Prevalence and mortality of chronic extracellular matrix dysregulated diseases: a nationwide register-based study

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Summary

Background Extracellular matrix (ECM) dysregulation, manifesting as fibrosis or tissue destruction, is a hallmark of many chronic diseases, leading to organ dysfunction and mortality. However, ECM-related diseases are rarely considered as a unified group, and their burden remains poorly defined. We aimed to quantify the burden of ECM-related diseases by estimating prevalence and mortality.

Methods We conducted a register-based study using Danish health registers. Chronic diseases were classified as ECM-related, either fibrotic or tissue destruction diseases, based on ICD-10 codes by field experts. Prevalence was estimated using the Danish National Patient Register, and mortality using the Danish Register of Causes of Death. Analyses were stratified by sex, and key analyses were replicated using the UK Biobank cohort (Application ID 31823).

Findings Among 1701 ICD-10 level-two disease codes, we identified 194 fibrotic diseases and 137 tissue destruction diseases, totalling 331 ECM-related diseases. 19% (1120068/5945094) of the population had a fibrotic disease, 30% (1772148/5945094) a tissue destruction disease, and 38% (2250048/5945094) an ECM-related disease, with higher prevalence among women. Mortality rates recorded as underlying causes were 381, 159 and 540 per 100,000 individuals for fibrotic, tissue destruction, and combined ECM-related diseases, accounting for 40% (22715/56795), 17% (9513/56795) and 57% (32228/56795) of deaths. Mortality was higher when ECM-related diseases were recorded as contributing causes of death. Mortality was higher among men.

Interpretation ECM-related diseases impose a substantial burden through high prevalence and mortality. Recognition of ECM dysregulation as a disease mechanism may inform therapeutic strategies and public health planning.

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Keywords: Extracellular matrix; Fibrosis; Tissue degradation; Disease burden; Prevalence; Mortality

Research in context

Evidence before this study

We searched PubMed and Google Scholar for studies published up to Jan 22, 2026, using combinations of the terms "extracellular matrix", "ECM", "fibrosis", "fibrotic diseases", "tissue destruction", "disease burden", "prevalence", and "mortality".

ECM remodelling is increasingly recognised as a shared mechanism across chronic diseases; however, ECM-related diseases are rarely assessed as a unified disease group. Few studies have systematically classified ECM-related diseases across organ systems. Even fewer have quantified their combined population-level burden in terms of prevalence and mortality rates. Previous estimates have suggested fibrosis contributes to up to 50 chronic diseases and may be linked to more than 35% of deaths in Western populations. However, comparable estimates that capture tissue destruction conditions are limited.

Added value of this study

We systematically classified ICD-10 level two diagnoses according to fibrotic or tissue destruction pathophysiology and quantified their population burden. We identified 194 fibrotic and 137 tissue destruction conditions, comprising 331 ECM-related diagnoses in total. In 2023, 19% of the Danish population had a fibrotic disease, 30% had a tissue destruction disease, and 38% had an ECM-related disease overall. In 2024, the mortality rates were 381, 159 and 540 per 100,000 individuals for fibrotic, tissue destruction, and combined ECM-related diseases (in total 40%, 17%, and 57% of all deaths).

By integrating diseases traditionally studied in isolation, this study provides a novel framework for quantifying the shared burden of ECM dysregulation at the population level.

Implications of all the available evidence

ECM-related diseases are common and are associated with substantial mortality. Treating ECM dysregulation as a shared disease framework could improve burden estimation and strengthen the rationale for research into therapies targeting common cellular effectors and ECM pathways, as well as inform disease surveillance, prevention strategies, and health policy prioritization.

Introduction

The extracellular matrix (ECM) is a dynamic and multifunctional component of all tissues. It provides structural support while actively modulating cellular behaviour and maintaining tissue homeostasis. Continuous and tightly regulated ECM remodelling is essential for maintaining tissue integrity, architecture, and function across all organs, and plays important roles in physiological and pathological processes including infection, inflammation, tissue repair, and regeneration.[1–3] When this balance is persistently disrupted, often in association with chronic inflammatory processes, ECM remodelling becomes dysregulated. It shifts towards either excessive matrix deposition (fibrosis) or excessive matrix degradation with tissue loss (tissue destruction).[2–7] Together, these processes define a broad group of chronic ECM-related diseases characterized by persistent dysregulation of ECM homeostasis and chronic ECM remodelling that contribute substantially to chronic morbidity and mortality.

Fibrotic diseases include idiopathic pulmonary fibrosis, chronic kidney disease, cardiovascular disease, systemic sclerosis, and liver cirrhosis, and are also implicated in most solid tumours.[4,6–11] Tissue destruction diseases include osteoarthritis, osteoporosis, rheumatoid arthritis, inflammatory bowel diseases, and atopic dermatitis.[12,13] Many of these conditions exhibit features of both fibrosis and tissue destruction. However, ECM-related diseases can be classified according to whether chronic ECM remodelling predominantly results in tissue gain (fibrosis) or tissue loss (tissue destruction) over time. This reflects the net direction of chronic ECM remodelling rather than transient or stage-specific variation. Despite typically being considered separately, these diseases share persistent dysregulation of ECM homeostasis as a common biological basis.[4]

Classifying ECM-related diseases as an overarching group may help link conditions with shared molecular processes currently studied in isolation. This may support the translation of therapies targeting the shared common ECM pathways. However, few studies have systematically defined shared ECM-related diseases across organ systems, and even fewer have quantified their combined population-level burdens.[14] Consequently, the prevalence and mortality attributable to ECM dysregulation are likely underestimated, limiting the recognition of ECM-related pathology as a major public health challenge.

The Danish health registries provide a unique opportunity to address these gaps through complete population coverage and long-term follow-up. In this study, we aimed to quantify the burden of ECM-related

chronic diseases by classifying ICD-10 level-two diagnoses according to ECM-related pathophysiology. Using Danish health registries, we estimated sex-specific prevalence and mortality rates for fibrotic diseases, tissue destruction diseases, and overall ECM-related diseases, and assessed mortality trends over a 25-year period. Danish registry data have been shown to be broadly representative of other Western populations, supporting the generalisability of findings beyond Denmark.[15,16] Key findings were externally replicated in the UK Biobank cohort.[17]

Methods

Study design and data sources

This register-based study included all individuals in Denmark with a civil registration number in the central person registry (CPR) from 1 January 1994 to 31 December 2023. Data were obtained from the Danish National Patient Register (NPR) and the Danish Cause of Death Register, which contain information on all hospital contacts and causes of death coded according to the Danish version of the International Classification of Diseases, 10th Revision (ICD-10). ICD-10 was introduced in Denmark on 1 January 1994.[15,16] The Danish health registries provide nationwide population coverage and complete longitudinal follow-up through the unique personal identification number assigned to all Danish residents. The registries are widely used for epidemiological research and have been extensively evaluated with generally high completeness and validity of recorded diagnoses and causes of death.[15,16] Data were available up to 2023 from the NPR and up to 2024 from the Cause of Death Register, with prevalence analyses covering 2013–2023 and mortality analyses including deaths from 1994 to 2024.

