Obesity and risk of diseases associated with hallmarks of cellular ageing: a multicohort study

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Summary

Background Ageing hallmarks, characterising features of cellular ageing, have a role in the pathophysiology of many age-related diseases. We examined whether obesity is associated with an increased risk of developing such hallmark-related diseases.

Methods In this multicohort study, we included people aged 38–72 years with data on weight, height, and waist circumference measured during a clinical examination at baseline between March 13, 2006, and Oct 1, 2010, from the UK Biobank with follow-up until Nov 12, 2021. To test reproducibility of the findings (replication analysis), we used data from people aged 40 years or older included in the Finnish Public Sector study and the Finnish Health and Social Support study who responded to the study surveys, had data on BMI, and were successfully linked to electronic health records from national registers up to Dec 31, 2016. Obesity and clinical characteristics were assessed at baseline. Via linkage to national health records, participants were followed up for 83 diseases related to nine ageing hallmarks (genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication). Outcomes were the first instance of hallmark-related disease, in addition to co-occurrence of three or more hallmark-related diseases and mortality.

Findings 496 530 adults (mean age 57·0 years [SD 8·1]) from the UK Biobank were included in the primary analysis, and 83 249 (mean age 48·2 years [6·4]) adults from the Finnish cohorts were included in the replication analysis. Median follow-up was 12·7 years (IQR 12·0–13·4) in the UK Biobank and 14·0 years (8·0–15·0) in the Finnish cohorts. After adjusting for demographic characteristics, lifestyle factors, and depression, UK Biobank participants with obesity (BMI ≥30·0 kg/m²) had a 1·40 (95% CI 1·38–1·41) times higher hazard ratio for the first hallmark-related disease than those with a healthy weight (BMI 18·5–24·9 kg/m²). The corresponding hazard ratios for three co-occurring diseases were 2·92 (95% CI 2·64–3·22) for deregulated nutrient sensing, 2·73 (2·46–3·02) for telomere attrition, 2·33 (2·10–2·60) for epigenetic alterations, 2·30 (2·14–2·48) for mitochondrial dysfunction, 2·23 (2·04–2·45) for stem cell exhaustion, 2·02 (1·89–2·16) for altered intercellular communication, 2·01 (1·89–2·15) for cellular senescence, 1·83 (1·67–2·00) for loss of proteostasis, and 1·39 (1·27–1·52) for genomic instability. These findings were replicated in the Finnish cohorts. In both studies, the associations between other risk factors (low education, unhealthy dietary factors [available only in the UK Biobank], smoking, high alcohol consumption, physical inactivity, and depression) and hallmark-related diseases were weaker than those with obesity. 45–60% of the excess mortality in people with obesity was attributable to hallmark-related diseases.

Interpretation Obesity might have an important role in the development of diseases associated with cellular ageing. Tackling ageing mechanisms could potentially help to reduce the disease and mortality burden resulting from the obesity epidemic.

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For the German translation of the abstract see Online for appendix 1

For the Finnish translation of the abstract see Online for appendix 2

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Introduction

Hallmarks of ageing characterise key features of cellular ageing, including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication.[1] Besides acting as indicators of the normal ageing process, each hallmark has a role in the disordered physiology of certain age-related diseases.[2,3] Primary hallmarks such as genomic instability, telomere attrition, epigenetic alterations, and loss of proteostasis are, for example, linked to an increased risk of various cancers.[2,4] Compensatory responses, termed antagonist hallmarks, initially counteract cellular damage but can become detrimental when persistent.[1] These responses include deregulated nutrient sensing, mitochondrial dysfunction, and cellular senescence, which might contribute to an increased risk of a wide range of

Research in context

Evidence before this study

Both human and animal studies suggest several shared mechanisms between obesity pathophysiology and primary, compensatory, and integrative hallmarks of cellular ageing. Furthermore, previous research has established links between each hallmark of ageing and risk of age-related diseases. We searched PubMed for studies on obesity and co-occurrence of hallmark-related diseases from database inception to Dec 20, 2023, without language or date restrictions, and identified more than 600 research articles that combined "obesity" and "cellular ageing" with "disease", "morbidity", or "disorder". Despite several reports on obesity and increased disease risk, there were no comprehensive analyses to determine the extent to which obesity might increase the risk of co-occurring hallmark-related diseases.

Added value of this study

We analysed longitudinal data from participants aged 38–72 years in the UK Biobank study and examined reproducibility of our findings in two community-based cohorts from Finland. Our study presents reproducible and robust population-level evidence that individuals with obesity (BMI ≥30·0 kg/m^2), compared with those with healthy weight (BMI 18·5–24·9 kg/m^2), are 1·4–2·4 times more likely to develop one or multiple diseases previously shown to be linked to hallmarks of cellular ageing. The associations between other risk factors and co-occurrence of multiple hallmark-related diseases, such as low education, unhealthy diet, smoking, high alcohol consumption, physical inactivity, and depression, were not as strong as those with obesity. Half of the excess mortality in people with obesity was attributable to hallmark-related diseases.

