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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	All flow cytometry data were acquired on an LSRII or FACSAria II (BD Biosciences) using FACSDiva v8.0.3 software. ATAC-seq DNA libraries were sequenced on an Illumina HiSeq 2500. RNA-seq DNA libraries were sequenced on an Illumina NextSeq 500. qPCR data were acquired on an Applied Biosystems 7500 Fast Real-Time PCR System. Histology slides were scanned with a NanoZoomer 2.0RS (Hamamatsu).
Data analysis	Flow Cytometry data were analyzed with FlowJo 10.3.0 software. Cardiac MRI data were analyzed with HOROS software. ATAC-seq data were analyzed using BWA-MEM, HOTSPOT2 and edgeR software. RNA-seq data were analyzed using Salmon, tximport, edgeR and clusterProfiler. ImageJ 1.51a was used for histology image analysis. SPSS 21.0 and GraphPad Prism 7.0c were used for statistical analysis.

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

Raw sequencing data are available from Gene Expression Omnibus, accession numbers GSE110639 and GSE124799.

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	No statistical methods were used to predetermine sample size. We did all experiments at least 2-3 times, with groups of at least n=3-5. From previous experience on either HSPC biology, niche factors, and inflammatory responses, we estimated how many mice we would approximately need.
Data exclusions	Statistical outliers (not more than one per experiment) were determined with the two-sided Grubbs' outlier test (GraphPad Prism) and excluded.
Replication	All experiments were reproduced at least once. All reproductions were successful.
Randomization	Mice were randomly assigned to groups at the start of experiments. For ApoE-/- mice, we determined leukocyte counts in all mice after 10 weeks of diet and allocated them into two groups of equal leukocyte counts to ensure same starting leukocyte levels prior to determining effects of exercise.
Blinding	Investigators were generally not blinded to group allocation. However, the analysis of the effect of exercise prior to cecal ligation and puncture as well as myocardial infarction and the effect of leptin inhibition after myocardial infarction were performed in a blinded fashion.

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 used for flow cytometry (all purchased from BioLegend unless indicated otherwise):
Biotin-conjugated antibodies (dilution for all 1:300): CD3 (100304, clone 145-2C11), CD4 (100404, clone GK1.5), CD8α (100704, clone 53-6.7), CD49b (108904, clone DX5), CD90.2 (105304, clone 30-H12), CD19 (115503, clone 6D5), B220 (103204, clone RA3-6B2), NK1.1 (108704, clone PK136), TER119 (116204, clone TER-119), CD11b (101204, clone M1/70), CD11c (117304, clone N418), Gr1 (108404, clone RB6-8C5).
PE-conjugated antibodies (dilution for all 1:300): B220 (103208, clone RA3-6B2), CD19 (115508, clone 6D5), CD3 (100206, clone 17A2), CD90.2 (140308, clone 53-2.1), CD49b (108908, clone DX5), CD103 (121406, clone 2E7), NK1.1 (108708, PK136) and Ter119 (116208, clone TER-119).
Antibodies conjugated to other fluorophores (dilution 1:300 unless stated otherwise): CD16/32-BV711 (101337, clone 93, 1:150), CD34-FITC (553733, clone RAM34, BD Biosciences, 1:150), CD48-AF700 (103426, clone HM48-1), CD115-BV421 (135513, clone AFS98), CD150-PerCP/Cy5.5 (115922, clone TC15-12F12.2), c-kit-PE/Cy7 (105814, clone 2B8, 1:150), Sca-1-BV605 (108133, clone D7, 1:150), BrdU-APC (552598, BD Biosciences, 1:50), Ki-67-FITC (11-5698-82, Thermo Fisher Scientific), CD11b-APC (101212, clone M1/70), CD45-BV711 (103147, clone 30-F11), F4/80-PECy7 (123114, clone BM8), Ly-6C-BV605 (128035, clone HK1.4), Ly-6G-FITC (127605, clone 1A8), B220-PE/Cy7 (103222, clone RA3-6B2), B220-APC/Cy7 (103224, clone RA3-6B2), CD3-PE (100206, clone 17A2), CD4-PerCP/Cy5.5 (100434, clone GK1.5), CD8α-BV711 (100748, clone 53-6.7), CD19-PE/Cy7 (115520, clone 6D5), CD19-APC/Cy7 (115530, clone 6D5), CD45.2-AF700 (109822, clone 104), NK1.1-APC/Cy7 (108730, clone PK136).