Study population

The study population was identified through the Danish Civil Registration System and included all individuals in Denmark with an active personal identification number between 1 January 1994 and 31 December 2024. At the end of 2024, 5945094 individuals were alive and residing in Denmark. Over the study period, a total of 8504378 unique individuals were included, comprising all individuals with an active CPR number who resided in Denmark at any point during the study period, including those who subsequently died or emigrated. Outcome data were obtained by linking the NPR and the Cause of Death Register with a separate dataset containing ICD-10 codes classified as fibrotic diseases, tissue destruction diseases, or non-ECM diseases. No exclusions were applied prior to data extraction, which means that the entire Danish population formed the basis of the analysis.

Disease definitions

This study classifies chronic diseases based on predefined operational definitions of chronic ECM remodelling phenotypes. The classification was designed to identify chronic diseases in which persistent dysregulation of ECM homeostasis, reflected by either fibrosis or tissue destruction, represents a defining feature of disease pathology.

Fibrotic diseases

Chronic disorders, in which chronic ECM dysregulation in the form of fibrosis has been described as a pathological feature or component of the disease. These conditions are characterised by excessive ECM formation relative to degradation, resulting in tissue remodelling, structural disruption, and impaired organ function.

Tissue destruction diseases

Chronic disorders, in which chronic ECM dysregulation in the form of excessive matrix degradation has been described as a pathological feature or component of the disease. These conditions are characterised by excessive ECM degradation relative to formation, resulting in tissue loss, structural disruption, and impaired organ function, with replacement of normal ECM by fibrillar collagen-rich matrix.

ECM-related diseases

Chronic disorders characterised by chronic ECM dysregulation and include both fibrotic diseases and tissue destruction diseases. This classification therefore captures conditions characterised either by excessive ECM formation or excessive ECM degradation as part of their pathology.

Non-ECM diseases

Disorders not characterized by chronic persistent dysregulation of ECM homeostasis according to the operational criteria applied in this study.

The operational definitions are provided in Appendix S1.

Disease classification

The classification focused exclusively on chronic diseases, reflecting the long-term nature of ECM dysregulation. All the Danish ICD-10 level two disease codes (in total: 1701) were reviewed and coded into one of four mutually exclusive categories: fibrotic diseases, tissue destruction diseases, non-ECM diseases, or unknown. Classification was based on the operational definitions (Appendix S1), literature evidence, disease biology, and clinical relevance. A panel of domain experts classified the ICD-10 codes. For each ICD-10 chapter, codes were independently assessed by two experts with relevant clinical expertise in that disease area

in a double-blinded, Delphi-inspired consensus process; a detailed description of the procedure is provided in Appendix S2. Where classification uncertainty arose, coders were required to consult at least three peer-reviewed publications describing the disease pathophysiology and its relationship to ECM remodelling. In cases of disagreement, a third expert adjudicated the final classification. Each ICD-10 code was assigned to one mutually exclusive category to prevent double counting.

Data integration and variable construction

Individual-level data from the NPR and Cause of Death Register were linked using pseudonymised identification numbers in the registries. The ECM classification dataset was linked to the registry data using ICD-10 diagnosis codes. Only primary and secondary diagnoses were included. For mortality analyses, the causes of death were categorised as underlying or contributing. A contributing cause indicator was defined as the presence of an ECM-related disease anywhere on the death certificate, regardless of whether it was recorded as the underlying cause of death or as an additional contributing cause. Fibrotic and tissue destruction diseases were analysed separately and combined into an overall ECM-related disease category.

Statistical analyses

Annual prevalence was estimated using a person-year dataset derived from the Danish Civil Registration System. Individuals were considered part of the population for a given year if they were alive and residing in Denmark on 31 December. Individuals were considered prevalent from their first recorded diagnosis onwards. For overall ECM-related disease, individuals were counted once, with onset defined by the earliest qualifying diagnosis. For the combined ECM disease category, individuals were counted once regardless of whether they met the criteria for fibrotic, tissue destruction, or both disease categories. ECM disease onset was defined as the earliest diagnosis across domains. Although prevalence was calculated for 1994–2023, only estimates from 2013 onwards are reported to encapsulate a 20-year look-back period and minimize potential bias due to left truncation. Prevalence estimates were calculated for the total population and stratified by sex. Age-specific prevalence was additionally calculated for 2023 and stratified by sex.

Mortality analyses covered the period 1994–2024. Annual mortality rates (MR) were calculated as deaths per 100,000 person-years, using the average population size between 1 January and 31 December as the denominator. MRs were computed separately for men and women and combined overall. Analyses were conducted for fibrotic, tissue destruction, and overall ECM-related diseases, considering both underlying and contributing causes of death. Temporal trends in mortality were evaluated using Poisson regression with calendar year entered as a continuous variable. Separate models were fitted for each disease group and for underlying and contributing causes. Sex-specific differences in temporal patterns were assessed through interaction terms between sex and calendar year. Temporal trends are presented as mortality rate ratios (MRR) per calendar year with corresponding 95% confidence intervals. Age-specific mortality rates were additionally calculated throughout the study period and stratified by sex.

For age-specific analyses, individuals younger than 40 years were combined into a single age category to comply with Danish registry data confidentiality requirements. For age-specific mortality analyses, calendar years were additionally aggregated into 2-year periods (with 2022–2024 presented as a 3-year period) to ensure robust estimates in small age- and sex-specific strata.

Prevalence and mortality estimates were derived from nationwide registry data covering the entire Danish population during the study period and thus represent population measures rather than sample-based estimates. Consequently, they are reported without accompanying standard errors or confidence intervals.

All statistical analyses were performed using R version 4.3.32024-02-29 and RStudio version 2023.12.1-402.

