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Supplementary information

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Aged bone marrow macrophages drive systemic aging and age-related dysfunction via extracellular vesicle-mediated induction of paracrine senescence

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Supplementary Information

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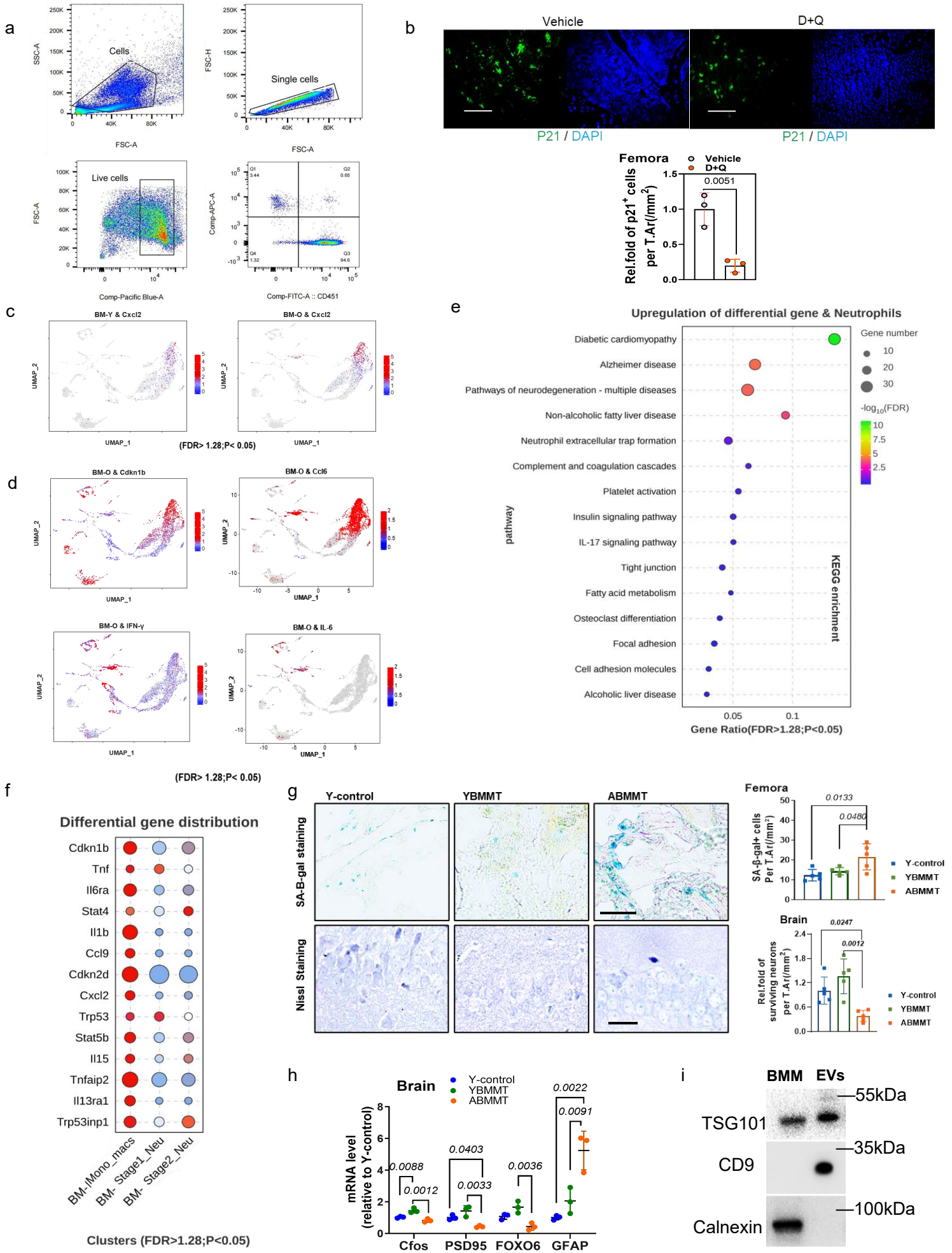
Supplementary Figure1

