Extended data 1: Impact of a history of early-life stress on object recognition memory and peripheral inflammatory signatures in mature adulthood.

a, Shown is a schematic representation of the MS paradigm performed in SD rats. **b,** Animals were tested for object recognition memory using the novel object recognition (NOR) task, wherein C and MS animals in mature adulthood (6-7 months) were first habituated to the NOR arena for 3 consecutive days prior to exposure on day 4 to two identical objects. Short-term object recognition memory was assessed on day 5 by replacing one of the identical objects with a novel object of similar dimensions. **c,** Short-term object recognition memory was assessed by determining the discrimination index in mature adult C and MS rats. Results are combined for both males (lighter shade) and females (darker shade) (C: n = 10 [6 males; 4 females], MS: 10 [6 males; 4 females]. **d,** Shown is a schematic representation of serum harvested from an independent cohort of mature adult C and MS rats for analysis of inflammation, aging-associated markers using immunoassay, as well as assessment of circulating cell free mtDNA (ccf-mtDNA) content using the MitoQuicLy method. Shown are graphs for the following serum markers in mature adult C and MS rats, namely **(e)** GDF15, **(f)** CRP, **(g)** IL1ß, **(h)** IFNγ, **(i)** TNFα, and **(j)** IL10, **(k)** IL4, **(l)** IL6, and **(m)** IL18 [C: n = 16 (8 males; 8 females), MS: n = 16 (8 males; 8 females)]. **n,** Shown is a graph for ccf-mtDNA using serum samples harvested from mature adult C and MS rats (C: n = 10 (6 males; 4 females), MS: n = 10 (6 males; 4 females). Data are represented as mean ± SEM and with individual data points depicted as dots in the graphs (males – lighter shade; females – darker shade). *$p < 0.05$ as compared to C; unpaired Student's *t*-test.

Extended data 2: A history of early-life stress impairs short and long-term object recognition memory in middle-aged male and female animals.

a, SD rats were subjected to early adversity using the maternal separation (MS) paradigm, which involved a daily separation (3 hours) of the litters from their dams from postnatal day 2 (P2) to P14, whilst control (C) litters were left undisturbed. **b,** Male and female animals from C and MS groups were tested for object recognition memory using NOR task, wherein middle-aged animals (13-15 months) were first habituated to the NOR arena for 3 consecutive days prior to exposure on day 4 to two identical objects. Short and long-term object recognition memory were assessed on day 5 and day 10 respectively, by replacing one of the identical objects with a novel object of similar dimensions. **c-f,** Graphs show short **(c-d)** and long-term **(e-f)** object recognition memory represented by determining the discrimination index in middle-aged male **(c, e)** and female **(d, f)** rats from C and MS groups. (C: n = 14 males; 9 females, MS: 14 males; 12 females). Data are represented as mean ± SEM and with individual data points depicted as dots in the graphs. *$p < 0.05$ as compared to C; unpaired Student's *t*-test.

Extended data 3: Object recognition memory impairment observed in middle-aged MS rats is comparable to aged control animals.

a, Shown is a schematic representation of the MS paradigm performed in SD rats. **b,** Animals from C and MS groups were tested for object recognition memory using NOR task, wherein middle-aged C and MS (13-15 months) as well as aged C (22 months) animals were first habituated to the NOR arena for 3 consecutive days prior to exposure on day 4 to two identical

objects. Short-term object recognition memory was assessed on day 5 replacing one of the identical objects with a novel object of similar dimensions. **c,** Short-term object recognition memory was assessed by determining the discrimination index in middle-aged C (n = 14 males), middle-aged MS (n = 14 males), and aged C animals (n = 18 males). Data are represented as mean ± SEM and with individual data points depicted as dots in the graphs. *p < 0.05 as compared to middle-aged C, one-way ANOVA followed by Tukey's post-hoc comparison.

Extended data 4: Correlation matrix depicting an association between novel object recognition and inflammatory markers in middle-aged control and MS animals.

a-b, Shown is a schematic representation of the NOR task performed in **(a)** middle-aged MS and **(b)** C animals, with serum harvested post NOR task for analysis of inflammatory markers using immunoassays. **c-d,** Shown is a correlation matrix denoting Pearson's correlation coefficient (r) evaluated between discrimination index scored by novel object recognition (NOR) task and several circulating inflammatory markers namely IL1ß, TNFα, IL10, IFNγ, CRP, GDF15 in middle-aged **(c)** MS and **(d)** C animals (C: n = 23 [14 males; 9 females], MS: 26 [14 males; 12 females]). The underlying matrix indicates nature and extent of association, with positive correlation represented in yellow and negative correlation represented in blue. Data represented as a Pearson's correlation coefficient ranging from -1 to +1 and derived from a comparison to NOR score of +1. *p < 0.05; unpaired Student's *t*-test.

