Proteomic organ-specific ageing signatures and 20-year risk of age-related diseases: the Whitehall II observational cohort study

Mika Kivimäki, Philipp Frank, Jaana Pentti, Markus Jokela, Solja T Nyberg, Acer Blake, Joni V Lindbohm, Hamilton Se-Hwee Oh, Archana Singh-Manoux, Tony Wyss-Coray, Linda Partridge

Summary

Background Biological ageing is known to vary among different organs within an individual, but the extent to which advanced ageing of specific organs increases the risk of age-related diseases in the same and other organs remains poorly understood.

Methods In this observational cohort study, to assess the biological age of an individual's organs relative to those of same-aged peers, ie, organ age gaps, we collected plasma samples from 6235 middle-aged (age 45–69 years) participants of the Whitehall II prospective cohort study in London, UK, in 1997–99. Age gaps of nine organs were determined from plasma proteins via SomaScan (SomaLogic; Boulder, CO, USA) using the Python package organage. Following this assessment, we tracked participants for 20 years through linkage to national health records. Study outcomes were 45 individual age-related diseases and multimorbidity.

Findings Over 123 712 person-years of observation (mean follow-up 19·8 years [SD 3·6]), after excluding baseline disease cases and adjusting for age, sex, ethnicity, and age gaps in organs other than the one under investigation, individuals with large organ age gaps showed an increased risk of 30 diseases. Six diseases were exclusively associated with accelerated ageing of their respective organ: liver failure (hazard ratio [HR] per SD increment in the organ age gap 2·13 [95% CI 1·41–3·22]), dilated cardiomyopathy (HR 1·65 [1·28–2·12]), chronic heart failure (HR 1·52 [1·40–1·65]), lung cancer (HR 1·29 [1·04–1·59]), agranulocytosis (HR 1·27 [1·07–1·51]), and lymphatic node metastasis (HR 1·23 [1·06–1·43]). 24 diseases were associated with more than one organ age gap or with organ age gaps not directly related to the disease location. Larger age gaps were also associated with elevated HRs of developing two or more diseases affecting different organs within the same individual (ie, multiorgan multimorbidity): 2·03 (1·51–2·74) for the arterial age gap, 1·78 (1·48–2·14) for the kidney age gap, 1·52 (1·38–1·68) for the heart age gap, 1·52 (1·12–2·06) for the brain age gap, 1·43 (1·16–1·78) for the pancreas age gap, 1·37 (1·17–1·61) for the lung age gap, 1·36 (1·26–1·46) for the immune system age gap, and 1·30 (1·18–1·42) for the liver age gap.

Interpretation Advanced proteomic organ ageing is associated with the long-term risk of age-related diseases. In most cases, faster ageing of a specific organ increases susceptibility to morbidity affecting multiple organs.

Funding Wellcome Trust, UK Medical Research Council, National Institute for Ageing, Academy of Finland.

Lancet Digit Health 2025; 7: e195–204

UCL Brain Sciences (Prof M Kivimäki FMedSci, P Frank PhD, J V Lindbohm MD PhD, Prof A Singh-Manoux PhD), **Institute of Healthy Ageing** (A Blake MSc, Prof L Partridge FMedSci), **and Research Department of Genetics, Evolution and Environment** (A Blake, Prof L Partridge), **University College London, London, UK; Clinicum** (Prof M Kivimäki, J Pentti MSc, S T Nyberg PhD, J V Lindbohm) **and Department of Psychology and Logopedics** (Prof M Jokela PhD), **University of Helsinki, Helsinki, Finland; Department of Public Health and Centre for Population Health Research, University of Turku, Turku, Finland** (J Pentti); **Broad Institute of MIT and Harvard, The Klarman Cell Observatory, Cambridge, MA, USA** (J V Lindbohm); **Graduate Program in Stem Cell and Regenerative Medicine** (H S-H Oh PhD), **The Phil and Penny Knight Initiative for Brain Resilience** (H S-H Oh, Prof T Wyss-Coray PhD), **Wu Tsai Neurosciences Institute** (H S-H Oh, Prof T Wyss-Coray), **and Department of Neurology and Neurological Sciences** (Prof T Wyss-Coray), **Stanford University, Stanford, CA, USA; Epidemiology of Ageing and Neurodegenerative Diseases, Université Paris Cité, Inserm U1153, Paris, France** (Prof A Singh-Manoux)

Correspondence to: Prof Mika Kivimäki, UCL Brain Sciences, University College London, London W1T 7NF, UK **m.kivimaki@ucl.ac.uk**

Introduction

Biological ageing impairs the functional and structural properties of cells, leading to the gradual degradation of physiological systems, diminished resilience, heightened susceptibility to diseases, and, ultimately, mortality.[1–3] It is also known that biological ageing progresses at varying rates, not only between individuals but also among different organs within the same individual.[4–7] With recent advancements in omics research enabling the measurement of thousands of circulating biomarkers from a single blood sample,[8] it has become possible to reliably quantify organ-specific ageing using plasma proteomics.[4]

In a groundbreaking study employing this method, organs undergoing accelerated ageing were found to be strongly linked to increased risk of specific disease states affecting those particular organs.[4] For instance, a heart ageing faster than expected for its chronological age exhibited the strongest association with heart diseases, whereas accelerated brain ageing was associated with an increased risk of cerebrovascular disorders. These findings lend support to the hypothesis that there are organ-specific relations between ageing and disease risk.[4] However, it remains uncertain whether these organ-specific repercussions represent the typical course of organ ageing. Research suggests that age-related changes at the cellular level, rather than being confined to specific organs, exert effects throughout the body.[9] For instance, age-related mitochondrial dysfunction, a hallmark of cellular ageing,

Research in context

Evidence before this study

Biological ageing progresses at different rates among individuals, influencing their risk of age-related diseases. Furthermore, there is variability in the ageing of different organs within the same individual, but the effect of this variation on disease risk remains unclear. We searched PubMed from database inception to April 8, 2024, with no language restrictions, using the terms "organ-specific aging" and "organ aging" and identified 88 studies. The results suggested that hallmarks of cellular ageing, such as epigenetic ageing clocks, affect multiple tissues, thus without strict organ specificity. In contrast, a study introducing a plasma proteome-based quantification of organ-specific ageing found that advanced heart ageing was associated with a doubling in the risk of heart failure in a cohort of 812 participants. Accelerated brain ageing, in turn, was associated with cerebrovascular disorders, and kidneys undergoing rapid ageing correlated with a higher prevalence of metabolic diseases. These findings lend support to the hypothesis that there are organ-specific relations between ageing and disease risk.

Added value of this study

We assessed the gaps between biological and chronological age in the arteries, heart, brain, lungs, intestines, liver, pancreas, kidneys, and immune system of 6235 middle-aged adults using plasma proteome signatures. We investigated whether accelerated ageing in each organ is associated with an increased risk of diseases either within the same organ (organ specificity) or in other organs. Organ age gaps were evaluated at a mean age of 55·7 years, using between 10 and 202 plasma proteins depending on the organ system, and overall organismal age gap assessment used 3907 proteins. Three key findings from the 20-year follow-up of 45 incident diseases across these nine organs offer new insights into the health effects of organ ageing. First, the associations between organ age gaps and the risk of 30 diseases linked accelerated organ ageing to a wider range of age-related diseases and over a longer follow-up than previous studies. Second, to our knowledge this is the first study to characterise variation in organ specificity, showing that the relationship between organ age gaps and disease risk depends on both the ageing organ and the disease. Although organ age gaps were often associated with diseases within the same organ, they were also linked to diseases across other organs. Strong support for organ specificity was found in only six of the 30 diseases. Third, our analysis of disease trajectories, which offers a novel perspective on organ ageing, suggests that faster ageing in one organ could increase the risk of developing diseases affecting multiple organs—a common outcome that substantially elevates the long-term risk of multiorgan multimorbidity.