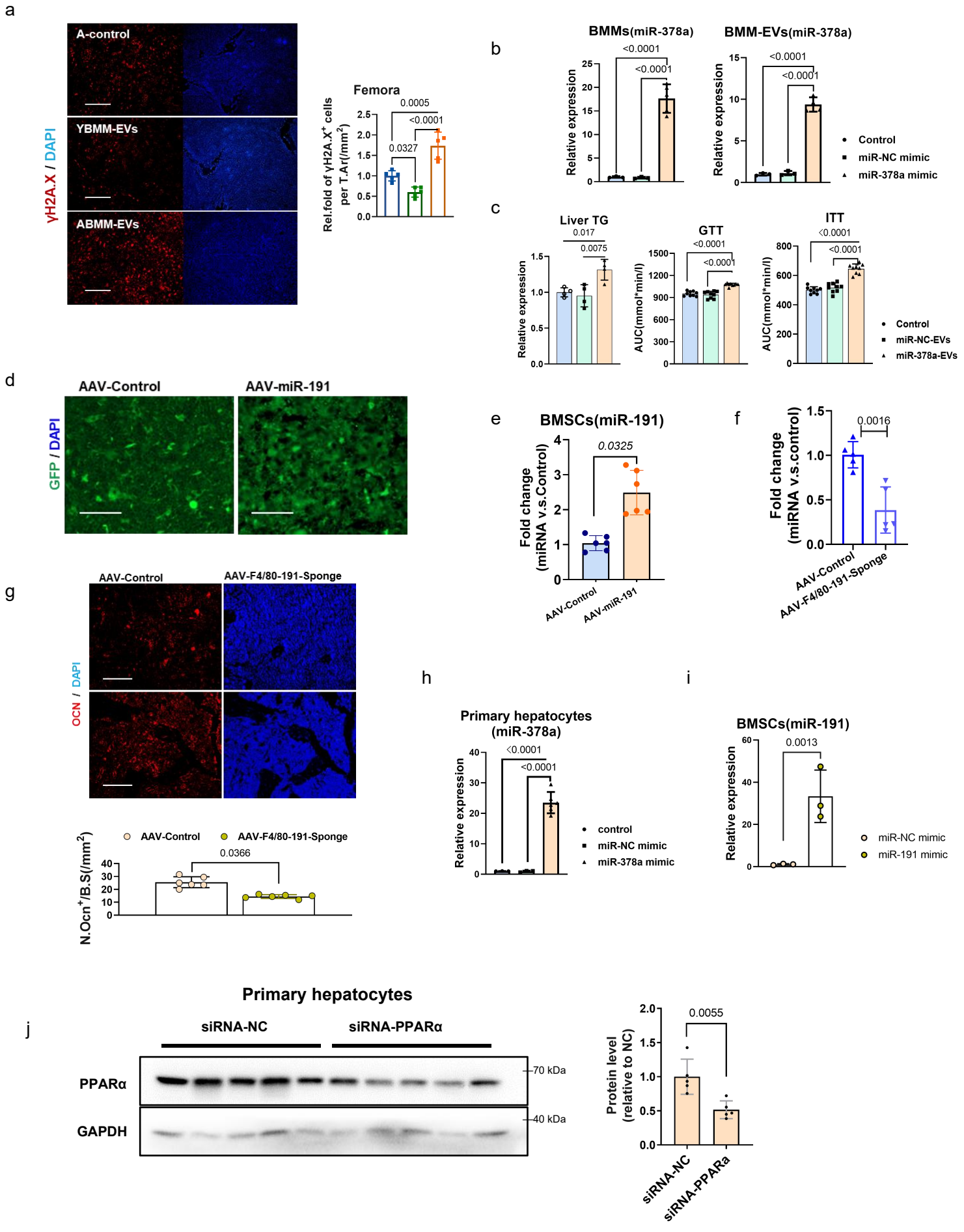


Supplementary Figures Legends

Supplementary Figure 1 Senescent BMMs cause senescence propagation to young mice. a, The gating figure of flow cytometry. **b,** Immunofluorescence staining of p21 in femoral bone sections (scale bar, 250μm; *n*=3 mice; 5~6 images per mouse). **c,** UMAP plots show the distribution of senescence-related genes in different cell types in young and old bone marrow (BM-Y, BM-O). **d,** UMAP plots show the expression and distribution of senescence-related genes in old bone marrow cells (BM-O). **e,** Bubble plot shows the KEGG enrichment pathways for the upregulated aging-related genes in neutrophils. **f,** Aging-related differential gene distribution in BMMs and neutrophils. **g,** Representative images of SA-β-gal staining in femur and Nissl staining in brain (scale bar, 250μm; *n*=5 mice; 5~6 images per mouse). **h,** The mRNA levels of C-fos, Psd95, Foxo6 and Gfap in the brain (*n*=3 mice). **i,** Western blot analysis of EV-related markers (*n*=3 mice).