Validation in UK Biobank

To externally validate our findings, we replicated selected analyses in the UK Biobank cohort (Application ID 31823), a large prospective cohort of approximately 500,000 participants,[17] As a selected cohort rather than a complete population registry, UK Biobank differs fundamentally from the Danish register-based data and is subject to selection bias. Therefore, it was not used to validate absolute prevalence estimates, which are derived from the entire Danish population.[17] Accordingly, UK Biobank was used exclusively for external validation of mortality estimates for 2024, which were compared with corresponding mortality rates derived from the Danish registry data.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, manuscript preparation, or the decision to submit the manuscript for publication.

Results

We classified 995 unique ICD10 codes into four major categories. The main groups were fibrotic diseases (n = 194) and tissue destruction diseases (n = 137), together constituting the total ECM-related disease

group (n = 331). The largest remaining group consisted of non-ECM diseases (n = 635). A smaller subset of codes (n = 29) could not be clearly categorised and were assigned as "unknown", as shown in Fig. 1a. The full classification list is provided in Appendix S3.

As shown in Fig. 1b, neoplasms were the largest proportion of fibrotic diseases (49%), whereas musculoskeletal diseases were the largest in tissue destruction diseases (33%).

Prevalence of ECM-related diseases

Since 2013, the prevalence of fibrotic, tissue destruction, and ECM-related diseases has remained relatively stable, with minor fluctuations.

In 2023, an estimated 19% of the Danish population lived with one or more fibrotic diseases (22.6% women, 15.1% men), 30% with one or more tissue destruction diseases (31.4% women, 28.3% men), and 38% with one or more ECM-related diseases (41.5% women, 34.2% men). Across all disease categories, the prevalence was consistently higher in women than in men. These patterns are shown in Fig. 2, while the prevalent ECM-disease distribution across ICD-10 chapters is presented in Appendix S5.

A pronounced age-related increase in prevalence was observed across all disease categories (Fig. 3). The prevalence of ECM-related diseases increased from 17.6% among individuals aged <40 years to 80.7% among those aged ≥85 years. Similarly, the prevalence of fibrotic diseases increased from 4.9% to 52.9%, and tissue destruction diseases increased from 14.4% to 67.7%. While women generally exhibited a higher prevalence across age groups, the female predominance in fibrotic diseases diminished with age, and prevalence became higher among men in the oldest age groups as shown in Fig. 3.

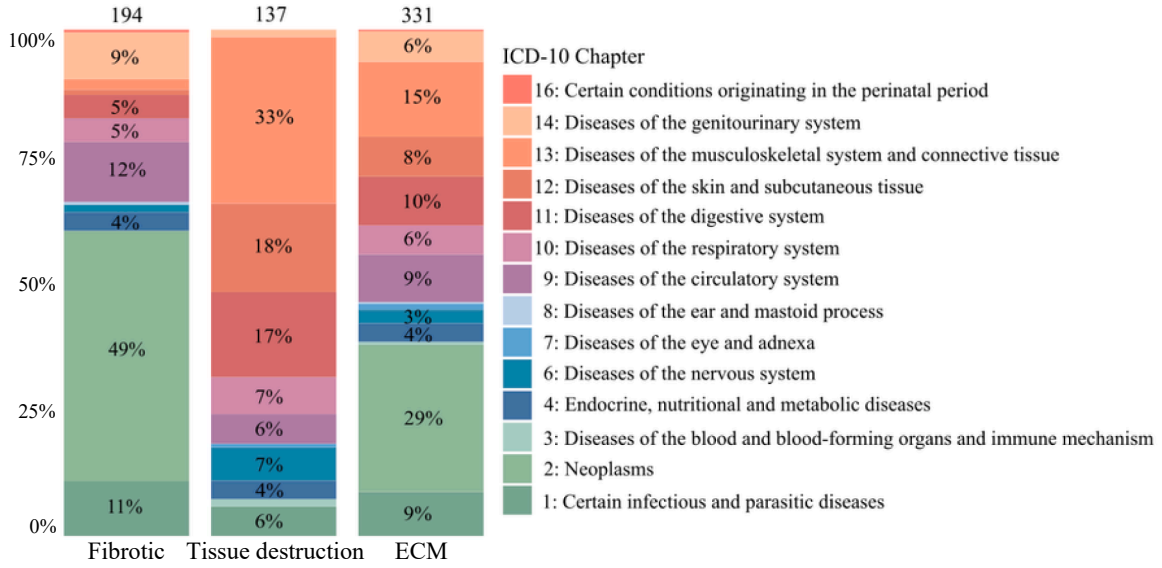
Mortality associated with ECM-related diseases

As depicted in Fig. 4, the crude mortality rates for diseases related to ECM in 2024 differed depending on the

1a Total number of diseases by ECM disease category. ECM-related diseases are classified as fibrotic diseases (characterised by excessive ECM formation) and tissue destruction diseases (characterised by excessive ECM degradation). Non-ECM and unknown diseases are shown in grey.

Disease category	Non-ECM	**Fibrotic**	**Tissue destruction**	Unknown	Total
Number of diseases	1341	**194**	**137**	29	1701

1b Proportion of diseases across disease categories by ICD 10 chapter- ECM diseases comprise fibrotic diseases and tissue destruction diseases within one unified group of diseases*.



**ICD-10 chapters representing less than 3% of the total are not labelled with percentages in the figure to improve readability. ICD-10 chapters not displayed in the figure or included in the legend contain no ECM-related diseases.*

Fig. 1: Distribution of extracellular matrix (ECM) related diseases.

