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Supplementary information

Biomarkers of ageing of humans and non-human primates

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Supplementary Table 1 | Examples of commonly used non-human primate species in ageing research[1,2]

Species	Scientific name	Average lifespan (years)	Maximum lifespan (years)	Genomic similarity with humans
Gray mouse lemur[a]	*Microcebus murinus*	8~10	18	91%
Squirrel monkey[b]	*Saimiri sciureus*	20	30	N/A
Common marmoset[b]	*Callithrix jacchus*	5~10	21	93%
Tufted capuchin[b]	*Sapajus apella*	10~17	45	N/A
African green monkey[c]	*Chlorocebus aethiops*	20	31	90%
Cynomolgus macaque[c]	*Macaca fascicularis*	25~30	39	93%
Rhesus macaque[c]	*Macaca mulatta*	25~40	40	93%
Japanese macaque[c]	*Macaca fuscata*	28~32	39	91%~93%
Olive baboon[c]	*Papio anubis*	25~30	38	94%
Chimpanzee[d]	*Pan troglodytes*	30~35	65	99%
Gorilla[d]	*Gorilla gorilla*	30~40	60	98%
Orangutan[d]	*Pongo pygmaeus*	50~60	60	97%

Primate classification: [a] Prosimian; [b] New World monkey; [c] Old World monkey; [d] Great ape. Abbreviation: N/A, not available.

Supplementary Table 2 | Representative surface biomarkers of cell senescence in primates

Surface biomarkers	General functions	Senescent cell types	Refs
uPAR$^{\uparrow; R\&P; H}$	A receptor involved in cellular migration, adhesion, and immune responses.	Primary human melanocytes^{CC}, human lung adenocarcinoma cells^{PT}, and diverse types of human pancreas cells^{PT}.	3,4
GPNMB$^{\uparrow; R\&P; H\&N}$	A transmembrane glycoprotein that plays a role in cell adhesion, migration, and immune system regulation.	Human umbilical vein endothelial cells^{CC}, leukocytes^{LS}, mesenchymal stem cells^{LS}, and monkey microglia^{PT}.	5-7
NKG2DLs$^{\uparrow; R\&P; H\&N}$, including MICA/B and ULBPs	A family of proteins that serve as ligands for the NKG2D receptor, involved in immune surveillance and immune cell activation.	Human fibroblasts^{CC}, hepatic stellate cells^{CC}, myeloma cells^{CC}, umbilical vein endothelial cells^{CC}, and monkey primary T cells^{CC}.	8-12
DPP4$^{\uparrow; R\&P; H}$	An enzyme that regulates peptide processing and is involved in glucose metabolism and immune regulation.	Human fibroblasts^{CC}.	13
PD-L1$^{\uparrow; P; H}$	A protein that inhibits the activity of T cells and is involved in immune evasion by some cancer cells.	Human fibroblasts^{CC}.	14
B2MG$^{\uparrow; P; H}$	A component of the major histocompatibility complex (MHC) class I molecule, involved in antigen presentation to the immune system.	Human cancer cells and fibroblasts^{CC}.	15
DEP1$^{\uparrow; P; H}$	A protein tyrosine phosphatase involved in the regulation of various cellular processes including cell adhesion	Human cancer cells and fibroblasts^{CC}.	15

	and signaling.		
ICAM-1↑; R&P; H	A cell surface protein that mediates cell-cell interactions and is involved in immune response and inflammation.	Human fibroblasts and vascular smooth muscle cells[CC].	16
NOTCH1↑; P; H	A transmembrane protein that plays a role in cell fate determination and differentiation during development.	Human fibroblasts[CC].	17
NOTCH3↑; R&P; H	A transmembrane receptor protein like NOTCH1 and involved in cell signaling pathways that regulate cell differentiation and proliferation.	Human fibroblasts and mammary epithelial cells[CC].	18
TNFRSF10D↑; P; H	A receptor for the cytotoxic ligand TRAIL, which is involved in the regulation of apoptosis.	Human mesenchymal stem cells[LS].	19
CYB5R1↑; R&P; H	An enzyme that plays a role in the electron transport chain.	Human fibroblasts and umbilical vein endothelial cells[CC].	20
SCAMP4↑; R&P; H	A protein involved in the intracellular transport of secretory proteins.	Human fibroblasts[CC].	21
FAT↑; R&P; H	A receptor involved in the recognition and phagocytosis of apoptotic cells, as well as playing a role in lipid metabolism and inflammation.	Human fibroblasts and bronchial epithelial cells[CC].	22
Ganglioside GD3↑; H	An acidic glycosphingolipid involved in cell adhesion, proliferation, and apoptosis.	Human fibroblasts[CC].	23

Note: "↑" indicates upregulated expression in senescent cells; "P" indicates expression change at the protein level; "R" indicates expression change at the RNA level; "H" indicates expression change in human cells; "N" indicates expression change in non-human primate cells; "CC" indicates cells cultured in vitro; "LS" indicates cells derived from live specimens; "PT" indicates cells within primary tissues.