Data are shown as mean ± SEM. *P< 0.05; **P< 0.01 were determined using two-tailed *t*-test and one-way ANOVA followed by Tukey's multiple comparison test.

Supplementary Figure2



Supplementary Figure 2 The effects of miR-378a and miR-191 on systemic aging *in vivo.* **a,** Immunofluorescence detection of γH2A.X in femur of aged mice after treatment with YBMM-EVs or ABMM-EVs (scale bar, 250μm; *n*=5 mice; 5~6 images per mouse). **b,** Expression levels of miR-378a in macrophage and macrophage-derived EVs after miR-378a mimic transfection (*n*=4 biological replicates). **c,** The hepatic triglyceride (TG) levels were measured in young recipients transplanted with macrophage-miR-378a-EVs (*n*=4 mice), and the AUC data of GTT and ITT (*n*=9 mice). **d-e,** The expression levels miR-191 in BMSCs of aged mice (22m, male mice) injected with AAV-miR-191 (scale bar, 250μm; *n*=6 mice). **f,** The expression levels miR-191 in BMMs of young mice (2m, male mice) injected with AAV-F4/80-miR-191-sponge (*n*=5 mice). **g,** Representative images of OCN immunofluorescence in femurs (scale bar, 250μm; *n*=6 mice; 5~6 images per mouse). **h,** Expression level of miR-378a in primary hepatocytes after miR-378a mimic transfection (*n*=6 biological replicates for miR-378a mimic; *n*=3 biological replicates for other groups). **i,** Expression level of miR-191 in BMSCs after miR-191 mimic transfection (*n*=3 biological replicates). **j,** Protein levels of PPARα in primary hepatocytes after siRNA-PPARα transfection (*n*=5 biological replicates).

Data are shown as mean ± SEM. *P< 0.05; **P< 0.01; ***P< 0.001; #P< 0.0001 were determined using two-tailed *t*-test in **f-g** and **j**, two-tailed *t*-test with a Welch's correction in **e** and **i**, and one-way ANOVA followed by Tukey's multiple comparison test in **a-c**, and **h**.

Table S1. Baseline characteristics according to initiation of either fenofibrate or simvastatin among patients with pre-diabetes

Variable list	Fenofibrate (n=1,602)	Simvastatin (n=6,384)	Standard difference
Demographics			
Age, mean (SD), y	63.5 (10.0)	63.0 (9.8)	0.049
Socioeconomic deprivation index score, mean (SD)	2.3 (1.6)	2.3 (1.6)	0.003
Women (%)	40.8	41.1	0.005
BMI, mean (SD), kg/m^2	29.6 (5.0)	29.5 (5.3)	0.006
Lifestyle factors			
Drinking (%)			0.036
None	16.6	16.8	
Past	3.2	3.3	
Current	75.5	74.5	
Missing data	4.7	5.4	
Smoking (%)			0.037
None	42.8	42.7	
Past	37.9	36.6	
Current	19.0	20.4	
Missing data	0.3	0.3	
Comorbidity (%)			
Hypercholesteremia*	73.7	74.2	0.011
Hypertriglyceridemia*	56.6	54.7	0.038
Hypertension	62.5	61.4	0.025
Transient ischemic attack	4.4	4.3	0.005
Ischemic heart disease	24.4	22.7	0.041
Myocardial infarction	9.9	9.6	0.007
Stroke	4.1	4.3	0.009
Osteoarthritis	25.4	22.5	0.068
Chronic kidney disease	9.9	9.5	0.013
Depression	16.6	14.7	0.051
Varicose veins	7.7	6.9	0.032
Venous thromboembolism	3.5	3.2	0.015
Chronic obstructive pulmonary disease	5.5	4.3	0.057
Pneumonia or infection	8.1	6.9	0.048
Osteoporosis	4.2	3.8	0.021
Fall	9.5	8.8	0.025
Cancer	9.3	10.1	0.028
Medication‡ (%)			
Nonsteroidal anti-inflammatory drugs	39.3	37.1	0.044
Opioids	14.9	13.1	0.050
Other statins	34.6	32.7	0.039
Corticosteroid	23.2	21.1	0.051
Thiazide diuretics	22.3	22.4	0.002
Antihypertensive	70.7	70.0	0.016
Antidiabetic	1.1	1.6	0.046