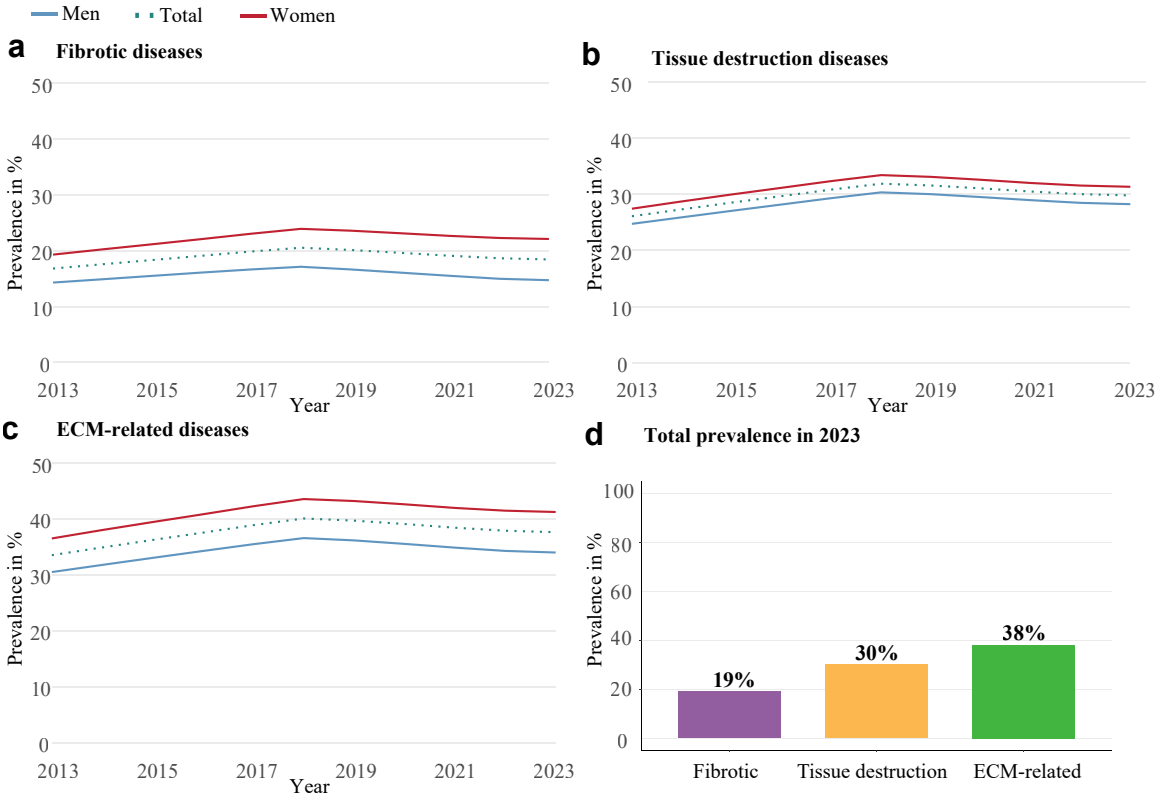


Fig. 2: Annual prevalence of fibrotic (a), tissue destruction (b), and extracellular matrix (ECM)-related diseases (c) in Denmark, 2013–2023, and total prevalence by disease group in 2023 (d).

disease category and whether the condition was identified as the underlying or a contributing cause of death.

Across all disease categories, mortality rates were higher when ECM-related diseases were recorded as contributing rather than underlying causes (Fig. 4a and b). For fibrotic diseases, the mortality rate was 381 per 100,000 as the underlying cause and 504 per 100,000 as a contributing cause. The corresponding rates for tissue destruction diseases were 159 and 250 per 100,000. Overall, ECM-related diseases accounted for 540 deaths per 100,000 as the underlying cause and 647 per 100,000 when contributing causes were included. The corresponding percentage distributions are presented in Appendix S6. The distribution of ICD-10 chapters among total deaths within each disease category in 2024 is presented in Appendix S6.

Similar patterns were observed in the UK Biobank cohort (Fig. 4a and b), with slightly higher mortality rates for fibrotic (Danish MR: 381 vs UK MR: 470 per 100,000) and overall ECM-related diseases (540 vs 623 per 100,000) compared with results from the Danish registry, while rates for tissue destruction diseases were broadly similar (159 vs 153 per 100,000) for the underlying causes. Similar patterns were observed for the contributing causes of death.

Trends in mortality associated with ECM-related diseases

Between 1994 and 2024, crude mortality rates for ECM-related disease groups declined substantially, with similar temporal patterns across fibrotic, tissue destruction, and overall ECM-related diseases. Rates gradually decreased from the mid-1990s to the early 2000s before stabilising. A marked discontinuity in 2006 coincided with Denmark's transition to electronic death certification, suggesting that part of the observed decline may reflect changes in reporting practices rather than changes in disease burden.[16]

Fibrotic diseases

Mortality due to fibrotic diseases declined between 1994 and 2024 (Fig. 5a and b). As the underlying cause of death, mortality rates fell from 498.6 deaths per 100,000 in 1994 to 381.1 deaths per 100,000 in 2024, with a gradual decline through the late 1990's and the early 2000s. When fibrotic diseases were recorded as contributing causes, mortality rates were higher, but followed a closely parallel pattern, decreasing from 663.6 deaths per 100,000 in 1994 to 504.7 deaths per 100,000 in 2024. The trends were similar for men and women, although men consistently exhibited slightly higher rates than women.

