RESEARCH ARTICLE

Comorbidity trajectories before and after the diagnosis of heart failure: A UK Biobank cohort study

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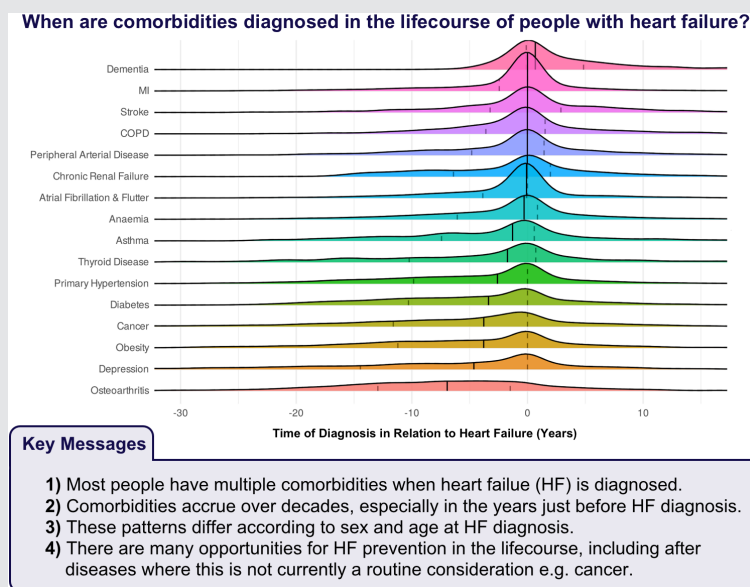|	
Aims	Heart failure (HF) is frequently associated with multiple comorbidities. We aimed to define their trajectory of accrual to identify opportunities for disease prevention.
Methods and results	We identified all participants in the UK Biobank cohort study diagnosed with HF prior to enrolment or during follow-up, who had disease occurrence data available from both primary and secondary care records (*n* = 9824). We established the time between diagnosis of HF and 16 common comorbidities to determine the rate and sequence of comorbidity accrual in relation to HF. Stratified analyses considered associations with sex and age at diagnosis of HF. In chronological sequence, HF was the median fourth diagnosis for men and women. As the age at HF diagnosis increased, HF came later in the sequence of diseases (median second in under 50 years to fifth in those aged 80–90 years). In all age strata, comorbidities accumulated for over a decade before HF and this accelerated in the years immediately before HF. The median time between comorbidity and HF diagnoses ranged from depression preceding HF by 10.7 years to dementia proceeding HF by 0.7 years; all comorbidities presented earlier in women. Atrial fibrillation/flutter was the commonest disease to immediately precede HF, followed by hypertension, cancer, myocardial infarction and osteoarthritis.
Conclusion	Heart failure is most often diagnosed in people with established multiple long-term conditions. There is a protracted window of opportunity during which interventions to prevent HF could be applied, often in disease contexts where this is not routine care, such as cancer and osteoarthritis.

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Graphical Abstract

When are comorbidities diagnosed in the lifecourse of people with heart failure?

Key Messages

1) Most people have multiple comorbidities when heart failue (HF) is diagnosed.
2) Comorbidities accrue over decades, especially in the years just before HF diagnosis.
3) These patterns differ according to sex and age at HF diagnosis.
4) There are many opportunities for HF prevention in the lifecourse, including after diseases where this is not currently a routine consideration e.g. cancer.

Time of diagnosis of comorbidities in relation to heart failure. COPD, chronic obstructive pulmonary disease; MI, myocardial infarction.

Introduction

An aging society and improving medical and public health practice mean that a growing proportion of people live with multiple long-term conditions (MLTC, also known as multimorbidity), which can be defined as two or more medical conditions.[1] A seminal cross-sectional analysis of 1.7 million people living in Scotland in 2007 revealed that a majority of people had MLTC by the age of 65−69.[2] By their nature, long-term conditions accumulate over time, imposing an increasing burden on individuals, although there is substantial inter-individual heterogeneity in the rate of accrual and the contributing conditions.[3,4] People with a larger number of medical conditions experience poorer quality of life and a greater burden of medical therapy; they also require substantially larger quantity healthcare resources, such as planned and emergency care contacts.[5]

Chronic heart failure (HF) is a common late phase in the natural history of many cardiovascular diseases, affecting millions of people globally.[6] Improving treatment over recent decades has been associated with improving survival rates and increasing contribution of non-cardiovascular events to mortality in people with HF.[7] This has been paralleled by an increasing prevalence of MLTC, such that people recently diagnosed with HF had a median of five other long-term conditions (from a possible 17 studied) in a large cross-sectional analysis conducted in England in 2014.[8] People with HF and a greater number of comorbidities experience greater loss of life expectancy, increased rates of both cardiovascular and non-cardiovascular death, and less commonly achieve optimal HF medical therapy.[9,10] Hence, prevention of HF in people with MLTC, and *vice versa*, is an important treatment goal. However, little is known about how and when diseases accrue in the lifecourse of people who develop HF, which hinders the targeting of preventative interventions to the right people at the right time. Therefore, we set out to define the trajectory of comorbidity development in people with HF in the UK Biobank (UKB) cohort study, with the goal of understanding preventative opportunities (*Graphical Abstract*).

Methods

Study cohort

The UKB is a prospective observational cohort study of 502 462 participants aged 37−73 years, recruited from 22 assessment centres across the United Kingdom (UK) between 2006 and 2010. It is an open access resource developed using UK Government and biomedical research charity funding, which set out to link wide-ranging phenotypic and healthcare record data. Further details of its design and conduct are available at https://www.ukbiobank.ac.uk and our prior publications.[11,12] UKB received ethical approval from the NHS Research Ethics Service (11/NW/0382); we conducted this analysis under application number 117090. All participants provided written informed consent and the research conforms with the principles outlined in the Declaration of Helsinki.