Anticoagulants	4.4	4.2	0.009
Aspirin	32.3	31.5	0.018
Antidepressant	16.8	16.3	0.012
Proton pump inhibitors	38.8	35.3	0.073
Benzodiazepine	13.9	13.0	0.026
Warfarin	4.2	3.9	0.012
Antiosteoporosis drugs	7.2	6.5	0.031
Nitrates	9.8	9.3	0.017
Bisphosphonates	3.3	2.8	0.028
Healthcare utilization, mean (SD)			
Hospitalizations‡	0.4 (1.0)	0.4 (1.0)	0.036
General practice visits‡	6.3 (5.4)	6.0 (6.0)	0.062
Specialist referrals‡	0.7 (1.1)	0.7 (1.2)	0.021

†The Socio-Economic Deprivation Index was measured by the Townsend Deprivation Index, which was grouped into quintiles from 1 (least deprived) to 5 (most deprived).

‡Frequency during the past 1 year.

*Hypercholesteremia was defined as a total cholesterol level above 5.0 mmol/L; hypertriglyceridemia was defined as a non-fasting triglyceride level above 2.3 mmol/L.

BMI, body mass index; n, number; y, years; SD, standard deviation.

Table S2. Baseline characteristics according to initiation of either fenofibrate or simvastatin among patients with pre-diabetes and diabetes

Variable list	Fenofibrate (n=7,236)	Simvastatin (n=28,086)	Standard difference
Demographics			
Age, mean (SD), y	62.2 (10.3)	62.0 (10.0)	0.015
Socioeconomic deprivation index score, mean (SD)	2.3 (1.6)	2.3 (1.6)	0.011
Women (%)	39.6	39.6	0.001
BMI, mean (SD), kg/m^2	31.0 (5.5)	30.9 (5.8)	0.010
Lifestyle factors			
Drinking (%)			0.047
None	22.8	22.7	
Past	3.9	3.7	
Current	65.8	64.7	
Missing data	7.6	8.8	
Smoking (%)			0.054
None	44.0	45.0	
Past	35.5	34.0	
Current	18.7	18.6	
Missing data	1.8	2.5	
Comorbidity (%)			
Hypercholesteremia*	53.1	55.6	0.050
Hypertriglyceridemia*	52.8	50.1	0.051
Hypertension	65.1	62.1	0.062
Transient ischemic attack	3.6	3.7	0.001
Ischemic heart disease	24.9	23.9	0.021
Myocardial infarction	10.3	10.2	0.005
Stroke	4.3	4.0	0.019
Osteoarthritis	22.6	21.3	0.031
Chronic kidney disease	10.2	8.3	0.066
Depression	15.1	14.3	0.023
Varicose veins	6.4	6.0	0.014
Venous thromboembolism	3.9	3.7	0.011
Chronic obstructive pulmonary disease	4.5	4.2	0.016
Pneumonia or infection	7.0	7.3	0.013
Osteoporosis	2.8	2.8	0.004
Fall	8.5	7.8	0.027
Cancer	8.6	8.7	0.002
Medication‡ (%)			
Nonsteroidal anti-inflammatory drugs	38.3	36.3	0.042
Opioids	14.7	13.2	0.042
Other statins	32.3	29.8	0.057
Corticosteroid	20.6	19.8	0.019
Thiazide diuretics	23.2	22.0	0.029
Antihypertensive	77.3	73.5	0.089
Antidiabetic	62.3	60.2	0.044
Anticoagulants	4.7	4.3	0.018

Aspirin	43.7	40.5	0.063
Antidepressant	15.8	15.2	0.016
Proton pump inhibitors	33.6	31	0.055
Benzodiazepine	12.6	11.5	0.034
Warfarin	4.4	4.1	0.014
Antiosteoporosis drugs	6.2	6.5	0.011
Nitrates	10.8	10.4	0.016
Bisphosphonates	2.7	2.5	0.013
Healthcare utilization, mean (SD)			
Hospitalizations‡	0.4 (1.0)	0.3 (1.0)	0.030
General practice visits‡	6.6 (6.3)	6.4 (6.6)	0.032
Specialist referrals‡	0.6 (1.1)	0.6 (1.1)	0.040

†The Socio-Economic Deprivation Index was measured by the Townsend Deprivation Index, which was grouped into quintiles from 1 (least deprived) to 5 (most deprived).

