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ORIGINAL ARTICLE

Healthcare resource use of patients with transthyretin amyloid cardiomyopathy

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Abstract

Aims Transthyretin amyloid cardiomyopathy (ATTR-CM) is the cardiac manifestation of transthyretin amyloidosis (ATTR). The aim of this study was to estimate healthcare resource use for ATTR-CM patients compared with heart failure (HF) patients, in Denmark, Finland, Norway, and Sweden.

Methods and results Data from nationwide healthcare registers in the four countries were used. ATTR-CM patients were defined as individuals diagnosed with amyloidosis and cardiomyopathy or HF between 2008 and 2018. Patients in the ATTR-CM cohort were matched to patients with HF but without ATTR-CM diagnosis. Resource use included number of visits to specialty outpatient and inpatient hospital care. A total of 1831 ATTR-CM and 1831 HF patients were included in the analysis. The mean number of hospital-based healthcare contacts increased in both the ATTR-CM and HF cohort during 3 years pre-diagnosis and was consistently higher for the ATTR-CM cohort compared with the HF cohort, with 6.1 [CI: 5.9–6.3] vs. 3.2 [CI: 3.1–3.3] outpatient visits and 1.03 [CI: 0.96–1.1] vs. 0.7 [CI: 0.7–0.8] hospitalizations. In the first year following diagnosis, patients with ATTR-CM continued to visit outpatient care (10.2 [CI: 10.1, 10.4] vs. 5.7 [CI: 5.6, 5.9]) and were admitted to hospital more frequently (3.3 [CI: 3.2, 3.4] vs. 2.5 [CI: 2.5, 2.6]) than HF patients.

Conclusions Transthyretin amyloid cardiomyopathy imposes a high burden on healthcare systems with twice as many outpatient specialist visits and 50% more hospitalizations in the year after diagnosis compared with HF patients without ATTR-CM. Studies to investigate if earlier diagnosis and treatment of ATTR-CM may lower resource use are warranted.

Keywords TTR amyloidosis; Healthcare resource use; Burden; Heart failure; Cardiomyopathy

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Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is the cardiac manifestation of transthyretin amyloidosis (ATTR), a disease characterized by tissue deposition of transthyretin fibrils that may affect several organs. ATTR-CM is often diagnosed late due to low awareness, or vague initial symptoms that affect several organs mimicking more common comorbidities.[1–4] It typically presents as heart failure with preserved ejection fraction, representing one of the few cases of heart failure with preserved ejection fraction where a disease-modifying treatment is now available.[5] Diagnostic delay and misdiagnosis is common[6] and contributes to low median survival, which has been estimated to be as short as 2.5–3.6 years depending on disease stage at diagnosis and to be half of that in other HF patients.[7,8] Timely diagnosis and treatment is expected to significantly improve life expectancy for patients with ATTR-CM up to 8 years depending on

type of ATTR-CM.[9] Therefore, early diagnosis of ATTR-CM is essential to ensure that patients can benefit from disease-modifying treatment in order to maximize quality of life and reduce the need for healthcare interactions.[9,10]

Although the epidemiology of ATTR-CM is beginning to emerge in published research using register data,[8,11–13] treatment patterns for ATTR-CM patients and their healthcare resource use are not well documented. There is a large body of work on the humanistic and economic burden of heart failure from around the world,[14–16] but only few studies on the healthcare resource use of ATTR-CM.[17–19] Existing studies have been limited to modelled resource use based on data collected from peer-reviewed journal articles, claims data covering only part of the country population, self-reported resource use, and did not compare resource use of ATTR-CM patients to that of a relevant population such as general HF patients not diagnosed with ATTR-CM.

The aim of the present study was to describe the healthcare resource use of patients with ATTR-CM aggregated over four Nordic countries in Europe; Denmark, Finland, Norway, and Sweden and to put this into context by comparing it with the resource use of a matched cohort of heart failure patients. This study is the first to investigate the resource use of ATTR-CM in a large multi-country study based on nationwide health register data.

