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Supplementary information

Roadmap for alleviating the manifestations of ageing in the cardiovascular system

In the format provided by the authors and unedited

Roadmap for alleviating manifestations of ageing in the cardiovascular system

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Supplementary Table 1: Ageing hallmarks in cells of the circulatory system

	Genomic Instability	Telomere attrition	Epigenetic alteration	Loss of proteostasis	Disabled macroautophagy	Altered intercellular communication	Chronic inflammation	Dysbiosis	Deregulated nutrient-sensing	Mitochondrial dysfunction	Cellular senescence	Stem cell exhaustion
												
Vascular cells												
Endothelial cells	1,2	3	4,5,6,7,8	9	9,10,11	12	13,14,15,16,17,18	19	20	21,22	23,24,25	15
Smooth muscle cells	1,2,26	1,27	4,28	29	30	31	32	33	34,35,36	21	37,38	39
Pericytes			40				40				40	
Cardiac cells												
Cardiomyocytes	41	41	41	42	43,44	41,45	46,47	48	49	41,50,51	41	
Cardiac fibroblasts	52		53			53	53		54,55	56	57	58
Circulatory cells												
Hematopoietic stem cells	59	60,61	60,62,63	64	65,66	67,68	17,69	69	70	71,72	60,73	74,75
Lymphoid lineage												
B cells		76,77	78	79	80	81	81	82,83,84	85	86	87	88
T cells	3	77,89	78,90	91-93	94,95	96,97	98,99,100		101,102	86,95,103,104	105,106	88
Natural killer cells		107				108,109,110	111,112,113,114	115	116-120		121,122,123	
Myeloid lineage												

Monocytes	124	125	126	127	128	128,129,130	131,132		133,134	133,134	125,131	74
Macrophages	135	136,137	138	139	136,140	141,142	138,143	144,145, 146	147,148	86	149,150, 151	
Granulocytes	152	153	152		152,154	155,156,157	156	158	134,159	86,160	161	74
Platelets		162	163	164	165	166,167,168	169,170		171	169,172	163	173
Erythrocytes		174				175			176,177		178	
Dendritic cells	179,180			181		129	182,183	184	185	186	187	188

Level of evidence	I,Human & other organisms	II,Human & other organisms	I,Only Human	II,Only Human	I,Only preclinical	II,Only prelinical	No effect	Unknown

Preclinical evidence: aged model or accelerated model of ageing.
Human evidence: aged model of cell or human tissue.
Evidence are (1) hallmark should manifest or happen during normal ageing, (2) experimental acceleration or increase of the hallmark accelerates normal ageing, and (3) experimental reduction of the hallmark slows normal ageing. Evidence I has at least 2 of the 3 above-mentioned point, while evidence II has only 1 of the above-mentioned point.
The numbers in the boxes refer to the corresponding citations in the bibliography.

Supplementary Table 2: Geropromoting mechanisms in human disease												
	Genomic Instability	Telomere attrition	Epigenetic alteration	Loss of proteostasis	Disabled macroautophagy	Altered intercellular communication	Chronic inflammation	Dysbiosis	Deregulated nutrient-sensing	Mitochondrial dysfunction	Cellular senescence	Stem cell exhaustion
												