‡Frequency during the past 1 year.

*Hypercholesteremia was defined as a total cholesterol level above 5.0 mmol/L; hypertriglyceridemia was defined as a non-fasting triglyceride level above 2.3 mmol/L.

BMI, body mass index; n, number; y, years; SD, standard deviation.

Table S3. Baseline characteristics according to initiation of either fenofibrate or simvastatin among patients with pre-diabetes and diabetes[#]

Variable list	Fenofibrate (n=6,749)	Simvastatin (n=25,923)	Standard difference
Demographics			
Age, mean (SD), y	62.0 (10.2)	61.9 (10.0)	0.011
Socioeconomic deprivation index score, mean (SD)	2.3 (1.6)	2.3 (1.6)	0.014
Women (%)	39.1	39.0	0.002
BMI, mean (SD), kg/m^2	31.0 (5.5)	30.9 (5.9)	0.010
Lifestyle factors			
Drinking (%)			0.054
None	22.7	23.0	
Past	3.8	3.6	
Current	65.8	64.3	
Missing data	7.7	9.1	
Smoking (%)			0.057
None	43.9	45.0	
Past	35.5	34.3	
Current	18.9	18.3	
Missing data	1.8	2.5	
Comorbidity (%)			
Hypercholesteremia[*]	52.9	55.2	0.045
Hypertriglyceridemia[*]	52.8	49.7	0.062
Hypertension	65.1	61.6	0.072
Transient ischemic attack	3.6	3.6	0.003
Ischemic heart disease	24.6	23.8	0.018
Myocardial infarction	10.1	10.0	0.005
Stroke	4.2	4.2	0.003
Osteoarthritis	21.8	20.7	0.028
Chronic kidney disease	9.9	8.2	0.061
Depression	15.0	13.8	0.034
Varicose veins	6.1	5.8	0.014
Venous thromboembolism	3.8	3.5	0.014
Chronic obstructive pulmonary disease	4.4	4.2	0.011
Pneumonia or infection	6.8	6.9	0.004
Osteoporosis	2.3	2.3	0.003
Fall	7.8	7.3	0.020
Cancer	8.6	8.4	0.009
Medication‡ (%)			
Nonsteroidal anti-inflammatory drugs	37.9	35.8	0.044
Opioids	14.3	13.1	0.036
Other statins	32.4	29.9	0.054
Corticosteroid	20.3	19.8	0.013
Thiazide diuretics	23.5	22.5	0.024
Antihypertensive	77.4	73.6	0.088
Antidiabetic	62.5	60.1	0.050
Anticoagulants	4.6	4.3	0.017

Aspirin	43.7	40.3	0.069
Antidepressant	15.6	14.9	0.018
Proton pump inhibitors	33.0	30.8	0.048
Benzodiazepine	12.3	11.6	0.022
Warfarin	4.3	4.0	0.015
Antiosteoporosis drugs	5.9	6.5	0.024
Nitrates	10.7	10.2	0.014
Bisphosphonates	2.4	2.1	0.015
Healthcare utilization, mean (SD)			
Hospitalizations‡	0.4 (1.0)	0.3 (1.0)	0.030
General practice visits‡	6.5 (6.3)	6.3 (6.9)	0.027
Specialist referrals‡	0.6 (1.1)	0.5 (1.1)	0.049

Patients with a history of major osteoporotic fracture were excluded.

†The Socio-Economic Deprivation Index was measured by the Townsend Deprivation Index, which was grouped into quintiles from 1 (least deprived) to 5 (most deprived).

‡Frequency during the past 1 year.

*Hypercholesteremia was defined as a total cholesterol level above 5.0 mmol/L; hypertriglyceridemia was defined as a non-fasting triglyceride level above 2.3 mmol/L.