Methods

Study design

This is a retrospective, observational cohort study using nationwide healthcare registers from four Nordic countries: Denmark, Finland, Norway, and Sweden. The same methodology was applied in all four countries to facilitate aggregation of country-level results. Patients were identified over the study period which ranged from the start of 2008 to the end of 2018. From identification, each patient was followed until death or the end of the study period. Detailed descriptions of methods have been published previously for a Sweden-specific prevalence study.[8]

The investigation conforms with the principles outlined in the Declaration of Helsinki and was approved by Ethical Review Boards and data holders.

Data sources

Data at the patient level were extracted from the patient registers and cause of death registers in each country and linked using pseudonymized personal identifiers. The patient registers contain data on inpatient as well as outpatient specialist visits, surgical procedures, and diagnoses [International Classification of Diseases 10th Revision (ICD-10)]. The cause of death register specifies the date and registered cause of death. Reporting to the national registers is mandatory, resulting in a high degree of completeness in the data. In Norway, data were available from 2008 to 2018 while data were available from 1998 to 2018 in the other countries.

Patient identification

As there was no diagnosis code available for ATTR-CM specifically during 2008 to 2018, ATTR-CM patients were defined as individuals diagnosed with amyloidosis (ICD-10: E85.0, E85.1, E85.2, E85.4, E85.8, and E85.9) and a diagnosis of HF (ICD-10: I50) or cardiomyopathy (CM, ICD-10: I42.0, I42.1, I42.2, I42.5, I42.8, I42.9, I43.1, I43.8) within 2 years of the amyloidosis diagnosis, between 2008 and 2018. The diagnosis date of HF/CM was defined as the patient's index date (date of inclusion in the ATTR-CM cohort) and is referred to as the time of ATTR-CM diagnosis throughout this manuscript. Patients with light-chain (AL) amyloidosis and multiple myeloma at any time were excluded, as were individuals who had undergone disease-modifying therapies such as liver, heart, or haematopoietic stem cell transplant prior to ATTR-CM diagnosis. To ensure at least 3 years of available data prior to diagnosis (lookback period), Norwegian patients diagnosed in 2008–2010 were excluded. In the other countries, a 3 year lookback period for patients diagnosed between 2008 and 2010 was available.

Patients with a HF diagnosis but without an ATTR-CM diagnosis were matched to patients in the ATTR-CM cohort. The diagnosis date for patients in the matched HF cohort was the date of the first recorded HF diagnosis between 2008 and 2018. One-to-one matching was based on birth year, sex, and calendar year of diagnosis.

Transthyretin amyloid cardiomyopathy patients that could not be matched were excluded from the ATTR-CM cohort. Analyses of resource use after diagnosis included resource use for both patients in the matched pair until one in the pair was lost to follow-up to avoid distortion of results by differences in survival.

Characteristics and outcomes

The Elixhauser comorbidity index[20] was calculated based on the three years before the diagnosis date. The index summarizes diagnoses in 31 disease categories into one numeric score; a patient receives a score of 1 for each category in which a diagnosis is registered and the scores are added up across categories to reflect the patient's overall comorbidity burden.

Resource use included all visits to specialist outpatient care (excl. surgeries), all hospitalizations (excl. surgeries), hospitalization days (summed up over all hospitalizations in a specified time period, excl. surgeries), and all surgical procedures (defined as visits with a primary all-cause surgical procedure code in the NCSP Classification of Surgical Procedures). One year before or after diagnosis refers to 365 days from the date of diagnosis; the year after diagnosis includes the date

of diagnosis. Year two before diagnosis refers to the period 730 to 365 days before diagnosis. In the analysis of resource use in 2018, only patients alive in 2018 were included. This analysis was included to show resource use per calendar year, independent of diagnosis date, for the latest available year of data. Annual resource use per calendar year gives an indication of the burden on the healthcare system and can be useful in health economics applications.

Statistical analyses

Individual level data were analysed separately for the four countries, using R Version 4.0.[21] Country-level results were aggregated and weighted by the patient numbers in the respective countries.