Cardiovascular system												
Hypertension	189,190, 191	190	192	193	193,194,195,196,197,198	199,200,201, 202	203,204	205,206	206,207,208, 209	195,196,210, 211	2,190	
Atherosclerosis	191,212	213,212	192	193	30,193, 214	199,215,216	204,217,218	219,220	207,208	214,221	190	222
Aneurysm/Arterial Dissection	223		224	225	226	199,215,227	228	229	228	230	231	231
ATTR Amyloidosis				223								
Atrial Fibrillation	232,233		232	234,235	234	236,237,238, 239,240	237,241,242	243	244	245,246,247	248	249
Non-AF arrhythmias	250		251,252	253	254	255,256	241,255,256	257	258	247,259	231	231,249
Age-related Heart Failure with preserved Ejection Fraction	260,261, 262,191	263,262, 264	265,262, 266	267,268, 269	267,270,271,195,272,273	274	103,204		207,275	103,195,261, 276	41,261, 277	
Cardiac Valve Degeneration	191	278	279	191		279	103,280		207	103,281	282	283
Brain												
Vascular Dementia	284,285	286,287	288,289, 290	291,292, 293	291,292,294	295,296,297, 298,299	103,203,300, 301	302,303	207,275,304, 305	103,306,307	308,309, 310	311
Alzheimer's Disease	312,313	314,315	289,290, 316	317,318, 319	317	320,321,322, 323	324,325	302	326,327,328	329	330	331
Parkinson's Disease	332	315,333, 334	335	336	337	338,339	340,341	342	343	344	345	346
Stroke	347,348, 349	350	347,351	352	353	354,355	356,357	358,359	360	361	347	

Kidney												
Chronic Kidney Disease	260	362,363	288	364,253, 365	195,271,366	215,367,368	103,204	369	370	103,306,371	231,372	231
Lung												
COPD/Emphysema		373,374, 375	376	377	378	49,379,380	379,381	382	383,384,385	386,378	379,387	388,389
Idiopatic Pulmonary Fibrosis		362,390, 391,374, 375,392	393	394,395	267,396	397	398,399	400	383	401,402	398,403, 404	405
Ear, nose, and throat diseases												
Presbycusis	406,407, 408		408,409, 410	411	407	412	407		413,414	415,416,417, 418,419	406,407	
Macular Degeneration/ Retinal atrophy	260,285, 420	421	288,422	423,424, 425	426,423	427	426,428. 429. 430	431	426,432,433	434	426,429	429,433
Cataracts	420,435, 212,285	212,213	288	436,437, 438	439,440	441	442,443		443	221,371	444	422
Liver												
Metabolic dysfunction-associated steatotic liver disease		445,446			447	447,448,449, 450	204	451,452	370	453,454,455, 456	457	458
Liver Fibrosis		362,446, 459,460	458	458	267	67,448,449,461	103,204	451	370	103,306,454, 455	462	458
Bone Marrow												
Myelodysplastic syndromes and Hematologic Neoplastic Disorders	420	463,464, 465,466	467,468	469	271	470,471	472	473	474,475,476	221,371,477		
Anemia	285	362,478, 479	480	481		482	103	483		103,484	485,285	485,285
Pancreas												
Diabetes	212,408	287,459, 212,213, 362	459,486	193	198,447	201,367,487, 488	204	452	207,208,489, 490	491,492	459	231

Systemic												
Osteoarthritis	212	213,362	288	493,494		495	103,495	369	207	103	444,496, 497,498	231
Osteoporosis	260,435, 408,420	287,213, 362,435	288,499	493,494	271	201,448,449, 500,501	103,502	369	207,369	103	444,501	458,501
Sarcopenia	260,435, 408,420	287,362, 435	288,499	493,494	267,271	201,448,449, 500	103,502	369	369	103	231,444	231,458
Infertility	435,212, 408,503	463,504, 212,505	499	493,494, 365	440	506,507	204	508	207	306	444	
Solid tumors	260,212, 285,420	463,212, 213,505	480,509, 510	511	271	449,512,513	217	514	207	371,455,515	459	
Graying/Loss of hair	212,408, 420,516	517,212, 213,505	499	364	267	215,449,518	103,502	369	207	103,306,371, 491	231	231,458
Skin alterations (tight skin, thin skin, hyperkeratosis)	212,408, 420,516	287,212, 213,505, 517	499	364,493, 494,253	267	67,215	103,502		207	103,371	231,498	231,458, 519

Light green: experimental evidence (genetic models, treatments)
Dark green: clinical evidence (randomized clinical trials with drugs acting on ageing hallmarks, genetic syndromes with accelerated ageing (references are highlighted in red)).
The numbers in the boxes refer to the corresponding citations in the bibliography.