Implications of all the available evidence

Epidemiological evidence shows that organ ageing, indicated by distinct plasma protein signatures, is associated with long-term risk of age-related diseases and multimorbidity, displaying diverse, mostly partial organ specificity. These findings highlight that organs within the human body function as an integrated system, where age-related dysfunction in one organ often affects other organs, increasing the likelihood of multiorgan involvement in disease processes. More work is needed before blood-based organ-specific proteomic signatures can be applied in clinical settings. However, plasma proteomic research, with its quick and non-invasive organ ageing assessment, holds promise for developing strategies to delay age-related diseases, improving diagnostics and treatments, and identifying at-risk groups for preventive measures.

increases the risk of cardiovascular and liver diseases, cancers affecting multiple sites, and neurodegenerative diseases such as dementia and Parkinson's disease.[10–12] This absence of strict organ specificity is consistent with the observation that organs function collaboratively. Consequently, age-related ailments affecting one organ might lead to systemic complications that affect multiple organs.[13,14] Hence, one might hypothesise that accelerated ageing of organs is more likely to contribute to multimorbidity than diseases localised to a single organ.

In this study of 6235 British adults, we explored two hypotheses: that faster ageing of an organ primarily contributes to morbidity of the same organ; and that it increases the risk of age-related diseases and their co-occurrence across multiple organs. We identified organ ageing signatures from plasma proteomics and tracked, over a two-decade follow-up period, the onset of 45 diseases shown to be linked to cellular ageing.[9]

Methods

Study design and participants

In the Whitehall II study, a prospective cohort study, all government employees aged 35–55 years working across 20 departments in London, UK, were invited to participate between Sept 10, 1985, and March 29, 1988. Of the 14121 invitees, 10308 (73·0%) agreed to participate.[15] Plasma samples for proteomic analyses were collected in a clinical examination between April 24, 1997, and Jan 8, 1999, when participants were aged 45–69 years, the baseline of the present analysis. Assessment of prevalent diseases before baseline and the follow-up of future diseases and deaths were based on linked electronic health records. Ethical approval for the Whitehall II study was obtained from the University College London Medical School Committee on the Ethics of Human Research (85/0938) and the London–Harrow and Scotland A Research Ethics Committees on the Ethics of Human Research. Informed written consent was obtained from all participants.

Organ ageing and baseline covariates

Plasma EDTA (edetic acid) samples drawn at baseline between 1997 and 1999 were stored at –80°C. Proteins were analysed using the SomaScan (SomaLogic; Boulder, CO, USA) version 4.0 assay for 2213 participants and the SomaScan version 4.1 assay for 4022 participants.[16] SomaScan uses the SOMAmer-based capture array, which quantifies the relative concentration of proteins or protein complexes in plasma. Standard SomaLogic normalisation, calibration, and quality control were done on all samples (appendix pp 3–4).

Using the Python package organage,[4] we computed a total of nine organ age gaps accounting for cohort characteristics (age and sex distribution). This package requires SomaScan data version 4.0 or version 4.1, age, and sex as inputs to compute Z scores (mean 0 [SD 1]) for organismal and organ-specific age gaps, ie, the biological age of an individual's organs or body relative to those of same-aged peers. The code automatically harmonises SomaScan versions 4.0 and 4.1.

The organage package was developed through the following steps.[4] Organ-specific plasma proteome was mapped using human organ bulk RNA sequencing data from the Genotype-Tissue Expression project.[17] Related genes were classified as organ enriched if they were expressed at least four times higher in one organ compared with any other organ, according to the definition proposed in the Human Protein Atlas (proteins with a high coefficient of variation or a low correlation between the two different versions of the SomaScan assay were removed).[18] A bagged ensemble of least absolute shrinkage and selection operator ageing models for different major organs was then conducted using the mutually exclusive organ-enriched proteins. An organismal ageing model using organ-nonspecific plasma proteins was also trained. These models were then validated in independent study populations.

In the present study, we determined age gaps in the arteries (14 proteins), brain (202 proteins), heart (ten proteins), immune system (173 proteins), intestine (33 proteins), kidney (12 proteins), liver (113 proteins), lung (nine proteins), and pancreas (34 proteins), in addition to an overall organismal age gap (3907 proteins; appendix pp 5–13).

See **Online** for appendix

For the **Python package organage** see https://github.com/hamiltonoh/organage

Incident age-related diseases and mortality

Our outcomes were new (incident) age-related diseases requiring hospital treatment, their co-occurrence, and mortality following the measurement of organ age. Dates and WHO ICD diagnostic codes of hospitalisations and deaths were retrieved from the UK National Health Service Hospital Episode Statistics database records and

