Supplementary Fig. 1 l Transition of cHMW adiponectin level in the longitudinal data of TOOTH study
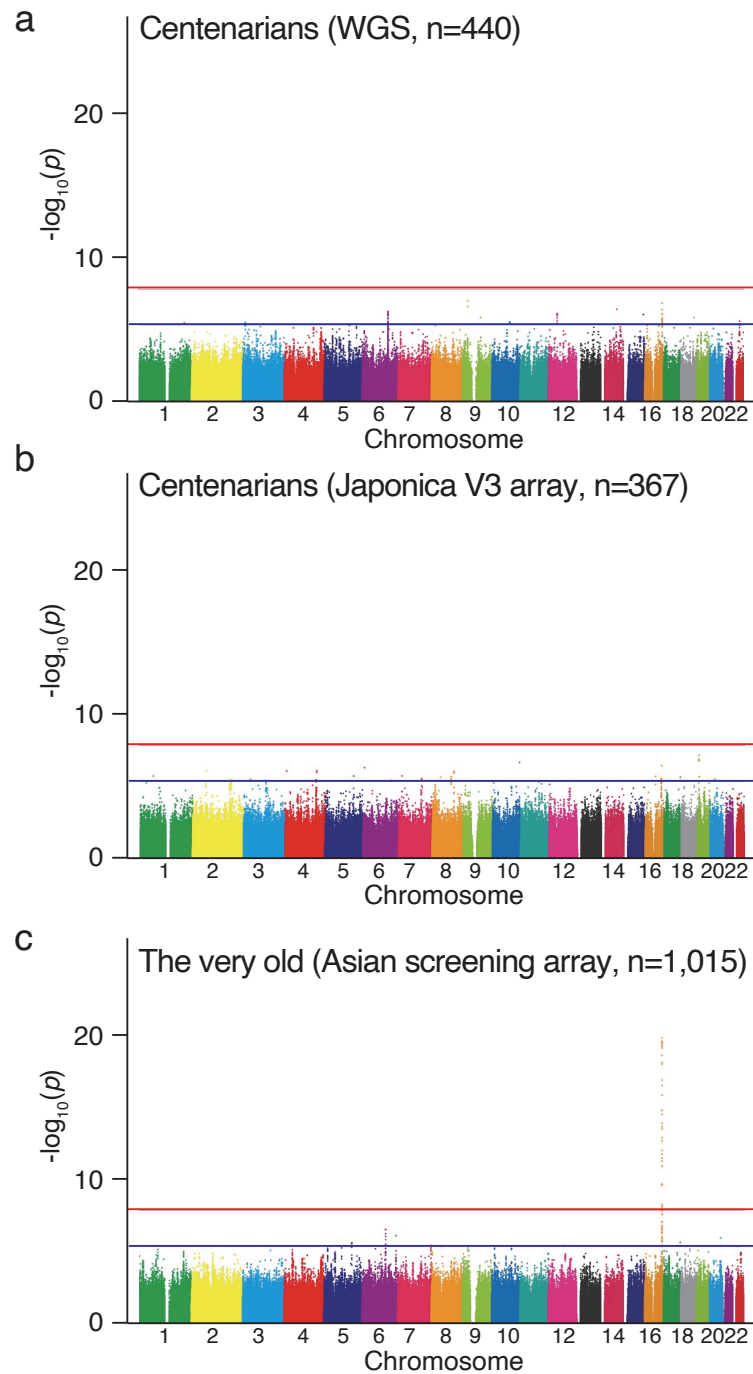
(a), Transition of cHMW adiponectin level at baseline and 3-year follow-up studies.
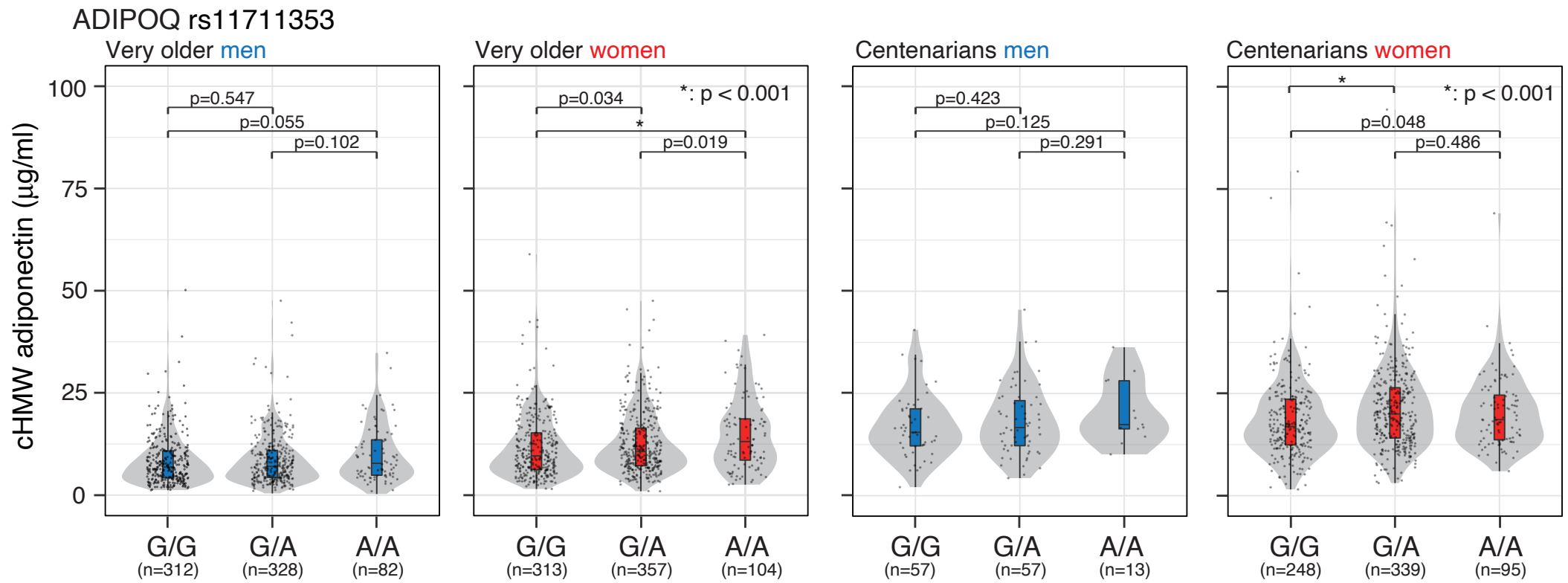
(b), Difference of cHMW adiponectin level between baseline and 3-year follow-up studies.