Supplementary Table 3: Lifestyle interventions as potential geroprotective and gerotherapeutic strategies for the cardiovascular system				
Experimental approaches	**Study design**	**Ageing hallmark affected**	**Effects on the circulatory system**	**Refs.**
Caloric restriction and dietary interventions				
8-week treatment program	RCT, 43 healthy adult males; 50-72 years	Epigenetic	↓Triglycerides ↑5-methyltetrahydrofolate	[520]
For Phase 2 of the CALERIE™ study participants were randomized 2:1 to either a 25% CR diet or an ad libitum diet for 2 years.	199 healthy young-to-middle-aged individuals	Senescence	↓Circulating biomarkers of ageing ↑Marker of metabolic health	[521]
2-year moderate CR (13%)	Multicentre, RCT, 238 healthy non-obese young and middle-aged; 21-50 years; men (72) and women (166)	↓ Oxidative stress ↓ Low-grade systemic inflammation ↑ Nitric oxide bioavailability	↓LDL-cholesterol, ↓Total cholesterol to HDL-cholesterol ratio ↓Blood pressure ↓CRP ↑Insulin sensitivity index ↓Metabolic syndrome severity score	[522]
6 months of 25% CR alone or in combination with exercise	RCT, 36 healthy non-obese men and women	↓ Inflammation	↓Body weight ↓Triacylglycerols CR+ exercise: ↓LDL-cholesterol ↓Diastolic blood pressure ↓ CRP in the controls versus CR+ exercise ↓ Estimated 10-year CVD risk by 29% in CR and 38% in the CR+ exercise (↔ control group)	[523]
8-week low-energy diet (810 kcal/daily)	Multicentre RCT, 2224 overweight individuals; 1504 women, 720 men with pre-diabetes	↓Inflammation	Men and Women: ↑Insulin sensitivity (35% of participants reverted to normoglycaemia) Men vs. Women: ↓Body weight ↓Metabolic syndrome Z-score ↓CRP ↓Fat mass ↓Heart rate Women vs. Men: ↓HDL cholesterol ↓Free-fat mass ↓Waist circumference ↓Pulse pressure	[524]
CR alone or in combination with exercise	RCT, 100 obese men and women with heart failure with preserved	↓ Inflammation	CR and exercise: ↑Peak oxygen consumption ↓LV hypertrophy ↓Diastolic dysfunction	[525]

	ejection fraction≥ 60 years		CR: ↓CRP ↓Total cholesterol ↓LDL-cholesterol	
12-months of CR (20%) or exercise	RCT, 48 normal weight and overweight middle-aged 29 women and 17men; 57±3 years	↓Inflammation	↓Body (fat) mass ↓LDL-cholesterol ↓Total cholesterol/HDL ratio ↓HOMA-IR index ↓ CRP	526
Fasting-mimicking diet (FMD): 3 cycles for 5 consecutive days per month for 3 months	RCT, 100 generally healthy participants (37 men; 42.2 ± 12.5 years and 63 women; 43.3 ± 11.7 years)	↑Nutrient signaling	↓Body mass index ↓Blood pressure ↓Fasting glucose ↓IGF-1 ↓Triglycerides ↓Total and low-density lipoprotein cholesterol ↓CRP	527
Long-term CR (11%) coupled with high intensity physical activity	Observational study; 54 healthy community-dwelling participants (29 men; 74.5 ± 0.7 years) and 25 women;74.7 ± 0.6 years	↑Nutrient signaling	↓Coronary heart disease ↓Body mass index ↑Plasma dehydroepiandrosterone ↓Mortality from age-associated diseases	528
Long-term CR (for an average of 6 years)	Observational study; 15 men and 3 women (range 35–82 years).	↓Inflammation	↓Body weight ↓Fat mass ↓Blood pressure ↓Total cholesterol ↓LDL-cholesterol ↓Total cholesterol to HDL-cholesterol ratio ↓Triglycerides ↑Fasting glucose ↓Fasting insulin ↓CRP ↓Carotid artery intima media thickness	529
Exercise training				
Lifelong exercise	Cross-sectional/observational study; 102 healthy seniors (>64 years of age) stratified into 4 groups: sedentary, casual, regular, competitive	↑Myocardial energetics ↑Expression of genes involved in fatty acid oxidation ↓Low-grade systemic inflammation	Regular exercisers vs. sedentary subjects: ↑Peak oxygen uptake ↑LV hypertrophy ↑LV distensibility ↓LV stiffness ↑LV compliance	530
Treadmill exercise	Observational study, 122,007 patients (53.4±12.6 years;	Unknown	Risk-adjusted all-cause mortality was inversely proportional to cardiorespiratory fitness and was lowest in elite performers.	531