We excluded all participants without record-level access to clinical events documented in primary care (UKB field ID 42040) since these are known to include more complete and timely records than hospital episode statistics (HES) or death registry data.[13] Within the subgroup of UKB with primary care record data ($n = 229\,944$), we then included only those participants with a diagnosis of HF (from primary care, HES or death registry data) at any time in life until the study censorship date of 24 April 2024. This resulted in a cohort of 9824 participants who developed HF. We applied no other inclusion or exclusion criteria.

Definitions of heart failure and comorbidities

All UKB field IDs and disease codes pertaining to our definition of HF, comorbidities and other participant characteristics are presented in online supplementary *Table Appendix S1*. We focused on the comorbid conditions included by Conrad *et al.*[8] in their analysis of MLTC in HF, since this allows comparison of our data with the most comprehensive published study of this phenomenon in the UK. They included 17 common long-term conditions, of which we excluded dyslipidaemia given that defining its onset is challenging and not all MLTC studies consider this as a primary disease (as opposed to a risk factor). For the remaining 16 conditions, the definitions applied by Conrad *et al.* were aligned with disease first occurrence data available through UKB. Where possible, we used UKB-defined first disease occurrence fields to aid reproducibility of our disease definitions; these included: obesity, chronic renal failure, atrial fibrillation/flutter, primary hypertension, myocardial infarction (either non-ST-elevation or ST-elevation), asthma, stroke, chronic obstructive pulmonary disease (COPD), dementia (of any cause), anaemia (of any cause), depression, thyroid disease (of any cause), diabetes (except pregnancy-associated), peripheral arterial disease (which includes aortic aneurysm) and cancer (of any type in the UKB cancer registry data). For osteoarthritis, no suitable collated UKB field ID or IDs were available, so we collated relevant read v2 and CTV3 codes from primary care records (field ID 42040—which is an actively updated dataset) and ICD-9/ICD-10 codes from hospital records (UKB Category 2006).

The first occurrence of any comorbidity was included when recorded either through primary care, HES, death registry or cancer registry data; self-reported occurrences were excluded, as were occurrences with invalid dates (prior to birth or in the future). For each comorbidity, we calculated the difference between its date of first diagnosis and the date of first HF diagnosis in order to understand the sequence and relative timing of comorbidity occurrence. To stratify the cohort by sex, we used UKB field ID 31. To stratify the cohort by age at HF diagnosis, we calculated age at HF diagnosis using the date of HF diagnosis in relation to the year and month of birth (UKB field IDs 34 and 52), deriving the following age at HF diagnosis strata: <50 years, 50–60 years, 60–70 years, 70–80 years and 80–90 years.

Statistical methods

We analysed UKB via the Research Access Platform secure cloud server (https://ukbiobank.dnanexus.com), using RStudio version 4.1.1. Analysis used the R suite 'tidyverse',[14] with plots were compiled using the embedded 'ggplot2' package, or the 'ggridges' (https://doi.org/10.32614/CRAN.package.ggridges) and 'networkD3' (https://doi.org/10.32614/CRAN.package.networkD3) packages. Continuous data are presented as mean and standard deviation, or median and interquartile range when non-normal. Categorical data are presented as percentage and number. Comparison of data between sexes uses unpaired *t*-tests for normally distributed continuous data, Mann–Whitney tests for non-normally distributed continuous data, and chi-squared tests for categorical data. Comparisons of continuous data across age at diagnosis of HF strata use Kruskal–Wallis tests. In a sensitivity analysis, we excluded participants diagnosed with HF after 24 April 2019 in order to define how a minimum 5-year observation period influenced the temporal distribution of comorbidity diagnoses in relation to HF diagnosis. All statistical tests were two-sided and statistical significance was defined as $p < 0.05$, Bonferroni adjusted to $p < 0.003$ when performing tests for each of the 16 long-term conditions assessed.

Results

Of 501 472 UK Biobank participants, 229 944 had available primary care clinical event records. Within this subgroup, we identified 9824 people (4.3%) with HF diagnosed up to the date of censorship on 24 April 2024. Their characteristics are illustrated in *Table 1*, showing a mean (standard deviation) age at HF diagnosis of 69.8 (9.9) years and a predominance of men (64%). During the observation period of 743 718 person-years, a total of 38 415 comorbid conditions (i.e. not including HF) were first diagnosed, equating to a median of 4 and mean of 3.91 (2.07) comorbidities per person. There were large differences in the prevalence of the 16 comorbidities we studied, ranging from dementia in 6.5% to atrial fibrillation/flutter in 51.1%.