Implications of all the available evidence

Given the large absolute and relative difference in hallmark-related disease risk between the two weight groups, the consistency of the present findings with the identified shared and reciprocal mechanisms in adiposity pathology and cellular ageing in previous human and animal studies, and the continuing increase in the prevalence of obesity globally, the potential obesity-related acceleration in cellular ageing might have important implications for population health.

age-related conditions, including those associated with metabolic disturbances (eg, type 2 diabetes, renal diseases, and fatty liver disease).[5–9] The cumulative effects of primary and compensatory damage—ie, integrative hallmarks, such as stem cell exhaustion and altered intercellular communication—are associated not only with conditions such as cardiovascular disease, osteoarthritis, and rheumatoid arthritis, but also with other diseases.[10–13] In total, tens of conditions have been identified to be related to each hallmark, with many of them shared across multiple hallmarks, reflecting the interconnected nature of the drivers of cellular ageing.[1,2,14]

The evidence supporting the associations between ageing hallmarks and diseases comes from various sources. Initial analyses, based on electronic health records from National Health Service (NHS) England general practice and hospitalisations of 3 million individuals, identified more than 200 diseases, with rates of onset increasing with chronological age.[15,16] These conditions span diverse organ systems and clinical specialties. Furthermore, by mining of 1·85 million abstracts on human ageing ("human aging corpus") extracted from PubMed using a 65-term taxonomy for the "hallmarks of ageing", researchers have been able to link a proportion of these conditions to specific hallmarks of cellular ageing.[2,16] Subsequently, 30 diseases most strongly related to each hallmark have been confirmed by identifying shared genes in the genome-wide association study catalogue; assessing whether proteins encoded by genes associated with the identified diseases showed significant enrichment of gene ontology terms related to the same ageing hallmark (gene set enrichment analysis); testing whether hallmark-related biological processes were enriched in the proteins representing the top hallmark-related diseases; and studying networks of diseases for co-occurrence within each hallmark.[2] Diseases that have passed this multistep validation process are considered to represent markers of cellular ageing at a pathological stage, at which impairments in the function and structure of cells and tissues are already associated with increased morbidity. As such, they complement biomarkers, such as telomere length and epigenetic ageing clocks, which are used to quantify biological and accelerated ageing without distinguishing between normal and pathological ageing.[17] So far, however, few studies have examined risk factors that drive the development of hallmark-related diseases.

In this study, we examined whether obesity is associated with increased risk of diseases previously shown to be related to the nine hallmarks of ageing.[2] Mechanistic studies suggest that these associations are biologically plausible because obesity seems to accelerate various aspects of cellular ageing.[18–21] This is supported by evidence from biomarker studies and animal models of telomere attrition, mitochondrial dysfunction, epigenetic alterations, and altered intercellular communication as possible intermediary factors linking obesity with the pathogenesis of age-related diseases.[11,22–24] To obtain robust results in our real-life study on humans, we focused on both incidence and co-occurrence of hallmark-related diseases. To provide context for our results, we compared the effect of obesity on hallmark-related diseases with that of other risk factors (such as low education, smoking,

dietary factors, and alcohol consumption). Additionally, we estimated the proportion of the association between obesity and mortality mediated by hallmark-related morbidity.

Methods

Study design and population

The primary analysis was based on data from the UK Biobank study, a prospective cohort study of UK adults. Among the individuals aged 38–72 years who participated in the UK Biobank, we included those with data on weight, height, and waist circumference measured during a clinical examination at baseline between March 13, 2006, and Oct 1, 2010. Follow-up of diseases linked to hallmarks of ageing through hospital admissions and deaths ended on Nov 12, 2021 (appendix 3 p 4).

To examine the reproducibility of the findings, we repeated main analyses in an independent population using pooled data from two Finnish cohort studies: the Finnish Public Sector (FPS) study and the Health and Social Support (HeSSup) study. The study population of FPS comprised men and women responding to questionnaire surveys between March 1, 2000, and June 30, 2002; March 1, 2004, and June 30, 2005; March 1, 2008, and Nov 30, 2009; or Dec 1, 2011, and Nov 30, 2013. Study participants were linked to electronic health records until Dec 31, 2016. In HeSSup, men and women living in Finland were sent a survey between June 7, 1998, and May 23, 2000, or between Jan 7, 2003, and Aug 12, 2003. Responders were linked electronically to national hospitalisation and mortality registers until Dec 31, 2016. From the Finnish studies, we included participants aged 40 years or older, who responded to the survey, had data on BMI, and were successfully linked to electronic health records from national registers up to Dec 31, 2016 (appendix 3 p 4).

Analyses of UK Biobank data were conducted under generic approval from the UK NHS National Research Ethics Service (2CFFAA23-CEC4-4AF0-9133-405139170B01). FPS was approved by the Helsinki Uusimaa Hospital District Ethics Committee (60/13/03/00/11) and HeSSup by the Turku University Central Hospital Ethics Committee. Participants provided informed consent for baseline assessments and register linkage. This study followed the STROBE guidelines.

Baseline assessment

Weight, height, and waist circumference at baseline were measured in the UK Biobank by trained staff using standard procedures. In FPS and HeSSup, weight and height were self-reported. We calculated BMI using the following formula: weight in kilograms divided by height in metres squared. Obesity was defined as a BMI of 30·0 kg/m² or higher, overweight as a BMI of 25·0–29·9 kg/m², and healthy weight as a BMI of 18·5–24·9 kg/m². Individuals with a BMI of less than 18·5 kg/m² were excluded from the primary and replication analyses. Waist circumference was categorised as high (≥102·0 cm in men and ≥88·0 cm in women), medium (94·0–101·9 cm in men and 80·0–87·9 cm in women), and healthy (<94·0 cm in men and <80·0 cm in women). The categories of waist-to-height ratio were high (≥0·6), medium (0·5 to <0·6), and healthy (<0·5).

In addition to age, sex, and, in the UK Biobank, ethnicity, baseline characteristics included self-reported educational qualification, dietary factors (mean intake of fruit, vegetables, read meat, processed meat, poultry, total fish, dairy milk, cheese, and fibre), smoking, alcohol consumption, physical activity, and depression (appendix 3 pp 4–5). In the analyses of the Finnish dataset, cohort was added as an additional covariate. Dietary data were not available in the Finnish cohorts.

See Online for appendix 3

Follow-up for hallmark-related diseases and mortality

UK Biobank participants were linked to the UK NHS Hospital Episode Statistics database for hospital admissions and the NHS Central Registry for mortality. The NHS delivers the majority of health-care services in the UK, including both inpatient and outpatient care. Record linkage was undertaken using a unique NHS identifier held by all UK residents. Participants of the Finnish cohorts were linked by their unique identification number to national hospital discharge (recorded by the Finnish Institute for Health and Welfare) and mortality (recorded by Statistics Finland) registries. These electronic health records included cause and date of hospitalisation or mortality, or both. In the UK Biobank and the Finnish cohort studies, diseases were coded according to WHO's ICD-10, capturing a total of 1204 three-character diagnostic codes.