Categorical variables are presented with frequency and proportion, and continuous variables are presented with mean and standard deviation. A 95% confidence interval was used to evaluate uncertainty around estimates and statistically significant differences between the ATTR-CM and HF patients on the aggregated results. The *z*-distribution was used to calculate confidence intervals for point estimates, and the binomial distribution was used for proportion estimates.

Results

Patient characteristics

In total, 1833 patients were identified as ATTR-CM patients with at least 3 years of lookback period of which 1831 patients could be matched to HF patients and were included in the analysis. The number of ATTR-CM patients identified in the Nordic countries ranged from 993 (54.2% of the study cohort) in Sweden to 197 (10.8%) in Denmark (*Table 1*).

Overall, the share of female ATTR-CM patients was 31%, with country-level shares varying between 20.3% in Denmark and 49.5% in Finland. The mean age ranged from 71.5 to 75.5 years across countries. Due to matching, the share of female patients and mean age at diagnosis were similar in the ATTR-CM and HF cohorts. The mean Elixhauser comorbidity index in total cohort of ATTR-CM patients was 4.74, with the lowest mean comorbidity index observed in Finland (3.19) and the highest in Sweden (5.13). In each country and overall, the mean Elixhauser comorbidity index levels were similar between the ATTR-CM and HF cohorts, although it was not used in the matching procedure.

Healthcare resource use in the years before diagnosis and in the first year after diagnosis

The mean number of outpatient visits, hospitalizations, hospitalization days, and surgeries for ATTR-CM and HF patients increased steadily in the three years leading to diagnosis with a sharp increase in the first year following diagnosis (*Figure 1*). In all years before and after diagnosis, resource use was higher among ATTR-CM patients compared with HF patients.

For the ATTR-CM patients, the mean number of outpatient visits increased from 4.8 [CI: 4.7–5.0] 3 years before diagnosis to 7.6 [CI: 7.4–7.8] in the year prior to diagnosis, while the number of visits for HF patients increased from 2.5 [CI: 2.4–2.6] to 4.2 [CI: 4.1–4.4], respectively. Across the entire 3 year pre-diagnosis period, the number of outpatient visits for ATTR-CM patients was 6.1 [CI: 5.9–6.3] compared with 3.2 [CI: 3.1–3.3] for HF patients. The same trend was observed for hospitalizations and hospitalization days. During the 3 year pre-diagnosis period, a mean number of 1.03 [CI: 0.96, 1.1] hospitalizations and 5.2 [CI: 5.1, 5.4] hospitalization days accumulated per patient in the ATTR-CM cohort compared with a mean of 0.7 [CI: 0.7, 0.8] hospitalizations and 3.7 [CI: 3.5, 3.8] hospitalization days in the HF cohort. The mean number of surgical procedures for the same period was 0.9 [CI: 0.8, 0.9] for the ATTR-CM cohort and 0.6 [CI: 0.5, 0.6] for patients in the HF cohort.

During the first year following diagnosis, the mean total number of hospital-based healthcare contacts continued to increase compared with pre-diagnosis years for both ATTR-CM and HF patients, and ATTR-CM patients utilized resources more than HF patients. The mean number of outpatient visits was higher among ATTR-CM patients (10.2 [CI: 10.1, 10.4]) than HF patients (5.7 [CI: 5.6, 5.9]). A statistically significant difference between ATTR-CM and HF was also observed for the mean number of hospitalizations (3.3 [CI: 3.2, 3.4] vs. 2.5 [CI: 2.5, 2.6]), hospitalization days (21.7 [CI: 21.5, 22] vs. 15.2 [CI: 15, 15.4]), and surgical procedures (1.7 [CI: 1.6, 1.8] vs. 1.06 [CI: 1.00, 1.12]).

Similar trends were observed in each of the included countries.