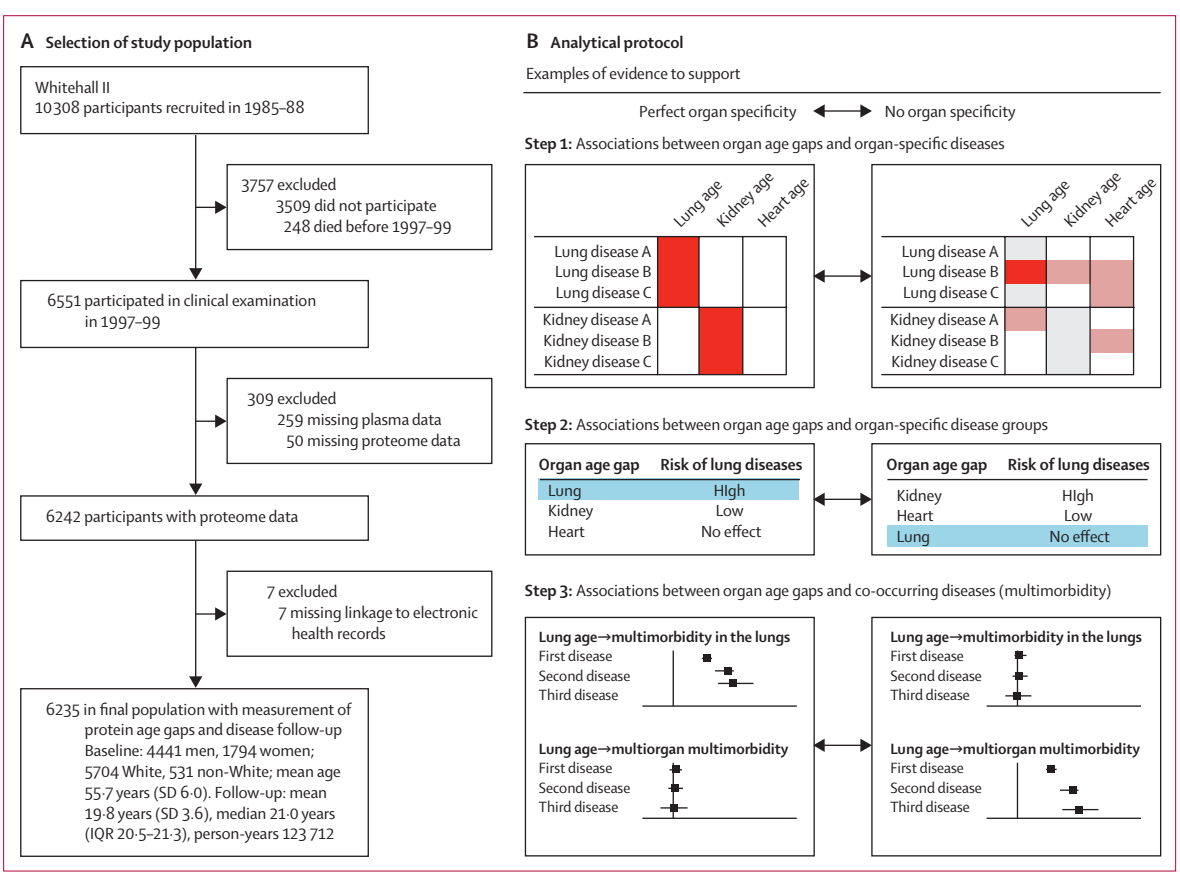


Figure 1: **Flow chart for sample selection and analytical approaches**

from mortality registers using individual National Health Service identification numbers for linkage until March 19, 2019. We measured prevalent and incident age-related diseases, including 45 diagnoses defined by Kuan and colleagues[19] and Fraser and colleagues.[9] This list of diseases has undergone extensive biological validation, including confirmation of an association between each disease and at least one hallmark of cellular ageing.[2] The selected 45 diseases met the following two criteria: they had a high enough incidence to facilitate powered analyses within the Whitehall II dataset; and they were diseases of the arteries, brain, heart, immune system, intestines, kidneys, liver, lungs, or pancreas. We classified the 45 diseases into nine partly overlapping organ-based subgroups as per ICD-10 classification (alphabetical order): arteries (four diseases), brain (five diseases), heart (eight diseases), immune system (ten diseases), intestines (two diseases), kidney (four diseases), liver (six diseases), lung (three diseases), and pancreas (three diseases). The diagnostic codes for all 45 diseases and their associations with hallmarks of cellular ageing are provided in the appendix (p 15).

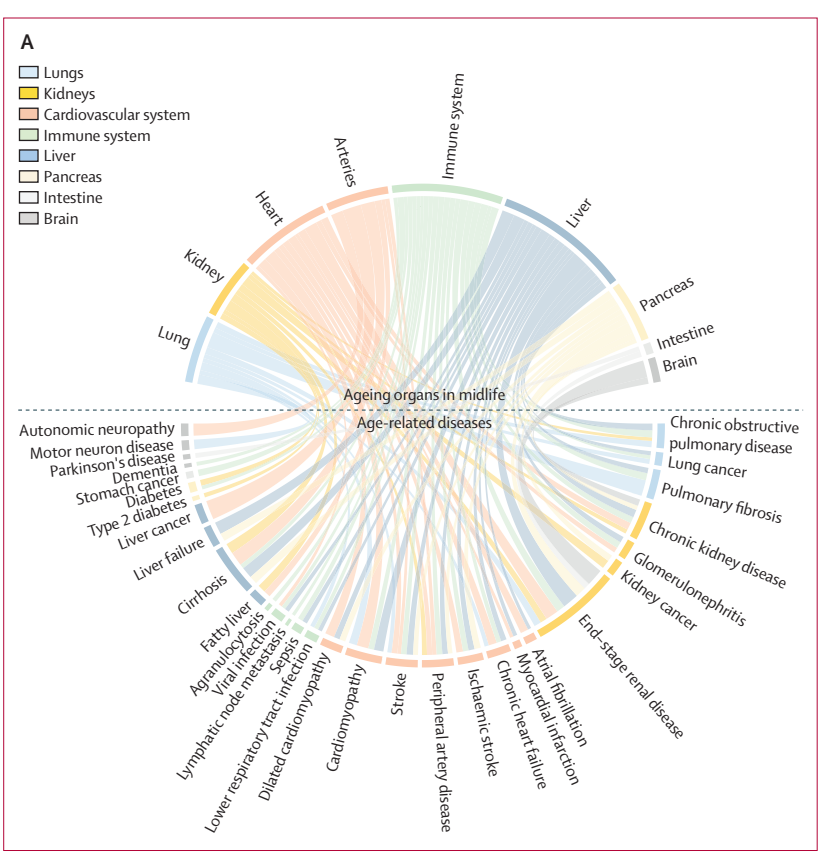
Statistical analysis

A detailed description of the statistical analyses is in the appendix (p 16). We examined the cross-sectional associations between all organ age gap measures using Pearson correlation coefficients. Participants were followed from the date of organ age assessment to the first record of the disease under investigation, death, or end of follow-up, whichever came first. Those who already had the disease(s) of interest at or before baseline were excluded from analyses on incident diseases, composite outcomes, and multimorbidities. To ensure triangulation, we used three different approaches (figure 1).[20]

First, we examined the age-adjusted, sex-adjusted, and ethnicity-adjusted associations of all nine organ age gaps with 45 incident age-related diseases at follow-up using separate Cox proportional hazards regression models. Hazard ratios (HRs) and 95% CIs were adjusted for age, sex, and ethnicity (model 1), and, additionally, for age gaps in organs other than the one under investigation (model 2). Associations of organ age gaps and the organismal age gap with mortality risk were also examined using Cox regression models. Given the substantial variation in the number of incident cases between diseases, we considered both effect size and statistical significance ($p<0·05$), with associations that had an HR of 1·2 or higher deemed relevant for public health. This threshold has also been used in previous studies.[21,22]

Second, in separate Cox models, we examined associations of the nine organ age gaps and organismal age gap with the risk of developing any disease related to specific organs in separate Cox models. In defining organ-specific outcomes, we combined diseases of the heart and arteries because they typically represent different presentations of the same systemic disease. Thus, the eight-organ-specific composite outcome comprised cardiovascular diseases (heart and arteries) and diseases of the nervous system (brain), immune system, intestines, kidneys, liver, lungs, and pancreas. HRs and 95% CIs for an organ age gap one SD higher were as specified in models 1 and 2.

Third, to examine multimorbidity within the group of diseases that are related to each organ age gap as outcomes, we constructed a multiorgan multimorbidity outcome for each organ age gap. For these outcomes, we selected diseases associated with the organ age gap (model 1), irrespective of organ specificity. We examined co-occurrence among the diseases included in each multiorgan multimorbidity outcome separately for each organ age gap. With data on diseases occurring during the entire follow-up, we first determined the odds ratio and 95% CI for each disease pair using logistic regression analysis adjusted for age, sex, and ethnicity. For each disease pair, the disease with the younger mean age at diagnosis was treated as the independent variable, and the disease with the older mean age at diagnosis was considered the dependent variable. We then calculated clustering coefficients (range 0–1, with a higher coefficient indicating stronger connections between the



(Figure 2 continues on next page)

diseases) for groups of diseases that related to each organ age gap by using the Barrat method of global network transitivity.

The associations between organ age gaps, organismal age gap, and multiorgan multimorbidity were examined in three separate Cox models, using the following outcomes: developing one disease versus no disease; developing two diseases versus one or no disease; and developing three diseases versus two or fewer diseases. These analyses were adjusted as specified in model 2. For comparison, we examined the associations of each organ age gap with multimorbidity within the same organ using separate Cox models (model 2). Post-hoc supplementary analyses are described in the appendix (pp 40–44). These analyses included repeating the main analysis after excluding lymph node metastasis from the composite outcome of immune system diseases and liver metastasis from the composite outcome of liver diseases. The rationale for these exclusions is that metastases typically occur in organs other than the site of the primary cancer.

