

Reporting Summary

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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

The data we used are from MarketScan Commercial Claims and Encounters and Medicare Supplementary (more than 100 million patients, from 2012 to 2017). Access to the MarketScan data analyzed in this manuscript is provided by the Ohio State University. The dataset is available from IBM at <https://www.ibm.com/products/marketscan-research-databases>. We included 7.23 million enrollees in Medicare Supplemental Database from the MarketScan dataset. Pharmacy prescriptions of sildenafil, diltiazem, losartan, glimepiride and metformin were identified by using RxNorm and National Drug Code (NDC).

Drug-target interactions were collected from the DrugBank database (v4.3), the Therapeutic Target Database (TTD, v4.3.02), and the PharmGKB database (December 01, 2018). All bioactivity data related to FDA-approved drugs were collected from three commonly used databases: ChEMBL(v20), BindingDB (December 15, 2018), and IUPHAR/BPS Guide to PHARMACOLOGY (December 15, 2018).

Signaling networks derived from low-throughput experiments were downloaded from Signalink (v2.0). Genes were annotated to their Entrez ID using the NCBI database (August 01, 2018, <https://www.ncbi.nlm.nih.gov>) as well as their official gene symbols from GeneCards (<http://www.genecards.org/>).

Data analysis

Expression data were subjected to R statistical processing using the limma/Bioconductor package (v3.13). Source codes for network proximity analysis and disease module identification are available: <https://github.com/ChengF-Lab/GPSnet>.

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. 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

The raw expression datasets in this study are downloaded from GEO database (<https://www.ncbi.nlm.nih.gov/geo/>, GSE65067, GSE74437, GSE74438, GSE64398, GSE53480, GSE56772, and GSE57583). In total, we collected a total of 34 transcriptomic datasets consisting of original brain microarray data (n=17) and bulk RNA-seq data (n=17) from 7 types of transgenic mouse models, including 5XFAD, APP/PS1, HO-TASTPM, Tg2576, TgCRND8, Tau P301L, and rTg4510. The detailed mutations and neuropathology for these models are provided in Supplementary Tables. Tissue/brain-specific expression data were downloaded from GTEx database (<https://www.gtexportal.org/home/>). Human protein-protein interactome and drug-target interactions are free available at <https://github.com/ChengF-Lab/endoAD>

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](https://www.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	The pharmacoepidemiology study utilized the MarketScan Medicare Claims database from 2012 to 2017. The dataset included individual-level diagnosis codes, procedure codes and pharmacy claim data for 7.23 enrollees in Medicare Supplemental Database from the MarketScan dataset. This big patient database offers statistical power for all population-based observations. The numbers of patients for each analysis using different subgroups are: (1) entire cohort, sildenafil n = 116,412; non-sildenafil n = 460,356; diltiazem n = 251,360; losartan n = 664,265; glimepiride n = 159,597; metformin n = 723,082. (2) patients without coronary artery disease (CAD), hypertension (HT), and type-2 diabetes (T2D), sildenafil n = 56,518; diltiazem n = 113,600; losartan n = 275,116; glimepiride n = 52,623; metformin n = 303,008 (3) CAD subgroup, sildenafil n = 19,093; diltiazem n = 51,771; losartan n = 111,592; glimepiride n = 30,083; metformin n = 91,705 (4) HT subgroup, sildenafil n = 49,541; diltiazem n = 119,097; losartan n = 339,940; glimepiride n = 74,018; metformin n = 275,328 (5) T2D subgroup, sildenafil n = 21,978; diltiazem n = 51,300; losartan n = 156,308; glimepiride n = 100,298; metformin n = 367,754 (6) comparisons for sex, sildenafil female n = 2,280 and male n = 114,132; non-sildenafil female n = 8,182 and male n = 452,174; diltiazem female n = 150,137 and male n = 101,223; losartan female n = 385,454 and male n = 278,811; glimepiride female n = 72,689 and male n = 86,908; metformin female n = 344,944 and male n = 378,138 (7) comparisons for age, sildenafil 65-74 n = 89,875 and ≥75 n = 26,537; non-sildenafil 65-74 n = 264,209 and ≥75 n = 196,147; diltiazem 65-74 n = 115,892 and ≥75 n = 135,468; losartan 65-74 n = 389,084 and ≥75 n = 275,181; glimepiride 65-74 n = 97,243 and ≥75 n = 62,354; metformin 65-74 n = 505,210 and ≥75 n = 217,872
Data exclusions	We used the de-identified health insurance claims for drug-disease outcome analysis, which doesn't apply to clinical data and doesn't require IRB approval. Data exclusions are not applicable.
Replication	Quantification data represent mean ± SD of three independent experiments for in vitro assays. We used the de-identified health insurance claims for drug-disease outcome analysis, which doesn't apply to clinical data and doesn't require IRB approval. Replication is not applicable.
Randomization	We used the de-identified health insurance claims for drug-disease outcome analysis, which doesn't apply to clinical data and doesn't require IRB approval. Randomization is not applicable.
Blinding	We used the de-identified health insurance claims for drug-disease outcome analysis, which doesn't apply to clinical data and doesn't require IRB approval. Blinding is not applicable.

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
☒	☐ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data

Methods

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

Antibodies

Antibodies used	Antibodies against CDK5 (Cat# A5730), GSK3 β (Cat# A2081), and phospho-GSK3B-Y216 (Cat# AP0261) were obtained from ABclonal Technology. CDK5-Phospho-Tyr15 (Cat# YP0380) was purchased from Immunoway (Plano, Texas, USA). horseradish peroxidase (HRP)-conjugated secondary antibody (Rabbit anti-Human IgG Secondary Antibody (Cat # PA1-28587)) tau (Phospho) [pT181] Human ELISA Kit (KHO0631, Invitrogen). The secondary antibody was IgG-conjugated Alexa Fluor 488 (111-545-003, Jackson ImmunoResearch).
Validation	All antibodies were validated by the specific companies before used. The validation of all primary antibodies for the species are available from the manufacturer's website.

Eukaryotic cell lines

Policy information about [cell lines](#)

Cell line source(s)	Human microglia HMC3 cells were obtained from American Type Culture Collection (ATCC, Manassas, VA). An AD patient-derived iPSC line HVRDi001-A-1 were purchased from WiCell.
Authentication	Human microglia HMC3 cells were verified (PCR assay) by ATCC and iPSCs were verified (PCR assay) by WiCell before use.
Mycoplasma contamination	All cell lines tested negative for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in the study.