	72 173 [59.2%] male)		Extremely high aerobic fitness was associated with benefit in older patients and those with hypertension.	
Cardiorespiratory fitness and mortality risk for different races, sex, and age	Observational study involving 750,302 U.S. veterans aged 30 to 95 years (mean age 61.3 ± 9.8 years) during a standardized exercise treadmill test	Unknown	↓Mortality by >50% across all age groups, races, and sex, independent of comorbidities upon moderate intensity physical exercise >150 minutes weekly.	[532]
Prolonged, sustained endurance training	Observational study, 12 healthy sedentary seniors (69.8±3 years; 6 women, 6 men) and 12 Masters athletes (67.8±3 years; 6 women, 6 men)	Unknown	↑Stroke volume ↔Contractility	[533]
4-year CR and physical activity	Multi-center, RCT, 5,145 volunteers (age 45-76 years), with established DM2 and overweight or obesity. Study follow-up: 11.5 years	Unknown	↔Risk of cardiovascular morbidity (heart attacks and stroke) or cardiovascular-related death	[534,535]
Abbreviations: CR: caloric restriction; CRP: C-reactive protein; HOMA-IR: homeostatic model assessment for insulin resistance; LDL: low-density lipoproteins; LV: left ventricle; HDL: high-density lipoproteins; RCT: randomized controlled trial				

Supplementary Table 4: Potential geroprotective and gerotherapeutic strategies on the cardiovascular system				
Experimental approaches	**Study design**	**Ageing Hallmark affected**	**Effects on the circulatory system**	**Refs.**
Current geroprotective and gerotherapeutic strategies used in human				
Senolytics				
Fisetin	RCT, fisetin two administrations of 2 mg/kg for three days – 2 weeks interval in between	Cell senescence	Endpoints: carotid femoral and brachial artery PWV. Ongoing	NCT06133634
Telomerase activators				
TA-65®	RCT, patients with MI >65 years old. TA-65® 16 mg/day, 12 months	Inflammation	↓hsCRP (-62%), ↓adverse events (-30%)	536
Anti-diabetic drugs				
Metformin	RCT, impaired glucose tolerance, metformin 850 mg bid, 3 years	Nutrient-sensing; gut microbiota	↓ risk of diabetes = risk of MACE	537
GLP-1RA	RCT, non-diabetic obese or overweight, semaglutide 2.4 mg/week, 3 years	Nutrient-sensing	↓ body weight ↓ risk of MACE	538,539
mTOR inhibitor				
Everolimus	RCT, patients with STEMI undergoing PCI, everolimus 7.5 mg/day (days 1-3) + 5.0 mg/day (days 4-5)	Nutrient-sensing, autophagy, inflammation	No difference in MI size or microvascular obstruction 30 days after the event	540
Polyamines				
Bifidobacterium animalis + Arginine	RCT, healthy adults, dietary supplementation for 12 weeks,	Gut microbiota, autophagy (↑ production of spermidine)	↑ brachial artery FMD	541
Sirtuins activators				
Nicotinamide mononucleotide (NMN)	RCT, healthy adults, nicotinamide mononucleotide 300, 600, or 900 mg/day vs placebo, 60 days	Epigenetic regulation; oxidative stress	↑ performance 6MWT = insulin-sensitivity	542
Resveratrol	Meta-analysis of RCTs, adults with metabolic syndrome, resveratrol 150-3000 mg/day, 1 week to 1 year	Epigenetic regulation; oxidative stress	↑ FMD	543
Anti-inflammatory				
Colchicine	RCT, patients with chronic coronary artery disease, 0.5 mg/day, 2.5 years	Inflammation	↓ risk of MACE	544
Canakinumib	RCT, patients with very-high cardiovascular risk and hsCRP >2 mg/L, canakinumab 50, 100,	Inflammation	↓ risk of MACE	218