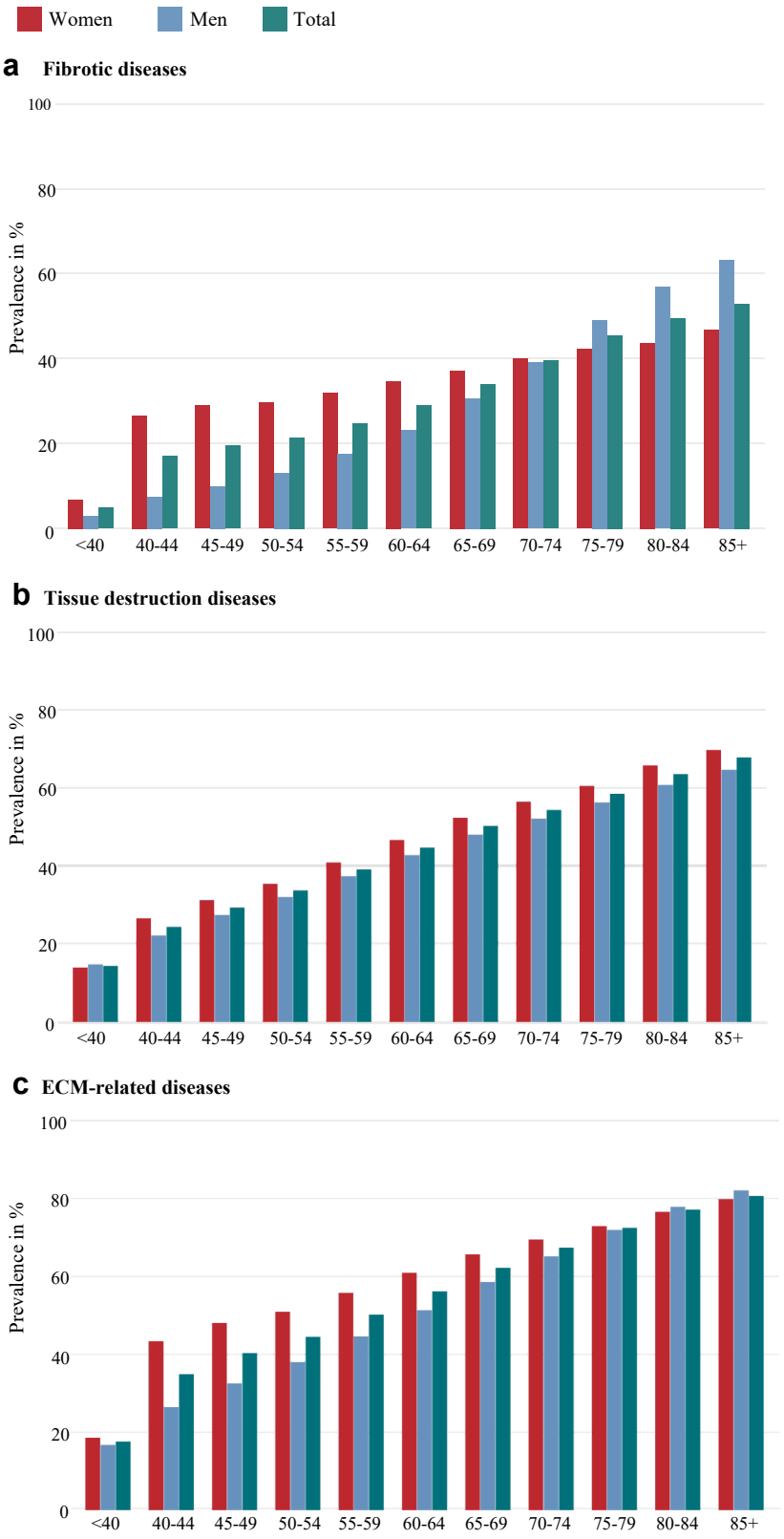


Fig. 3: Age- and sex-specific prevalence of fibrotic (a), tissue destruction (b), and extracellular matrix (ECM)-related diseases (c) in 2023. Individuals younger than 40 years were grouped into a single category to comply with Danish registry data confidentiality regulations.

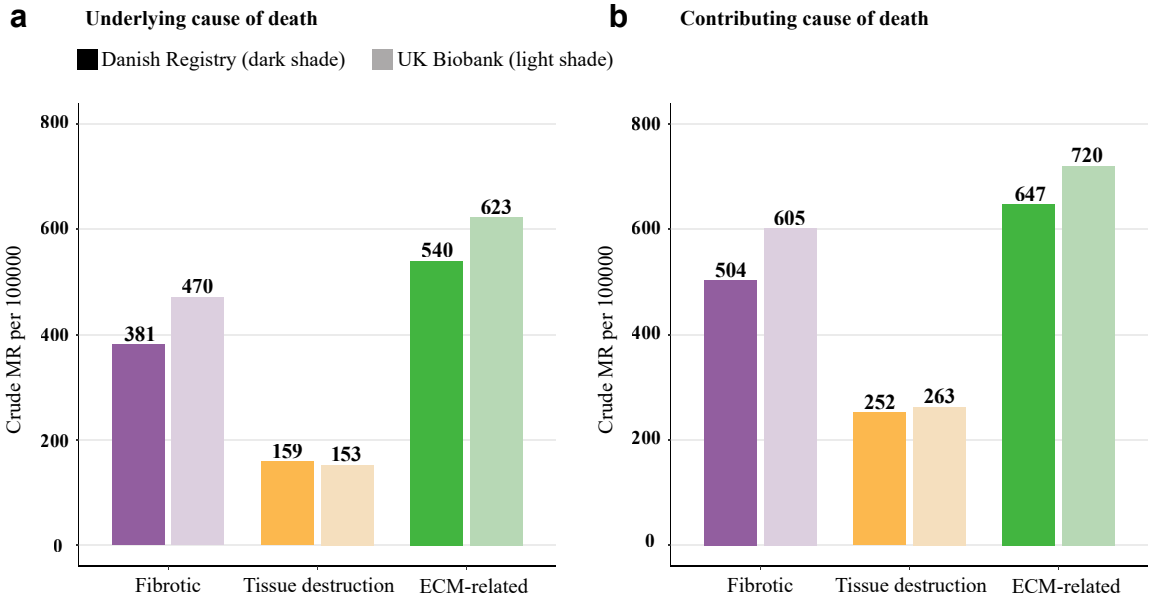


Fig. 4: Crude mortality rates for fibrotic, tissue destruction, and extracellular matrix (ECM)-related diseases by cause of death in Denmark in 2024, compared with mortality rates from the UK Biobank cohort 2019, showing (a) underlying cause of death and (b) contributing cause of death. Fibrotic diseases are shown in purple, tissue destruction diseases in blue, and ECM-related diseases in green. For each disease category, darker shades represent Danish Registry estimates and lighter shades represent UK Biobank estimates.

Poisson regression analyses confirmed a significant annual decline in mortality from fibrotic diseases for both underlying and contributing causes from 1994 to 2024 (Appendix S8). Mortality rate ratios indicated a stronger relative decline among women compared with men over time, as reflected by a significant sex-by-year interaction.

Tissue destruction diseases

Mortality from tissue destruction diseases declined between 1994 and 2024 (Fig. 5c and d). As the underlying cause of death, mortality rates decreased from 204.2 deaths per 100,000 in 1994 to 159.6 deaths per 100,000 in 2024. When recorded as contributing causes, mortality was higher but followed a similar pattern, decreasing from 323.4 deaths per 100,000 in 1994 to 252.3 deaths per 100,000 in 2024. The trends were nearly identical for both men and women.

Poisson regression analyses demonstrated significant long-term declines in mortality for tissue destruction diseases, with sex-specific differences in temporal trends that were smaller than those observed for fibrotic diseases (Appendix S8).

ECM-related diseases

Combining all ECM-related diseases, mortality declined between 1994 and 2024 (Fig. 5e and f). When ECM diseases were recorded as the underlying cause of death, mortality decreased from 702.9 deaths per 100,000 in 1994 to 540.6 deaths per 100,000 in 2024. Mortality was higher when ECM diseases were listed as contributing causes, declining from 853.5 deaths per 100,000 in 1994 to 647.5 deaths per 100,000 in 2024. Across both the underlying and contributing causes, the trends for men and women were closely aligned, with men consistently exhibiting slightly higher mortality but without substantial divergence over time.