We measured an individual's vulnerability to specific hallmark-related diseases and multimorbidity based on diagnostic codes defined by Kuan and colleagues[15] and Fraser and colleagues[2] (appendix 3 p 3). For each hallmark, these include 27–30 diseases shown to be strongly associated with the specific hallmark, including conditions linked to a single hallmark as well as those shared by two or more hallmarks, totalling 83 diseases.

We defined multimorbidity as the co-existence of two or more hallmark-related diseases in the same individual and analysed two and three co-occurring hallmark-related diseases as separate outcomes, with the latter representing a more advanced stage of multimorbidity. Considering the disease-free status of participants at baseline, the relatively long period over which age-related diseases develop and the follow-up duration of the UK Biobank being less than 15 years, our study was not well powered to analyse multimorbidities with four or more co-existing diseases as an outcome.

Statistical analysis

Detailed descriptions of the statistical analyses are provided in appendix 3 (pp 5–6, 28–34). Briefly, we

defined hallmark-related disease from the first onset of a disease linked to a specific ageing hallmark. Co-occurrence of multiple hallmark-related diseases were defined as the onset of the second and the third disease within an ageing hallmark. In addition, we constructed an overall hallmark-related disease outcome and an overall hallmark-related disease co-occurrence outcome, defined as the onset of the first and third disease linked to any of the nine ageing hallmarks, respectively.

We examined associations between BMI categories at baseline and risk of first hallmark-related diseases and co-occurrence of hallmark-related diseases at follow-up in separate Cox proportional hazards regression models, excluding participants who had any of the studied hallmark-related diseases at baseline. In the basic models, hazard ratios (HRs) and 95% CIs for obesity with healthy weight as the reference were adjusted for age, sex, and ethnicity in the UK Biobank, and for age, sex, and cohort in the Finnish cohort studies. In multivariable adjusted analyses, we additionally adjusted effect estimates for education, dietary factors (in UK Biobank participants alone), smoking, physical activity, alcohol consumption, and depression. We performed several sensitivity and subgroup analyses to confirm the robustness of our findings.

In addition, we compared the associations of obesity with hallmark-related multimorbidity with those of other risk factors with hallmark-related multimorbidity. We also estimated the proportion of the association between obesity and mortality mediated by hallmark-related diseases in a subgroup with no hallmark-related diseases at baseline using Cox regression models.

To examine the reproducibility of the findings from the analysis based on the UK Biobank (primary analysis), analyses on the associations between obesity and hallmark-related diseases and multimorbidity were repeated using the Finnish cohorts (replication analysis). Furthermore, using repeat obesity data available in the Finnish cohorts (two to four surveys), we calculated the proportion of individuals who developed hallmark-related multimorbidity during the 16-year follow-up period compared with those who did not. The analysis was based on a backward timescale starting from the diagnosis of hallmark-related multimorbidity (cases) or the end of the follow-up (non-cases).