Antibodies used for in vivo experiments:
Mouse Leptin/OB Antibody (AF498, R&D Systems) and Normal Goat IgG Control (AB-108-C, R&D Systems).

Validation	All antibodies used for flow cytometry were previously validated for flow cytometry on murine cells by the respective manufacturers. In vitro and in vivo validation of the anti-leptin antibody was previously performed by Konstantinides et al. (Konstantinides S, Schäfer K, Neels JG, Dellas C, Loskutoff DJ. Inhibition of endogenous leptin protects mice from arterial and venous thrombosis. Arterioscler Thromb Vasc Biol 2004, 24(11): 2196-2201).

Animals and other organisms

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

Laboratory animals	The following mouse strains were used in this study: C57BL/6J, C57BL/6-Tg(UBC-GFP)30Scha/J, B6.SJL-PtprcaPepcb/BoyJ, B6.129P2-Apoetm1Unc/J, Nestin-GFP, LeptinRcre-R26-YFP and -R26-Tdtomato, OCN-GFPtopaz, CD45.1STEM, and B6.Cg-Tg(Prrx1-cre/ERT2,-EGFP)1Smkm/J crossed with B6.129P2-Leprtm1Rck/J. Seven- to eight-week-old mice of both genders were used for experiments.
Wild animals	This study did not involve wild animals.
Field-collected samples	This study did not involve field-collected samples.
Ethics oversight	All experiments were approved by the Subcommittee on Animal Research Care at Massachusetts General Hospital. All efforts were made to minimize suffering.

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	The population characteristics for The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) are described in Ridker et al. (Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ; CANTOS Trial Group. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017, 377(12): 1119-1131). Multivariate regression analyses were used to address for effects after adjustment for age, gender, body mass index, education level, history of heart failure and hemoglobin A1c. From the Athero-Express registry, 913 participants (mean age of 68.9 years, 73.1% males) were included in this study. Patient characteristics of the Athero-Express cohort are in detail listed in Supplementary Table 3.
Recruitment	CANTOS: Patient recruitment was performed at participating centers in 39 countries. Patients were eligible for enrollment if they had a history of myocardial infarction and a blood level of high-sensitivity C-reactive protein of 2 mg or more per liter despite the use of aggressive secondary prevention strategies. Additional details on patient recruitment are listed in in Ridker et al. (Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ; CANTOS Trial Group. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017, 377(12): 1119-1131). Athero-Express: Patient recruitment was performed at University Medical Center Utrecht (UMCU, the Netherlands). Patients undergoing carotid endarterectomy or femoral vascular procedures were eligible for enrollment. Additional details on patient recruitment are listed in Verhoeven et al. (Verhoeven BA , Velema E, Schoneveld AH, de Vries JP, de Bruin P, Seldenrijk CA, de Kleijn DP, Busser E, van der Graaf Y, Moll F, Pasterkamp G. Athero-express: differential atherosclerotic plaque expression of mRNA and protein in relation to cardiovascular events and patient characteristics. Rationale and design. Eur J Epidemiol. 2004, 19(12): 1127-33) and Hellings et al. (Hellings WE, Moll FL, de Kleijn DP, Pasterkamp G. 10-years experience with the Athero-Express study. Cardiovasc Diagn Ther. 2012, 2(1): 63-73).
Ethics oversight	CANTOS: The study protocol was approved at participating centers by the responsible institutional review board or ethics committee, as applicable in the 39 countries involved. An independent data and safety monitoring committee oversaw the trial. Athero-Express: The study protocol was approved by the medical ethics committee of the UMCU.

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

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Sample preparation is described in detail in the Methods section.
Instrument	LSRII (for flow cytometry) and FACSAria II (for cell sorting), both BD Biosciences.
Software	FACSDiva v8.0.3 (for acquisition) and FlowJo v10.3.0 (for analysis).
Cell population abundance	The purity of sorted cells was >95%.
Gating strategy	The gating strategy is described in the Methods section and gating strategies are provided either in main figures or extended data figures. All samples were pre-gated on viable and single cells (FSC-A vs FSC-W, and SSC-A vs SSC-W).

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.