Poisson regression analyses confirmed a significant annual reduction in ECM-related mortality and a modest but statistically significant sex-by-year interaction, indicating slightly faster relative declines among women (Appendix S8).

Age-specific mortality trends

Mortality increased markedly with age across all disease categories, with the highest mortality rates observed among individuals aged ≥70 years. Temporal declines were observed across most age-specific strata for both underlying and contributing causes of death (Appendix S9).

Discussion

ECM dysregulation, manifesting as fibrosis or tissue destruction, represents a fundamental process across a wide spectrum of chronic diseases. Despite this shared biological basis, ECM-related pathology is still rarely conceptualised as a unified disease group, contributing to an incomplete understanding of its population-level burden. This study addresses this gap by showing that

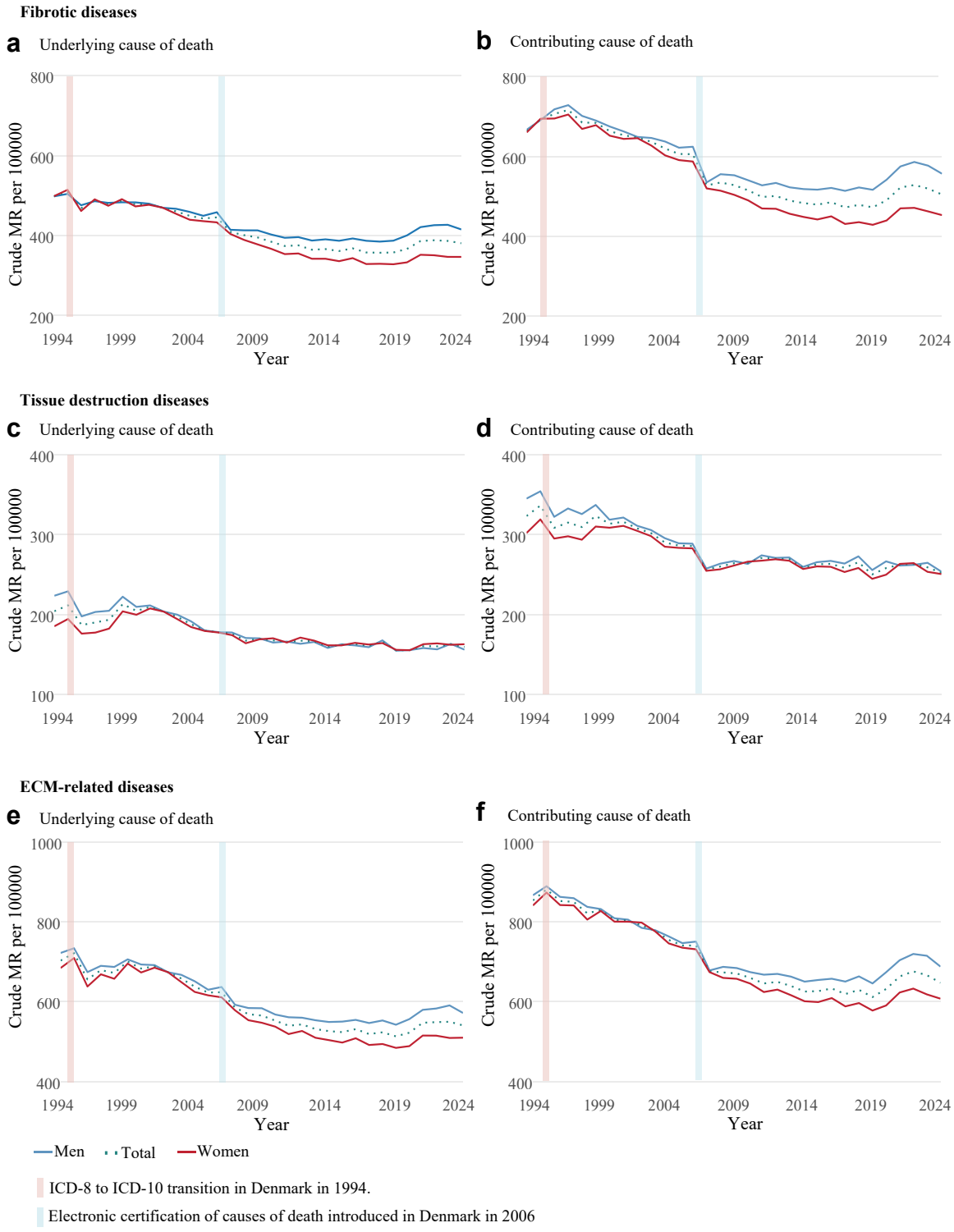


Fig. 5: Temporal trends in crude mortality rates (MR) for fibrotic (a, b), tissue destruction (c, d), and extracellular matrix (ECM)-related diseases (e, f) in Denmark, 1994–2024.

persistent dysregulation of ECM homeostasis can be understood as a shared biological basis underlying a broad range of diseases across different organ systems.

ECM-related diseases represent a substantially larger burden of disease than previously recognised,[14] encompassing 331 chronic diseases. 38% of the population live with at least one ECM-related disease, and ECM-related diseases contribute substantially to mortality, accounting for 647 deaths per 100,000 individuals in 2024 when contributing causes of death are considered, corresponding to 68% of all deaths (Appendix S6).

We identified 194 fibrotic diseases and 137 tissue destruction diseases, comprising 331 ECM-related conditions, far exceeding the approximately 50 fibrotic conditions reported in earlier studies.[14] This difference likely reflects the methodological choices. Previous studies primarily focused on diseases with well-established ECM remodelling, whereas we systematically assessed ICD-10 level-two codes and classified them through a Delphi-inspired expert consensus process with independent, blinded evaluation by disease-area experts. In addition, neoplasms were classified individually rather than aggregated, resulting in the identification of numerous cancer entities with fibrotic pathology. Conversely, diseases characterised primarily by matrix degradation rather than excessive matrix deposition, such as chronic obstructive pulmonary disease and rheumatoid arthritis were classified as tissue destruction diseases or non-ECM-related diseases, consistent with the applied pathophysiological definition.[5,12,13,18] Together, these methodological differences explain the broader disease spectrum identified and highlight the value of a granular, reproducible framework for studying ECM-related pathology across organ systems.