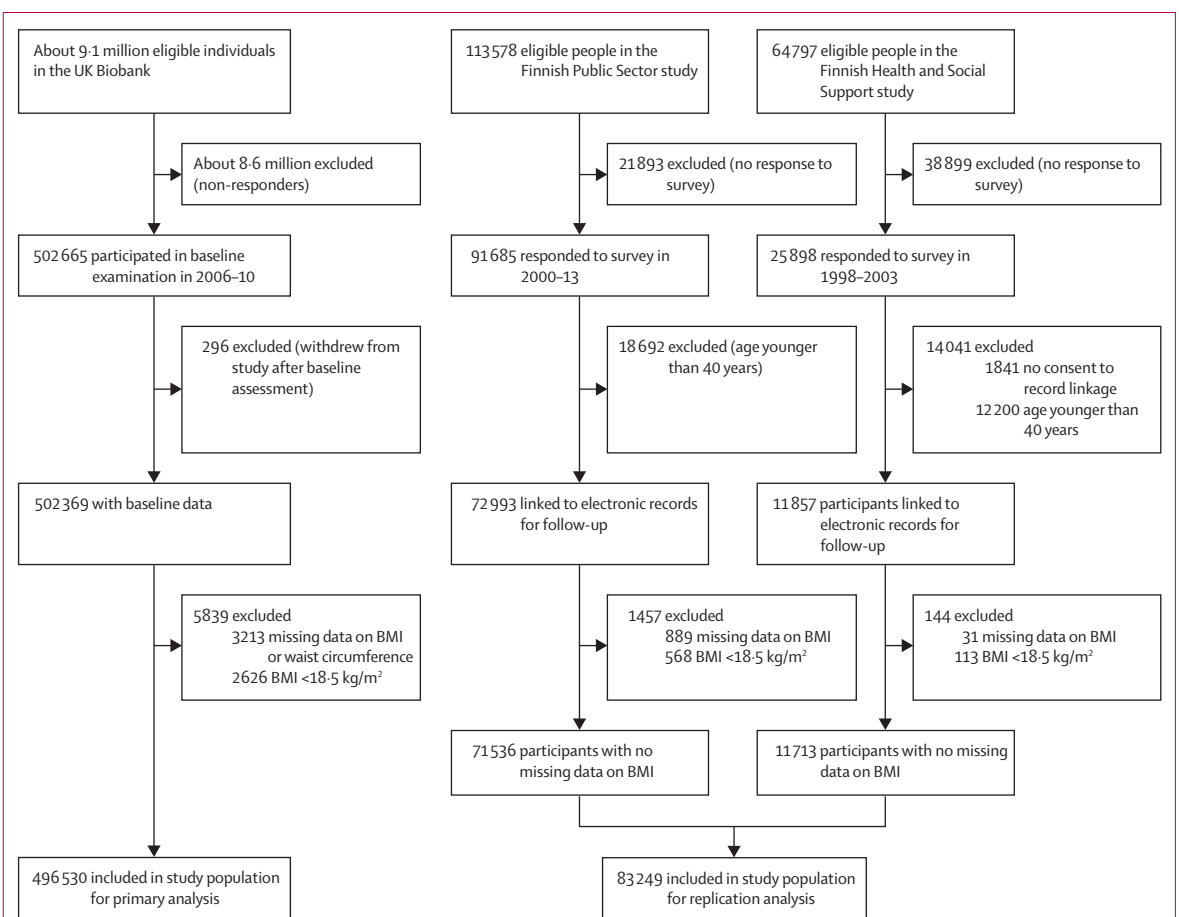

Figure 1: **Selection of participants for primary and replication analyses**

All analyses were performed using SAS statistical software (version 9.4).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of the 502 665 adults in the eligible population from the UK Biobank, 496 530 (98·8%) had complete data on height, weight, and waist circumference; were successfully linked to national health registers; and were included in the sample for primary analysis (figure 1). From all 117 583 participants in the Finnish cohorts, 83 249 (70·8%) were aged 40 years or older, had data on height and weight, and were successfully linked to national health records. The mean age of UK Biobank participants at the time of obesity assessment (baseline) was 57·0 years (SD 8·1; appendix 3 p 7). 122 172 (24·6%) participants had obesity based on BMI. In the Finnish cohorts, the mean age was 48·2 years (SD 6·4), and 12 275 (14·7%) participants had obesity based on BMI.

In the UK Biobank, median follow-up was 12·7 years (IQR 12·0–13·4). The incidence of the first hallmark-related disease per 1000 person-years was 27·6 (95% CI 27·4–27·9) in participants with healthy weight and 38·0 (37·6–38·3) in those with obesity. The cumulative incidence of first hallmark-related disease reached 30% (95% CI 29–31) at age 62 years in the healthy weight group, whereas it was reached 5 years earlier at age 57 years in participants with obesity (appendix 3 p 9).

Obesity was associated with 52 hallmark-related diseases (45 after Bonferroni correction; table 1; appendix 3 p 10). Notable exceptions where obesity was not associated with hallmark-related diseases included osteoporosis, glaucoma, Parkinson's disease, and dementia.

The association of obesity with any first-occurring hallmark-related disease followed a dose–response pattern across healthy weight, overweight, and obesity (table 2; appendix 3 p 12). The age-adjusted, sex-adjusted, and ethnicity-adjusted HR was 1·13 (95% CI 1·11–1·14) for overweight and 1·44 (1·43–1·46) for obesity, with the corresponding HRs being 1·11 (1·10–1·13) and 1·40 (1·38–1·41) after multivariable adjustment (table 2). These findings on obesity were robust to Bonferroni correction (appendix 3 p 12).

Network analysis showed strong inter-relationships among diseases within each hallmark, with the clustering coefficients varying between 0·76 (loss of proteostasis) and 0·92 (stem cell exhaustion; appendix 3 p 13). The incidence of developing at least three co-occurring hallmark-related diseases was 6·8 (95% CI 6·6–6·9) per 1000 person-years in participants with obesity and 3·4 (3·3–3·5) per 1000 person-years in those with healthy weight. Increase in co-occurrence of multiple hallmark-related diseases started at about age 50 years, and the 10% cumulative incidence of three co-occurring hallmark related diseases was reached at age 72 years among

	Related mechanisms	HR (95% CI) of obesity for three selected diseases per hallmark*
Primary hallmarks of ageing		
Genomic instability	DNA damage including DNA repair deficiencies, mutations, chromosome breakage, and DNA breaks (both single-stranded and double-stranded); transposable elements; mitochondrial DNA damage (eg, mitochondrial DNA mutations)	Bowel cancer 1·26 (1·18–1·34); breast cancer 1·15 (1·10–1·21); thyroid cancer 1·49 (1·18–1·89)
Telomere attrition	Decreased telomere length including decreased leukocyte telomere length	Chronic heart failure 3·70 (3·40–4·03); coronary heart disease 1·98 (1·90–2·06); type 2 diabetes 7·63 (6·40–9·10)
Epigenetic alterations	DNA methylation; histone modifications including histone acetylation and histone methylation; gene transcription including coding RNA and non-coding RNA (eg, microRNA)	Kidney cancer 1·94 (1·71–2·21); liver cancer 1·88 (1·60–2·22); stomach cancer 1·77 (1·51–2·08)
Loss of proteostasis	Chaperone; proteolysis including protein aggregation, autophagy, and proteasome; endoplasmic reticulum stress (eg, unfolded protein response)	Cataract 1·26 (1·23–1·29); plasma cell cancer 1·21 (1·04–1·40); type 2 diabetes 7·63 (6·40–9·10)
Antagonist hallmarks of ageing		
Deregulated nutrient sensing	Insulin resistance; dyslipidaemia; nutrient-sensing pathways including insulin and IGF signalling, AMP-activated protein kinase, mTOR complex 1, and sirtuin 1	Type 2 diabetes 7·63 (6·40–9·10); fatty liver 8·79 (6·64–11·62); hypertension 2·13 (1·92–2·36)
Mitochondrial dysfunction	Mitochondrial toxicity including reactive oxygen species; mitochondrial bioenergetics including electron transport chain and Krebs cycle; mitochondrial dynamics including mitochondrial turnover (eg, mitochondrial degradation and biogenesis)	Sepsis 1·78 (1·69–1·89); cardiomyopathy 1·64 (1·34–2·02); chronic kidney disease 2·56 (2·18–3·01)
Cellular senescence	Immunosenescence; senescence-associated secretory phenotype; senescence markers	Cirrhosis 2·33 (1·96–2·77); osteoarthritis 2·62 (2·55–2·70); viral infections 1·47 (1·37–1·58)
Integrative hallmarks of ageing		
Stem cell exhaustion	Stem cell differentiation; progenitor cell; stem cell self-renewal	Anaemia 1·57 (1·48–1·66); osteoarthritis 2·62 (2·55–2·70); myocardial infarction 1·76 (1·67–1·85)
Altered intercellular communication	Inflammatory signalling including inflammaging and inflammation; neural signalling (neurotransmitters); hormonal signalling (hormones)	Thyroid disease 1·43 (1·27–1·61); lower respiratory tract infection 1·56 (1·51–1·61); rheumatoid arthritis 1·47 (1·29–1·68)