	150 mg s.c. every 3 months, 3.7 yrs			
Future perspectives for geroprotective and gerotherapeutic interventions.				
Caloric restriction mimetics				
Spermidine supplementation	Spermidine supplementation to drinking water starting from the age of 4 months (life-long) or 18 months (late-in-life) of C57BL/6J female mice	Autophagy, Mitochondrial dysfunction, Epigenetics, Senescence, Inflammation	10-15% extension in median lifespan, depending on age at when treatment is initiated ↑ endothelial function, vascular stiffness	195
NAD+ Precursors (nicotinamide, nicotinamide riboside, and nicotinamide mononucleotide)	Supplementation to 4 months to 28 months old C57BL/6J mice, Dahl salt-sensitive rats, ZSF1 obese rats, or mouse model of dilated cardiomyopathy	Mitochondrial dysfunction, Epigenetics, DNA stability, inflammation, senescence	0-5% extension in median lifespan depending on age when treatment is initiated ↓ cardiac hypertrophy and diastolic dysfunction, protecting from HFpEF and dilated cardiomyopathy ↓ vascular remodelling and endothelial dysfunction	545,211,546,547,548
Genetic therapies				
systemic VEGFA overexpression in the circulation (1.5-2 fold)	VEGF transgenic mice	Mitochondrial dysfunction, Senescence, Inflammation	up to 48% in male mice and 39% in female mice extended lifespan ↑ perfusion and oxygenation of tissues ↓ loss of capillaries	449
ACBP neutralization	i.p. injection to 8 week old C57BL/6J female mice	Autophagy, Inflammation, Senescence	Reduced chemotherapy-induced cardiac senescence and dysfunction	549
Mitochondria				
Mitochondria-targeted antioxidants	i.p. injection to 24-month-old C57BL/6 mice	Mitochondrial dysfunction, Inflammation	↑ neurovascular coupling, cerebral microvascular and cognitive functions	307
mTOR inhibitor				
Rapamycin	Microencapsulated rapamycin incorporated in the chow diet starting at 270 days or 600 days in mice	Nutrient-sensing, autophagy, inflammation	14% for females and 9% for males extended lifespan	550
Parabiosis				
heterochronic parabiosis	Anastomosis surgery up to 3 months in 3- to 22-month old mice	Epigenetics, Proteostasis, Senescence, Inflammation	6-week extension in median lifespan of old mice after detachment Global multi-omic improvement ↑ endothelial function and different tissue functions	461,551,500
Senolytic				
Dasatinib and quercetin	bi-weekly administration starting at 24-27 months of age	Senescence	36% higher lifespan and 64.9% lower mortality hazard	552

			↑ maximal walking speed, hanging endurance, grip strength, treadmill endurance, and daily activity	
Small molecules compounds				
Taurine supplementation	Daily oral administration to 14 months old female mice for 10 to 12 months.	All hallmarks	12% in female and 10% in male mice lifespan extension ↑ energy expenditure, bone mass, and muscle functions ↓ depression, anxiety-like behaviours, and reduced insulin resistance.	[553]
anti-IL-11	75-week-old mice for 25 weeks	Inflammation	25% in female and 22.5% in male mice median lifespan extension ↑ metabolism and muscle functions	[554]

Abbreviations:
6MWT: 6-minute walk test; FMD: flow-mediated dilation; HFpEF: heart failure with preserved ejection fraction; hsCRP: high-sensitivity C-reactive protein; i.p.: intraperitoneal; MACE: major adverse cardiovascular event; MI: myocardial infarction; PCI: percutaneous coronary intervention; PWV: pulse wave velocity; RCT: randomized controlled trial; STEMI: ST-elevation myocardial infarction.

