

Reporting Summary

Nature Research 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 Research 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	Details of software used by each study included in genome-wide meta-analyses (as listed in Supplementary Table 1 and main text): BOLT-LMM (v2.3.2, v2.3.4), EPACTS, GEMMA v0.94.1, GenABEL, ProbABEL (v0.4.5), IMPUTE, MACH2QTL, matlab, MiniMac, Plinkv1.07, PLINKv1.9, QUICKTEST 0.95, R, RareMetalWorker, SNPTest (v2, v2.5), SHAPEIT3, IMPUTE2, IMPUTE4. Some studies used in-house genome-wide analysis code which was study specific and so is not available. References are provided in the Methods for where software/code can be accessed. Specific versions of software (e.g. R) are listed where information was supplied by studies. RNA Seq data was processed using bcl2fastq2 Conversion Software v2.19, trimmomatic v0.36, hisat2, samtools, picard metrics, picard tools, Stringtie.
Data analysis	METAL; GCTA; Stata v14, v16; BOLT-LMM; LOFTEE; IGV; Variant Effect Predictor b38; PLINK v1.9, v1.90b4.4; SMR; DEPICT; LDSC-SEG; MAGENTA; Excel; SAIGE-GENE; LOFTEE; UCSC Lifter; Downstreamer; MAGMAv1.08; LDPRED; Radial-MR; R (v2.14.1). References are provided in the Methods for where software/code can be accessed.

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 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

Data availability statement:

Full genome-wide association summary statistics for the discovery meta-analysis are available from the ReproGen website (www.reprogen.org).

MII Oocyte dataset EGAS00001004947

SMR <https://cns.genomics.com/software/smr/#eQTLsummarydata>

Tabula Muris <https://tabula-muris.ds.czbiohub.org/>

LDSC-SEG <https://github.com/bulik/ldsc/wiki/Cell-type-specific-analyses>

RNA-seq samples <https://www.ebi.ac.uk/ena>

Human oocyte expression analyses: GSE107746, GSE107746

Source data for Fig. 1 are available from the ReproGen website.

Source data for Fig. 2-3; Extended Data Fig. 4, 8-10 are available.

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	Genome-wide meta-analyses were performed using all available study cohorts who agreed to participate. This was an increase in the sample size compared with previous published analyses that identified 56 genetic signals (n=70,000 vs n=200,000, Day, F.R. et al. Nat. Genet. 10, 1–19 (2017)). Similarly, the Mendelian Randomization (MR) analyses used the largest available GWAS summary statistics. We have previously demonstrated the ability to detect causal relationships based on summary statistics from smaller GWAS sample sizes. For the mouse model of environmentally-induced low ovarian reserve, power was determined based on effect sizes for gene expression differences observed in Aiken et al FASEB J. 30, 1548–56 (2016).
Data exclusions	For genome-wide meta-analyses, standard quality control criteria were applied by two analysts independently and only studies passing these checks were included in the meta-analyses. Within each individual study contributing genetic data, standard genotype qc protocols were followed.
Replication	A sample of 294,828 women from 23andMe, Inc was used as a replication cohort. We observed high concordance in effect estimates for the 290 signals identified in our main results with the replication analyses with nearly all variants at least nominally associated. We also evaluated the 290 signals identified by our main analyses in 78,317 women of East Asian ancestry, finding broad replication, consistent with previous observations (PMID: 29773799). Pathway and enrichment analyses were carried out using multiple software packages to explore consistency of results. Gene expression analyses in human oocytes were based on z-scores to enable comparison between data sources. The MII Oocytes single-cell RNA-seq dataset generated in this study was based on 11 MII oocytes. We used processed RNA-seq data of Fetal Primordial Germ Cells from Li et al (2017, Accession code: GSE86146) [PMID:28457750] from 17 human female embryos; and from Zhang et al (2018, Accession code GSE107746) [PMID: 30472193] ovarian tissue from 7 adult donors. For analysis of gene expression in mouse environmentally-induced low ovarian reserve models, gene expression was measured in 8 biologically independent animals from different litters in each group. For sChek1, Chek1 cKO, and Chek2 mice, experiments were performed in multiple mice and litters as detailed in the results. To test the natural breeding efficiency, cages were set with one or two adult (2-months or 12-month-old) control or females with a male of proven fertility. Litter sizes and dates of delivery were registered for all litters obtained during a period for up to one year.
Randomization	NA for population genetic analyses - all subjects with the available phenotype were included. For mouse environmentally-induced low ovarian reserve models, mice were randomized to different diets. There was no significant difference in the pre-culling litter size between obesogenic and control litters. Equal sex ratios within the litters were maintained as far as possible. For sChek1, Chek1 cKO, and Chek2 mice no randomization of the oocytes was performed as at each stage only the material necessary for the experiment was collected. All experiments were carried out using litter mate controls or with animals of closely related parents as controls.
Blinding	NA for genome-wide analyses - all subjects with the available phenotype were included. No blinding during data collection/analyses for mouse models. In the case of the environmentally-induced low ovarian reserve models, this was because mice were fed different diets. In the case of the Chek1, Chek1 cKO, and Chek2 models, this was as mice were genotyped two times, initially upon weaning and again before experimental procedures were carried out.