The cHMW adiponectin level is gradually increasing during very old.

a Centenarians (WGS, n=440)

b Centenarians (Japonica V3 array, n=367)

c The very old (Asian screening array, n=1,015)

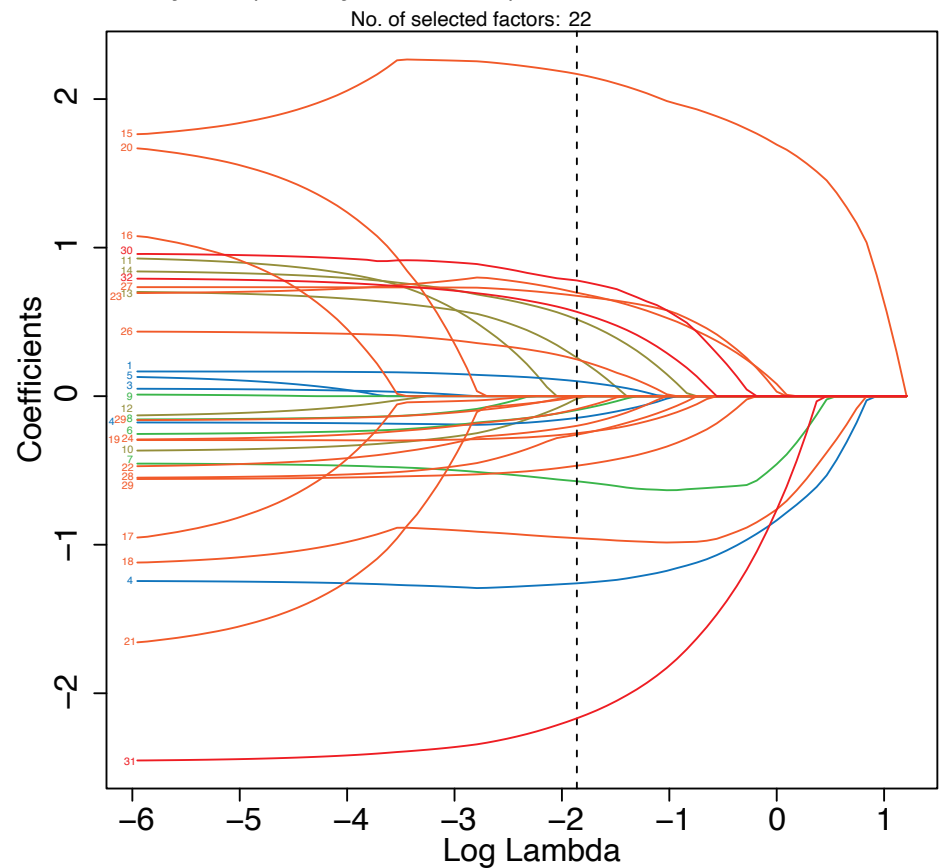**Supplementary Fig. 2 l GWAS for cHMW adiponectin level**

(a), GWAS for cHMW adiponectin level in centenarians (n=440) determined by whole genome sequencing (WGS). (b), GWAS for cHMW adiponectin level in centenarians (n=367) determined by genotyping by DNA microarray (Japonica V3 array) and DNA sequence imputation. (c), GWAS result for cHMW adiponectin level in the very old (n=1,015) determined by genotyping using DNA microarray (Asian screening array, Illumina) and DNA sequence imputation.

Supplementary Fig. 3 | Distribution of cHMW adiponectin level in rs11711353 (ADIPOQ) genotypes of the very old and centenarians

(a) The very old (85-89yo, n=1,314)

No. of selected factors: 22

(b) Centenarians (100-yo, n=352)

No. of selected factors: 7

Basic information (5)
1 Age
2 BMI
3 SBP
4 Years of education
5 Smoking history

Pysical and Cognitive function(4)
6 IADL score
7 Hand grip
8 Cognitive impairment
9 WHO5 score

Disease histories (5)
10 Heart disease
11 Diabetes
12 Cancers
13 Renal disease
14 Fracture

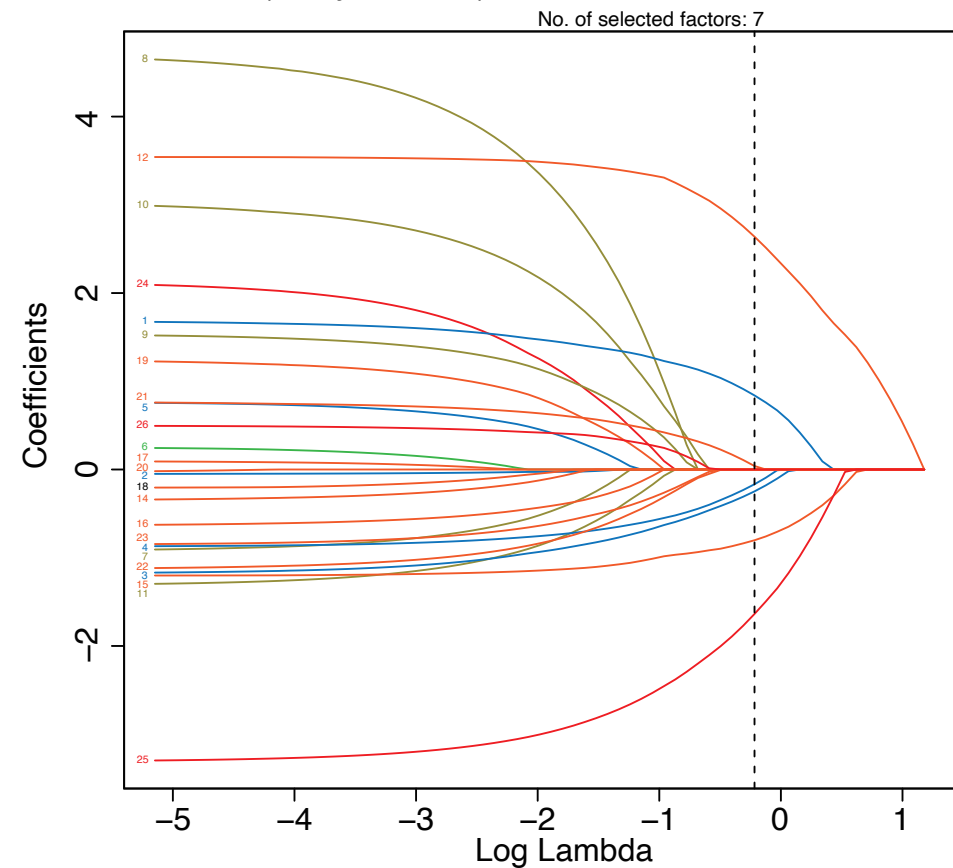Biomarkers in blood (15)
15 HDLC
16 TCHO
17 LDLC
18 TG
19 CHE
20 AST
21 ALT
22 γGTP
23 LDH
24 UA
25 ALB
26 CstC
27 NTproBNP
28 HBA1c
29 IL6