Figure 2 shows that the higher mean number of hospital-based healthcare contacts in the ATTR-CM cohort was partly driven by a higher share of patients using resources and partly due to a larger number of resource intensive patients in the ATTR-CM cohort compared with the HF cohort. The share of patients with at least one visit was higher for all three years prior diagnosis. In Years 3, 2, and 1 before diagnosis, the share of the resource intensive patients with three or more visits was 11.1 [CI: 7.8, 14.4], 13.0 [CI: 9.7, 16.4], and 9.7 [CI: 6.3, 13.1] percentage points higher in the ATTR-CM than the HF group. For hospitalizations, there was a less pronounced difference in the share of patients with at least one hospitalization between the cohorts. The share of patients with three or more hospitalizations was lower in ATTR-CM than HF in Year 3 before diagnosis (1.7% [CI: 1.1%, 2.3%] vs. 5.6% [CI: 4.5%, 6.6%]), but was higher in Year 2 (11.0% [CI: 9.6%, 12.5%] vs. 6.8% [CI: 5.7%, 8.0%]) and Year 1 (19.3% [CI: 17.5%, 21.5%] vs. 16.1% [CI: 14.4%, 17.8%]) before diagnosis.

Table 1 Patient characteristics at diagnosis

	Denmark		Finland		Norway[a]		Sweden		Total study population	
	ATTR-CM (*N* = 197, 10.8%[b])	HF (*N* = 197, 10.8%)	ATTR-CM (*N* = 321, 17.5%)	HF (*N* = 321, 17.5%)	ATTR-CM (*N* = 320, 17.5%)	HF (*N* = 320, 17.5%)	ATTR-CM (*N* = 993, 54.2%)	HF (*N* = 993, 54.2%)	ATTR-CM (*N* = 1831)	HF (*N* = 1831)
Females, *n* (%)	40 (20.3)	40 (20.3)	159 (49.5)	159 (49.5)	75 (23.4)	75 (23.4)	296 (29.8)	296 (29.8)	570 (31.1)	570 (31.1)
Age at diagnosis, mean (SD)	71.5 (12.0)	71.52 (12.0)	73.6 (10.2)	73.6 (10.2)	75.5 (12.3)	75.5 (12.2)	72.8 (11.4)	72.8 (11.4)	73.4 (3.4)	73.5 (3.4)
Elixhauser comorbidity index, mean (SD) [CI]	3.23 (2.11) [2.94, 3.53]	3.21 (2.03) [2.93, 3.49]	3.19 (1.95) [2.97, 3.4]	2.82 (1.65) [2.64, 3.0]	5.08 (2.36) [4.83, 5.34]	4.59 (2.34) [4.33, 4.85]	5.13 (2.41) [4.98, 5.28]	5.30 (2.35) [5.15, 5.45]	4.74 (1.51) [4.67, 4.81]	4.67 (1.48) [4.61, 4.74]

ATTR-CM, transthyretin amyloid cardiomyopathy; CI, confidence interval; HF, heart failure; SD, standard deviation.
[a]To ensure at least three years of available data prior to diagnosis (lookback period), Norwegian patients diagnosed in 2008–2010 were excluded.
[b]Percentages refer to proportion of patients from that country of all ATTR-CM/HF patients.

By study design, 100% of patients had at least one visit or hospitalization in the year of diagnosis. The share of resource intensive patients was higher in the year following diagnosis among patients with ATTR-CM. Of all ATTR-CM patients, 76.6% [CI: 74.7%, 78.6%] had three or more outpatient visits compared with 65.6% [CI: 63.4%, 67.8%] in the HF cohort and 45.5% [CI: 43.2%, 47.8%] of ATTR-CM patients were hospitalized three or more times compared with 39.2% [CI: 36.9%, 41.4%] of HF patients.