Men were diagnosed with HF at a younger age than women (69.3 [9.9] vs. 70.5 [9.5] years; $p < 1 \times 10^{-10}$) and had fewer comorbid conditions (3.83 [2.00] vs. 4.05 [2.05] comorbidities per person; $p = 3.1 \times 10^{-5}$) during the observation period. Whilst some comorbidities had a similar prevalence in men and women, myocardial infarction, atrial fibrillation/flutter, peripheral arterial disease and diabetes were more common in men, whilst asthma, obesity, anaemia, depression, thyroid disease and osteoarthritis were more common in women (all $p < 0.003$). When stratified according to age at HF diagnosis, there was a small increase in the number of comorbidities from those aged <50 to those aged 70–80, after which this plateaued. Cancer, chronic renal failure, dementia and osteoarthritis showed the largest increase in prevalence with rising age at HF diagnosis, whilst the opposite was noted for obesity, diabetes and depression.
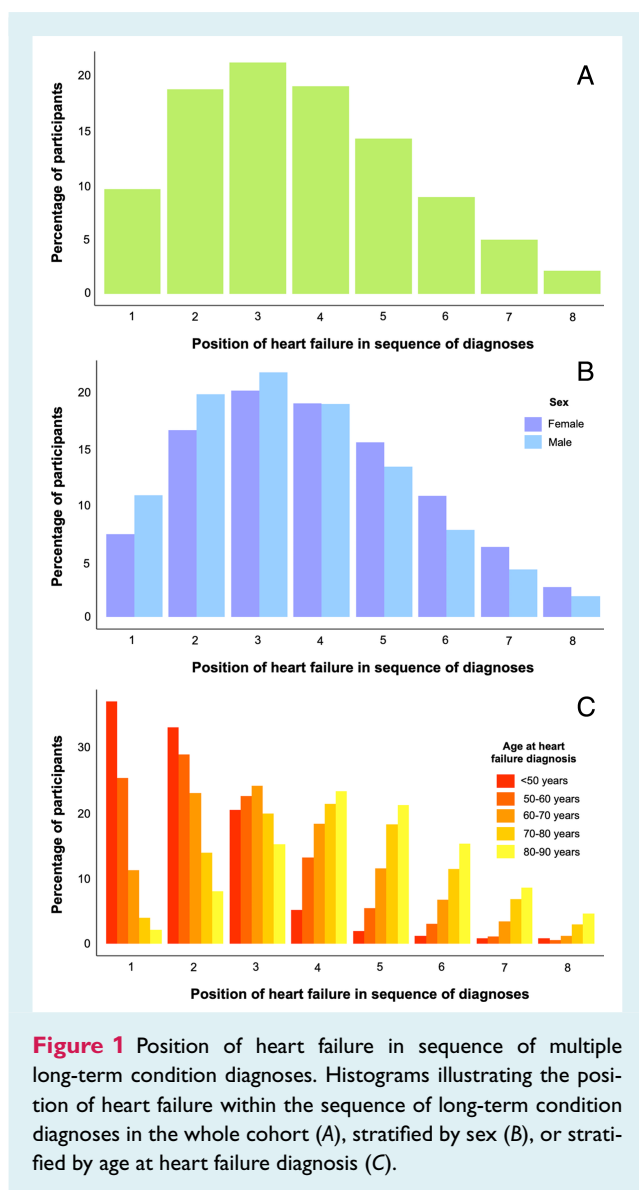
Sequence and chronology of heart failure in the trajectory of multiple long-term condition accrual

When considered amongst the chronological sequence of MLTC accrual, HF was the median fourth diagnosis received. *Figure 1A* illustrates the distribution of these data, with fewer than 10% of people having HF as their first MLTC diagnosis. When stratified by sex, a subtle rightward shift is noted in women (*Figure 1B*), indicating that HF is a later diagnosis in the sequence of MLTC accrual in women (Mann–Whitney $p < 1 \times 10^{-10}$), although HF remains the median fourth diagnosis in men and women. When

Table 1 Participant characteristics

	Total (n = 9824)	Sex		Age at diagnosis of HF (years)				
		Male (n = 6284, 64.0%)	Female (n = 3540, 36.0%)	<50 (n = 255, 2.6%)	50–60 (n = 1201, 12.2%)	60–70 (n = 3173, 32.3%)	70–80 (n = 4540, 46.2%)	80–90 (n = 655, 6.7%)
Age at diagnosis of HF, years	69.8 (9.9)	69.3 (9.9)	70.5 (9.5)	–	–	–	–	–
White ethnicity, n (%)	9122 (92.8)	5854 (93.2)	3268 (92.3)	223 (87.5)	1067 (88.8)	2932 (92.4)	4278 (94.2)	622 (95.0)
Non-white ethnicity, n (%)	684 (7.0)	418 (6.7)	266 (7.5)	<50 (11.8)	130 (10.8)	236 (7.4)	255 (5.6)	<50 (5.0)
No. of comorbidities	3.91 (2.07)	3.83 (2.00)	4.05 (2.05)	3.22 (1.99)	3.36 (2.01)	3.75 (2.04)	4.03 (2.01)	4.02 (1.85)
Comorbidities, n (%)								
MI	2653 (27.0)	1870 (29.8)	783 (22.1)	64 (25.1)	339 (28.2)	880 (27.7)	1226 (27.0)	144 (22.0)
Asthma	751 (7.6)	414 (6.6)	337 (9.5)	<50 (7.5)	93 (7.7)	239 (7.5)	355 (7.8)	<50 (6.9)
Stroke	1022 (10.4)	662 (10.5)	360 (10.2)	<50 (9.0)	112 (9.3)	318 (10.0)	490 (10.8)	79 (12.1)
Obesity	2944 (30.0)	1785 (28.4)	1159 (32.7)	82 (32.2)	373 (31.1)	997 (31.4)	1333 (29.4)	159 (24.3)
Cancer	3405 (34.7)	2122 (33.8)	1283 (36.2)	<50 (12.5)	303 (25.2)	1070 (33.7)	1736 (38.2)	264 (40.3)
Chronic renal failure	3175 (32.3)	2033 (32.4)	1142 (32.3)	54 (21.2)	322 (26.8)	957 (30.2)	1587 (35.0)	255 (38.9)
COPD	1908 (19.4)	1217 (19.4)	691 (19.5)	<50 (15.7)	168 (14.0)	603 (19.0)	973 (21.4)	124 (18.9)
Dementia	637 (6.5)	405 (6.4)	232 (6.6)	<50 (2.4)	<50 (2.9)	142 (4.5)	381 (8.4)	73 (11.1)
Atrial fibrillation/flutter	5021 (51.1)	3337 (53.1)	1684 (47.6)	114 (44.7)	460 (38.3)	1542 (48.6)	2539 (55.9)	366 (55.9)
Primary hypertension	3838 (39.1)	2393 (38.1)	1445 (40.8)	90 (35.3)	471 (39.2)	1265 (39.9)	1756 (38.7)	256 (39.1)
Anaemia	3535 (36.0)	2140 (34.1)	1395 (39.4)	76 (29.8)	352 (29.3)	1113 (35.1)	1750 (38.5)	244 (37.3)
Diabetes	2973 (30.3)	2008 (32.0)	965 (27.3)	78 (30.6)	395 (32.9)	1010 (31.8)	1336 (29.4)	154 (23.5)
Depression	1562 (15.9)	868 (13.8)	694 (19.6)	61 (23.9)	213 (17.7)	488 (15.4)	700 (15.4)	100 (15.3)
Thyroid disease	1127 (11.5)	502 (8.0)	625 (17.7)	<50 (16.1)	126 (10.5)	363 (11.4)	503 (11.1)	94 (14.4)
PAD	1088 (11.1)	803 (12.8)	285 (8.1)	<50 (8.6)	127 (10.6)	357 (11.3)	508 (11.2)	74 (11.3)
Osteoarthritis	2776 (28.3)	1526 (24.3)	1250 (35.3)	<50 (14.5)	237 (19.7)	783 (24.7)	1472 (32.4)	247 (37.7)
No comorbidities	284 (2.9)	197 (3.1)	87 (2.5)	<50 (7.5)	65 (5.4)	102 (3.2)	87 (1.9)	<50 (1.7)