The mortality analyses showed important differences across disease groups. Neoplasms (ICD-10 chapter 2) were the primary driver of mortality among fibrotic diseases, accounting for 68.0% of fibrotic deaths when underlying causes of death were considered and 62.9% when contributing causes of death were included (Appendix S7). Respiratory diseases (ICD-10 chapter 10) and diseases of the nervous system (ICD-10 chapter 6) contributed most substantially to mortality within tissue destruction diseases (Appendix S7). Notably, mortality was substantially higher when ECM-related diseases were recorded as contributing causes of death, highlighting that ECM pathology frequently modifies disease trajectories rather than acting as the primary cause.[19] This highlights the importance of considering contributing causes when estimating disease burden.

The contrasting patterns observed across prevalence and mortality suggest that sex differences in disease progression and survival may play an important role.[19–21] This pattern is consistent with the well-described mortality-morbidity paradox, whereby women experience higher morbidity while men experience higher mortality across chronic diseases.[19,22] Potential explanations include hormonal differences, sex differences in healthcare utilisation, with women more likely to seek care and be diagnosed earlier, as well as higher levels of risk behaviours and later disease presentation among men.[20–23] A similar pattern is observed for ICD-10 Chapter 13 (musculoskeletal system and connective tissue diseases), which has the highest prevalence among ECM-related diseases (~17%, Appendix S5) and a higher prevalence in women (approximately 5 percentage points higher than men; Appendix S5). Despite this, the chapter accounts for <5% of ECM-related deaths, both as underlying and contributing causes (Appendix S7), indicating a clear dissociation between disease burden and mortality. This is exemplified by osteoporosis, which is highly prevalent, especially among women, but rarely a direct cause of death. These findings support the importance of considering sex-specific patterns in surveillance and prevention strategies.

The combination of high prevalence and declining mortality suggests that more individuals are living longer with ECM-related diseases This pattern likely reflects improved diagnosis and treatment but also indicates a persistent burden of chronic disease.[19,20,23] Potential contributors include advances in chronic disease management, implementation of national cancer screening programmes, and greater emphasis on early disease detection and treatment. Notably, the prevalence was higher for tissue destruction diseases than for fibrotic diseases, whereas mortality showed the opposite pattern. This divergence suggests that tissue destruction diseases more often represent chronic conditions lived with over extended periods, while fibrotic diseases are more strongly associated with fatal disease trajectories. These findings underscore that improvements in survival may coexist with substantial ongoing disease burden, with important implications for quality of life and healthcare utilisation. The future trajectory of fibrotic diseases may also be influenced by the introduction of novel disease-modifying therapies. For example, resmetirom and semaglutide have demonstrated promising effects on MASH resolution and fibrosis-related outcomes, potentially altering the natural history of an important subset of fibrotic diseases.[24,25] Improved treatment may delay disease progression and extend survival, thereby influencing future estimates of disease burden.

This interpretation is consistent with the presence of mixed ECM phenotypes across disease courses. Pancreatic cancer provides a representative example, exhibiting both ECM deposition and degradation during progression, while the long-term disease trajectory is dominated by stromal accumulation, resulting in a predominantly fibrotic outcome.[26]

The identification of 331 diseases characterized by ECM remodelling in this study highlights the broad

relevance of ECM-related pathology and suggests potential opportunities for therapeutic repositioning. This is particularly relevant given that several major domains of pharmaceutical research and development including oncology, immunology, metabolic diseases, central nervous system disorders, and cardiovascular conditions are also characterised by substantial ECM alterations. Shared ECM-related mechanisms across these therapeutic areas may offer opportunities for cross-indication drug development and drug repurposing strategies.

The major strength of this study lies in its nationwide coverage, long follow-up, and systematic classification of ECM-related diseases using transparent criteria and blinded expert review, as well as the external validation of findings in the UK Biobank cohort.

Nevertheless, several limitations merit consideration. First, ECM-related diseases were defined as chronic diseases characterized by persistent dysregulation of ECM homeostasis, reflected by either fibrosis or tissue destruction. This classification should not be interpreted as implying absence of ECM involvement in diseases categorized as non-ECM diseases, as ECM biology contributes to the function and pathology of virtually all tissues. Rather, the classification was intended to identify diseases in which persistent dysregulation of ECM homeostasis represents a defining feature of disease pathology. Furthermore, this does not imply that ECM dysregulation is a primary cause or driver of disease onset but rather reflects its recurrent involvement across chronic disease processes. Consequently, causal inference regarding ECM dysregulation cannot be made within this framework, as the classification is based on previously reported pathological and mechanistic descriptions rather than primary causal evidence. Second, manual classification of ICD-10 codes introduces potential information bias,[27] although this was mitigated through independent coding and adjudication. Third, NPR includes only hospital contacts, potentially underestimating prevalence for conditions commonly managed in primary care. For example, Jørgensen et al. (2016) have reported that approximately 80% of patients with type 2 diabetes in Denmark are treated in primary care settings.[28] Furthermore, prevalence estimates in this study were restricted to diagnoses recorded from 1995 onwards, which may have resulted in underestimation by missing earlier disease onset. To mitigate this limitation, we applied a 20-year retrospective observation window, increasing the likelihood that chronic cases were captured through subsequent hospital contacts. Fourth, misclassification in the Cause of Death Register, particularly for contributing causes and unspecified diagnoses, may bias mortality estimates, and changes in coding practices over time likely contributed to the observed discontinuity around 2006.[16,29] Finally, although UK Biobank provided independent validation, it is not fully representative of the general population. Findings therefore primarily reflect Northern European populations and healthcare systems and may not generalise to other settings.[17,30]

In conclusion, ECM-related diseases represent a substantial and widespread disease burden, with high prevalence and a major contribution to population mortality, particularly when contributing causes of death are considered. Although mortality has declined over the past 25 years, it remains substantial and, together with persistent prevalence and pronounced sex-specific patterns, highlights the need to recognise ECM pathology as a shared framework for therapeutic strategies, epidemiological research, and public health planning.