Abbreviations: B2MG, β-2-microglobulin; CYB5R1, cytochrome B5 reductase 1; DEP1, density-enhanced phosphatase 1; DPP4, dipeptidyl peptidase 4; FAT, fatty acid translocase, also known as cluster of differentiation 36 (CD36); GPNMB, glycoprotein nonmetastatic melanoma protein B; ICAM-1, intercellular adhesion molecule 1; MICA/B, MHC class I polypeptide-related sequence A/B; NKG2DLs, natural killer group 2D ligands; NOTCH1/3, Notch receptor 1/3; PD-L1, programmed cell death ligand 1, also known as CD274; SCAMP4, secretory carrier-associated membrane protein 4; TNFRSF10D, tumor necrosis factor receptor superfamily member 10D, also known as CD264; ULBPs, UL16-binding proteins; uPAR, urokinase plasminogen activator receptor.

Supplementary Table 3. Representative ageing biomarkers at the tissue level in primates

Tissue types	Structural changes	Functional changes	Cellular alterations	Molecular markers
Skin	Epidermal thinning, flattening of the dermis and epidermis, decreased dermal collagen density, erosion of the spinous layer and the basal layer, and hair follicle miniaturization.	Wrinkles, reduced elasticity, and altered pigmentation.	Reduced endothelial cells, melanocytes, Langerhans cells, and pericytes, increased immune cell infiltration, and senescence of fibroblasts and melanocytes.	KRT10$^{\downarrow; P; H; LS}$, KRT14$^{\downarrow; P; H; LS}$, KRT15$^{\downarrow; P; H; LS}$, COL17A1$^{\downarrow; P; H; LS}$, and a panel of senomarkers (Supplementary Table 4).

The central nervous system	Brain atrophy, reduced cortical thickness, decreased gray matter volume and white matter integrity.	Increased cerebrovascular injuries, altered connectivity patterns, impaired brain glucose metabolism, declined cognitive functions and motor skills, and neural degenerations.	Increased senescent neurons and disproportion of oligodendrocytes and microglia.	BCAN$^{\downarrow; P; H; LS}$, NfL$^{\uparrow; P; H; LS}$, CHIT1$^{\uparrow; R\&P; H\&N; LS\&PT}$, and a panel of senomarkers (Supplementary Table 4).
The cardiovascular system	Valve calcification and stenosis, fat deposition in epicardium, increased cross-sectional area of cardiomyocytes (indicating hypertrophy), vessel wall thickening, vascular calcification, increased cardiac and vascular fibrosis, and enlarged vessel lumens.	Diastolic and systolic dysfunction, impaired conduction systems, increased vascular stiffness, endothelial dysfunction, and an increased risk of cardiovascular diseases.	Cardiomyocyte loss and hypertrophy, immune cell infiltration, decreased endothelial cells, increased fibroblasts and smooth muscle cells, and disturbed intercellular communications.	Ang II$^{\uparrow; P; H\&N; LS\&PT}$, ACE$^{\uparrow; R\&P; H\&N; LS\&PT}$, cTnT$^{\uparrow; P; H; LS}$, BNP$^{\uparrow; P; H; LS}$, SAA1/2$^{\uparrow; P; H; PT}$, SAP$^{\uparrow; P; H; PT}$, IGHA$^{\uparrow; P; H; PT}$, GAS6$^{\uparrow; P; H; PT}$, COMP$^{\uparrow; P; H; PT}$, C4A$^{\uparrow; P; H; PT}$, FOXP1$^{\downarrow; R\&P; H\&N; PT\&CC}$, FOXO3A$^{\downarrow; R\&P; H\&N; PT\&CC}$, ferrous ion$^{\uparrow; H; LS}$, ACSL4$^{\uparrow; R\&P; H; LS}$, ALOX15$^{\uparrow; R\&P; H; LS}$, and a panel of senomarkers (Supplementary Table 4).
Lungs	Airway dilation and calcification, bronchial wall thickening, alveolar enlargement,	Decreased elastic recoil and compliance, impaired respiratory capacity,	A decrease in the proportion of alveolar epithelial cells (particularly type 2 cells), basal cells, and	ACE2$^{\uparrow; R\&P; H\&N; LS\&PT}$, FTL$^{\downarrow; R\&P; H; LS\&PT}$, SAP$^{\uparrow; P; H; PT}$, and a panel of senomarkers (Supplementary

	loss of lung parenchymal density, and increased fibrosis and fat deposition.	diminished gas exchange efficiency, increased residual end-expiratory lung volume, and a heightened risk of pulmonary diseases.	proliferating natural killer (NK)/T cells, accompanied by an increase in the proportion of fibroblasts during human lung ageing; reduced alveolar epithelial type 2 cells, alveolar macrophages, and dendritic cells, along with an increase in capillary endothelial cells in lung tissues of patients with age-associated chronic obstructive pulmonary disease; an increase of immune cells like mast cells, plasmocytes, and $CD8^+$ T cells with lung ageing in cynomolgus monkeys.	Table 4).
Liver	Reduced liver volume, increased thickness of the sinusoidal endothelium, decreased frequency of endothelial fenestrations,	Impaired regenerative capacity and drug detoxification, disturbances in glucose and lipid metabolism, reduced	Increased proportion of immune cells including neutrophils and Kupffer cells, and dysfunction of hepatocytes and sinusoidal endothelial cells.	ACSL4$^{\uparrow; R; N; PT}$, SCAD$^{\uparrow; R\&P; H; LS}$, CYP1A2$^{\uparrow; P; H; PT}$, PCSK9$^{\uparrow; R\&P; H; LS\&PT}$, SREBP2$^{\uparrow; R\&P; H\&N; PT\&CC}$, SAP$^{\uparrow; P; H; PT}$, alkaline phosphatase$^{\uparrow; P; H; LS}$, γ-