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
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used Rhodamine (TRITC)-AffiniPure Donkey Anti-Rabbit IgG (711-025-152, Jackson Immuno Research)

Validation As detailed on manufacturer's web site.

Animals and other organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research

Laboratory animals For mouse environmentally-induced low ovarian reserve model, female C57BL/6J mice were used. All animal experiments were carried out under the UK Home Office Animals (Scientific Procedures) Act (1986, United Kingdom). Female C57BL/6J mice were randomized to be fed ad libitum either a standard laboratory chow diet (7% simple sugars/3% fat; Special Dietary Services, Witham, UK) or an obesogenic diet. sChek1, Chek1 cKO, and Chek2 mice: lines were maintained in a C57BL6 (Chek1cKO) or C57BL/6-129Sv (Chek2 and sChek1) mixed background, respectively. Breeding cages were set in a conventional way with strict specific pathogen-free barrier and mice used for experiments were kept in individual ventilated cages (IVC). 12h light exposure was provided. Temperature, relative humidity and air changes per hour were 22 °C (+/-2 °C), 55% +/-10 %, and 17 respectively. Food and water were provided ad libitum. Age of mice included in specific experiments is detailed in the results.

Wild animals The study did not involve wild animals.

Field-collected samples The study did not involve samples collected from the field.

Ethics oversight For mouse environmentally-induced low ovarian reserve models: All animal experiments underwent ethical review by the University of Cambridge Animal Welfare and Ethical Review Board and were carried out under the UK Home Office Animals (Scientific Procedures) Act (1986, United Kingdom). sChek1, Chek1 cKO, and Chek2 mice: Mouse work at the University of Copenhagen (sChek1) was licensed under 2016-15-0202-00043 by the Danish Animal Experiments Inspectorate (Dyreforsøgstilsynet, Denmark). Mouse work at UAB (Chek2) was approved by the UAB and the Catalan Ethics Committee for Animal Experimentation (CEEAAH 1091; DAAM6395). Mouse work at CCHMC (Chek1) was performed according to the guidelines of the Institutional Animal Care and Use Committee (protocol no. IACUC2018-0040) approved by CCHMC. The Chek1 cKO, Zp3-Cre embryology was conducted at the Institute of Animal Physiology and Genetics CAS in Libeňov (Czech Republic), abiding by the policies of the Expert Committee for the Approval of Projects of Experiments on Animals of the Academy of Sciences of the Czech Republic (# 43-2015).

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

Human research participants

Policy information about [studies involving human research participants](#)

Population characteristics For studies included in the genome-wide analyses, details of sample size, mean age and mean age at natural menopause for each study are provided in Supplementary Table 1. We included women with age at natural menopause (ANM) from age 40 to 60 inclusive. ANM was derived from self-reported questionnaire data by each study (details of questions are provided in Supplementary Table 1) and was the age at last naturally occurring menstrual period followed by at least 12 consecutive months of amenorrhea. Exclusions were women with menopause caused by hysterectomy, bilateral ovariectomy, radiation or chemotherapy, and those using HRT before menopause.

Recruitment A range of study cohorts with data on post-menopausal European women were included in the genome-wide analyses - these included various study designs e.g. population cohort studies (e.g. UK Biobank), cancer studies (e.g. BCAC), and longitudinal studies (e.g. ALSPAC).

Ethics oversight

For studies included in the genome-wide analyses, within each of the studies, each participant provided written informed consent and the study protocol was approved by the institutional review board at the parent institution. Research on RNA expression in human eggs was carried out according to the Helsinki II declaration and was conducted in accordance with national regulation on research on human subjects and material. The research was approved by the Scientific Ethical Committee of the Capital Region of Denmark (Videnskabsetisk Komite) in accordance with Danish National regulation (H-2-2011-044; extension license amm. Nr. 51307; license holder: Claus Yding Andersen and H-1604473; license holder: Eva R. Hoffmann; H-16027088 granted to Marie Louise Grøndahl). GDPR approval was obtained from the national data agency (SUND-2016-60, Eva R Hoffmann and HGH-2016_086 to Marie Louise Grøndahl).

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