Supplementary Table 5. Clinical applicability of biological clocks and surrogate ageing markers							
Biological clocks	**Approach/ Strategy**	**Predictive value for lifespan**	**Evidence level I, II, III**	**Predictive value for health span**	**Evidence level I, II, III**	**Therapeutic response**	**Evidence level I, II, III**
Deep learning-based haematological ageing clock*, [555]	Several deep learning-based predictors of biological age trained upon population-specific 20 blood biochemistry biomarkers and haematological cell count datasets	Associated with all-cause mortality	I	N/A		N/A	
DNAmAge[556]	At the molecular level, DNAm age is a proximal readout of a collection of innate ageing processes that conspire with other, independent root causes of ageing to the detriment of tissue function. DNAm age is defined as estimated ("predicted") age.	Associated with increased risk for all-cause mortality	I	Associated with risk for incident CV disease, stroke, different types of cancer, Parkinson's disease and dementia	II	Diet and lifestyle treatment leads to a decrease in DNAmAge. Vitamin D may slow down epigenetic ageing.	II
GlycanAge± [556,557]	Biological age test which determines biological age by measuring chronic inflammation through blood test. A panel of molecular measures based on glycans attached to immunoglobulin G antibodies associated with chronological age.	N/A		Associated with multiple diseases, among others CV disease and diabetes.	I	N/A	
PhenoAge and GrimAgeæø[556]	Both are epigenetic clocks that measure changes in DNA methylation levels at specific CpG sites that are highly correlated with calendar age.	Associated with all-cause mortality	I	Associated with risk of cancer, Alzheimer's disease, CHD. Predictive ability for age-at-menopause. Associated with multiple age-related clinical phenotypes (walking speed, frailty, and cognitive functions).	I	Significant reduction of PhenoAge by CR for 2 years. Reduction of GrimAge by plant-food-rich diet and exercise. Treatment with human umbilical cord plasma reduced GrimAge.	II
DunedinPoAm and DunedinPACE[556]	Rate measure based on comparison of longitudinal change over time in 18 biomarkers of organ-system integrity among individuals who are all at the same chronological age.	Associated with all-cause mortality	I	Associated with incidence of multiple chronic diseases, including dementia and disability.	I	Significant reduction of DunedinPACE by CR for 2 years	II

Multiomic biological age estimation based on KDM[556]	Derived from modelling associations of biomarkers with chronological age in a reference sample and then applying parameters derived from these models in the target dataset to compute participants' biological age values.	N/A		May be a sign of healthy ageing.	I	N/A	
Ageing.AI, Deep Transcriptomic and Proteomic Clocks[556]	AI-based blood clocks, based on haematological parameters, transcriptomic and proteomic data.	Associated with all-cause mortality.	I	N/A		N/A	
Proteomic clocks[558,559]	Proteomic clocks include protein-based biomarkers, they consist of an intermediate phenotype that is most proximal to age-related diseases, and thus may provide more accurate information on ageing and age-related pathologies.	May predict CV death	I	Screening of prostate cancer, prediction of CV events in CCS patients. Associated with body and liver fat, body mass, alcohol consumption, physical activity, conversion from pre-diabetes to DM	I	N/A	
Metabolomic clock[558]	Metabolomic clocks measure the structural and functional building blocks of an organism (through measurement of all metabolites and low-molecular-weight molecules in biological specimens) as a powerful link between genotype and phenotype in aging and age-related diseases.	Associated with all-cause, CV, cancer- and infection-related mortality	I	Associated with the risk of CV disease and functionality in individuals with advanced age.	I	N/A	
Inflammatory ageing clock[560]	A metric for age-related chronic inflammation based on blood immune biomarkers to aid in prediction of important ageing phenotypes and provide insights into the mechanisms leading to vascular ageing.	Associated with exceptional longevity in centenarians	II	Associated with multimorbidity, immunosenescence, frailty and CV ageing.	II	N/A	
Immune aging (IMM-AGE) score[561]	A high-dimensional trajectory of immune ageing that describes a person's immune status better than chronological age,	Better performance in predicting mortality in older	II	N/A		N/A	