Genetic factors (3)
30 SEX
31 *CDH13* rs4783244
32 *ADIPOQ* rs11711353

Basic information (5)
1 Age
2 BMI
3 SBP
4 Education categry
5 Smoking history

Pysical and Cognitive function(1)
6 ADL score

Disease histories (5)
7 Heart disease
8 Diabetes
9 Cancers
10 Renal disease
11 Fracture

Biomarkers in blood (12)
12 HDLC
13 TCHO
14 LDLC
15 TG
16 CHE
17 γGTP
18 UA
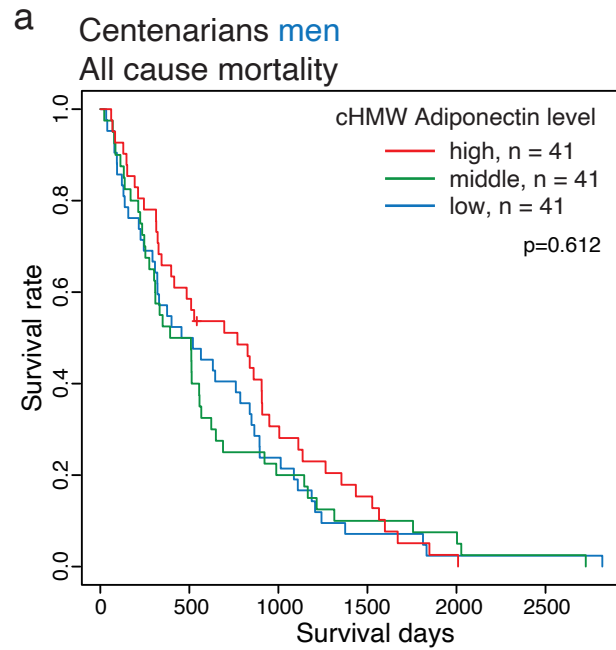19 ALB
20 CstC
21 NTproBNP
22 HBA1c
23 IL6

Genetic factors (3)
24 SEX
25 *CDH13* rs4783244
26 *ADIPOQ* rs11711353

Supplementary Fig. 4 | LASSO with five-fold cross-validation against 1,314 very old and 352 centenarians
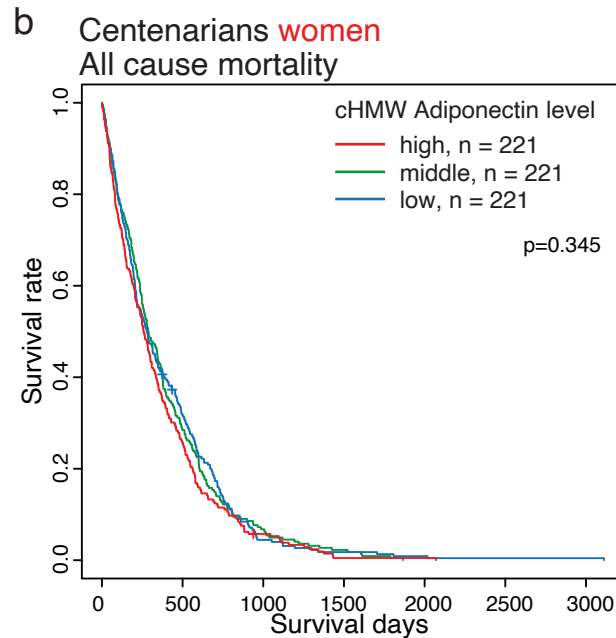
(a), LASSO with five-fold validation analysis against 1,314 very old. As a result of five-fold cross-validation, 22 factors shown in black in the bottom column were selected for further multivariate regression analysis. (b), LASSO with five-fold validation analysis against 352 centenarians. As a result of five-fold cross-validation, 7 factors shown in black in the bottom column were selected for further multivariate regression analysis.