HR=hazard ratio. *HR for obesity versus healthy weight adjusted for age, sex, and ethnicity. The full list of obesity hallmark-related disease associations is provided in appendix 3 (p 10).

Table 1: **Hallmarks of ageing and related mechanisms with illustrative examples of hallmark-related diseases associated with obesity in the UK Biobank**

	Participants	Cases	Basic model* HR (95% CI)	Multivariable adjusted† HR (95% CI)
UK Biobank				
First disease				
Healthy weight	137 235	47 642	1 (ref)	1 (ref)
Overweight	171 628	69 998	1·13 (1·11–1·14)	1·11 (1·10–1·13)
Obesity	91 737	43 413	1·44 (1·43–1·46)	1·40 (1·38–1·41)
Second disease				
Healthy weight	137 235	16 593	1 (ref)	1 (ref)
Overweight	171 628	26 946	1·16 (1·14–1·18)	1·14 (1·12–1·16)
Obesity	91 737	18 617	1·65 (1·62–1·69)	1·56 (1·53–1·60)
Third disease				
Healthy weight	137 235	5916	1 (ref)	1 (ref)
Overweight	171 628	10 308	1·19 (1·15–1·22)	1·16 (1·12–1·20)
Obesity	91 737	7743	1·84 (1·78–1·90)	1·70 (1·65–1·77)
Finnish cohorts				
First disease				
Healthy weight	38 335	8258	1 (ref)	1 (ref)
Overweight	26 719	7703	1·27 (1·23–1·31)	1·25 (1·21–1·29)
Obesity	10 586	3654	1·72 (1·66–1·79)	1·66 (1·60–1·73)
Second disease				
Healthy weight	38 335	2131	1 (ref)	1 (ref)
Overweight	26 719	2220	1·29 (1·21–1·37)	1·26 (1·19–1·34)
Obesity	10 586	1174	1·93 (1·79–2·07)	1·83 (1·70–1·97)
Third disease				
Healthy weight	38 335	572	1 (ref)	1 (ref)
Overweight	26 719	688	1·40 (1·25–1·57)	1·35 (1·21–1·51)
Obesity	10 586	446	2·59 (2·29–2·94)	2·37 (2·08–2·69)

A healthy weight was defined as a BMI of 18·5–24·9 kg/m², overweight was defined as a BMI of 25·0–29·9 kg/m², and obesity was defined as a BMI of 30·0 kg/m² or higher. HR=hazard ratio. *Adjusted for age, sex, and ethnicity (UK Biobank) or cohort (Finnish cohorts). †Adjusted for age, sex, ethnicity (UK Biobank), cohort (Finnish cohorts), education, dietary factors (UK Biobank), smoking, physical activity, alcohol consumption, and depression.

Table 2: **Associations of obesity with any hallmark-related diseases and disease co-occurrence**

participants with obesity and 77 years among those with a healthy weight (appendix 3 p 9). The age-adjusted, sex-adjusted, and ethnicity-adjusted HR for three co-occurring hallmark-related diseases was 1·19 (95% CI 1·15–1·22) for overweight and 1·84 (1·78–1·90) for obesity (table 2), with both estimates being significant after Bonferroni correction (appendix 3 p 12). The corresponding HRs were 1·16 (95% CI 1·12–1·20) and 1·70 (1·65–1·77) after multivariable adjustment.

For three co-occurring hallmark-related diseases as the outcome, age-adjusted, sex-adjusted, and ethnicity-adjusted HRs for obesity versus healthy weight varied between 1·48 (95% CI 1·35–1·61) for genomic instability and 3·25 (2·95–3·59) for deregulated nutrient sensing. The corresponding HRs were 1·39 (95% CI 1·27–1·52) and 2·92 (2·64–3·22) after multivariable adjustment (figure 2). Further analyses (appendix 3 pp 14–18) showed that the association between obesity and co-occurrence of hallmark-related diseases was consistent across men (1·79, 95% CI 1·70–1·87) and women (1·89, 1·80–1·99; appendix 3 p 17), and remained robust after controlling for the competing risk of death and multiple testing (Bonferroni) and excluding the two most common conditions (osteoarthritis and cataract) from the definition of hallmark-related disease co-occurrence. There was no indication of effect modification by ethnicity ($p_{interaction}$=0·58). Additionally, using waist circumference and waist-to-height ratio to define obesity resulted in similar HRs for obesity and co-occurrence of hallmark-related diseases (appendix 3 p 19).

Obesity was more strongly associated with co-occurrence of three hallmark-related diseases than other risk factors, including education, dietary factors, smoking, physical activity, alcohol consumption, and depression at baseline (figure 3A; for details, see appendix 3 p 20). In participants with no hallmark-related diseases at baseline and after adjustment for age, sex, and ethnicity, individuals with obesity had a 1·37 times (95% CI 1·32–1·42) higher risk of mortality than those with a healthy weight. The corresponding HR was 1·31 (95% CI 1·27–1·36) in multivariable-adjusted analyses (figure 3B). A total of 44·8% (95% CI 40·2–51·1) of the multivariable-adjusted excess risk of mortality in individuals with obesity was mediated through hallmark-related diseases (figure 3B).