Where fewer than 50 cases are noted in a condition, the precise number of participants is not provided to reduce the risk of deanonymization.
COPD, chronic obstructive pulmonary disease; HF, heart failure; MI, myocardial infarction; PAD, peripheral arterial disease.

Figure 1 Position of heart failure in sequence of multiple long-term condition diagnoses. Histograms illustrating the position of heart failure within the sequence of long-term condition diagnoses in the whole cohort (*A*), stratified by sex (*B*), or stratified by age at heart failure diagnosis (*C*).

stratified by age at HF diagnosis, a marked difference in the position of HF in the sequence of MLTC accrual is noted (Kruskal−Wallis $p < 1 \times 10^{-10}$) (*Figure 1C*). Specifically, HF was the median second diagnosis in people with HF diagnosed under 50 years of age, rising to the median fifth diagnosis in people diagnosed with HF aged 80−90 years. Hence, HF is typically diagnosed in the context of established MLTC.

In order to understand the kinetics of MLTC accrual during the lifecourse of people with HF, we plotted out the number of comorbidities (i.e. excluding HF) over time expressed in relation to the diagnosis of HF (i.e. with negative time representing prior to HF). Notably, data after the diagnosis of HF pertain to a diminishing population as participants die or reach the date of censorship. As people with a greater number of accumulated comorbidities are likely to be older, they are more likely to die which results in a levelling off or reduction in the apparent burden of comorbidities per person. To minimize this phenomenon, we only present data

according to strata of age at HF diagnosis (*Figure 2*). As expected, the number of comorbidities rises over time and is higher in people with HF diagnosed at an older age. However, irrespective of age at HF diagnosis, comorbidities accumulate (at differing rates) for at least 20 years prior to HF diagnosis and accumulate more rapidly around 5 years before HF diagnosis. This period of accelerated comorbidity diagnosis continues for approximately another 5 years after HF diagnosis and then tapers off, especially in those diagnosed with HF later in life. These data illustrate a protracted period of MLTC accrual prior to HF.

Timing of individual comorbidity diagnoses in relation to heart failure

To understand the timing of specific comorbidity diagnoses in relation to HF diagnosis, we constructed Ridgeline plots for each comorbidity (*Figure 3*), again with negative time denoting prior to HF. Importantly, the amplitudes of these are not proportional to the prevalence of a comorbidity, allowing a specific focus on the temporal distribution of each comorbidity diagnosis in relation to HF diagnosis. To simplify interpretation, the median and interquartile range is illustrated in each comorbidity Ridgeline (and *Table 2*), and these are ordered according to median time, showing that osteoarthritis is the earliest forerunner of HF and dementia is the latest comorbidity to develop, with a majority of dementia diagnoses occurring after HF. Most cases of some comorbidities present over a narrow period (e.g. myocardial infarction and atrial fibrillation/flutter, with interquartile ranges of 2.4 and 3.9 years, respectively), whereas others present over protracted periods (e.g. depression and cancer, with interquartile ranges of 14.4 and 11.6 years, respectively).

For eight of the studied comorbidities (osteoarthritis, depression, obesity, cancer, diabetes, hypertension, atrial fibrillation/flutter and myocardial infarction), three quarters of cases were diagnosed prior to or synchronously with HF, with the remaining cases diagnosed after HF. However, it should be noted that with longer follow-up, a greater proportion cases of each comorbidity would be expected to be diagnosed after HF. To address this possibility, we performed a sensitivity analysis including only participants diagnosed with HF on or before 24 April 2019 ($n = 1819$), giving 5 years of follow-up in those not dying during the period (online supplementary *Table S2*). As expected, in comparison with our primary analysis, this modestly reduced the interval between HF and comorbidity diagnoses (because there was more time for comorbidities to develop after HF diagnosis, whereas no more could develop before HF) leading a more than 1-year change for thyroid disease, diabetes, cancer, depression and osteoarthritis intervals. Overall, these data emphasize that different comorbidities often have distinct kinetic profiles in relation to the onset of HF.