a
Centenarians men
All cause mortality

cHMW Adiponectin level
— high, n = 41
— middle, n = 41
— low, n = 41

p=0.612

b
Centenarians women
All cause mortality

cHMW Adiponectin level
— high, n = 221
— middle, n = 221
— low, n = 221

p=0.345

Supplementary Fig. 5 | Survival time analysis for all-cause mortality against the three quantile groups of cHMW adiponectin levels in centenarians men and women
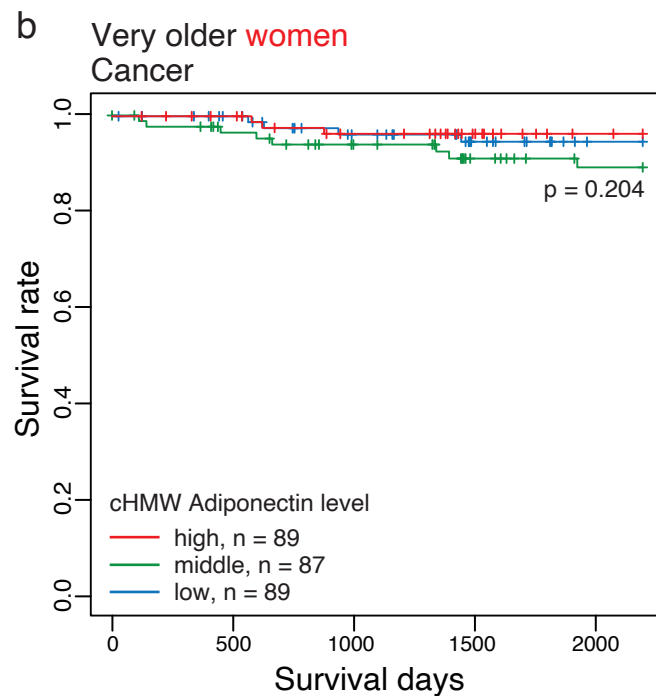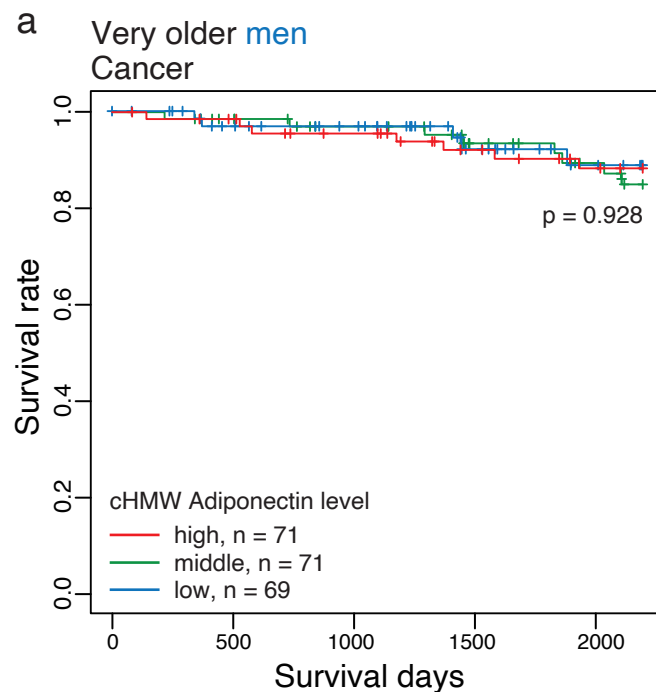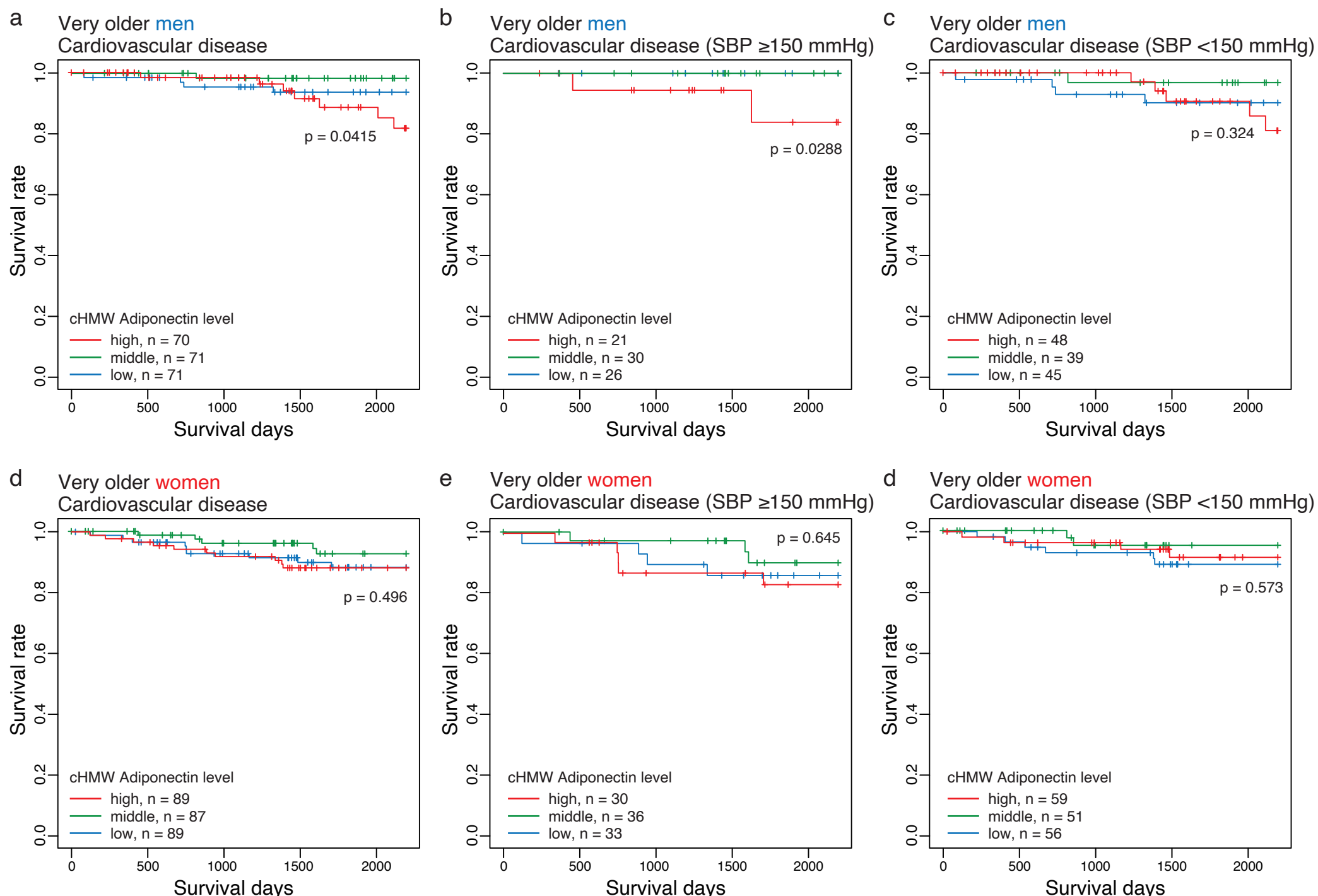
(a), Survival analysis for all-cause mortality of Centenarian men grouped by cHMW adiponectin level. No significant difference among the three cHMW adiponectin level different groups was observed.
(b), Survival analysis for all-cause mortality of Centenarian women grouped by cHMW adiponectin level. No significant difference among the three cHMW adiponectin level different groups was observed.