In replication and supplementary analyses, the findings from the Finnish cohort studies were consistent with those observed in the UK Biobank and did not differ between the two Finnish cohorts ($p_{interaction}$=0·23; figures 2, 3; table 2; appendix 3 pp 21–25). A total of 60·4% (95% CI 43·9–95·4) of the obesity–mortality association was mediated through hallmark-related diseases (median follow-up 14·0 years [IQR 8·0–15·0]). Furthermore, over the maximum 16-year follow-up period of 48 270 Finnish cohort participants with repeat weight measurements (mean 2·4 [SD 1·1], range 2–4), obesity was consistently more prevalent among participants who developed multiple co-occurring hallmark-related diseases than among those who did not (appendix 3 pp 26–27). In addition, we observed a dose–response pattern: compared with participants who consistently maintained a healthy weight, the HR for co-occurrence of hallmark-related diseases was 1·98 (95% CI 1·48–2·65) times higher among participants with obesity in one measurement and increased to 2·99 (2·41–3·71) for those with obesity in two measurements (appendix 3 p 26).

Discussion

The findings of this observational multicohort study suggest that obesity might have an important role in the development of diseases that have been shown to be associated with cellular ageing.[2] First, we observed a more than two times higher risk of disease co-occurrence related to deregulated nutrient sensing, telomere attrition, epigenetic alterations, mitochondrial dysfunction, stem cell exhaustion, and altered intracellular communication among individuals with obesity than in those with a healthy weight. The risk of developing multiple diseases associated with the loss of

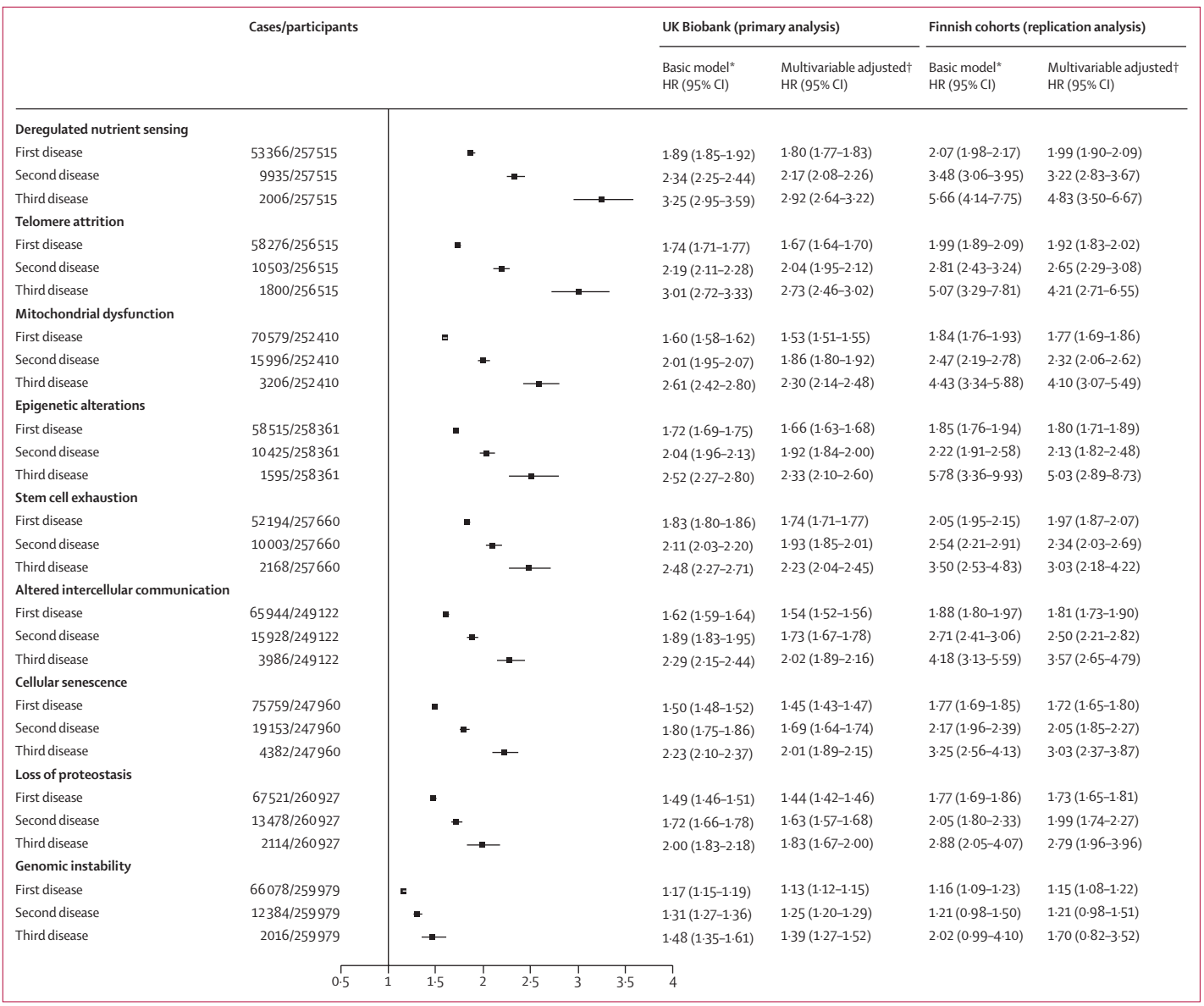

Figure 2: **Association of obesity with specific hallmark-related diseases and disease co-occurrence**
HR=hazard ratio. *Adjusted for age, sex, and ethnicity (UK Biobank) or cohort (Finnish cohorts). †Adjusted for age, sex, ethnicity (UK Biobank), cohort (Finnish cohorts), education, dietary factors (UK Biobank), smoking, physical activity, alcohol consumption, and depression.

proteostasis was nearly twice as high, whereas the risk associated with genomic instability was 1·4 times higher. Second, the association of obesity with co-occurrence of multiple hallmark-related diseases was stronger than those of other risk factors, including low education, smoking, high alcohol consumption, physical inactivity, diet, and depression. Third, about half of obesity-related mortality was attributable to hallmark-related diseases. These findings were reproducible in men and women and across two different study populations and were not dependent on the method used to assess obesity.