	and elevated fat deposition, fibrosis, and inflammation.	hepatic blood flow, and an increasing incidence of liver diseases.		glutamyltransferase$^{\uparrow; P; H; LS}$, cholesterol$^{\uparrow; H; LS}$, triglycerides$^{\uparrow; H; LS}$, and a panel of senomarkers (Supplementary Table 4).
The immune system	Reduced size and weight of the thymus and spleen, decreased number and volume of lymph nodes, and expanded yellow bone marrow.	Dysregulated immunity, immunosenescence, compromised immune defense against infections and malignancies, and increased autoimmunity and systemic inflammation.	Decreased thymocytes, dendritic cells, naive B and T cells, and memory B cells, increased fat cells, monocytes and memory T cells, and declined diversity of B and T cells.	CD28$^{\downarrow; P; H; LS}$, CD45RA$^{\downarrow; P; H; LS}$, CD38$^{\downarrow; R\&P; H; LS}$, CXCR3$^{\uparrow; P; H; LS}$, GZMK$^{\uparrow; R\&P; H; LS}$, GAS6$^{\uparrow; P; H; PT}$, TIMP3$^{\uparrow; P; H; PT}$, NKG2C$^{\downarrow; R; H; LS}$, PD-1$^{\uparrow; P; H; LS}$, IgG$^{\uparrow; P; H; PT}$, NEAT1$^{\uparrow; R; H; LS}$, MALAT1$^{\uparrow; R; H; LS}$, and a panel of senomarkers (Supplementary Table 4).
Adipose tissue	Reduced subcutaneous white adipose tissue, increased visceral fat, declined brown and beige adipose tissue, and increased fat deposits in non-adipose tissues, such as bone marrow, heart, and skeletal muscle.	Impaired thermogenesis, heightened inflammation, and metabolic disturbances.	Reduced but enlarged adipocytes and increased immune cells and inflammatory adipose progenitor cells.	PLAU$^{\uparrow; R\&P; H; LS}$, THBD$^{\uparrow; R\&P; H; LS}$, IgG$^{\uparrow; P; H; LS}$, PPARγ$^{\downarrow; P; H; LS}$, leptin$^{\downarrow; R\&P; H; LS}$, C/EBPα$^{\uparrow; R; H; LS}$, PCCA$^{\downarrow; R; H; LS}$, IRS1$^{\downarrow; R; H; LS}$, ESR1$^{\downarrow; R; H; LS}$, and a panel of senomarkers (Supplementary Table 4).
The musculoskeletal system	Muscle fiber atrophy, increased type I	Declined muscle strength and	Increased immune cell infiltration and	FOXO3$^{\downarrow; R\&P; H\&N; PT}$, SESN1$^{\downarrow; R\&P; H\&N; LS\&PT}$,

	fibers, declined type II fibers, activated inflammation and apoptosis, and increased fat accumulation in the skeletal muscle; reduced mineral density and increased marrow fat accumulation in the bone; extracellular matrix remodeling, heightened inflammation, and reduced thickness of articular cartilage, as well as structural degenerations in the synovium.	mass, bone loss, and increased cartilage stiffness, which contribute to restricted mobility and age-related conditions such as sarcopenia, osteoporosis, and osteoarthritis.	decreased muscle stem cell and endothelial cell populations in the skeletal muscle; dysregulated osteoblasts, osteoclasts, adipocytes, mesenchymal stem cells, and hematopoietic stem cells in the bone; reduced chondrocytes and increased immune cells in joints.	METTL3$^{\downarrow; P; N; PT}$, m^{6}A$^{\downarrow; N; PT}$, PCCA$^{\downarrow; R; H; LS}$, BMP$^{\uparrow; H; LS}$, COL1A2$^{\uparrow; P; H; LS}$, FOXO1$^{\downarrow; R\&P; H; LS}$, α-Klotho$^{\downarrow; P; H; LS}$, serum osteocalcin$^{\downarrow; P; N; LS}$, serum 25-hydroxyvitamin D$^{\downarrow; N; LS}$, urinary pyridinoline$^{\uparrow; N; LS}$, urinary deoxypyridinoline$^{\uparrow; N; LS}$, phosphatidylcholine$^{\uparrow; N; LS}$, lysophosphatidylcholine$^{\uparrow; N; LS}$, and a panel of senomarkers (Supplementary Table 4).
Kidneys	Reduced kidney volume, surface roughening, nephron loss, glomerulosclerosis, tubular atrophy, compensatory hypertrophy of remaining nephrons, interstitial fibrosis, and increased extracellular matrix components.	Declined glomerular filtration rate, impaired excretion of metabolic waste and regulation of fluid balance, and an increased risk of chronic kidney disease.	Decreased density and hypertrophy of podocytes, and increased immune cells.	CD45$^{\uparrow; P; N; PT}$, WT1$^{\downarrow; P; H; LS}$, podocin$^{\downarrow; P; H; LS}$, FN$^{\uparrow; P; H\&N; PT\&CC}$, α-SMA$^{\uparrow; P; H; CC}$, WNT9A$^{\uparrow; P; H; LS}$, GSK3β$^{\uparrow; P; H; LS}$, histone crotonylation$^{\uparrow; P; H; LS}$, ZFYVE21$^{\downarrow; P; H; LS}$, albumin$^{\uparrow; P; H; LS}$, renin$^{\uparrow; P; H; LS}$, α-Klotho$^{\downarrow; P; H\&N; LS\&PT}$, urea nitrogen$^{\uparrow; H; LS}$, creatinine$^{\uparrow; H\&N; LS}$, and a panel