Healthcare resource use in 2018

In the final year of the study (1 January to 31 December 2018), a total of 708 ATTR-CM patients and 708 HF patients were still alive (diagnosed before 2018 and both patients in matched pair alive on 1 January 2018, or included at diagnosis in 2018). The mean number of hospital-based healthcare contacts among the ATTR-CM patients was higher than for the matched HF patients (*Figure 3*). Compared with HF patients, ATTR-CM patients had, on average, more specialized outpatient visits (8.7 [CI: 8.4–9] vs. 4.7 [CI: 4.5, 4.9]), more hospitalizations (1.9 [CI: 1.8–2.1] vs. 1.4 [CI: 1.3, 1.5]), and more surgeries (1.4 [CI: 1.3–1.5] vs. 0.9 [CI: 0.8, 1]). The mean number of hospitalized days was also higher for ATTR-CM patients than HF patients (9.7 [CI: 9.4–10] vs. 7.2 [CI: 7, 7.5]).

Discussion

This is the first multi-country study characterizing and quantifying healthcare resource use of ATTR-CM and the first study to assess the number and type of interactions with specialist healthcare services in comparison with a matched cohort of HF patients without ATTR-CM diagnosis. The analysis revealed some consistent patterns in the ATTR-CM patient pathway: an increase in the level of healthcare resource use in the years before diagnosis and in the year following diagnosis, as well as higher levels of resource use of ATTR-CM patients compared with HF patients. The annual increase in hospital-based resource use before diagnosis was driven both by an increase in patients using healthcare resources at least once per year and the increase in the number of resource intensive patients with three or more outpatient specialist visits or hospitalizations per year.

The patterns of increased use of specialist care leading up to diagnosis were similar in the ATTR-CM and matched HF cohort; however, the mean number of outpatient visits, hospitalizations, hospitalization days, and surgeries was significantly higher for the ATTR-CM cohort in all three years prior diagnosis and the year following diagnosis. Also, the share of resource intensive patients was higher in the ATTR-CM cohort compared with the HF cohort. Independent of timing regarding diagnosis, resource use was higher for ATTR-CM patients compared with HF patients in the year 2018, the most recent year of available data.

Figure 1 The mean number of outpatient visits, hospitalizations and hospitalization days in the years before diagnosis (Years 3 to 1) and year directly following and including diagnosis (Year 0). The dotted lines represent the mean number for the entire pre-diagnosis period. The error bars represent 95% confidence intervals. ATTR-CM, transthyretin amyloid cardiomyopathy; HF, heart failure.