BMI, body mass index; n, number; y, years; SD, standard deviation.

Table S4. Baseline characteristics according to initiation of either fenofibrate or simvastatin among patients with pre-diabetes and diabetes[#]

Variable list	Fenofibrate (n=7,201)	Simvastatin (n=27,924)	Standard difference
Demographics			
Age, mean (SD), y	62.1 (10.2)	61.9 (10.0)	0.015
Socioeconomic deprivation index score, mean (SD)	2.3 (1.6)	2.3 (1.6)	0.019
Women (%)	39.5	39.5	<0.001
BMI, mean (SD), kg/m^2	31.0 (5.5)	31.0 (5.9)	0.003
Lifestyle factors			
Drinking (%)			0.049
None	22.7	22.8	
Past	3.9	3.5	
Current	65.8	64.9	
Missing data	7.5	8.8	
Smoking (%)			0.056
None	43.9	45.3	
Past	35.6	34.0	
Current	18.8	18.4	
Missing data	1.8	2.4	
Comorbidity (%)			
Hypercholesteremia[*]	53.2	55.5	0.046
Hypertriglyceridemia[*]	53.0	50.4	0.052
Hypertension	65.0	62.0	0.062
Transient ischemic attack	3.6	3.7	0.002
Ischemic heart disease	24.8	23.6	0.029
Myocardial infarction	10.4	9.8	0.018
Stroke	4.3	4.0	0.015
Osteoarthritis	22.6	21.4	0.028
Chronic kidney disease	10.2	8.2	0.066
Depression	15.1	14.1	0.027
Varicose veins	6.3	6.2	0.008
Venous thromboembolism	3.9	3.7	0.014
Chronic obstructive pulmonary disease	4.5	4.0	0.027
Pneumonia or infection	7.0	7.0	0.001
Osteoporosis	2.8	2.8	0.003
Fall	8.6	7.6	0.036
Cancer	8.6	8.7	0.004
Medication‡ (%)			
Nonsteroidal anti-inflammatory drugs	38.2	36.4	0.038
Opioids	14.8	13.3	0.043
Other statins	33.3	29.7	0.077
Corticosteroid	20.6	19.8	0.019
Thiazide diuretics	23.2	22.5	0.017
Antihypertensive	77.3	73.5	0.089
Antidiabetic	62.3	60.3	0.040
Anticoagulants	4.7	4.1	0.028

Aspirin	43.7	40.2	0.071
Antidepressant	15.7	15.0	0.019
Proton pump inhibitors	33.6	31.1	0.053
Benzodiazepine	12.5	11.7	0.024
Warfarin	4.3	3.8	0.027
Antiosteoporosis drugs	6.2	6.6	0.017
Nitrates	10.8	10.2	0.019
Bisphosphonates	2.7	2.3	0.021
Healthcare utilization, mean (SD)			
Hospitalizations‡	0.4 (1.0)	0.3 (1.0)	0.046
General practice visits‡	6.6 (6.3)	6.4 (7.2)	0.026
Specialist referrals‡	0.6 (1.1)	0.5 (1.1)	0.049

Patients with a history of dementia were excluded.

†The Socio-Economic Deprivation Index was measured by the Townsend Deprivation Index, which was grouped into quintiles from 1 (least deprived) to 5 (most deprived).

‡Frequency during the past 1 year.

*Hypercholesteremia was defined as a total cholesterol level above 5.0 mmol/L; hypertriglyceridemia was defined as a non-fasting triglyceride level above 2.3 mmol/L.

BMI, body mass index; n, number; y, years; SD, standard deviation.

Table S5. Life expectancy between patients treated with fenofibrate and simvastatin at different ages