The present analyses on the co-occurrence of multiple hallmark-related diseases focused on nine specific multimorbidities, contributing to the diverse body of evidence linking obesity with multimorbidity or multiple long-term conditions.[25] Previous studies, unlike our current investigation, have not specifically focused on conditions related to the hallmarks of cellular ageing. Consequently, they do not typically capture the age-related increased vulnerability to bacterial and viral infections, lower respiratory tract infections, and sepsis. The risk of these diseases tends to increase with cellular senescence (immunosenescence),[26] impaired intercellular communication (inflammaging),[11] and mitochondrial dysfunction (defective mitophagy contributing to inflammaging).[27] For this reason, they were included

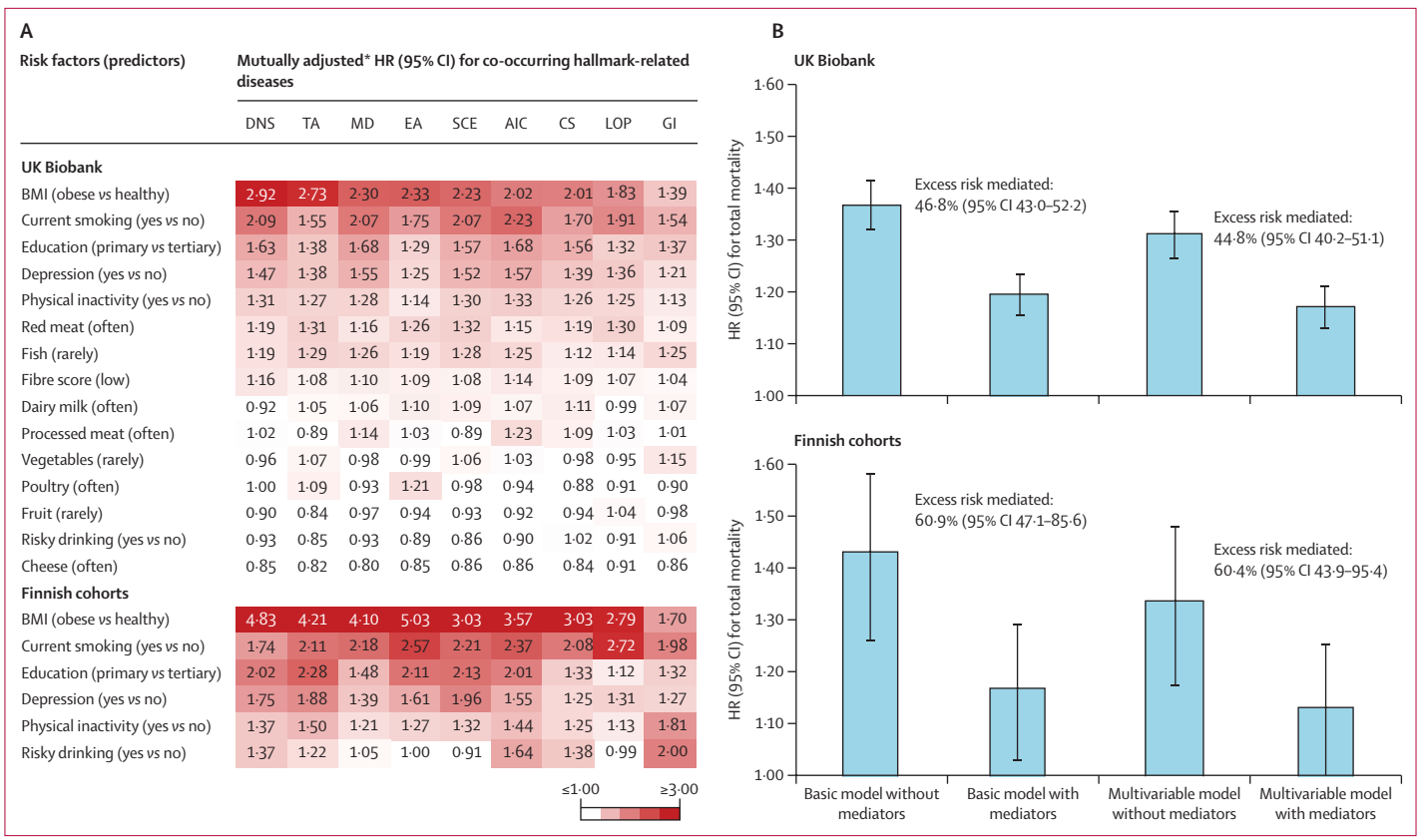

Figure 3: **Obesity, risk factors, and co-occurrence of hallmark-related diseases (A) and excess mortality risk for obesity mediated through hallmark-related diseases (B)**
A healthy weight was defined as a BMI of 18·5–24·9 kg/m², and obesity was defined as a BMI of 30·0 kg/m² or higher. (A) Numbers are mutually adjusted HRs for obesity and other risk factors at baseline in relation to co-occurrence of three or more hallmark-related diseases at follow-up (full data are available in appendix 3 pp 20, 25). (B) The basic and multivariable-adjusted HR for obesity versus healthy weight at baseline for total mortality in participants initially free of hallmark-related diseases with and without additional adjustment for hallmark-related diseases after baseline. The percentage of the obesity–mortality association mediated through the onset of hallmark-related diseases after baseline is also shown. AIC=altered intercellular communication. CS=cellular senescence. DNS=deregulated nutrient sensing. EA=epigenetic alterations. GI=genomic instability. HR=hazard ratio. LOP=loss of proteostasis. MD=mitochondrial dysfunction. SCE=stem cell exhaustion. TA=telomere attrition. *Adjusted for age, sex, ethnicity (UK Biobank), cohort (Finnish cohorts), and all of the listed risk factors.

in our analyses. By contrast, multimorbidity outcomes in previous studies have included conditions not directly associated with the hallmarks of ageing, such as mental disorders (depression, anxiety, and psychological or emotional conditions). These conditions were excluded from our outcome measures.