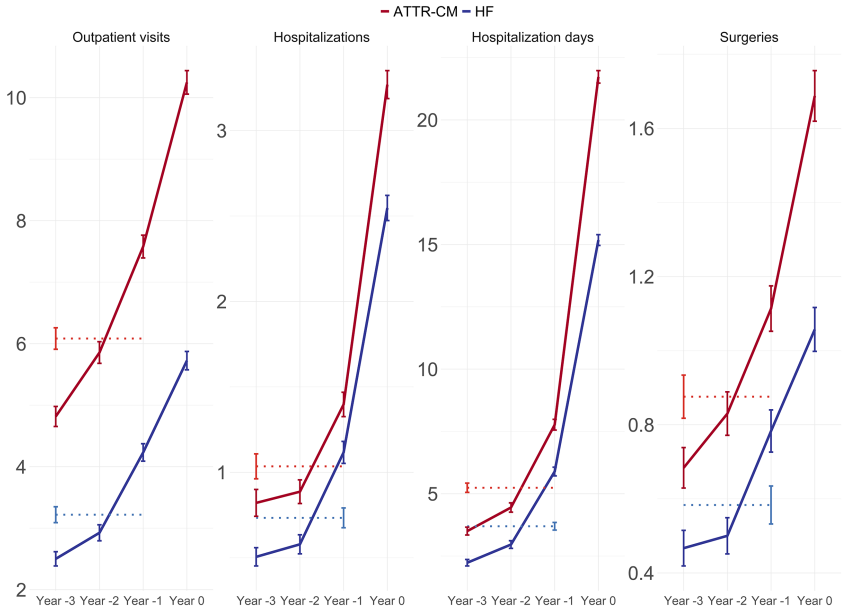
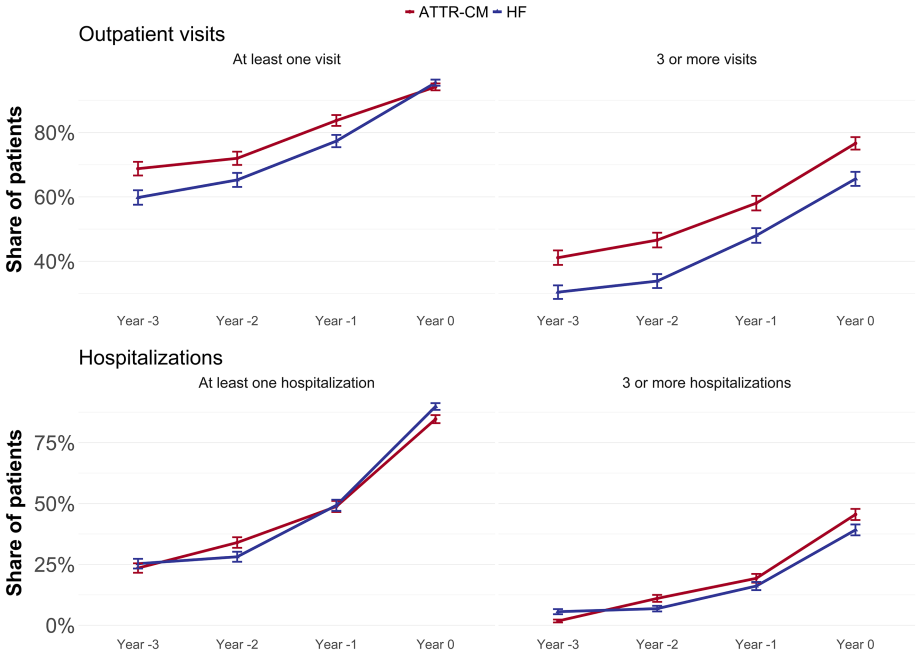


Figure 2 Share of patients with at least one and three or more outpatient visits/hospitalizations in the three years before diagnosis (Years 3 to 1). The error bars indicate 95% confidence intervals. ATTR-CM, transthyretin amyloid ardiomyopathy; HF, heart failure.



The relatively lower use of healthcare resources in HF patients compared with ATTR-CM patients in the year following diagnosis may indicate less severe symptoms in this cohort and may also reflect the availability of effective treatment for HF in the years of 2008–2018. At the same time, the severity of ATTR-CM at the time of diagnosis becomes evident by the fact that 44% of the ATTR-CM cohort was admitted to hospital three or more times in the year after diagnosis,

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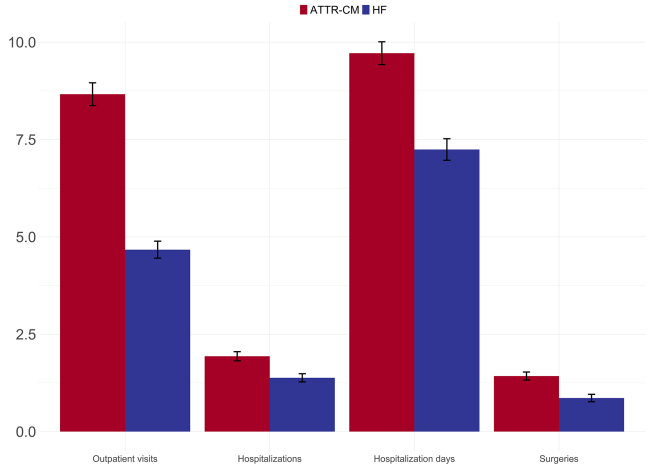
Figure 3 The mean number of outpatient visits, hospitalizations, hospitalizations days, and surgeries in 2018. The error bars indicate 95% confidence intervals. ATTR-CM, transthyretin amyloid cardiomyopathy; HF, heart failure.



which is higher compared with a previous single country study estimate of 30%.[22] This likely illustrates the difficulty in correctly treating ATTR-CM and the importance of earlier diagnosis.