We used Python version 3.10 to construct organ age gap variables, R version 4.3.3 to compute clustering coefficients, and SAS version 9.4 to perform all other statistical analyses (appendix pp 45–52).

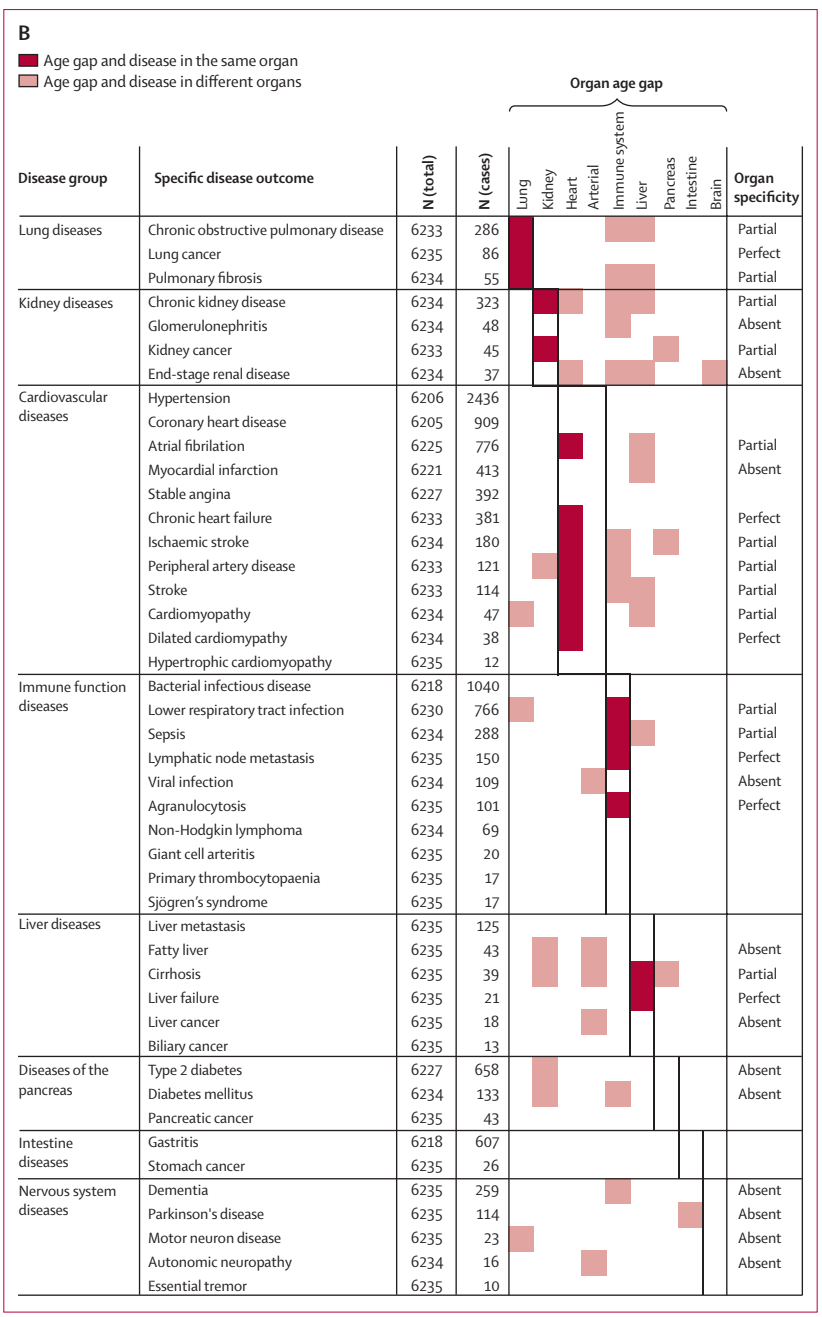
Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication.

Results

Extended results are in the appendix (pp 17–44). 6235 participants had valid data on proteomic organ-specific age gaps and linked records on age-related diseases, forming the analytical sample of this study (figure 1). Any differences in mean age (56·1 years *vs* 55·7 years), sex distribution (66·9% male and 33·1% female *vs* 71·2% male and 28·8% female), and mortality rate (10·1 per 1000 person-years *vs* 8·6 per 1000 person-years) between the eligible population and study participants were small.

Pearson correlations for the cross-sectional associations between these age gap measures were low or moderate, ranging from –0·08 to 0·37 (appendix pp 22–24). These correlation coefficients were higher among participants with prevalent age-related diseases at baseline (r=0·22–0·53, n=110). Over 123712 person-years of observation (mean follow-up 19·8 years [SD 3·6]), and after excluding disease cases at or before baseline, higher organ age gaps were associated with an elevated risk of 32 out of the 45 age-related diseases, with HRs per SD increment of 1·20 or higher after adjustment for age, sex, and ethnicity (figure 2A), and an elevated risk of 30 diseases after an additional mutual adjustment for organ-specific age gaps (figure 2B, appendix pp 25–27). For six diseases, we observed perfect organ specificity (ie, diseases that were only associated with the respective organ age gap): liver failure (age-adjusted, sex-adjusted, ethnicity-adjusted, and other age-gap-adjusted HR 2·13 per SD increment [95% CI 1·41–3·22] in the liver age gap), dilated cardiomyopathy (HR 1·65 per SD increment [1·28–2·12] in the heart age gap), chronic heart failure (HR 1·52 per SD increment [1·40–1·65] in the heart age



Disease group	Specific disease outcome	N (total)	N (cases)	Organ specificity
Lung diseases	Chronic obstructive pulmonary disease	6233	286	Partial
	Lung cancer	6235	86	Perfect
	Pulmonary fibrosis	6234	55	Partial
Kidney diseases	Chronic kidney disease	6234	323	Partial
	Glomerulonephritis	6234	48	Absent
	Kidney cancer	6233	45	Partial
	End-stage renal disease	6234	37	Absent
Cardiovascular diseases	Hypertension	6206	2436	
	Coronary heart disease	6205	909	
	Atrial fibrilation	6225	776	Partial
	Myocardial infarction	6221	413	Absent
	Stable angina	6227	392	
	Chronic heart failure	6233	381	Perfect
	Ischaemic stroke	6234	180	Partial
	Peripheral artery disease	6233	121	Partial
	Stroke	6233	114	Partial
	Cardiomyopathy	6234	47	Partial
	Dilated cardiomyopathy	6234	38	Perfect
	Hypertrophic cardiomyopathy	6235	12	
Immune function diseases	Bacterial infectious disease	6218	1040	
	Lower respiratory tract infection	6230	766	Partial
	Sepsis	6234	288	Partial
	Lymphatic node metastasis	6235	150	Perfect
	Viral infection	6234	109	Absent
	Agranulocytosis	6235	101	Perfect
	Non-Hodgkin lymphoma	6234	69	
	Giant cell arteritis	6235	20	
	Primary thrombocytopaenia	6235	17	
	Sjögren's syndrome	6235	17	
Liver diseases	Liver metastasis	6235	125	
	Fatty liver	6235	43	Absent
	Cirrhosis	6235	39	Partial
	Liver failure	6235	21	Perfect
	Liver cancer	6235	18	Absent
	Biliary cancer	6235	13	
Diseases of the pancreas	Type 2 diabetes	6227	658	Absent
	Diabetes mellitus	6234	133	Absent
	Pancreatic cancer	6235	43	
Intestine diseases	Gastritis	6218	607	
	Stomach cancer	6235	26	
Nervous system diseases	Dementia	6235	259	Absent
	Parkinson's disease	6235	114	Absent
	Motor neuron disease	6235	23	Absent
	Autonomic neuropathy	6234	16	Absent
	Essential tremor	6235	10	

Figure 2: **Prospective associations of proteomic organ-specific age gaps with 45 incident diseases related to different organs**

Statistically significant (p<0·05) associations with a hazard ratio per SD higher organ ageing equal to or higher than 1·20 for each incident disease after adjustment for age, sex, and ethnicity (A) and after adjustment for age, sex, ethnicity, and other organ ageing gaps (B).