		adults than the epigenetic clock.					
Surrogate ageing markers							
CMR radiomics[562,563]	CMR radiomics may be used for detailed cardiovascular phenotyping, by providing multiple quantifiers of ventricular shape and myocardial texture.	N/A		Associated with cardiac ageing	I	N/A	
Echocardiographic heart ageing patterns[564]	A standard Doppler echocardiogram able to detect distinct heart ageing patterns (associations of age with LV mass, geometry, diastolic function, LA volume, and aortic root size) which reflect different biological susceptibilities to age-dependent diseases and provide a new tool for personalising timeliness and intensity of prevention.	Associated with all-cause and CV mortality	I	Predictive value for biological age, CV and non-CV events	I	N/A	
ECG-based heart age[565]	ECG can reflect physiological status of the heart better than chronological age through specific ECG patterns.	Associated with all-cause and CV mortality	I	Associated with HF, stroke, CAD, AMI, AF and DM	I	N/A	
Retinal age gap[566,567]	The retinal age gap is the difference between the biological age of the retina -assessed by deep learning- and a person's chronological age. A positive value indicates an 'older' appearing retina.	Associated with all-cause mortality and mortality attributable to non-CV and non-cancer disease.	I	Associated with risk of stroke. Predictive value for biological age	I	N/A	
CXR-age[568]	Estimation of a patient's age from CXR based on radiological findings.	Associated with all-cause and CV mortality	I	N/A		N/A	
Visible age-related signs**[569]	Assumes that presence of visible age-related signs is a marker of the actual biological age of an individual.	Associated with all-cause mortality in older people	I	Increased risk of IHD and AMI. Correlated with innate immunity at	I	N/A	

				transcriptome level			
PWV	Marker of arterial stiffness, the velocity at which the pressure waves, generated by the systolic contraction of the heart, propagates along the arterial tree, usually between the common carotid and the common femoral artery.	Increased PWV values associated with all-cause and CV mortality[570-574]	I	Associated with diabetes, hypertension, stroke, CAD, hypertrophic cardiomyopathy, myocardial fibrosis, early mild diastolic HF, sleep-disordered breathing in post-stroke patients.[574-582] Determinant of myocardial ischemic threshold[583]		Only 2 studies[584,585] have showed in an indirect way that an improvement in outcomes is mediated through improvement in PWV. Large geroscience studies should confirm lifespan or healthspan extension clinical benefit induced by treatments leading to arterial stiffness regression.	III
Carotid IMT[586-589]	A quick, safe and bedside test that measures the thickness of the carotid artery wall at paired segments.	Associated with CV mortality	I	Associated with traditional CV factors	II	The extent of intervention effects on carotid IMT progression predicted the degree of CV risk reduction.	I
Carotid plaque parameters ***,[590,591]	Carotid plaque parameters include plaque presence, number, thickness, area and volume.	Associated with all-cause and CV mortality	I	Associated with traditional CV factors	I	N/A	
CAC score[592-594]	CAC score measures the amount of calcified plaque in coronary arteries by computed tomography scan.	Associated with all-cause, CV, cancer and CHD mortality	I	Associated with traditional CV factors. CAC progression associated with risk of AMI. May predict incident cancer, CKD, COPD, and dementia.	I	N/A	