Age interval, y	Simvastatin, y (95% CI)	Fenofibrate, y (95% CI)	Difference in LE, y (95% CI)*
40-44	35.52 (35.43 to 35.62)	36.22 (36.05 to 36.40)	-0.70 (-0.90 to -0.50)
45-49	31.21 (31.12 to 31.29)	31.49 (31.31 to 31.66)	-0.28 (-0.48 to -0.09)
50-54	27.23 (27.15 to 27.32)	27.35 (27.18 to 27.52)	-0.12 (-0.31 to -0.07)
55-59	23.49 (23.41 to 23.57)	23.70 (23.54 to 23.87)	-0.21 (-0.40 to -0.03)
60-64	20.11 (20.03 to 20.19)	20.28 (20.11 to 20.44)	-0.17 (-0.35 to -0.02)
65-69	16.94 (16.86 to 17.02)	17.48 (17.30 to 17.66)	-0.54 (-0.74 to -0.35)
70-74	14.12 (14.03 to 14.21)	15.24 (15.05 to 15.44)	-1.12 (-1.33 to -0.91)
75-79	11.80 (11.70 to 11.90)	13.25 (13.04 to 13.47)	-1.45 (-1.69 to -1.22)
80-84	9.85 (9.74 to 9.96)	11.66 (11.43 to 11.89)	-1.81 (-2.07 to -1.56)
≥85	8.63 (8.33 to 8.83)	11.34 (11.14 to 11.44)	-2.71 (-3.14 to -2.01)

Y, year; 95% CI, 95% confidence interval; LE, life expectancy.

* The difference in life expectancy was calculated as the estimated life expectancy in patients treated with simvastatin minus that in patients treated with fenofibrate.

Table S6. KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Antibodies		
Mouse monoclonal anti-p-γH2AX	Santa Cruz	CAT#sc-517348; RRID: AB_2783871
Mouse monoclonal anti-p21	Santa Cruz	CAT#sc-6246; RRID: AB_628073
Mouse monoclonal anti-p53	Cell signaling Technology	CAT#2524s; RRID: AB_331743
Rabbit monoclonal anti-p-IR	Cell signaling Technology	CAT#3024s; RRID: AB_331253
Rabbit monoclonal anti-IR	Cell signaling Technology	CAT#3025s; RRID: AB_2280448
Rabbit polyclonal anti-p-AKT	Cell signaling Technology	CAT#9271s; RRID: AB_329825
Rabbit polyclonal anti-AKT	Cell signaling Technology	CAT#9272s; RRID: AB_329827
Rabbit polyclonal anti-p-GSK3β	Cell signaling Technology	CAT#9336s; RRID: AB_331405
Rabbit monoclonal anti-GSK3β	Cell signaling Technology	CAT#9315s; RRID: AB_490890
Mouse monoclonal anti-PPARα	Santa Cruz	CAT#sc-398394; RRID: AB_2885073
Mouse monoclonal anti-PSD95	Santa Cruz	CAT#sc-32290; RRID: AB_628114
Mouse monoclonal anti-GluR-1	Santa Cruz	CAT#sc-55509; RRID: AB_629532
Rabbit polyclonal anti-IBA1	Proteintech	CAT#10904-1-AP; RRID:AB_2224377
Rat monoclonal anti-F4/80	Abcam	CAT#ab6640; RRID:AB_1140040
Mouse monoclonal anti-Osteocalcin	Takara	CAT#M188; RRID: AB_2935810
Chemicals, Peptides, and Recombinant Proteins		
Recombinant human M-CSF protein	Proteintech	CAT#HZ-1192
Dasatinib	LC labs	CAT#D-3307
Quercetin	Sigma-Aldrich	CAT# Q4951
Fenofibrate	Sigma-Aldrich	CAT#F6020
Percoll	GE Healthcare Life Sciences	CAT# 17-0891-01
PKH26	Sigma-Aldrich	CAT# PKH26GL-1KT
Protease Inhibitor Cocktail	Selleck	CAT#B14001
Phosphatase Inhibitor Cocktail	Selleck	CAT#B15001