	N (total)	N (cases)	Model 1	Model 2
Outcome: any incident disease of the lungs (three diagnoses)				
Age gap in lungs	6232	382	1·49 (1·35–1·64)	1·42 (1·28–1·56)
Age gap in immune system	6232	382	1·41 (1·31–1·51)	1·36 (1·26–1·48)
Age gap in liver	6232	382	1·39 (1·26–1·52)	1·37 (1·23–1·53)
Age gap in pancreas	6232	382	1·17 (1·06–1·29)	1·10 (0·99–1·23)
Age gap in kidneys	6232	382	1·14 (1·03–1·26)	1·06 (0·95–1·17)
Age gap in arteries	6232	382	1·10 (0·99–1·21)	0·99 (0·89–1·10)
Age gap in intestines	6232	382	1·07 (0·96–1·18)	0·97 (0·87–1·08)
Age gap in heart	6232	382	1·07 (0·97–1·18)	0·97 (0·88–1·08)
Age gap in brain	6232	382	0·91 (0·82–1·01)	0·70 (0·62–0·78)
Outcome: any incident cardiovascular disease (12 diagnoses)				
Age gap in heart	6167	2903	1·13 (1·09–1·17)	1·13 (1·09–1·18)
Age gap in immune system	6167	2903	1·07 (1·03–1·11)	1·08 (1·03–1·12)
Age gap in lungs	6167	2903	1·02 (0·99–1·06)	1·03 (0·99–1·06)
Age gap in liver	6167	2903	1·04 (1·00–1·08)	1·02 (0·98–1·07)
Age gap in arteries	6167	2903	1·00 (0·97–1·04)	1·00 (0·96–1·04)
Age gap in intestines	6167	2903	0·95 (0·92–0·99)	0·95 (0·91–0·99)
Age gap in brain	6167	2903	0·97 (0·93–1·01)	0·94 (0·90–0·98)
Age gap in pancreas	6167	2903	0·96 (0·92–0·99)	0·94 (0·91–0·98)
Age gap in kidneys	6167	2903	0·93 (0·90–0·97)	0·94 (0·90–0·98)
Outcome: any incident disease related to immune system (ten diagnoses)				
Age gap in immune system	6211	1635	1·20 (1·15–1·25)	1·17 (1·12–1·23)
Age gap in lungs	6211	1635	1·16 (1·11–1·22)	1·13 (1·08–1·19)
Age gap in liver	6211	1635	1·16 (1·11–1·22)	1·11 (1·05–1·18)
Age gap in heart	6211	1635	1·14 (1·08–1·19)	1·10 (1·05–1·16)
Age gap in kidneys	6211	1635	1·07 (1·02–1·12)	1·05 (1·00–1·10)
Age gap in pancreas	6211	1635	1·05 (1·00–1·10)	1·01 (0·96–1·07)
Age gap in intestines	6211	1635	1·03 (0·98–1·08)	0·99 (0·94–1·04)
Age gap in arteries	6211	1635	1·02 (0·97–1·07)	0·97 (0·92–1·02)
Age gap in brain	6211	1635	0·99 (0·94–1·04)	0·88 (0·83–0·93)
Outcome: any incident liver disease (six diagnoses)				
Age gap in liver	6235	215	1·20 (1·05–1·36)	1·23 (1·06–1·43)
Age gap in arteries	6235	215	1·21 (1·06–1·38)	1·19 (1·03–1·36)
Age gap in immune system	6235	215	1·17 (1·03–1·32)	1·13 (0·99–1·30)
Age gap in pancreas	6235	215	1·13 (0·99–1·28)	1·10 (0·95–1·27)
Age gap in kidneys	6235	215	1·10 (0·96–1·26)	1·09 (0·95–1·25)
Age gap in heart	6235	215	1·05 (0·92–1·20)	1·01 (0·87–1·16)
Age gap in lungs	6235	215	1·04 (0·91–1·19)	1·00 (0·87–1·15)
Age gap in intestines	6235	215	0·98 (0·85–1·12)	0·92 (0·80–1·06)
Age gap in brain	6235	215	0·87 (0·76–1·00)	0·75 (0·65–0·87)
Outcome: any incident kidney disease (four diagnoses)				
Age gap in heart	6231	386	1·40 (1·28–1·52)	1·27 (1·16–1·39)
Age gap in kidneys	6231	386	1·27 (1·15–1·40)	1·25 (1·13–1·38)
Age gap in liver	6231	386	1·46 (1·33–1·60)	1·23 (1·10–1·37)
Age gap in immune system	6231	386	1·36 (1·26–1·46)	1·20 (1·10–1·31)
Age gap in pancreas	6231	386	1·27 (1·15–1·40)	1·15 (1·04–1·28)
Age gap in brain	6231	386	1·37 (1·24–1·51)	1·12 (1·01–1·25)
Age gap in arteries	6231	386	1·15 (1·04–1·28)	1·02 (0·92–1·14)
Age gap in lungs	6231	386	1·09 (0·99–1·20)	1·00 (0·91–1·10)
Age gap in intestines	6231	386	0·99 (0·90–1·10)	0·83 (0·75–0·92)

(Table continues on next page)

gap), lung cancer (HR 1·29 per SD increment [1·04–1·59] in the lung age gap), agranulocytosis (HR 1·27 per SD increment [1·07–1·51] in the immune system age gap), and lymphatic node metastasis (HR 1·23 per SD increment [1·06–1·43] in the immune system age gap). Partial organ specificity (diseases associated with age gaps in the respective organ and other organs) was observed for 12 diseases, including chronic kidney disease and cirrhosis, each of which was associated with as many as four organ age gaps. Another 12 diseases were not associated with the respective organ age gap, suggesting no organ specificity. These included end-stage renal disease (linked to heart, immune system, liver, and brain age gaps), fatty liver (heart and arterial age gaps), viral infections (arterial age gap), diabetes (kidney and immune system age gaps), dementia (immune system age gap), and Parkinson's disease (intestine age gap).

In the analysis of eight composite outcomes of organ-specific diseases, a larger lung age gap showed stronger associations with lung diseases than age gaps in other organs (table, appendix pp 28–29). We also observed organ specificity in relation to the heart age gap, which showed the strongest association with cardiovascular diseases; the immune system age gap, which was most strongly associated with diseases of the immune system; and the liver age gap, which was most strongly associated with liver diseases. Other organ age gaps were also associated with these organ-specific disease groups, suggesting that organ specificity was partial. Diseases of the pancreas, intestines, and nervous system were not associated with age gaps of the respective organ, suggesting no organ specificity for these organ age gaps. Individuals with a large organismal age gap had an increased risk of diseases of the kidneys, pancreas, nervous system, liver, immune system, intestines, and cardiovascular system (appendix p 30).