Sirtuins[558]	Sirtuin proteins comprise a group of nutrient- and stress-responsive factors that regulate diverse cellular processes to promote health span.	Associated with lifespan	I	Associated with multiple mechanisms of CV disease	II	CR was associated with an increased expression of SIRT1 and SIRT1 was suggested as the main mediator of prolonged lifespan after CR.	
Hs-cTnT[595,596]	Newer type of biomarker which helps to diagnose heart injury and acute coronary syndrome earlier.	Associated with all-cause and CV mortality	I	Increased in older people. Associated with structural heart disease (left ventricular hypertrophy), CHD and HF.	I	N/A	
hs-CRP[218,597,598]	A marker of inflammation with established relationship with atherothrombotic disease.	Associated with all-cause and CV mortality	I	Increased in older populations. Improves CV disease prediction.	I	Achievement of on-treatment CRP <2 mg/L leads to significant reduction of both CV and all-cause mortality.	I
Serum BNP[599-601]	Method for detection of heart failure by measuring the amount of BNP or its prohormone NT-proBNP in the bloodstream.	Associated with all-cause mortality	I	Increased in aged individuals, age-related impairment of left atrial strain positively correlates with higher BNP levels. Marker of increased risk of HF in older adults. Inversely associated with walking speed, chair rise speed, balance time, and grip strength.	II	N/A	
IL-6 [601,602]	Important in ageing and age-related disease and has been called the "gerontologist's	Independent predictor of all-	II	Increased in older populations.	II		

	cytokine". IL-6 plays a key role in the acute phase response, in metabolic control and in the pathogenesis of many chronic diseases.	cause mortality, CV and non-CV mortality		Inversely associated with walking speed, chair rise speed, balance time, and grip strength. Associated with iron deficiency, reduced LVEF and AF in HF patients.			
Urinary BNP[558]	Method for detection of heart failure by measuring the amount of BNP in the urine.	Associated with all-cause mortality	II	May diagnose HF	II	N/A	
Urinary FPA[603]	Urinary FPA is probably a valuable marker of low-grade activation of coagulation, particularly in chronic conditions.	Associated with CV mortality	II	Independent predictor of CV events in patients presenting with chest pain (AMI and angina pectoris)	II		

I - Evidence from large representative population samples. II - Evidence from small, well designed but not necessarily representative samples. III - Evidence from non-representative surveys, case reports.
* Visible age-related signs included male pattern baldness, earlobe crease, and xanthelasmata-alone or in combination.
** In this deep learning-based haematological ageing clock 20 blood biochemistry markers were included.
¶ Epigenetic clocks, based on a set of DNA methylation measures associated with chronological age.
ǝ Epigenetic clocks, based on a set of DNA methylation measures associated with ''clinical phenotypic age measures'' (a panel of age associated molecular and physiological biomarkers, measured in blood).
⁋ KDM applied to over 900 principal component transformed biomarkers (metabolites, proteins, genomics, and clinical measures).
Abbreviations: DNA, deoxyribonucleic acid; CV, cardiovascular; CpG, 5'—C—phosphate—G—3'; CHD, coronary heart disease; CR, calorie restriction; KDM, Klemera and Doubal method; AI, artificial intelligence; CCS, chronic coronary syndrome; DM, diabetes mellitus; CMR, cardiovascular magnetic resonance; LV, left ventricular; LA, left atrium; ECG, electrocardiogram; HF, heart failure; CAD, coronary artery disease; AMI, acute myocardial infarction; AF, atrial fibrillation; CXR, chest X-ray; IHD, ischemic heart disease; PWV, pulse wave velocity; IMT, intima media thickness; CAC, coronary artery calcium; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; SIRT1, sirtuin 1; hs-cTnT, high-sensitive cardiac troponin T; hs-CRP, high-sensitivity C-reactive protein; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro B-type natriuretic peptide; IL-6 interleukin-6; LVEF, left ventricular ejection fraction; FPA, fibrinopeptide.

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