				of senomarkers (Supplementary Table 4).
The reproductive system	Decreased number of primordial follicles, increased follicular atresia, and fibrosis in ovaries; thickening of the basement membrane and seminiferous tubule walls, increased accumulation of lipofuscin, fibrosis, lipids, and extracellular matrix in testes.	Reduced ovarian reserve and oocyte counts, hormonal imbalance, increased inflammation, stiffness, and vascular damage in ovaries; impaired spermatogenesis, decreased sperm concentration, and abnormal testosterone production in testes.	Loss of oocytes, disproportion and dysfunction of stromal and granulosa cells in ovaries; decreased number and failed differentiation of spermatogonial stem cells, disproportion and dysfunction of spermatogonia, Sertoli cells, and Leydig cells.	APOE$^{\uparrow; R\&P; H\&N; LS\&PT}$, CD38$^{\uparrow; R; H; LS}$, gasdermin D$^{\uparrow; P; H; LS}$, C/EBPδ$^{\uparrow; R; H; LPT}$, RICTOR$^{\uparrow; R; H; PT}$, MT-ATP6$^{\downarrow; R; H; PT}$, FOXP1$^{\downarrow; R\&P; H; LS}$, IDH1$^{\downarrow; R\&P; H\&N; LS\&PT}$, PRDX4$^{\downarrow; R\&P; H\&N; LS\&PT}$, IGFBP7$^{\uparrow; R\&P; H; LS}$, TIMP1$^{\uparrow; P; H; LS}$, collagen$^{\uparrow; P; H\&N; LS\&PT}$, SOX9$^{\downarrow; P; H\&N; LS\&PT}$, WT1$^{\downarrow; P; N; PT}$, PTCH1$^{\downarrow; P; H; LS}$, AMH$^{\downarrow; P; H; LS}$, testosterone$^{\downarrow; H; LS}$, and a panel of senomarkers (Supplementary Table 4).

Note: "$^{\uparrow}$" indicates upregulation during ageing; "$^{\downarrow}$" indicates downregulation during ageing; "^{P}" indicates expression change at the protein level; "^{R}" indicates expression change at the RNA level; "^{H}" indicates human samples; "^{N}" indicates non-human primate samples; "^{CC}" indicates cultured cells; "^{LS}" indicates live specimens; "^{PT}" indicates primary tissues.

Abbreviations: ACE, angiotensin-converting enzyme; ACSL4, acyl-CoA synthetase long-chain family member 4; ALOX15, arachidonate 15-lipoxygenase; AMH, anti-Mullerian hormone; Ang II, angiotensin II; APOE, apolipoprotein E; α-SMA, α-smooth muscle actin; BMP, bis(monoacylglycero)phosphate; BCAN, brevican; BNP, B-type natriuretic peptide; C4A, complement 4A; CD28, cluster of differentiation 28; C/EBPβ,

CCAAT/enhancer-binding protein-β; CHIT1, chitotriosidase 1; COL17A1, collagen type XVII α 1; COMP, cartilage oligomeric matrix protein; cTnT, cardiac troponin T; CXCR3, C-X-C motif chemokine receptor 3; CYP1A2, cytochrome P450 1A2;ESR1, estrogen receptor 1; FN, fibronectin; FOXP1, forkhead box P1; FTL, ferritin light chain; GAS6, growth arrest-specific protein 6; GSK3β, glycogen synthase kinase 3β; GZMK, granzyme K; IDH1, isocitrate dehydrogenase 1; IgG, immunoglobulin G; IGFBP7, insulin-like growth factor-binding protein 7; IGHA1, immunoglobulin heavy constant alpha 1; IRS1, insulin receptor substrate 1; KRT10, keratin 10; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; METTL3, methyltransferase-like 3; m^6A, N^6-methyladenosine; MT-ATP6, mitochondrially-encoded ATP synthase 6; NEAT1, nuclear paraspeckle assembly transcript 1; NfL, neurofilament light chain; NKG2C, natural killer group 2 member C; PD-1, programmed cell death protein 1; PCCA, propionyl-CoA carboxylase subunit α; PCSK9, proprotein convertase subtilisin/kexin type 9; PLAU, urokinase-type plasminogen activator; PPARγ, peroxisome proliferator-activated receptor-γ; PRDX4, peroxiredoxin 4; PTCH1, Patched 1; RICTOR, RPTOR independent companion of mTOR complex 2; SAA1/2, serum amyloid A1/2; SAP, serum amyloid P-component; SCAD, short-chain acyl-CoA dehydrogenase; SREBP2, sterol regulatory element-binding protein 2; SESN1, sestrin 1; SOX9, SRY-box transcription factor 9; THBD, thrombomodulin; TIMP1, tissue inhibitor of metalloprotease 1; WNT9A, Wnt family member 9A; WT1, Wilms's tumor 1; ZFYVE21, zinc finger FYVE-type containing 21.