Analyses examining disease co-occurrence were based on diseases associated with organ age gaps with p values of less than 0·05 and an HR of 1·2 or greater after adjustment for age, sex, and ethnicity, irrespective of the location of the disease (figure 3). The odds ratio for 104 disease pairs was higher than 5, suggesting that an individual with a disease associated with a specific organ age gap has high odds of developing another disease associated with the same organ age gap (appendix pp 31–36). The corresponding clustering coefficients for these sets of diseases varied between 0·79 and 0·93 for organ age gaps (no clustering coefficient could be estimated for the two diseases associated with age gaps in the intestines and brain).

Larger organ age gaps were associated with an increased risk of multiorgan multimorbidity (figure 4, appendix p 37). After adjustment for age, sex, ethnicity, and age gaps in other organ age gaps, the HRs for developing two or three co-occurring organ-age-related diseases were 2·03 (95% CI 1·51–2·74) for the arterial age gap, 1·78 (1·48–2·14) for the kidney age gap,

1·52 (1·38–1·68) for the heart age gap, 1·52 (1·12–2·06) for the brain age gap, 1·43 (1·16–1·78) for the pancreas age gap, 1·37 (1·17–1·61) for the lung age gap, 1·36 (1·26–1·46) for the immune system age gap, and 1·30 (1·18–1·42) for the liver age gap. The corresponding HR for the organismal age gap was 1·30 (1·21–1·41; appendix p 38).

In the analysis of multimorbidity within the same organ (appendix pp 14, 39), the HRs adjusted for age, sex, ethnicity, and the eight other organ-specific age gaps tended to be weaker: 1·41 (95% CI 1·05–1·89) for the lung age gap, 1·32 (1·20–1·46) for the heart age gap, and 1·28 (1·14–1·43) for the immune system age gap (no associations with multimorbidity in the respective organ for age gaps in the kidneys, liver, pancreas, arteries, and brain; figure 4).

Post-hoc analyses (appendix pp 40–44) confirmed that the exclusion of secondary malignancies from the composite outcomes of immune system and liver diseases did not alter the associations with organ age gaps. Furthermore, the findings of the associations between organ age gaps and multiorgan multimorbidity remained statistically significant after additional adjustments for smoking, alcohol consumption, physical activity, obesity, and socioeconomic status. We also found that the organismal age gap and age gaps in all organs except the intestines and brain were associated with total mortality. The age-adjusted, sex-adjusted, and ethnicity-adjusted HRs per SD higher age gap varied from 0·99 (95% CI 0·93–1·05) for the brain age gap to 1·23 (1·17–1·29) for the immune system age gap, with the strongest association evident for the organismal age gap (HR 1·30 [1·23–1·38]).

	N (total)	N (cases)	Model 1	Model 2
(Continued from previous page)				
Outcome: any incident disease related to pancreas (three diagnoses)				
Age gap in kidneys	6227	729	1·23 (1·14–1·32)	1·22 (1·14–1·32)
Age gap in immune system	6227	729	1·05 (0·98–1·13)	1·11 (1·02–1·19)
Age gap in arteries	6227	729	1·05 (0·97–1·13)	1·08 (1·00–1·17)
Age gap in pancreas	6227	729	0·96 (0·89–1·03)	1·03 (0·95–1·11)
Age gap in brain	6227	729	0·92 (0·86–1·00)	0·98 (0·90–1·06)
Age gap in lungs	6227	729	0·97 (0·91–1·05)	0·97 (0·90–1·05)
Age gap in heart	6227	729	0·90 (0·84–0·97)	0·96 (0·89–1·04)
Age gap in intestines	6227	729	0·86 (0·80–0·93)	0·86 (0·79–0·93)
Age gap in liver	6227	729	0·85 (0·79–0·92)	0·86 (0·79–0·93)
Outcome: any incident disease related to intestines (two diagnoses)				
Age gap in immune system	6218	622	1·13 (1·05–1·22)	1·13 (1·05–1·22)
Age gap in liver	6218	622	1·08 (1·00–1·17)	1·09 (0·99–1·19)
Age gap in arteries	6218	622	1·08 (1·00–1·17)	1·08 (0·99–1·17)
Age gap in pancreas	6218	622	1·03 (0·96–1·12)	1·01 (0·93–1·10)
Age gap in kidneys	6218	622	1·03 (0·95–1·11)	1·01 (0·94–1·10)
Age gap in intestines	6218	622	1·00 (0·93–1·09)	0·98 (0·90–1·07)
Age gap in lungs	6218	622	0·99 (0·91–1·07)	0·97 (0·89–1·05)
Age gap in heart	6218	622	0·98 (0·91–1·06)	0·96 (0·88–1·04)
Age gap in brain	6218	622	0·96 (0·89–1·04)	0·90 (0·83–0·99)
Outcome: any incident disease related to the nervous system (five diagnoses)				
Age gap in immune system	6234	375	1·16 (1·06–1·27)	1·13 (1·05–1·22)
Age gap in liver	6234	375	1·08 (0·97–1·19)	1·09 (0·99–1·19)
Age gap in arteries	6234	375	1·14 (1·03–1·27)	1·08 (0·99–1·17)
Age gap in pancreas	6234	375	1·07 (0·97–1·19)	1·01 (0·93–1·10)
Age gap in kidneys	6234	375	1·07 (0·96–1·18)	1·01 (0·94–1·10)
Age gap in intestines	6234	375	1·13 (1·02–1·25)	0·98 (0·90–1·07)
Age gap in lung	6234	375	1·09 (0·99–1·21)	0·97 (0·89–1·05)
Age gap in heart	6234	375	1·15 (1·05–1·26)	0·96 (0·88–1·04)
Age gap in brain	6234	375	0·98 (0·88–1·08)	0·90 (0·83–0·99)

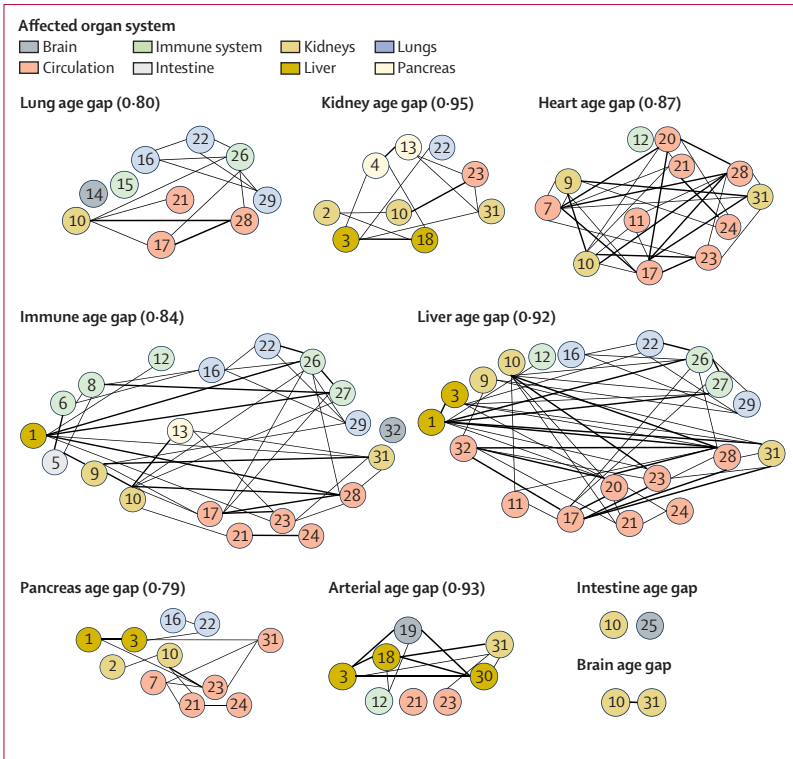
Data are n or hazard ratio (95% CI). Model 1 is adjusted for age, sex, and ethnicity. Model 2 is adjusted for age, sex, ethnicity, and age gaps in organs other than the one under investigation.