The consequences of delayed ATTR-CM diagnosis were examined in a recent literature review, demonstrating disease progression due to delayed and misdiagnoses after extensive and long examination periods.[6] This revealed multi-faceted adverse impacts on patients, some of whom undergo inappropriate tests and ineffective treatments during evaluations by multiple healthcare providers, while their disease worsens. An English analysis of healthcare data for 524 patients before and after ATTR-CM diagnosis, demonstrated a median of 17 (interquartile range 9–27) hospital visits in the three years before diagnosis.[22] This is in line with the mean number of visits in our study, suggesting multiple missed diagnostic opportunities causing a strain on both patient and healthcare resources.

Although the comorbidity index differed between countries, it was consistently similar between ATTR-CM and HF patients within each country. This shows that between-country differences are more likely due to differing coding practices than due to large differences in patient populations. The similar comorbidity index in ATTR-CM and HF patients indicates that higher resource use in ATTR-CM was not primarily driven by differences in comorbidities and suggests that the condition of ATTR-CM patients is deteriorating more rapidly, increasing the need for further hospital visits. This is further highlighted by the excess mortality in ATTR-CM patients compared with HF patients.[8]

One strength of this study is the use of data from national datasets across the four Nordic countries over a long period of time, from 2008 to 2018. The employed register data include all hospital-based contacts, visits, hospitalizations, and surgeries, for the whole population and is thus one of the most reliable sources for estimating resource use. However, due to data availability estimated resource use was limited to healthcare contacts that took place in specialty care and potentially significant amounts of resources used in primary care, home treatment or institutional care were not included. This means that our results underestimated the total resource use of ATTR-CM and HF patients.

Moreover, ATTR-CM and HF patients were identified based on recorded diagnoses while ATTR-CM is known to be underdiagnosed. As there was no specific ATTR-CM diagnosis code available during the years covered in this study, ATTR-CM patients were identified using a combination of several diagnoses based on clinical expertise and experience with coding practice in the Nordic countries. Despite these efforts, it can be the case that some non-ATTR-CM patients were included and that some ATTR-CM patients were missed. Further, the coded records did not provide enough diagnostic details to distinguish between types of ATTR-CM (hereditary or wild-type). For the HF cohort, it was not possible to identify subtypes or severity of HF, due to a lack of detail in the available diagnosis codes.

In conclusion, ATTR-CM is a severe disease, and our results indicate a higher burden on healthcare systems compared with matched patients with non-ATTR HF, both in the years leading to diagnosis and after diagnosis is established. The diagnosis appears to be achieved only after numerous interactions with healthcare services in the years before a diagnosis is made. Some of this healthcare resource use can potentially be mitigated with earlier diagnosis.

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Conflict of interest

R.L., J.L.H., and A.F. are employed by Quantify Research and funded by Pfizer to conduct this study; Quantify Research is a consultancy and works with a range of different pharmaceutical companies. K.J., M.H.R., A.M.S., and M.V. are Pfizer employees and hold Pfizer stock and/or stock options. J.K. received support from Pfizer for her collaboration in this manuscript as well as grants or contracts from Sanofi-Genzyme, Pfizer, and The Finnish Foundation for Cardiovascular Research. J.K. also received consulting fees and honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Sanofi-Genzyme, Pfizer, Bayer, Takeda, Amgen, and Chiesi as well as payment for expert testimony from Sanofi-Genzyme, Pfizer, Bayer, Takeda, and Amgen. J.K. has received support for participation on a Data Safety Monitoring Board or Advisory Board from Sanofi-Genzyme, Pfizer, Bayer, Takeda, Amgen, and Chiesi and is supported by Amgen for Leadership or fiduciary role in other board, society, committee, or advocacy group. E.G. has received grants and honoraria for lectures from Pfizer. F.G. has received support from Pfizer for work on the present manuscript and consulting fees from Pfizer, Alnylam, and Ionis. J.G.S. has no conflict of interests.

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