Supplementary Table 4 | Representative senomarkers for predicting tissue ageing in primates

Tissue types	Senomarkers	Refs
Skin	$p16^{INK4a\uparrow; P; H; LS}$, $p21^{CIP1\uparrow; P; H\&N; LS\&PT}$, lipofuscin$^{\uparrow; H; LS}$, γ-H2AX$^{\uparrow; P; H; LS}$, 8-oxodG/8-OHdG$^{\uparrow; H; LS}$, PCNA$^{\downarrow; P; H; LS}$, Ki-67$^{\downarrow; P; H; LS}$, ERVs$^{\uparrow; P; H\&N; LS\&PT}$, miR-31$^{\uparrow; R; H; LS}$, etc.	24-30

The central nervous system	SA-β-gal$^{\uparrow; P; H\&N; PT}$, p16$^{INK4a \uparrow; P; H; LS}$, γ-H2AX$^{\uparrow; P; N; PT}$, H3K9me3$^{\downarrow; P; H\&N; LS\&PT}$, H3K27me3$^{\downarrow; P; N; PT}$, Lamin B1$^{\downarrow; P; H\&N; LS\&PT}$, Lamin B2$^{\downarrow; P; H\&N; LS\&PT}$, LINE-1$^{\uparrow; P; N; PT}$, ERVs$^{\uparrow; P; H\&N; LS\&PT}$, Aβ$^{\uparrow; P; H\&N; PT\&CC}$, tau$^{\uparrow; P; N; PT}$, TMEM106B$^{\uparrow; P; H; LS}$, IL-6$^{\uparrow; P; H; LS}$, MMP3$^{\uparrow; P; N; PT}$, MMP9$^{\uparrow; P; N; PT}$, GDF15$^{\uparrow; P; H; LS}$, lipofuscin$^{\uparrow; N; PT}$, 4-HNE$^{\uparrow; H\&N; PT\&CC}$, GPNMB$^{\uparrow; R; N; PT}$, somatic mutations$^{\uparrow; H; PT}$, etc.	6,24,31-36
The cardiovascular system	SA-β-gal$^{\uparrow; P; H\&N; PT\&CC}$, lipofuscin$^{\uparrow; N; PT}$, p21$^{CIP1 \uparrow; R\&P; H\&N; PT\&CC}$, γ-H2AX$^{\uparrow; P; H; LS}$, 8-oxodG/8-OHdG$^{\uparrow; H; LS}$, S100A8$^{\uparrow; P; N; PT}$, S100A9$^{\uparrow; P; N; PT}$, IL-1β$^{\uparrow; R\&P; N; PT}$, IL-6$^{\uparrow; P; H; PT}$, IL-7$^{\uparrow; R\&P; H\&N; PT\&CC}$, TNF-α$^{\uparrow; P; N; PT}$, MCP-1$^{\uparrow; P; H; LS}$, MMP2$^{\uparrow; P; H\&N; LS\&PT}$, MMP9$^{\uparrow; R\&P; H\&N; LS\&PT}$, HP1$^{\downarrow; P; N; PT}$, H3K9me3$^{\downarrow; P; N; PT}$, Lamin B1$^{\downarrow; P; N; PT}$, Lamin B2$^{\downarrow; P; N; PT}$, CCL17$^{\uparrow; P; H; LS}$, GDF15$^{\uparrow; P; H; LS}$, IGFBP7$^{\uparrow; P; H; LS}$, spermidine$^{\downarrow; H; PT}$, NAD^{+} $^{\downarrow; H; LS}$, SIRT2$^{\downarrow; R\&P; H\&N; PT\&CC}$, somatic mutations$^{\uparrow; H; PT}$, etc.	24,37-50
Lungs	SA-β-gal$^{\uparrow; P; N; PT}$, lipofuscin$^{\uparrow; H; PT}$, p16$^{INK4a \uparrow; P; H; PT}$, p21$^{CIP1 \uparrow; P; H; PT}$, γ-H2AX$^{\uparrow; P; H; LS}$, 8-oxodG/8-OHdG$^{\uparrow; H; LS}$, S100A8$^{\uparrow; P; N; PT}$, TNF-α$^{\uparrow; P; N; PT}$, IL-6$^{\uparrow; P; H; PT}$, IL-7$^{\uparrow; R\&P; N; PT}$, IL-8$^{\uparrow; P; H; PT}$, ERVs$^{\uparrow; P; N; PT}$, LINE-1$^{\uparrow; P; H; LS}$, GDF15$^{\uparrow; P; H; LS}$, CRP$^{\uparrow; P; H; LS}$, cGAS$^{\uparrow; P; H; LS}$, telomere length$^{\downarrow; H; LS}$, etc.	24,38,51-55