Contributors

RCC, CLB, SB and MAK conceptualised the study and developed the methodology. CLB, ACBJ, DJL, FG, KH, JHM, SHN, SL, MAK performed the classification of all diseases into ECM-related categories (fibrotic diseases, tissue destruction diseases, non-ECM diseases, and unknown conditions) according to the predefined classification framework. RCC and SB had access to and verified the underlying data. RCC performed the data curation and data visualisation, and CLB, SB and MAK interpreted the results. CLB, SB and MAK supervised the project. RCC, CLB, SB and MAK wrote the original manuscript. All authors (RCC, CLB, AH, ACBJ, DJL, DK, FG, FR, GS, JHM, KH, NW, PGC, RK, SLF, SHN, SL, SH, TMM, SB, MAK) critically reviewed and edited the manuscript for important intellectual content. All authors (RCC, CLB, AH, ACBJ, DJL, DK, FG, FR, GS, JHM, KH, NW, PGC, RK, SLF, SHN, SL, SH, TMM, SB, MAK) approved the final version of the manuscript.

Data sharing statement

Applications for data access can be submitted to the Danish Health Data Authority (forskerservice@sundhedsdata.dk). Researchers must meet the requirements outlined on the Authority's website: https://english.sundhedsdatastyrelsen.dk/health-data-and-registers/research-services. Data access requests are typically processed within 3–6 months.

Declaration of interests

CLB holds stocks in Nordic Bioscience A/S and is founder of ISECMP.

AH serves as a board member of the International Society of Extracellular Matrix Biology Pharmacology and as chairwoman of the Danish Society for Matrix Biology.

ACBJ serves as an unpaid executive board member of the FNIH Biomarker Consortium and is a shareholder in Nordic Bioscience A/S.

DJL holds stock options in Nordic Bioscience A/S.

DK reports consulting and advisory activities related to trial design and drug development in fibrosis for AbbVie, Amgen, Argenx, AstraZeneca, Boehringer Ingelheim, BMS, Cabaletta, Galderma, Gossamer, Liquidia, Mirador, Miltenyi, NKarta, Novartis, Pharmosa, Philikos, Scleroderma Research Foundation, and Zura Bio.

FG is a shareholder in Nordic Bioscience A/S.

FR reports consulting fees from AbbVie, Abivax, Adiso, Adnovate, Agomab, Alimentiv, Allakos, Allergan, Anaptys, Arena, AstraZeneca, Bausch & Lomb, Boehringer Ingelheim, Cabaletta, Cage, Cellarity, Celgene/BMS, Celltrion, CDISC, Celsius, Chemomab, Cowen, 89Bio, Empress, Enveda, Equillium, Eugit, Falk, Ferring, Flow Therapeutics, Forth Therapeutics, Frequency Therapeutics, Galapagos, Galmed, Genentech, Gilead, Gossamer, Granite, GSK, Guidepoint, Helios, Helmsley, Horizon Therapeutics, Image Analysis Limited, Imidomics, Index Pharma, Janssen, JT Pharma, Koutif, Landos, Lassen, Lilly, Medbiopharma, Merck, Mestag, Metacrine, Mirador, Mirum, Mobius, Mopac, Morphic, Myka Labs, Nxera, Ono, Organovo, Origo, Palisade, Pfizer, Pharvaris, Pliant, Prometheus Biosciences, Radyus, Receptos, RedX, Roche, Rubix, Samsung, Sanofi, Sironax, SRT, Surmodics,

Surrozen, Takeda, Techlab, Tentarix, Teva, Thabor, Theravance, Thetis, Tillerts, Transcenta, Tr1x Bio, UCB, Ventus, Versant, Viatris, Virgo, Xencor, and Ysios. FR also reports advisory board participation for AbbVie, Abivax, Adiso, Adnovate, Agomab, Alimentiv, Allakos, Allergan, Anaptys, Arena, AstraZeneca, Bausch & Lomb, Boehringer Ingelheim, Cabaletta, Cage, Cellarity, Celgene/BMS, Celltrion, CDISC, Celsius, Chemomab, Cowen, 89Bio, Empress, Enveda, Equillium, Eugit, Falk, Ferring, Flow Therapeutics, Forth Therapeutics, Frequency Therapeutics, Galapagos, Galmed, Genentech, Gilead, Gossamer, Granite, GSK, Guidepoint, Helios, Helmsley, Horizon Therapeutics, Image Analysis Limited, Imidomics, Index Pharma, Janssen, JT Pharma, Koutif, Landos, Lassen, Lilly, Medbiopharma, Merck, Mestag, Metacrine, Mirador, Mirum, Mobius, Mopac, Morphic, Myka Labs, Nxera, Ono, Organovo, Origo, Palisade, Pfizer, Pharvaris, Pliant, Prometheus Biosciences, Radyus, Receptos, RedX, Roche, Rubix, Samsung, Sanofi, Sironax, SRT, Surmodics, Surrozen, Takeda, Techlab, Tentarix, Teva, Thabor, Theravance, Thetis, Tillerts, Transcenta, Tr1x Bio, UCB, Ventus, Versant, Viatris, Virgo, Xencor, and Ysios.

JHM is employed by Nordic Bioscience A/S.

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NW is employed by Nordic Bioscience A/S.

RK reports consulting activities for BioLamina, Sweden.

SLF reports travel support to attend the ECM Pharmacology Congress in Copenhagen, Denmark, in June 2026.

SHN reports research grants from Innovation Fund Denmark and Horizon Europe Marie Skłodowska-Curie Actions, honoraria from LEO Pharma, and ownership of stocks in Nordic Bioscience A/S.

SL is employed by Nordic Bioscience A/S and holds shares and RSUs in Nordic Bioscience Holding A/S.

SH reports research grants from the Dutch Heart Foundation, AstraZeneca, CSL Behring, IMI2-CARDIATEAM, DCM NEXT, ZonMW-Metacor, NWO and Dutch Heart Foundation DCM Precise, KIC-DEMAND Partnership NWO-Hartstichting, and the Dutch National CardioResource; consulting activities for AstraZeneca, Ribocure Life Sciences, and Merck; honoraria from Pfizer; leadership roles within committees of the European Society of Cardiology and Heart Failure Association; and membership of the European Reference Network for rare low prevalence and complex diseases of the heart (ERN GUARD-Heart).

TMM reports consulting fees from AbbVie, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, GlaxoSmithKline, IQVIA, Insmed, Merck, Pfizer, Pliant, PureTech, RedX, Sanofi, Trevi, United Therapeutics, and Vicore, and board participation for IQVIA, United Therapeutics, and Gossamer.

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MAK holds stock options in Nordic Bioscience A/S.

All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2026.101901.

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