Protein Ladder	Thermo Fisher Scientific	CAT#26617
insulin	Novo Nordisk	J20160057
Critical commercial assays		
Senescence β-Gal Staining Kit	Solarbio	CAT#G1580
ExoQuick™-TC reagent	SBI	CAT#EXOTC10A-1
Evo M-MLV RT Master Mix	Accurate Biology	CAT#AG11706
All-in-One miRNA qPCR Kit	GeneCopoeia	CAT#QP010
BCA protein assay kits	Thermo Fisher Scientific	CAT# 23227
Triglyceride (TG) kit	Elabscience	CAT# E-BC-K261-M
Glucometer monitor	Roche	ACCU-CHEK Active
Experimental Models: Cell Lines		
Bone marrow-derived macrophage	This paper	N/A
Primary hepatocyte	This paper	N/A
Bone marrow mesenchymal stem cell	This paper	N/A
Experimental models: Organisms/strains		
Mouse: C57BL/6J	SLAC Laboratory	N/A
Mouse: miR-378a floxed mice	GemPharmatech CO., Ltd	T007903
Oligonucleotides		
PCR primer for genotype: miR-378a-floxed 5'arm-forward: CAC TTG CTG CCG TAC TTT CAC G	GemPharmatech CO., Ltd	T007903
PCR primer for genotype: miR-378a-floxed 5'arm- reverse: CCA ACT GAC CTT GGG CAA GAA CAT	GemPharmatech CO., Ltd	T007903
PCR primer for genotype: miR-378a-floxed 3'arm-forward: TAC TCT TGC CGT TCA TGT GCG	GemPharmatech CO., Ltd	T007903
PCR primer for genotype: miR-378a-floxed 3'arm- reverse: AAG ATG GCT CCT ACC AAA GGT AGC	GemPharmatech CO., Ltd	T007903
RT-PCR primer: Mki67 Forward: 5'-AATCCAACTCAAGTAAACGGGG-3'	This paper	N/A
RT-PCR primer: Mki67 Reverse: 5'-TTGGCTTGCTTCCATCCTCA-3'	This paper	N/A
RT-PCR primer: Cdkn1a Forward: 5'-CCTGGTGATGTCCGACCTG-3'	This paper	N/A

RT-PCR primer: Cdkn1a Reverse: 5'-CCATGAGCGCATCGCAATC-3'	This paper	N/A
RT-PCR primer: Cdkn2a Forward: 5'-ACATCAAGACATCGTGCGATATT-3'	This paper	N/A
RT-PCR primer: Cdkn2a Reverse: 5'-CCAGCGGTACACAAAGACCA-3'	This paper	N/A
RT-PCR primer: IL-1β Forward: 5'-GCAACTGTTCCTGAACTCAACT-3'	This paper	N/A
RT-PCR primer: IL-1β Reverse: 5'-ATCTTTTGGGGTCCGTCAACT-3'	This paper	N/A
RT-PCR primer: IL-6 Forward: 5'-TAGTCCTTCCTACCCCAATTTCC-3'	This paper	N/A
RT-PCR primer: IL-6 Reverse: 5'-TTGGTCCTTAGCCACTCCTTC-3'	This paper	N/A
RT-PCR primer: TNF-α Forward: 5'-CCCTCACACTCAGATCATCTTCT-3'	This paper	N/A
RT-PCR primer: TNF-α Reverse: 5'-GCTACGACGTGGGCTACAG-3'	This paper	N/A
RT-PCR primer: Cxcl1 Forward: 5'-CTGGGATTCACCTCAAGAACATC-3'	This paper	N/A
RT-PCR primer: Cxcl1 Reverse: 5'-CAGGGTCAAGGCAAGCCTC-3'	This paper	N/A
RT-PCR primer: Cxcl10 Forward: 5'-CCAAGTGCTGCCGTCATTTTC-3'	This paper	N/A
RT-PCR primer: Cxcl10 Reverse: 5'-GGCTCGCAGGGATGATTTCAA-3'	This paper	N/A
RT-PCR primer: MMP10 Forward: 5'-GAGCCACTAGCCATCCTGG-3'	This paper	N/A
RT-PCR primer: MMP10 Reverse: 5'-CTGAGCAAGATCCATGCTTGG-3'	This paper	N/A
RT-PCR primer: MMP13 Forward: 5'-CTTCTTCTTGTTGAGCTGGACTC-3'	This paper	N/A
RT-PCR primer: MMP13 Reverse: 5'-CTGTGGAGGTCACTGTAGACT-3'	This paper	N/A
Software and algorithms		
Data-analysis software	Bruker MicroCT	Version 1.9
3-dimensional model visualization software	Bruker MicroCT	Version 2.0
NRecon image reconstruction software	Bruker MicroCT	Version 1.6
Prism 8	Graphpad	http://www.graphpad.com/
Image Lab	BioRad	http://www.bio-rad.com/en-us/product/image-lab-software

ChemiDoc XRS imaging system	BioRad	http://www.bio-rad.com/en-us/product/chemidoc-imaging-systems/chemidoc-xrs-system