Liver	SA-β-gal$^{\uparrow; P; H\&N; PT\&CC}$, p21$^{CIP1 \uparrow; P; H\&N; LS\&PT}$, γ-H2AX$^{\uparrow; P; H; LS}$, S100A8$^{\uparrow; P; N; PT}$, S100A9$^{\uparrow; P; N; PT}$, IL-1β$^{\uparrow; R\&P; N; PT}$, IL-6$^{\uparrow; R\&P; N; PT}$, MMP9$^{\uparrow; P; N; PT}$, TNF-α$^{\uparrow; P; N; PT}$, Lamin B1$^{\downarrow; P; H\&N; PT\&CC}$, H3K9me3$^{\downarrow; P; N; PT}$, ERVs$^{\uparrow; P; N; PT}$, APOE$^{\uparrow; P; H; LS}$, GPNMB$^{\uparrow; P; H; PT}$, etc.	24,43,50,56-59
The immune system	SA-β-gal$^{\uparrow; P; H; LS\&CC}$, p16$^{INK4a \uparrow; R\&P; H; LS}$, p21$^{CIP1 \uparrow; R\&P; H; LS}$, p53$^{\uparrow; R\&P; H; LS}$, H3K9me3$^{\downarrow; P; H; PT}$, ROS$^{\uparrow; H; LS}$, telomere length$^{\downarrow; H; LS}$, IL-6$^{\uparrow; P; H\&N; LS\&PT}$, IL-8$^{\uparrow; R\&P; H; LS\&CC}$, etc.	50,60-65
Adipose tissue	SA-β-gal$^{\uparrow; P; H\&N; LS\&PT}$, p16$^{INK4a \uparrow; R\&P; H; LS}$, p21$^{CIP1 \uparrow; R\&P; H; LS}$, p53$^{\uparrow; P; H; LS}$, Ki-67$^{\downarrow; P; H; LS}$, PCNA$^{\downarrow; R\&P; H; LS}$, γ-H2AX$^{\uparrow; P; H; LS}$, TAF$^{\uparrow; H; LS}$, IL-6$^{\uparrow; R; H; LS}$, IL-8$^{\uparrow; R; H; LS}$, CXCL10$^{\uparrow; R; H; LS}$, MCP-1$^{\uparrow; R\&P; H; LS}$, etc.	66-70
The musculoskeletal system	SA-β-gal$^{\uparrow; P; H; LS}$, p16$^{INK4a \uparrow; R\&P; H; LS}$, p21$^{CIP1 \uparrow; R\&P; H; LS}$, TAF$^{\uparrow; H; LS}$, Lamin B1$^{\downarrow; P; N; PT}$, H3K9me3$^{\downarrow; P; H\&N; LS\&PT}$, HP1$^{\downarrow; P; H; LS}$, ERVs$^{\uparrow; P; H; LS}$, S100A8$^{\uparrow; P; H; LS}$, S100A9$^{\uparrow; P; H; LS}$, IL-1β$^{\uparrow; R; N; PT}$, IL-6$^{\uparrow; R\&P; H\&N; LS\&PT}$, CCL2$^{\uparrow; R; H; LS}$, CCL3$^{\uparrow; R; H; LS}$, TGF-β$^{\uparrow; R; H; LS}$, SIRT5$^{\downarrow; P; H\&N; LS\&PT}$, etc.	43,71-79
Kidneys	SA-β-gal$^{\uparrow; P; H; LS\&CC}$, p16$^{INK4a \uparrow; R\&P; H; LS}$, p21$^{CIP1 \uparrow; R\&P; H\&N; LS\&PT}$, p53$^{\uparrow; P; H; CC}$, p-Rb$^{\downarrow; P; H; CC}$, Ki-67$^{\downarrow; P; H; LS}$, γ-H2AX$^{\uparrow; P; H; CC}$, SASP factors like IL-1β and IL-6$^{\uparrow; R; H;}$	24,80-85