Next, we explored sex differences in the timing of specific comorbidity diagnoses in relation to HF diagnosis. Ridgeline plots (online supplementary *Figure Appendix S1*) and summary data (online supplementary *Table S3*) show that most comorbidities developed earlier, in relation to HF diagnosis, in women than men. This was most pronounced for cancer which developed a median of 7.1 years before HF in women, versus 2.6 years before
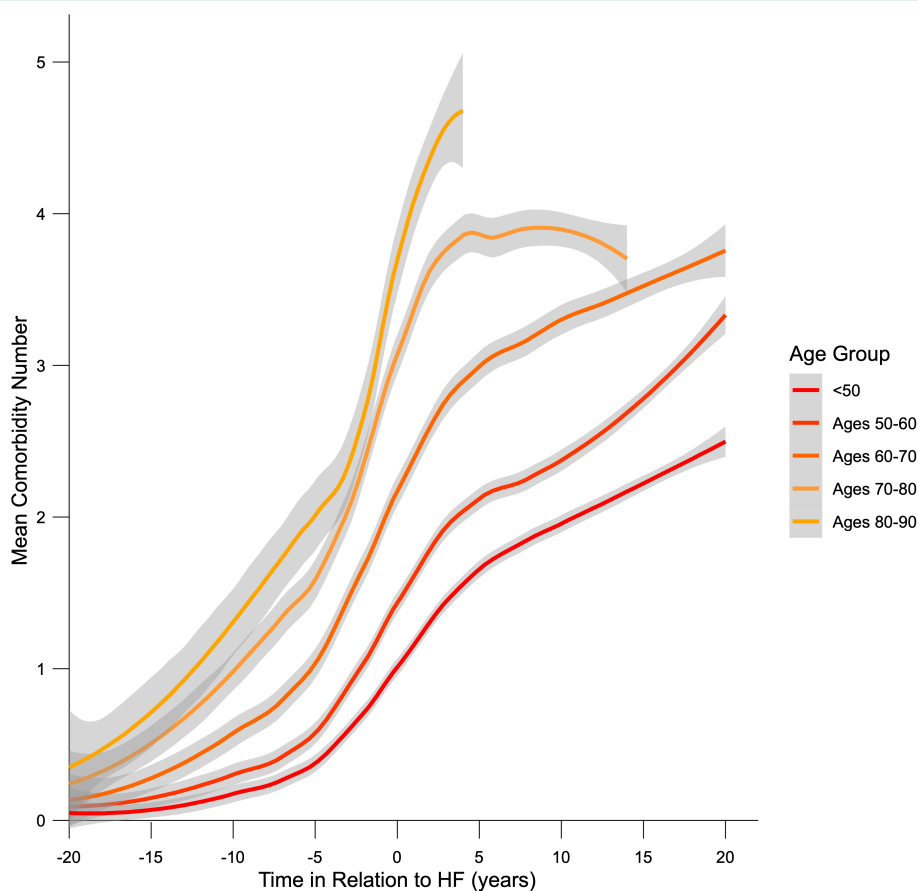
Figure 2 Chronology of comorbidity accrual. For strata at age of heart failure (HF) diagnosis, the mean (and 95% confidence interval of the mean in grey shading) number of non-HF comorbidities are plotted against time relative to HF diagnosis (i.e. negative time denoting prior to HF).

HF in men. Depression, obesity, thyroid disease and asthma also predated HF by at least 2 years more in women than men. We also generated Ridgeline plots (online supplementary *Figure S2*) and summary data (online supplementary *Table S4*) to address how age at HF diagnosis is associated with the timing of specific comorbidity diagnoses in relation to HF diagnosis. As expected from earlier analyses (*Figure 1C*), in people developing HF before 50 years of age, the majority of cases of each comorbidity developed years after HF (ranging from median of 0 years for myocardial infarction to 13.2 years for dementia). Conversely, in people developing HF aged 80–90 years, the majority of cases of each comorbidity developed years before HF (ranging from median of −11.7 for osteoarthritis to −0.1 years for dementia). Intermediate strata exhibited a spectrum of timings in between these extremes. These data emphasize that sex and age at HF diagnosis are associated with distinct kinetics in the timing of comorbidity development in relation to HF diagnosis.

Finally, we generated a Sankey plot to illustrate the diagnoses occurring immediately before and after HF (*Figure 4*), since the former represent times of opportunity to prevent future HF and the latter opportunities to mitigate comorbidity progression in established HF. Notably, this plot does not illustrate diagnoses coded simultaneously with HF, since these are unlikely to represent new opportunities to prevent disease. However, summary data for this plot in *Table 3* also include synchronous diseases and, as expected, these most often include myocardial infarction (7.3% of HF cases) and atrial fibrillation/flutter (10.9% of HF cases). Atrial fibrillation/flutter is also the most common diagnosis prior to HF (12.9%), with cancer (8.4%), hypertension (7.8%), myocardial infarction (7.0%) and osteoarthritis (7.0%) forming the top five prior diagnoses. Regarding diagnoses after HF, these were more evenly distributed, with atrial fibrillation/flutter (6.8%), anaemia (6.3%), chronic renal failure (6.3%), hypertension (4.9%) and cancer (4.4%) forming the five commonest diagnoses immediately after HF. These data illustrate both well-established and under-appreciated opportunities for disease prevention, especially before HF.