a

Very older men
Cancer

Survival rate

p = 0.928

cHMW Adiponectin level
— high, n = 71
— middle, n = 71
— low, n = 69

Survival days

b

Very older women
Cancer

Survival rate

p = 0.204

cHMW Adiponectin level
— high, n = 89
— middle, n = 87
— low, n = 89

Survival days

Supplementary Fig. 6 | Survival time analysis for cancer-cause mortality against the three quantile groups of cHMW adiponectin levels in very older men and women
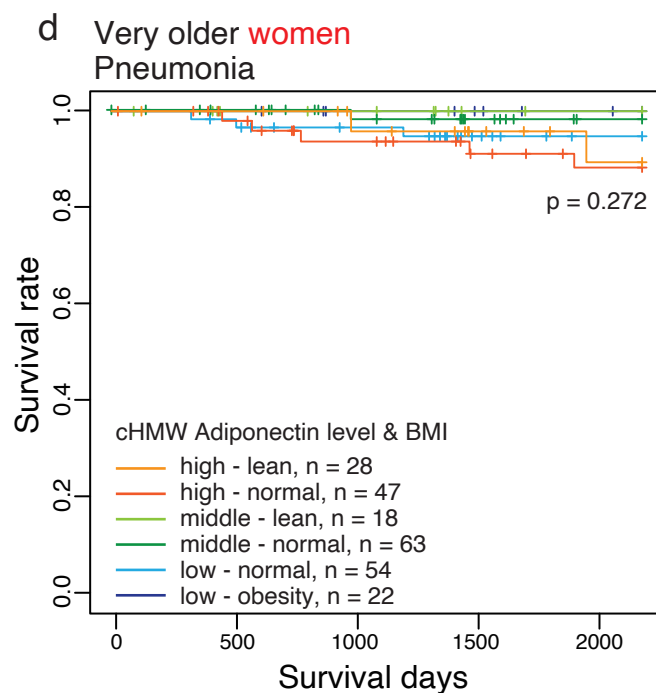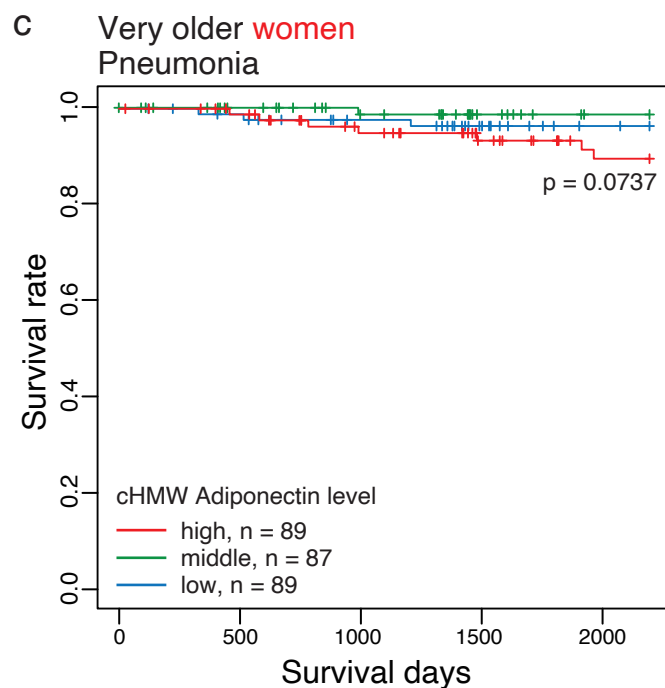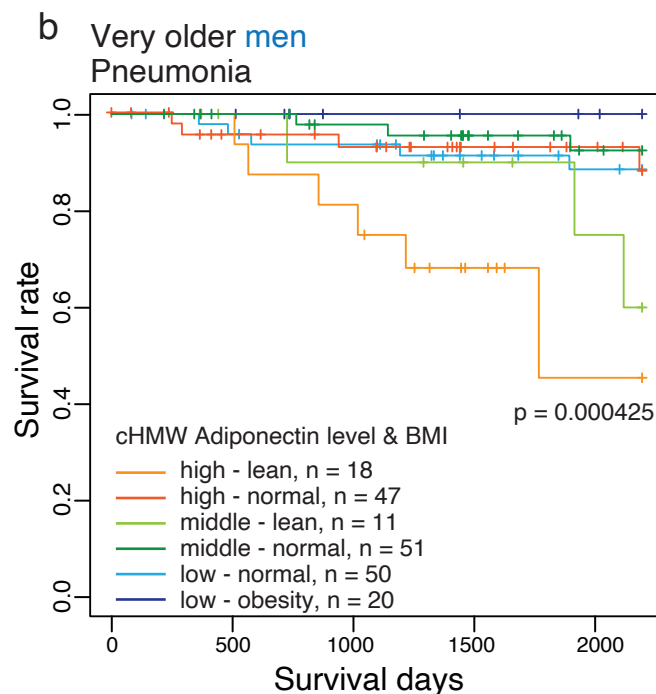
(a), Survival analysis for cancer-cause mortality of very older men grouped by cHMW adiponectin level. There was no significant difference among the three cHMW adiponectin level groups in very older men. (b), Survival analysis for cancer -cause mortality of very older women grouped by cHMW adiponectin level. There was no significant difference among the three cHMW adiponectin level different groups in very older women.