Table: **Prospective associations between proteomic organ-specific age gaps and the 20-year incidence of organ-specific age-related disease**

Discussion

Our 20-year follow-up supports organ-specific ageing, as indicated by a distinct proteomic signature, as part of the aetiology of age-related morbidity. The findings suggest diverse, mostly partial organ specificity in the links between accelerated organ ageing and health outcomes. First, the rates of ageing between different organs showed only modest correlations, aligning with the notion that biological ageing progresses at slightly varying rates among different organs within the same individual. Second, individuals with a fast-ageing organ faced an increased risk of 30 out of the 45 age-related diseases examined. We observed strict organ specificity for only six diseases. In contrast, the likelihood of developing the other 24 diseases was influenced by age acceleration in both the respective organ and other organs, or solely by age acceleration in other organs. Third, individuals with fast-ageing lungs had a higher risk of developing lung diseases than those with age acceleration in other organs. Similar patterns were observed with fast-ageing hearts and cardiovascular diseases, fast-ageing immune systems and immune diseases, and fast-ageing livers and liver diseases. However, advanced ageing in other organs also increased the risk of these organ-specific disease outcomes. Fourth, advanced ageing in almost all organs was linked to a higher long-term risk of multiorgan multimorbidity. Most associations with single-organ multimorbidity were weaker.

In the present study, the six diseases with complete organ specificity were dilated cardiomyopathy, chronic heart failure, liver failure, agranulocytosis, lung cancer, and lymphatic node metastasis. Lymphatic node metastasis is a secondary malignancy typically resulting from the spread of cancer cells from a primary tumour in another organ. Thus, the observed associations suggest that advanced organ age, in addition to increasing the risk of disease in the respective organ (ie, acting as a risk factor), could make disease progression in the respective organ more likely (ie, affecting the course of pre-existing disease and serving as a prognostic factor).



Disease	Mean age at diagnosis, years
1 Liver failure	69·2
2 Kidney cancer	69·8
3 Cirrhosis	70·6
4 Type 2 diabetes	70·6
5 Stomach cancer	70·7
6 Lymphatic node metastasis	70·8
7 Dilated cardiomyopathy	70·9
8 Agranulocytosis	70·9
9 Glomerulonephritis	71·0
10 End-stage renal disease	71·5
11 Myocardial infarction	71·6
12 Viral Infection	71·6
13 Diabetes, other or non-specified	71·6
14 Motor neuron disease	71·7
15 Non-Hodgkin lymphoma	72·0
16 Lung cancer	72·1
17 Cardiomyopathy	72·2
18 Fatty liver	72·3
19 Autonomic neuropathy	72·5
20 Atrial fibrillation	72·8
21 Stroke	73·4
22 Chronic obstructive pulmonary disease	73·9
23 Peripheral arterial disease	74·0
24 Ischaemic stroke	74·1
25 Parkinson's disease	74·1
26 Lower respiratory tract infection	74·2
27 Sepsis	74·7
28 Chronic heart failure	75·1
29 Pulmonary fibrosis	75·3
30 Liver cancer	76·0
31 Chronic kidney disease	76·4
32 Dementia	78·3

Figure 3: **Associations between diseases related to each proteomic organ-specific age gap**
Each number in parentheses is the clustering coefficient. The number in each circle indicates the disease. The link between the circles shows an association between a disease pair with a statistically significant (p<0·05) OR of 5 or higher, including only diseases associated with ageing organs. Diseases are in order of increasing mean age at diagnosis. A thin line between diseases denotes an OR of 5·00–9·99, and a thick line indicates an OR of 10·00 or higher. The colour of each circle indicates the organ system affected by the disease. Low numbers prevented estimation of some associations between rare diseases (appendix pp 31–36). OR=odds ratio.

The partial organ specificity we observed in most of the diseases and comorbidities is biologically plausible.[23] Organ systems are interconnected and dependent on each other. Accordingly, our findings showed that advanced ageing in a specific organ increases the risk of multiorgan morbidities, and that rapid ageing in several parts of the body raises the chance of developing a disease in a specific organ. Indeed, the effects of cellular ageing are widespread.[3]

In addition to the lungs, heart, and immune system, our findings highlight the crucial role of the kidneys in the pathogenesis of age-related diseases. The kidneys perform essential functions in waste removal, fluid balance, chemical regulation, blood pressure control, and hormone production. In our study, advanced kidney ageing was linked to a wide range of diseases, affecting not only the kidneys but also the liver, pancreas, lungs, and cardiovascular system. Additionally, the kidneys appeared to be sensitive to damage from almost any major organ, as faster ageing in nearly all organs increased the risk of kidney diseases.

The present findings confirm several previous observations. We found a tendency of age-related diseases to cluster within the same individuals, resulting in the co-occurrence of diseases across multiple organs, a phenomenon also reported in other study populations.[24–26] We replicated the results from US cohorts showing that organ ageing correlates with age-related diseases, that heart ageing is linked to cardiovascular disease risk, and that faster-ageing organs are associated with higher mortality.[4] In the LonGenity study with 812 participants, for instance, individuals with accelerated heart ageing had a 2·5-fold increased 15-year risk of heart failure.[4] The corresponding HR in our 20-year follow-up was 1·6-fold. In the LonGenity study, excess risk of mortality was 1·2 or higher for accelerated heart, arterial, brain, immune system, intestine, liver, and organismal ageing.[4] We observed similar effect sizes for associations of heart, immune system, liver, and organismal ageing. In our study, the strongest risk factor for total mortality was organismal ageing.