Discussion

Our findings have a number of novel and potentially important implications for the prevention and treatment of HF and its
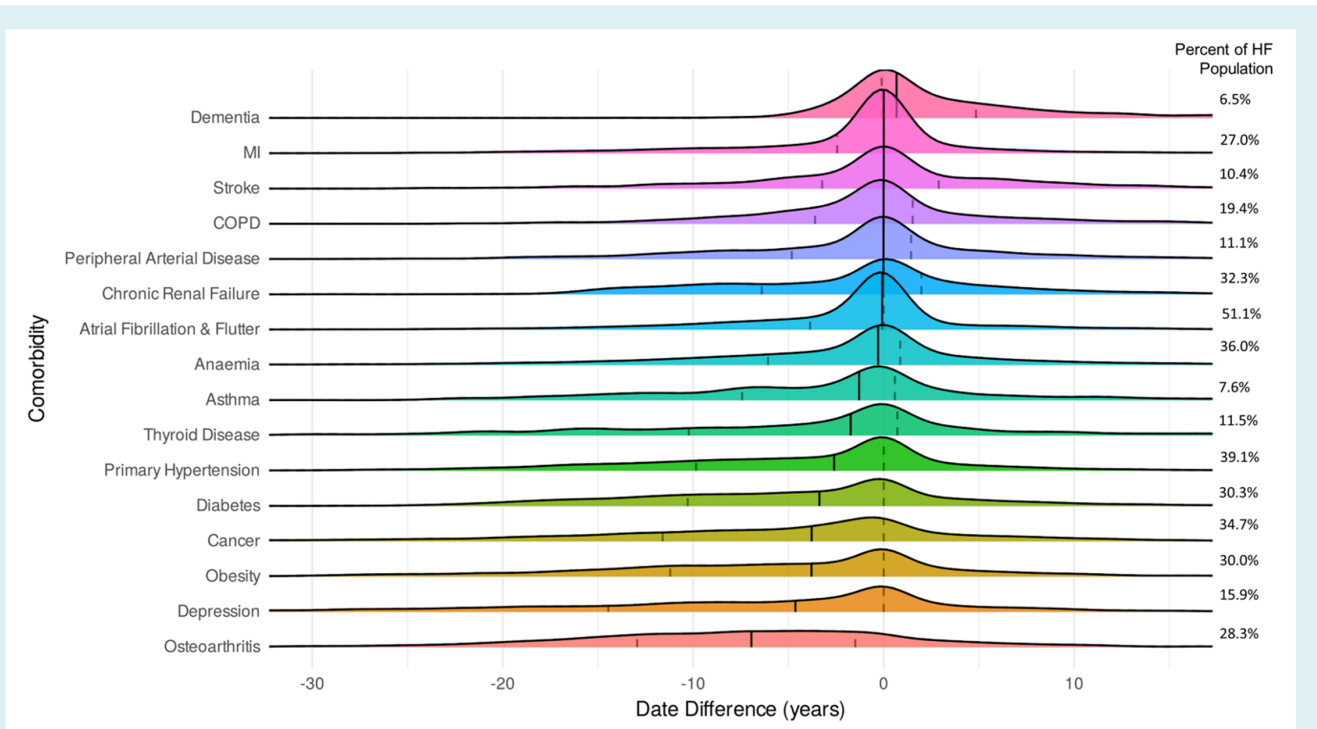
Figure 3 Chronology of comorbidity diagnoses in relation to heart failure (HF) diagnosis. Ridgeline plot illustrating the chronological distribution of comorbidity diagnoses in relation to HF diagnosis. The amplitude of Ridgelines does not relate to comorbidity prevalence, the data for which are noted to the right of the plot for reference. COPD, chronic obstructive pulmonary disease; MI, myocardial infarction.

Table 2 Timing of comorbidity diagnoses in relation to heart failure diagnosis

Comorbidity	Time in relation to HF (years)
Osteoarthritis	−6.9 (−12.9 to −1.5)
Depression	−4.6 (−14.4 to 0.0)
Obesity	−3.8 (− 11.2 to 0.0)
Cancer	−3.8 (−11.6 to 0.0)
Diabetes	−3.4 (−10.3 to 0.0)
Primary hypertension	−2.6 (−9.8 to 0.0)
Thyroid disease	−1.7 (−10.2 to 0.7)
Asthma	−1.3 (−7.4 to 0.6)
Anaemia	−0.3 (−6.1 to 0.9)
Atrial fibrillation/flutter	−0.1 (−3.9 to 0.0)
Chronic renal failure	0.0 (−6.4 to 2.0)
Peripheral arterial disease	0.0 (−4.8 to 1.4)
COPD	0.0 (−3.6 to 1.5)
Myocardial infarction	0.0 (−2.4 to 0.0)
Stroke	0.0 (−3.2 to 2.9)
Dementia	0.7 (−0.1 to 4.8)

Data presented as median (first quartile to third quartile) and are also illustrated in *Figure 3*. Negative numbers denote comorbidity diagnoses predating HF, for example with −6.9 (−12.9 to −1.5) for osteoarthritis denoting 50% of cases predating HF by 6.9 years, 25% of cases predating HF by 12.9 years, and 75% of cases predating HF by 1.5 years.
COPD, chronic obstructive pulmonary disease; HF, heart failure.

comorbidities. First, HF tends to be diagnosed after a sustained period of disease accrual, often spanning over a decade, with an accelerated phase closer to the diagnosis of HF. This suggests that there is a protracted opportunity to address modifiable risk factors for HF in people entering the early phase of MLTC. Indeed, we show that hypertension, obesity and diabetes are common antecedents of HF, and it is well established that optimization of these can reduce incident HF. However, cancer and osteoarthritis were also common precursors of HF, raising the question of whether traditional cardiovascular risk modification could benefit future health in these circumstances. Moreover, understanding why diseases like cancer and osteoarthritis commonly precede HF could lead to additional approaches to reduce incident HF. Our data also highlight opportunities to prevent comorbidity accrual after the diagnosis of HF; in particular, most cases of dementia develop after HF, yet this is not currently considered in the approach to HF care.[15]