Supplementary Fig. 7 | Survival time analysis for cardiovascular disease-cause mortality against the three quantile groups of cHMW adiponectin levels in very older men and women
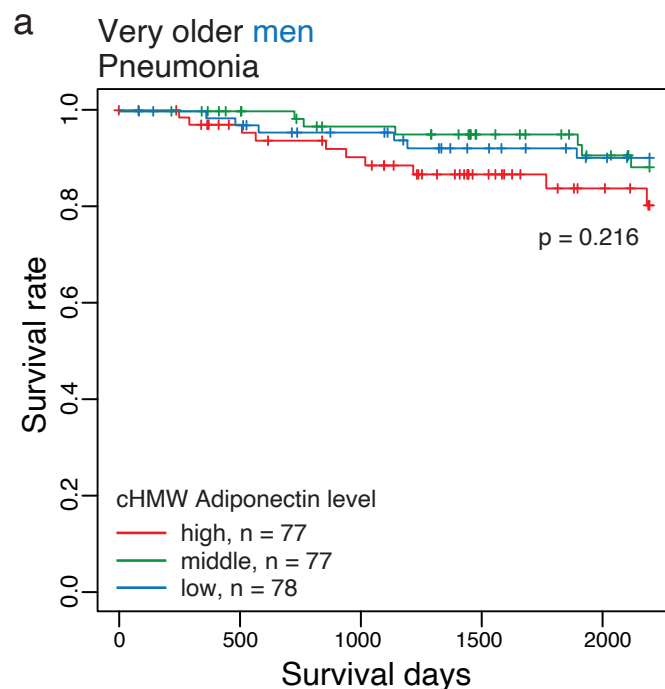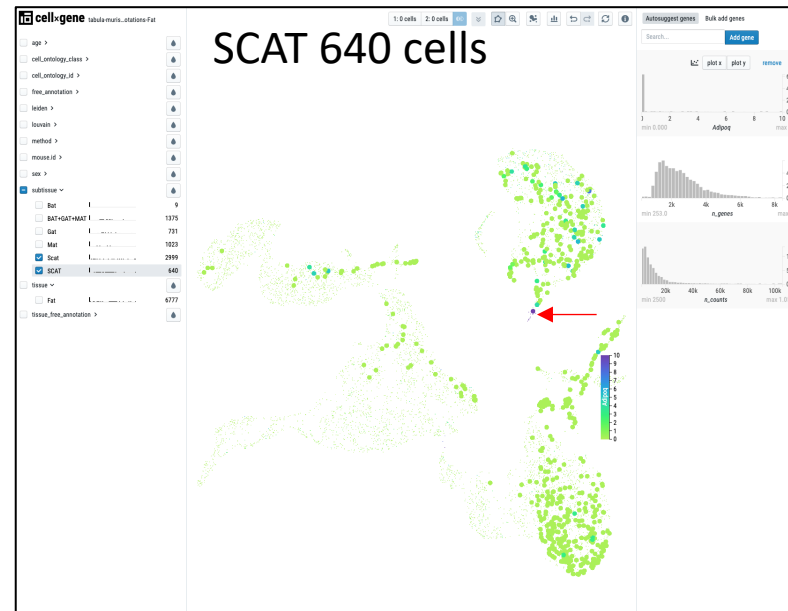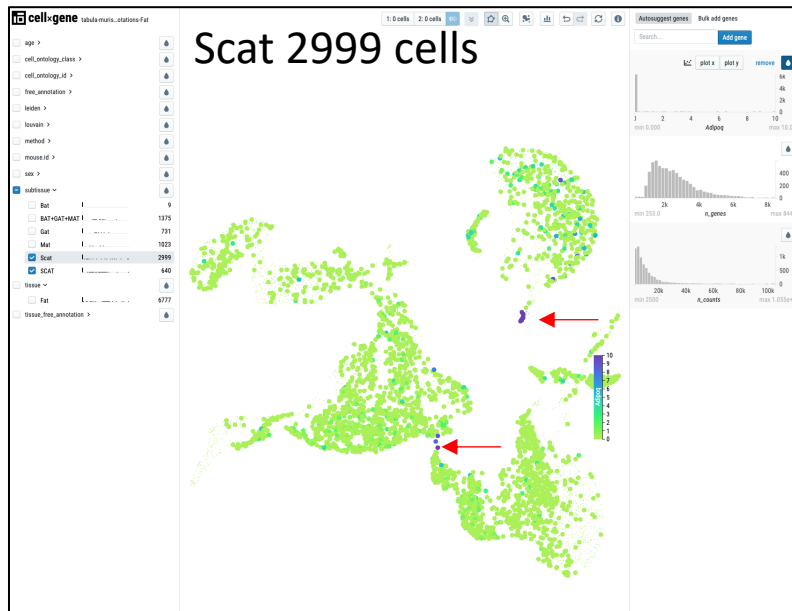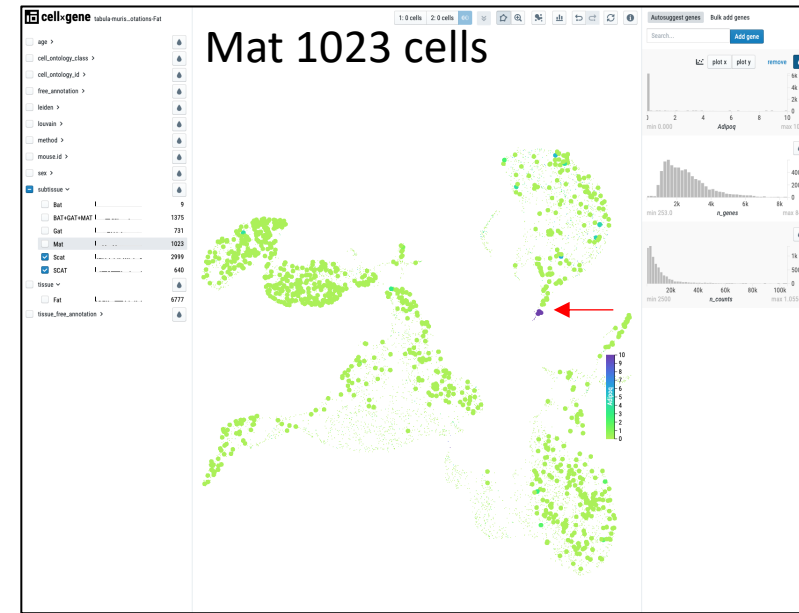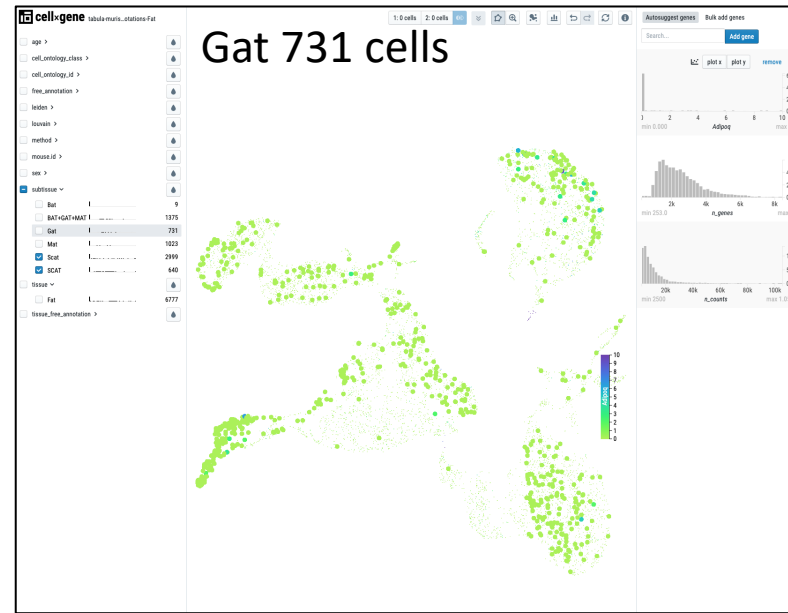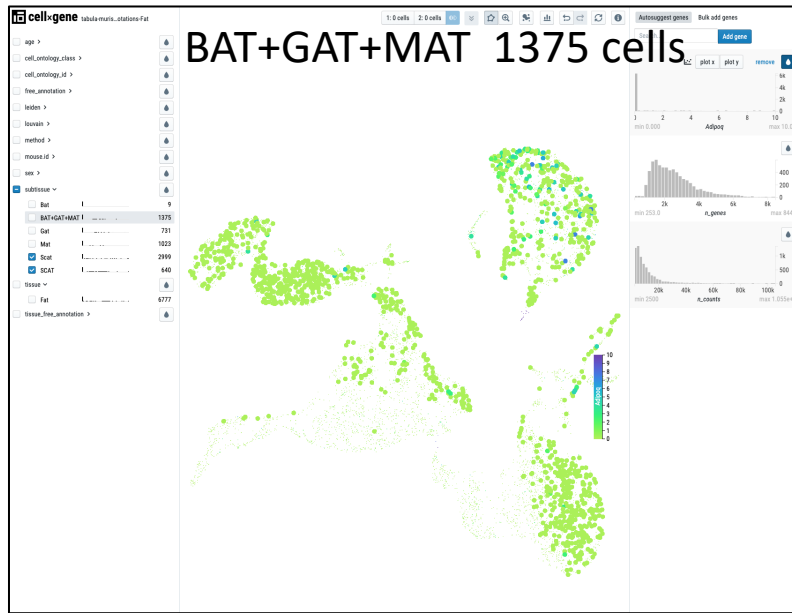
(a) Survival analysis for cardiovascular-cause mortality in very older men grouped by cHMW adiponectin level. The high cHMW adiponectin group in very older men showed a significant cardiovascular-cause mortality difference. (b), Survival analysis for cardiovascular-cause mortality in very oldere men grouped by cHMW adiponectin level and high blood pressure (SBP ≥ 150mmHg). The high cHMW adiponectin group in very older men with high blood pressure (SBP ≥ 150mmHg) showed a significant cardiovascular-cause mortality difference. (c), Survival analysis for cardiovascular-cause mortality in very older men grouped by cHMW adiponectin level without high blood pressure (SBP < 150mmHg). No significant cardiovascular-cause mortality difference was observed among three cHMW adiponectin level groups without high blood pressure in very older men. (d), Survival analysis for cardiovascular-cause mortality in very older women grouped by cHMW adiponectin level. No significant cardiovascular-cause mortality difference was observed among three cHMW adiponectin level groups in very older women. (e), Survival analysis for cardiovascular-cause mortality in very older women grouped by cHMW adiponectin level and high blood pressure (SBP ≥ 150mmHg). No significant cardiovascular-cause mortality difference was observed among three cHMW adiponectin level groups with high blood pressure (SBP ≥ 150mmHg) in very older women. (f), Survival analysis for cardiovascular-cause mortality in very older women grouped by cHMW adiponectin level and no high blood pressure (SBP < 150mmHg). No significant cardiovascular-cause mortality difference was observed among three cHMW adiponectin level groups without high blood pressure (SBP < 150mmHg) in very older women.