In our long-term follow-up, faster ageing of the immune system emerged as the strongest long-term risk factor for incident dementia, and faster ageing of the intestines was the strongest risk factor for Parkinson's disease. These findings are consistent with longitudinal studies that have linked circulating inflammatory markers (such as C-reactive protein, IL-6, and α-1-antichymotrypsin)[27] and severe peripheral systemic infections to a higher risk of dementia,[28,29] and a

	Multiorgan multimorbidity			Multimorbidity in the same organ		
	N (total)	N (cases)	HR (95% CI)*	N (total)	N (cases)	HR (95% CI)*
Lung age gap						
First disease	6223	1234	1·22 (1·15 to 1·29)	6232	382	1·42 (1·28 to 1·56)
Second disease	6223	444	1·36 (1·24 to 1·49)	6232	41	1·41 (1·05 to 1·89)
Third disease	6223	146	1·37 (1·17 to 1·61)	6232	<10	Not estimated
Kidney age gap						
First disease	6220	1184	1·21 (1·14 to 1·28)	6231	386	1·25 (1·13 to 1·38)
Second disease	6220	339	1·38 (1·24 to 1·53)	6231	56	1·28 (1·00 to 1·65)
Third disease	6220	106	1·78 (1·48 to 2·14)	6231	10	1·31 (0·72 to 2·38)
Heart age gap						
First disease	6203	1493	1·28(1·22 to 1·34)	6185	1533	1·28 (1·22 to 1·34)
Second disease	6203	601	1·46 (1·37 to 1·57)	6185	835	1·25 (1·17 to 1·34)
Third disease	6203	258	1·52 (1·38 to 1·68)	6185	355	1·32 (1·20 to 1·46)
Immune age gap						
First disease	6218	1786	1·23 (1·17 to 1·29)	6211	1635	1·17 (1·12 to 1·23)
Second disease	6218	872	1·26 (1·19 to 1·34)	6211	651	1·16 (1·08 to 1·25)
Third disease	6218	445	1·36 (1·26 to 1·46)	6211	221	1·28 (1·14 to 1·43)
Liver age gap						
First disease	6196	1980	1·14 (1·08 to 1·20)	6235	215	1·23 (1·06 to 1·43)
Second disease	6196	963	1·22 (1·14 to 1·31)	6235	35	1·28 (0·90 to 1·83)
Third disease	6196	528	1·30 (1·18 to 1·42)	6235	<10	Not estimated
Pancreas age gap						
First disease	6225	927	1·13 (1·06 to 1·21)	6227	729	1·03 (0·95 to 1·11)
Second disease	6225	262	1·32 (1·17 to 1·50)	6227	103	1·06 (0·86 to 1·31)
Third disease	6225	75	1·43 (1·16 to 1·78)	6227	<10	Not estimated
Arterial age gap						
First disease	6229	412	1·24 (1·12 to 1·37)	6205	2514	1·02 (0·98 to 1·07)
Second disease	6229	41	2·03 (1·51 to 2·74)	6205	274	1·04 (0·92 to 1·18)
Third disease	6229	<10	Not estimated	6205	52	1·17 (0·87 to 1·56)
Brain age gap*						
First disease	6234	323	1·14 (1·01 to 1·28)	6234	375	0·87 (0·78 to 0·98)
Second disease	6234	37	1·52 (1·12 to 2·06)	6234	44	0·84 (0·60 to 1·17)

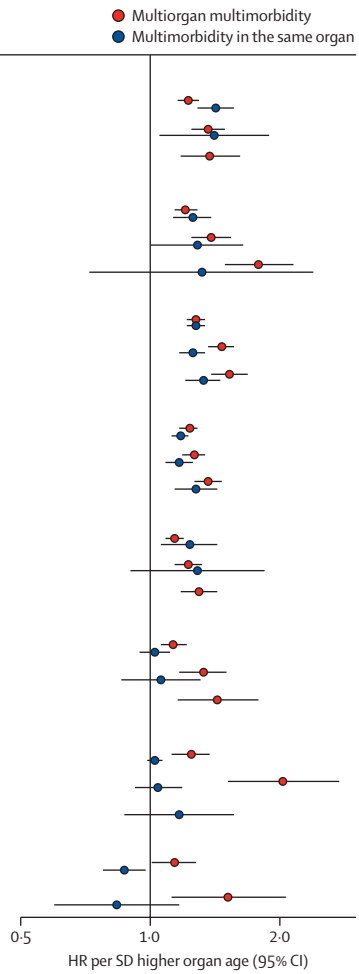


Figure 4: **Prospective associations of proteomic organ-specific age gaps with developing one, two, and three age-related diseases during a 20-year follow-up**
For each ageing organ, multiorgan outcomes include diseases related to ageing of that organ with an HR of 1·20 or higher and p value less than 0·05. In contrast, multimorbidity in the same organ refers to the risk of diseases within the ageing organ itself (appendix p 15). HR=hazard ratio. *HR for the third disease was not estimated due to insufficient case numbers (n<10).

compromised intestinal barrier, as part of the overall immune system, to Parkinson's disease.[30] Furthermore, recent proteome-wide analyses suggest a role for inflammation in the aetiology of neurodegeneration.[31–33]

This study has several limitations. As our analyses were conducted within an occupational cohort study, participants were generally likely to be healthier than the general population. Further research is needed to examine the generalisability of our findings in more diverse populations, including those of low-income and middle-income countries. Our study relied on observational data, so we are unable to confirm the causality of the associations observed. The assessment of proteins at baseline provided a snapshot of participants' organ age. Future studies should measure organ age repeatedly to more accurately assess future disease risk. Incidence rates of some age-related diseases were low, reducing our ability to confirm robust associations for these rare health outcomes. Our use of electronic health records shares limitations with most other large multi-outcome cohort studies, including the inability to detect undiagnosed diseases and those rarely leading to hospitalisation. However, an advantage of using linkage data to national electronic health records is that it enables the inclusion of all participants in the analyses, not just those who continued to participate in follow-up examinations. In our study, differences in lifestyle, obesity, and socioeconomic status did not explain the observed links with age-related diseases. Further analyses are needed to identify drivers of organ age acceleration and related morbidity.

More work is needed before organ-specific proteomic signatures can be applied in clinical settings. A better understanding of these signatures could potentially offer tailored prevention strategies for age-related diseases, contribute to disease-specific risk calculators, facilitate new organ-specific therapeutic opportunities, provide

prognostic information for individuals living with diseases, and offer intermediary outcomes for interventions aimed at reducing age-related diseases. Plasma-based organ age signatures are attractive due to their quick and easy assessment, whereas existing methods to study individual organs, such as tissue biopsies and imaging, are expensive, invasive, or require equipment not available in all health-care settings.

Contributors

All authors participated in designing the study, generating hypotheses, interpreting the data, and critically reviewing the report. MK, with PF, had the primary responsibility for writing this paper. JP and MJ performed data analyses. All authors had access to all the pseudonymised data reported in the study. JP, PF, and MK accessed and verified the data. All authors read and approved the final version of the manuscript and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests. Hamilton Se-Hwee is Co-founder and Scientific Advisor of Tealomics.

Data sharing

Data, protocols, and other metadata of the Whitehall II study are available for sharing within the scientific community. Bona fide researchers interested in accessing the data can apply through the Dementias Platform UK (https://www.dementiasplatform.uk) or the Whitehall Scientific Committee (https://www.ucl.ac.uk/psychiatry/research/mental-health-olderpeople/whitehall-ii/data-sharing). Statistical code and complete summary data for figures and tables are provided in the appendix (pp 3–52). Individual-level data might be restricted by consent, confidentiality, or privacy laws or considerations. These policies apply to both clinical and proteomic data.

Acknowledgments

The study, MK, and AS-M were supported by the Wellcome Trust (221854/Z/20/Z), the UK Medical Research Council (MR/S011676/1), and the National Institute on Aging (National Institutes of Health), USA (R01AG056477, R01AG062553). MK, JP, and STN were supported by the Academy of Finland (350426) and the Finnish Foundation for Cardiovascular Research (a86898). PF was supported by the Wellcome Trust (221854/Z/20/Z) and JVL by Academy of Finland (339568) and Päivikki and Sakari Sohlberg Foundation. Some proteins were measured as an academic–industry partnership project beween University College London and SomaLogic, which provided expertise in plasma proteins and funded 2213 SomaScan assays.

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