Extended data 5: Impact of early-life stress on complete blood count measures in mature adult and middle-aged male animals.

a, Shown is a schematic representation of the MS paradigm performed in SD rats, with blood harvested from C and MS animals in mature adulthood or middle-aged life for assessment of complete blood count. **b-c,** Shown is a table for complete blood count measures namely white blood cells (WBCs), red blood cells (RBCs), platelets, haemoglobin, hematocrit in blood harvested from **(b)** adult and **(c)** middle-aged C and MS male animals (C: n = 6, MS: n = 6). Data are represented as mean ± SEM. *p < 0.05 as compared to C; unpaired Student's *t*-test.

Extended data 6: Early-life stress does not alter neuroinflammatory signatures in the hippocampi of mature adult animals.

a, Shown is a schematic representation of the maternal separation (MS) paradigm followed by assessing neuroinflammation-associated signatures in the hippocampus in mature adulthood, namely NLRP3 inflammasome marker expression, and immunofluorescence studies to assess activation of microglia using Iba1. **b,** Shown are representative western blots for hippocampal protein expression of NLRP3, ASC, and NF-κB in mature adult C and MS rats, along with β-actin used as a protein loading control. **c,** Graph depicts relative protein expression for NLRP3 inflammasome markers namely NLRP3, ASC, and NF-κB in the hippocampi of adult C and MS rats. Data is represented as a fold change of middle-aged C rats (mean ± SEM) with protein expression normalized to β-actin (C: n = 4 males, MS: n = 4 males). **d-g,** Graphs represent the number of activated microglia/mm^2 in the hippocampal subfields namely **(d)** CA1, **(e)** CA3, **(f)** DG, and **(g)** hilus from adult C and MS rats (C: n = 6 males, MS: n = 6 males). Data are

represented as mean ± SEM, with individual data points depicted as dots in the graphs. *p < 0.05 as compared to C; unpaired Student's *t*-test.

Extended data 7: Early-life stress does not disrupt mitochondrial health and function in the hippocampi of mature adult animals.

a, Shown is a schematic representation of the maternal separation (MS) paradigm followed by assessing mtDNA content, cellular ATP levels and mtROS production in hippocampi of adult C and MS animals. **b,** Graphs represent relative mtDNA content in hippocampi derived from adult C and MS male and female animals (C: n = 19 [10 males; 9 females], MS: n = 19 [10 males; 9 females]). **c,** graphical representation of relative cellular ATP levels assessed in hippocampi derived from mature adult C and MS male and female animals (C: n = 14 [7 males; 7 females], MS: n = 14 [7 males; 7 females]). **d**, Graph represents mitochondrial reactive oxygen species (mtROS) production in the form of hydrogen peroxide in mitochondria (mtH_2O_2) harvested from hippocampi of mature adult C and MS rats (C: n = 5 males, MS: n = 5 males). Data are represented as mean ± SEM, with individual data points depicted as dots in the graphs (males – lighter shade; females – darker shade). *p < 0.05 as compared to C; unpaired Student's *t*-test.

Extended data 8: Impact of nicotinamide supplementation on peripheral inflammatory markers in middle-aged rats with a history of early-life stress.

a, Shown is a schematic representation of the paradigm for nicotinamide (NAM; 100 mg/kg/day) supplementation through drinking water commencing from 8 months of age for 5 months (CD and MSD: age-matched C and MS animals with regular drinking water; CN and MSN: age-matched C and MS animals with NAM supplemented drinking water). Serum was harvested for analysis of inflammation-associated markers using immunoassays. **b-e**, Shown are graphs for serum markers namely **(b)** eNAMPT, **(c)** IL6, **(d)** IL10, and **(e)** TNFα levels in middle-aged CD, MSD, CN and MSN male and female animals (CD: n = 19 [11 males; 8 females], MSD: n = 16 [8 males; 8 females], CN: n = 18 [10 males; 8 females], MSN: n = 23 [15 males; 8 females]). Data are the mean ± SEM with individual data points depicted as dots in the graphs (males – lighter shade; females – darker shade). $^{*}p$ < 0.05 (Interaction effect on Two-way ANOVA between the variables of MS and NAM); $^{@}p$ < 0.05 (compared with CD: Control group on regular drinking water, Tukey's post-hoc test); $^{₹}p$ < 0.05 (compared with MSD: MS group on regular drinking water, Tukey's post-hoc test).