	CC, etc.	
The reproductive system	SA-β-gal↑; P; H&N; PT&CC, lipofuscin↑; H&N; LS&PT, γ-H2AX↑; P; H&N; LS&PT, 8-oxodG/8-OHdG↑; H&N; LS&PT, ROS↑; H; LS, 4-HNE↑; N; PT, p21CIP1↑; R&P; H&N; LS&PT, SASP factors↑; R&P; H&N; LS&PT, Ki-67↓; P; N; PT, lysosome number↑; H; LS, lysosomal pH↓; H; LS, etc.	86-94

Note: "↑" indicates upregulation during ageing; "↓" indicates downregulation during ageing; "P" indicates expression change at the protein level; "R" indicates expression change at the RNA level; "H" indicates human samples; "N" indicates non-human primate samples; "CC" indicates cultured cells; "LS" indicates live specimens; "PT" indicates primary tissues.

Abbreviations: 4-HNE, 4-hydroxynonenal; 8-oxodG/8-OHdG, 8-hydroxy-2'-deoxyguanosine; Aβ, amyloid-β; CCL17, C-C motif chemokine ligand 17; CRP, C-reactive protein; CXCL10, C-X-C motif chemokine ligand 10; ERVs, endogenous retroviruses; GDF15, growth differentiation factor 15; GPNMB, glycoprotein nonmetastatic melanoma protein B; H3K9me3, histone H3 lysine 9 trimethylation; HP1, heterochromatin protein 1; IGFBP7, insulin-like growth factor binding protein 7; IL-6, interleukin-6; LINE-1, long interspersed nuclear element 1; MCP-1, monocyte chemoattractant protein 1; miR-31, microRNA-31; MMP3, matrix metalloproteinase 3; NAD^+, nicotinamide adenine dinucleotide; PCNA, proliferating cell nuclear antigen; $p16^{INK4a}$, also known as CDKN2A (cyclin-dependent kinase inhibitor 2A); $p21^{CIP1}$, also known as CDKN1A (cyclin-dependent kinase inhibitor 1A); p53, tumor protein 53; p-Rb, phosphorylated retinoblastoma protein; ROS, reactive oxygen species; S100A8, S100 calcium-binding protein A8; SA-β-gal, senescence-associated β-galactosidase; SASP, senescence-associated secretory phenotype; SIRT2, sirtuin 2; TAF, telomere-associated foci; TGF-β, transforming growth factor β; TMEM106B, transmembrane protein 106B; TNF-α, tumor necrosis factor α; γ-H2AX, phosphorylated histone H2AX.

Supplementary Table 5 | Representative examples for common ageing biomarkers in primates at the organismal level

Molecular biomarkers	Refs
IL-1β$^{\uparrow; P; N; LS}$, IL-6$^{\uparrow; P; H; LS}$, CRP$^{\uparrow; P; H; LS}$, IL-23R$^{\uparrow; P; H; LS}$, GDF15$^{\uparrow; P; H; LS}$, S100A8$^{\uparrow; P; H\&N; LS\&PT}$, S100A9$^{\uparrow; P; H\&N; LS\&PT}$, NfL$^{\uparrow; P; H; LS}$, VCAM-1$^{\uparrow; P; H; LS}$, HERV-K envelope protein$^{\uparrow; P; H; LS}$, TNF-α$^{\uparrow; P; H; LS}$, ox-LDL$^{\uparrow; P; H; LS}$, PAPPA$^{\uparrow; P; H; LS}$, PSG4$^{\uparrow; R\&P; H; LS\&PT}$, KCNQ1OT1$^{\uparrow; R; H; LS}$, GAS6$^{\uparrow; P; H; LS\&PT}$, COMP$^{\uparrow; P; H; LS\&PT}$, CHI3L1$^{\uparrow; P; H; LS}$, NOTCH3$^{\uparrow; P; H; LS}$, ITLN1$^{\uparrow; P; H; LS}$, EFEMP1$^{\uparrow; P; H; LS}$, HTRA1$^{\uparrow; P; H; LS}$, LTBP2$^{\uparrow; P; H; LS}$, Activin A$^{\uparrow; P; H; LS}$, TNFsRII$^{\uparrow; P; H; LS}$, serum total protein$^{\downarrow; P; H; LS}$, bioavailable testosterone$^{\downarrow; P; H; LS}$, AMH$^{\downarrow; P; H; LS}$, Klotho$^{\downarrow; P; H; LS}$, uridine$^{\downarrow; H; LS}$, taurine$^{\downarrow; H\&N; LS}$, MANF$^{\downarrow; P; H; LS}$, 8-oxoG$^{\uparrow; H\&N; LS}$, DNA methylation of LINE-1$^{\downarrow; H; LS}$, DNAmAge$^{\downarrow; N; LS\&PT}$, telomere length$^{\downarrow; H; LS\&PT}$, somatic mutations$^{\uparrow; H\&N; PT}$, etc.	30,50,95-125

Note: "$^{\uparrow}$" indicates upregulation during ageing; "$^{\downarrow}$" indicates downregulation during ageing; "^{P}" indicates expression change at the protein level; "^{R}" indicates expression change at the RNA level; "^{H}" indicates human samples; "^{N}" indicates non-human primate samples; "^{LS}" indicates live specimens; "^{PT}" indicates primary tissues.

Abbreviations: 8-oxoG, 8-oxo-guanine; AMH, anti-Mullerian hormone; CHI3L1, chitinase-3 like-protein-1; COMP, cartilage oligomeric matrix protein; CRP, C-reactive protein; DNAmAge, DNA methylation age; EFEMP1, EGF-containing fibulin extracellular matrix protein 1; GAS6, growth arrest-specific protein 6; GDF15, growth differentiation factor 15; HERV-K, human endogenous retrovirus K; HTRA1, HtrA serine peptidase 1; IL-1β, interleukin 1β; IL-23R, IL-23 receptor; ITLN1, intelectin 1; KCNQ1OT1, KCNQ1 opposite strand transcript 1; LINE-1, long interspersed nuclear element 1; LTBP2, latent transforming growth factor beta binding protein 2; MANF, mesencephalic astrocyte-derived neurotrophic factor; NfL, neurofilament light; NOTCH3, Notch receptor 3; ox-LDL, oxidized low-density lipoprotein; PAPPA, pregnancy-associated plasma protein A; PSG4, pregnancy-specific beta-1-glycoprotein 4; S100A8, S100 calcium-binding protein A8; TNF-α: tumor necrosis factor α; TNFsRII, tumor necrosis factor soluble receptor II; VCAM-1, vascular cell adhesion molecule-1.