a Very older men
Pneumonia

Survival rate vs Survival days

p = 0.216

cHMW Adiponectin level
— high, n = 77
— middle, n = 77
— low, n = 78

b Very older men
Pneumonia

Survival rate vs Survival days

p = 0.000425

cHMW Adiponectin level & BMI
— high - lean, n = 18
— high - normal, n = 47
— middle - lean, n = 11
— middle - normal, n = 51
— low - normal, n = 50
— low - obesity, n = 20

c Very older women
Pneumonia

Survival rate vs Survival days

p = 0.0737

cHMW Adiponectin level
— high, n = 89
— middle, n = 87
— low, n = 89

d Very older women
Pneumonia

Survival rate vs Survival days

p = 0.272

cHMW Adiponectin level & BMI
— high - lean, n = 28
— high - normal, n = 47
— middle - lean, n = 18
— middle - normal, n = 63
— low - normal, n = 54
— low - obesity, n = 22

Supplementary Fig. 8 | Survival time analysis for pneumonia-cause mortality against the three quantile groups of cHMW adiponectin levels in very older men and women
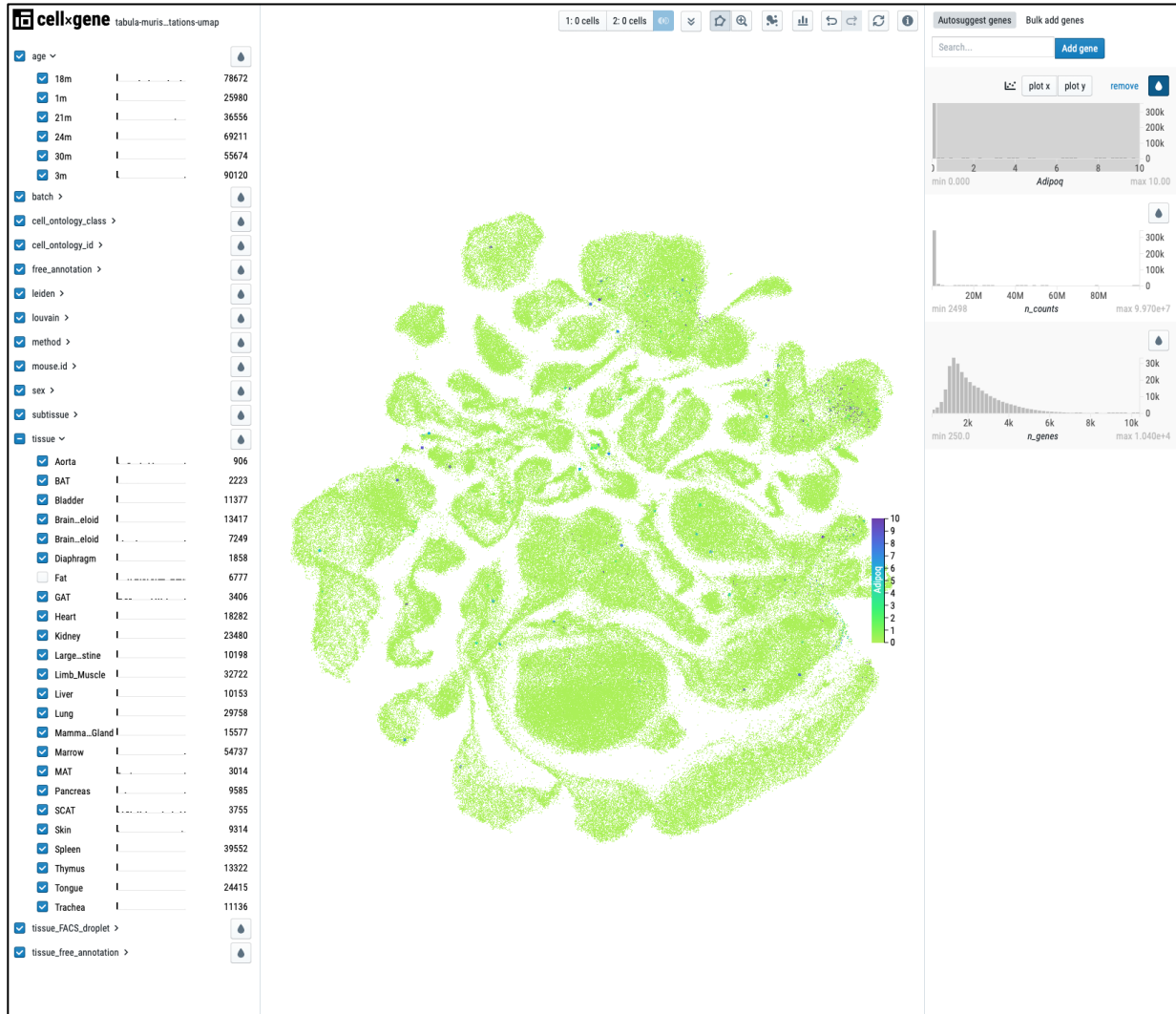
(a) Survival analysis for pneumonia-cause mortality in very older men grouped by cHMW adiponectin level. There was no significant pneumonia-cause mortality difference among three cHMW adiponectin level groups in very older men. (b) Survival analysis for pneumonia-cause mortality in very older men grouped by combination cHMW adiponectin level and BMI (lean BMI<18.5, normal BMI 18.5 ~ 25.0, obesity BMI ≥ 25.0). The high cHMW adiponectin group with low BMI (SBP ≥ 150mmHg) in very older men showed a significant pneumonia-cause mortality difference. (c) Survival analysis for pneumonia-cause mortality in very older women grouped by cHMW adiponectin level. There was no significant pneumonia-cause mortality difference among three cHMW adiponectin level groups in very older women. (d) Survival analysis for pneumonia-cause mortality in very older women grouped by combination cHMW adiponectin level and BMI (lean BMI<18.5, normal BMI 18.5 ~ 25.0, obesity BMI ≥ 25.0). There was no significant pneumonia-cause mortality difference in any combination cHMW adiponectin level groups and BMI in very older women.
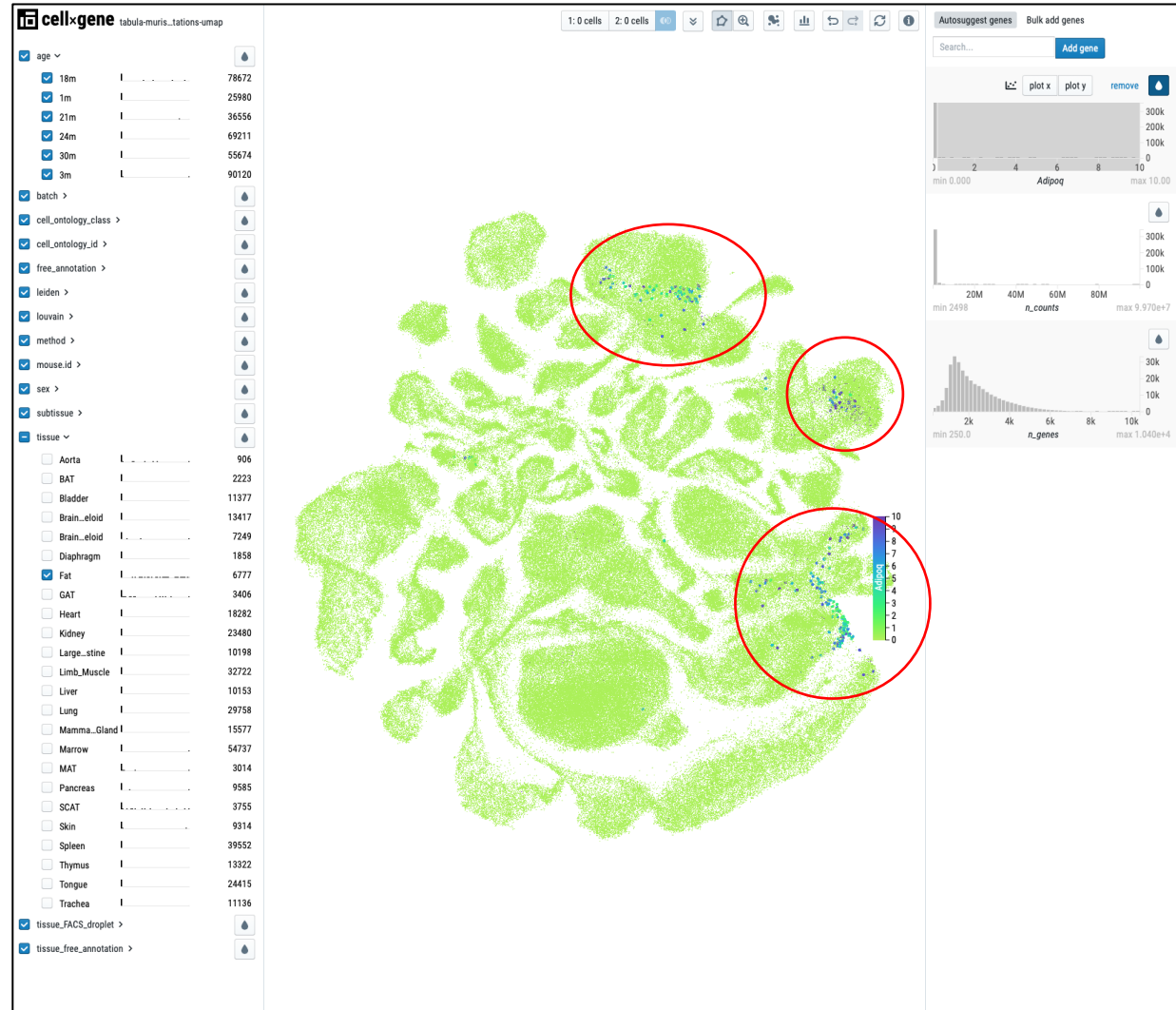
Supplementary Fig. 9 | Adiponectin mRNA expression analysis of single-cell RNA-seq for four kinds of mouse adipose tissue.

We re-analyzed single-cell RNA-seq results (https://tabula-muris-senis.ds.czbiohub.org/fat/droplet/) for four kinds of mouse adipose tissues including brown adipose tissue (Bat), gonadal adipose tissue (Gat), mesenteric adipose tissue (Mat), and subcutaneous adipose tissue (Scat). Dots with the blue color indicated adiponectin-expressed cells. These single-cell RNA-seq results suggested that Scat is one of the major adiponectin-expressed cells in adipose tissues.

Supplementary Fig. 10 | Ectopic expression of adiponectin with aging in mouse

We re-analyzed single-cell RNA-seq results of 24 kinds of tissue in 1, 3, 18, 21, 24, 30 months (https://tabula-muris-senis.ds.czbiohub.org/fat/droplet/). Major adiponectin-expressed cells were adipose tissue and no obvious ectopic adiponectin expression was observed in the time series of mouse cells.