The current results are consistent with interventional, experimental, mechanistic, and mendelian randomisation studies suggesting that obesity, weight changes, and dietary choices have multiple effects on whole-body physiology, different tissues, and the functional and structural properties of cells, including regulation of gene expression. More specifically, individuals with obesity have been shown to be characterised by heightened adipokine synthesis, increased lipid production, increased activity of the sympathetic nervous and renin–angiotensin–aldosterone systems, and increased mechanical stress, affecting the entire body and specific organs.[19] Studies also indicate that reducing obesity through bariatric surgery or pharmacotherapy can normalise hormonal and vagal signalling, thereby enhancing intestinal nutrient sensing.[28,29] In addition, gastric bypass surgery might extend telomere length.[30] Furthermore, caloric restriction, a non-clinical approach to obesity reduction, can activate AMP-dependent kinase and the sirtuin family of proteins, inhibit IGF1 and mTOR-dependent activities, modulate mitochondrial activity, and delay age-related pathologies.[21,31] Mendelian randomisation studies support a causal association between obesity and accelerated epigenetic ageing,[32] although this relationship might be bidirectional such that DNA methylation also contributes to fat accumulation. In the light of the converting findings from our investigation and those from other studies, obesity is linked to excess risk of pathology related to deregulated nutrient sensing, telomere attrition, mitochondrial dysfunction, and epigenetic alterations, but it remains unclear whether these associations are causal, attributable to similarities in processes related to obesity and cellular ageing, or due to effects of cellular ageing on central obesity.[18,33]

Numerous, often inter-related biological, environmental, and behavioural factors might influence the risk

of the 83 multi-aetiological conditions related to hallmarks of cellular ageing. In our study, individuals with obesity had a higher relative risk of hallmark-related diseases than those with other factors such as low education, unhealthy diet, smoking, high alcohol consumption, physical inactivity, and depression. Importantly, the association between obesity and hallmark-related diseases remained significant even after adjusting for these factors. These findings suggest that obesity plays an independent part as a risk factor or risk mediator for hallmark-related diseases.

Although obesity was associated with heightened risk of the majority of hallmark-related diseases in our study, this was not the case for all of them, suggesting that there are also important differences in processes driving obesity and cellular ageing. For example, we observed no obesity-related risk elevation for hallmark-related conditions of osteoporosis, glaucoma, and Parkinson's disease.[2] In addition, there was no direct association between obesity and dementia. This is likely to be an artifact, resulting from the relatively short 13-year follow-up in the included cohort studies. The preclinical phase of dementia during which weight loss is common is typically longer than a decade. Thus, increased dementia risk in individuals with obesity can be observed only when weight assessment is taken 10–20 years before symptomatic disease.[34,35]

The present results should be interpreted in the context of the study's limitations. Low participation in the UK Biobank (5·5% of those eligible to participate) might have introduced selection bias, although reproducibility in the Finnish cohorts with higher response rates suggests that major bias is unlikely. Meaningful analyses of the effects of weight loss on diseases associated with cellular ageing were not possible due to lack of data distinguishing intentional from unintentional weight changes. Self-reported weight and height in the Finnish cohorts might have introduced reporting bias, potentially affecting associations in the replication analysis. However, consistency with UK Biobank results, where measurements were taken, suggests this bias is unlikely to be significant. Additionally, dietary factors not fully assessed in our study (eg, different fatty acids, certain vitamins, and natural dietary antioxidants) and active metabolites from gut microbiota could influence hallmark-related diseases, potentially affecting the validity of multivariable-adjusted analyses. Furthermore, self-administered survey instruments for covariate measurement might be less accurate than direct measurements of weight and height, contributing to potential overestimation of the independent effects of obesity. Our use of electronic health records shares the limitations with most other large multi-outcome cohort studies, including the inability to detect undiagnosed conditions and those rarely leading to hospitalisation. This might attenuate disease incidence but is not considered a source of substantial error to relative risks.

We determined a person's vulnerability to specific hallmark-related diseases, as defined by Kuan and colleagues[15] and Fraser and colleagues,[2] rather than using direct examinations of cellular changes. Future investigations should integrate measurement of cellular mechanisms into cohort studies to determine the entire pathway from obesity to altered cellular ageing and the consequent increase in cellular-age-associated morbidities. Further research is also needed to examine the generalisability of our findings in more diverse populations and in low-income and middle-income countries.

In conclusion, the present epidemiological evidence supports a life course model of cellular-age-associated disease accumulation in individuals with obesity. This model suggests that the excess risk of individual diseases associated with cellular ageing is followed by an increased prevalence of cellular-ageing-related multimorbidity after the age of 50 years. These findings and the large proportion of obesity-related deaths attributable to cellular-ageing-associated diseases imply that tackling ageing mechanisms could potentially help to reduce the disease and mortality burden resulting from the obesity epidemic.

Contributors

All authors participated in designing the study, generating hypotheses, interpreting the data, and critically reviewing the report. MK 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 and MK accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Researchers registered with the UK Biobank can apply for access to the database by completing an application. The application must include a summary of the research plan, data fields required, any new data or variables that will be generated, and payment to cover the incremental costs of servicing an application (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access). In FPS and HeSSup, pseudonymised questionnaire data, as used in this study, can be shared by request to JE (jenni.ervasti@ttl.fi) and JP (jaana.e.pentti@helsinki.fi). Linked health records require separate permission from the Findata, which is the Health and Social Data Permit Authority in Finland. Statistical code and complete summary data for figures and tables are provided in appendix 3 (pp 19–22).

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