The wider disease context of HF is increasingly important, as evidenced by the large and growing contribution of non-cardiovascular events to hospitalization and mortality in people with HF.[7,16,17] Moreover, evidence-based care of HF is harder to achieve and sustain in people with wider health problems.[10,18] The work of Conrad et al.[8] has previously shown a significant burden of MLTC in people with HF, rising from three to five non-HF comorbidities per person between 2002 and 2014. Their work in a large nationally representative sample of the UK population broadly agrees with our finding that MLTC
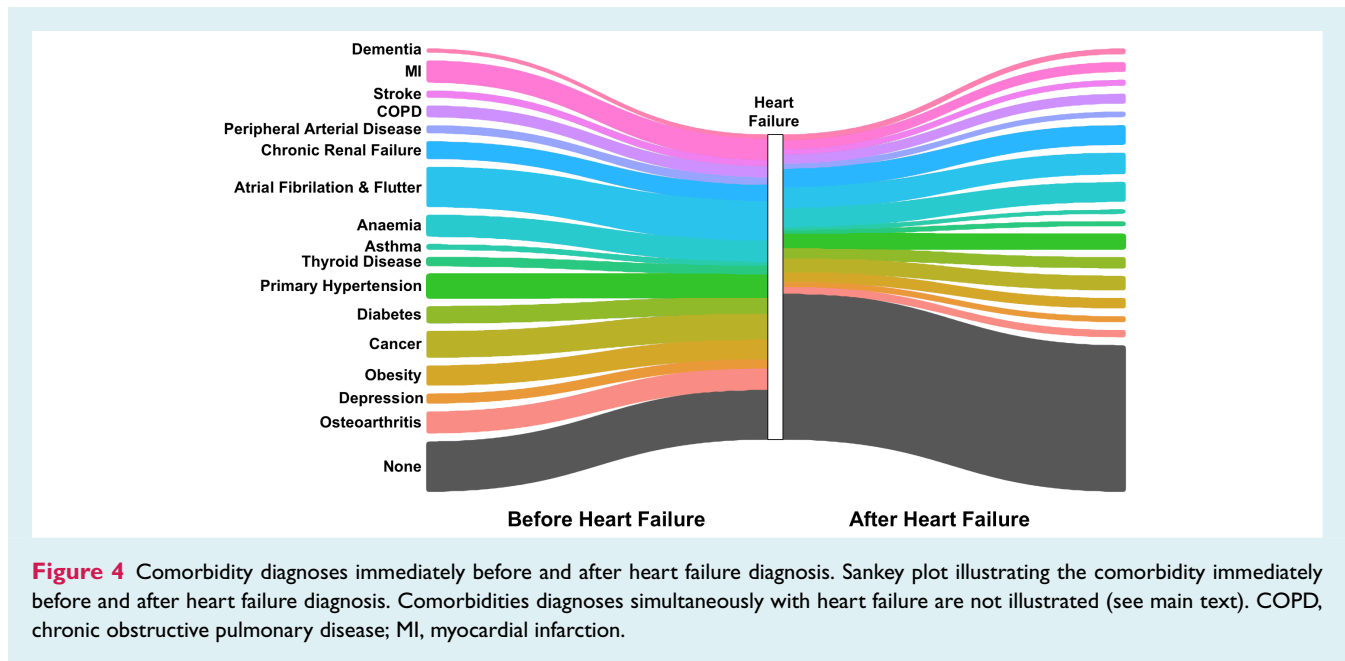
Figure 4 Comorbidity diagnoses immediately before and after heart failure diagnosis. Sankey plot illustrating the comorbidity immediately before and after heart failure diagnosis. Comorbidities diagnoses simultaneously with heart failure are not illustrated (see main text). COPD, chronic obstructive pulmonary disease; MI, myocardial infarction.

Table 3 Comorbidities diagnosed immediately before, after or synchronous with heart failure diagnosis

Comorbidity	Immediately before HF	Synchronous with HF	Immediately after HF
Dementia	105 (1.1)	70 (0.7)	156 (1.6)
Myocardial infarction	690 (7.0)	714 (7.3)	298 (3.0)
Stroke	204 (2.1)	102 (1.0)	168 (1.7)
COPD	358 (3.6)	263 (2.7)	299 (3.0)
Peripheral arterial disease	240 (2.4)	121 (1.2)	159 (1.6)
Chronic renal failure	549 (5.6)	265 (2.7)	617 (6.3)
Atrial fibrillation/flutter	1268 (12.9)	1069 (10.9)	664 (6.8)
Anaemia	683 (7.0)	299 (3.0)	620 (6.3)
Asthma	129 (1.3)	65 (0.7)	90 (0.9)
Thyroid disease	262 (2.7)	85 (0.9)	120 (1.2)
Primary hypertension	762 (7.8)	408 (4.2)	482 (4.9)
Diabetes	528 (5.4)	243 (2.5)	324 (3.3)
Cancer	824 (8.4)	<50 (0.4)	435 (4.4)
Obesity	631 (6.4)	242 (2.5)	308 (3.1)
Depression	297 (3.0)	80 (0.8)	169 (1.7)
Osteoarthritis	688 (7.0)	<50 (0.5)	206 (2.1)
None	1606 (16.3)	6698 (68.2)	4714 (48.0)

Data presented as *n* (%). Where fewer than 50 cases are noted in a condition, the precise number of participants is not provided to reduce the risk of deanonymization.
COPD, chronic obstructive pulmonary disease; HF, heart failure.

is established at the point of HF diagnosis. However, in spite of considering the same comorbidities, our data suggest a slightly lower comorbidity burden at HF diagnosis, probably resulting from our cohort being 7 years younger, along with UK Biobank participants being healthier than the UK population.[19]

Our data provide a lifecourse context to what has been shown at the moment of HF diagnosis, thereby identifying potential windows of opportunity for prevention of HF and its comorbidities. At a population level, it is striking that long-term conditions accrued for approximately two decades in advance of HF, irrespective

of the age at which HF developed, with the rate of accrual being much faster in older groups. There was also a notable phase of accelerated disease accrual around the time of HF, with peaks of many comorbidities at this time. It is important to acknowledge that some of these diagnoses may simply reflect the greater medical attention at the point of HF diagnosis, although others are likely to genuine reflect newly developing pathology. We cannot discern the relative contributions of these, and it is important to note that disease diagnoses are often delayed from disease onset. Whilst some individuals developed HF as their first or second major health problem, especially in younger people, the clear majority had a protracted period of MLTC, including many non-cardiovascular diseases, prior to the diagnosis of HF. This suggests that interventions to reduce HF risk could be targeted over an extended period of life, often in disease settings (such as osteoarthritis) where current practice would not consider this, or even as part of novel services designed to improve outcomes for people with MLTC. Collectively, our data emphasize the need for all clinicians to think beyond secondary prevention of index diseases, and more broadly consider the future disease trajectory of individuals/populations to more effectively use these preventative opportunities.

Whilst simple interventions like optimization of blood pressure are likely to be useful in many HF prevention settings, addressing the reasons why multiple diseases cluster together may have a larger therapeutic overall impact. One example of this is emerging data on 'innate immune training' induced by one disease leading to an inflammatory state that promotes accumulation of other diseases. Indeed, pre-clinical models show that stroke promotes HF, and that HF promotes kidney disease.[20,21] Further support comes from *post-hoc* analyses of the CANTOS trial, showing that interleukin-1β inhibition reduced incident anaemia, gout, osteoarthritis, lung cancer and HF in addition to its primary endpoint of atherosclerotic cardiovascular events.[22–27] Much

greater understanding is still needed from mechanistic, epidemiological and applied health research, but considering diseases in clusters has significant potential to improve the efficacy of treatment and mitigate its burden.