Supplementary Box 1 | Sex differences during ageing in tissues beyond the reproductive system

Ageing exhibits profound sex-specific disparities across non-reproductive tissues, driven by hormonal, genetic, and environmental factors. These differences manifest in tissues like the brain, cardiovascular system, liver, and immune system, with implications for ageing phenotypes and disease susceptibility.

Brain

Cognitive decline and neurodegenerative diseases associated with brain ageing display marked sex differences. In a clinical study involving more than 1200 participants, it was observed that women exhibited superior cognitive function during the ageing process relative to men[126]. However, in contrast, a longitudinal investigation spanning four years in marmosets demonstrated that female individuals tend to experience cognitive deterioration at an earlier stage compared to their male counterparts[127], indicating that species-specific mechanisms may underlie these differences. Upon diagnosis of mild cognitive impairment (MCI) or Alzheimer's disease (AD) dementia, women tend to experience a more rapid decline in cognitive function compared to men. Additionally, throughout the progression of AD, differences are observed in the rates and patterns of brain atrophy between men and women, with women typically exhibiting faster brain atrophy during the MCI stage[128]. In rhesus monkeys, sex differences in motor decline emerge with age: males show greater slowing in complex motor tasks, independent of striatal atrophy, pointing to sex-specific neural circuit vulnerabilities[129].

Cardiovascular system

Cardiovascular ageing exhibits distinct sex-specific differences in both phenotypic manifestations and disease susceptibility[130,131]. In terms of ageing phenotypes, women demonstrate greater age-related left ventricular wall thickening, concentric remodeling, and diastolic dysfunction compared to men, while men exhibit more

eccentric hypertrophy and systolic dysfunction. Vascular ageing in women is marked by accelerated arterial stiffness postmenopause and heightened microvascular dysfunction, whereas men show earlier and more severe plaques. Regarding disease susceptibility, women are more prone to heart failure with preserved ejection fraction and non-obstructive coronary artery disease.

Liver

In the liver, sex hormones significantly influence ageing-related conditions. Non-alcoholic fatty liver disease and hepatocellular carcinoma are more prevalent in men than in premenopausal women[132], suggesting a potential protective effect of estrogen. This disparity diminishes in postmenopausal women, indicating the importance of hormonal status in age-related chronic liver disease progression. Additionally, men exhibit higher rates of hepatic fibrosis and hepatobiliary malignancies[133,134], potentially due to sex-specific differences in immune regulation, metabolic pathways, and hormones.

Immune system

The immune system undergoes pronounced sex-specific ageing. Men typically show higher levels of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, contributing to increased inflammaging[135]. This is associated with a higher risk of age-related diseases such as cardiovascular disorders and certain cancers. Epigenomic analyses reveal male-specific erosion of B cell regulatory loci and amplified innate immune responses post-65 years[136]. Furthermore, compared to women, men typically show lower levels of T cell activation and experience a more rapid progression of T cell senescence with ageing[137].

Supplementary Box 2 | Representative clocks for ageing prediction

Notable examples of DNA methylation clocks include Horvath's clock[138], Hannum's clock[139], PhenoAge[140], GrimAge[141], DunedinPACE[142], Skin & Blood clock[143], Retroelement-Age[144], PRC2-AgeIndex[145], and their derivatives such as GrimAge2[146].

ATAC-clock and miRNA age are developed from ageing-associated chromatin accessibility alterations and miRNA expression patterns, respectively[147,148]. These clocks, closely aligned with gene expression dynamics, may complement DNA methylation clocks and serve as auxiliary ageing biomarkers.

Clocks based on transcriptomic, proteomic, or metabolomic data have been proven to be promising biomarkers for the prediction of ageing, disease susceptibility, and intervention effectiveness[24,50,97,149-153].

Immune clocks or inflammatory clocks, derived from age-related fluctuations in circulating immune cells and proteins, also have the potential to track ageing and relevant disease phenotypes[154,155].

Advances in single-cell sequencing technologies have propelled the development of ageing clocks with higher resolution, contributing to a more nuanced understanding of cellular heterogeneities in the ageing process[156-159].

Notably, ageing-specific profiles of skin, oral, or gut microbiomes can also be developed as clocks for predicting chronological age and individual health[160-163].

Like facial imaging clocks, retinal photographs or images of eye corners have been utilized to indicate biological ageing of individuals[164,165].

Clinical ageing clocks have been developed using a comprehensive array of over 150 clinical parameters, encompassing derived health scores, medical examination data, as well as clinical laboratory and blood chemistry analyses[166]. These models act as potential indicators of healthy ageing and provide promising targets for clinical

interventions.

Composite ageing clocks, based on multi-omics data spanning different molecular dimensions or multimodal measurements that incorporate multiple phenotypic traits and molecular parameters, have demonstrated robust capacities in predicting ageing and assessing the outcomes of interventions[167-169].

Beyond these aspects mentioned above, other types of biomarkers, such as those relying on wearable sensor data like sleep or movement patterns, could introduce new paradigms for predicting ageing and health[170].

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