Our data also suggest important associations of age and sex with the nature and rate of MLTC accrual. These may help to better understand the associations between HF and specific comorbidities, along with being important considerations for optimal disease prevention approaches in these populations. One interesting example is the substantially longer period by which cancer pre-dated HF in women. This could be in keeping with some data suggesting pre-menopausal women experience lower rates of anthracycline chemotherapy cardiotoxicity.[28] It is also possible that the cancer women experience less cardiotoxic therapy regimens, by virtue of differing type or stage, but our data do not allow us to explore this. However, many other comorbidities were diagnosed earlier in relation to HF in women, so some of the sex differences for cancer timing in relation to HF may be part of a more generalized phenomenon. Much more work is needed to understand this interesting observation and elucidate clinically relevant messages. Regarding our data stratified by the age of HF diagnosis, these suggest that HF prevention should be a priority in people with accumulating MLTC (especially older women), whereas in younger people developing HF early in their disease trajectory need clinicians to focus on wider MLTC prevention. These distinct approaches have the shared goal of reducing disease complexity by focusing on the differing disease trajectories each group faces in later life.

Two of the precursors to HF that we identified warrant further discussion. Cancer and osteoarthritis are non-cardiovascular disorders already known to be associated with a higher risk of incident HF, with particularly good evidence for the former.[29,30] Indeed, there are established clinical guidelines advocating traditional cardiovascular prevention approaches for people receiving the most cardiotoxic cancer therapy,[31] although adherence to such approaches is low and declines after cancer therapy.[32] This is important given the high confidence that many cancer therapies have cardiovascular sequelae that can be monitored and mitigated. Consideration or modification of future HF risk is not currently included in guidelines on osteoarthritis care, possibly reflecting a lack of mechanistic understanding. It must be emphasized that our analyses cannot determine causal relationships between cancer or osteoarthritis and HF, and that other long-term conditions we did not study may also contribute to HF. However, even if the relationships we noted are not causal, they are still of value in defining periods of HF risk during the lifecourse of many people. As noted earlier, this complexity of considering multiple single diseases in parallel, rather than as related disease clusters, may underpin these missed opportunities. Changing this approach will require understanding of how these diseases interact with HF, robust clinical evidence that interventions can target multiple diseases, and involvement of patients to develop approaches that are acceptable and minimize treatment burden.

Although our analysis has led to potentially important findings, we must also address its limitations. First, and as alluded to earlier, UK Biobank is not representative of the general UK population, especially in terms of age, ethnicity and socioeconomic deprivation,

and exhibits a 'healthy cohort' effect.[19] This means that we may have underestimated the prevalence of MLTC in people with HF, and that our findings may not reliably generalize to the wider UK population or beyond. Whilst valuable methods are emerging to recalibrate data from UK Biobank to the wider UK population,[33] unfortunately these are not yet applicable to the temporal data we have analysed. Second, whilst we have lifecourse data in all participants prior to HF, we do not have systematic follow-up for the remainder of the lifecourse, due to participants reaching the censorship date. This biases our analysis of the distribution of incident diseases to the time before HF and also complicates analysis after HF given that the most multimorbid participants are more likely to die, both due to their accumulated disease and older age. Our sensitivity analysis goes some way to addressing this and suggests only a modest effect on our estimates of disease timing in relation to HF, but this should still be carefully considered when using our data. Third, MLTC research is hampered by a lack of consensus on which conditions to consider. Whilst recent attempts have been made to seek consensus,[34] we elected to replicate definitions used in the most robust available study in HF, also allowing us to contrast our data with that from a large UK primary care cohort. However, applying other combinations of long-term conditions, such as the larger and non-overlapping list from the recent consensus paper,[34] might lead to differing conclusions. Moreover, it is important to acknowledge the debate on what constitutes a long-term condition versus a risk factor for disease, which is pertinent to factors like obesity. Whilst we elected to include obesity as a common antecedent of HF also included by Conrad *et al.*,[8] the Delphi consensus of Ho *et al.*[34] ultimately excluded obesity from their MLTC definition, emphasizing an ongoing area of uncertainty in MLTC research. Fourth, misclassification of HF and other long-term conditions in routine care and its subsequent coding is a limitation of healthcare record-based research and may add noise to our dataset. This is especially important for our definition of osteoarthritis, which relied in part on primary care codes, meaning that our findings for this condition must be used more cautiously. It is also important to note that we assumed comorbid conditions were chronic in nature, but this is unlikely in every case given the possibility of remission (e.g. in anaemia or obesity). Unfortunately, UK Biobank data, and electronic health record data more broadly, do not encompass disease remission and so we could not encompass this in our analyses. Finally, we do not attempt to subclassify HF or its comorbidities, for example based on severity, and nor can we account for disease remission. These again reflect a challenge for the field of MLTC research that will require more advanced data handling and analytical approaches. This issue is most pertinent to the classification of HF into that with preserved or reduced left ventricular ejection fraction. Approximately half of HF is associated with preserved ejection fraction, which is associated with older age, female sex and a greater burden of comorbidities.[35] Although this would have been an important factor to include in our stratified analyses, most (>85%) UK Biobank primary care records do not currently include ejection fraction coding for people with HF, and these appear to under-represent HF with preserved ejection fraction.[36] Moreover, the cardiac imaging data in UK Biobank are

generally not performed at the time of HF diagnosis and so are not informative. Hence, we could not perform these important analyses.

Conclusions

Heart failure is typically diagnosed after a sustained period of disease accrual, often spanning more than a decade, with an accelerated phase closer to the diagnosis of HF. This represents an important window of opportunity for measures to prevent HF, including in the context of diseases, such as cancer and osteoarthritis, where future HF risk is not systematically addressed. Beyond traditional HF prevention approaches, further research is needed to understand the shared basis of these diseases, which may allow the development of interventions addressing multiple conditions.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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