

## Original article

## Lack of seasonality in occurrence of pericarditis, myocarditis, and endocarditis



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## ABSTRACT

**Purpose:** The etiology of pericarditis, myocarditis, and endocarditis is predominantly infectious, and infections often show seasonal variation. Little is known, however, about seasonal patterns in these cardiopathies.

**Methods:** Using Danish health care registries, we identified all patients with a first-time hospital-based diagnosis of pericarditis, myocarditis, or endocarditis between 1994 and 2016. We estimated peak-to-trough ratios from fitted sine curves to measure the intensity of seasonal variation in occurrence during the study period. Because randomness will lead to small apparent seasonal patterns, we also conducted a plasmode simulation to assess the degree of seasonality that randomness would produce.

**Results:** Crude peak-to-trough ratios of monthly frequencies summarized over a year were small. We estimated a peak-to-trough ratio of 1.10 (95% confidence interval [CI], 1.05–1.14) for pericarditis, 1.11 (95% CI, 1.02–1.21) for myocarditis, and 1.01 (95% CI, 1.00–1.07) for endocarditis. The simulated mean peak-to-trough ratios found after randomly reassigning the monthly frequencies within each year were 1.04 (95% CI, 1.00–1.09) for pericarditis, 1.04 (95% CI, 1.00–1.13) for myocarditis, and 1.04 (95% CI, 1.00–1.10), for endocarditis.

**Conclusion:** The data indicate no important seasonal variation in the occurrence of pericarditis, myocarditis, and endocarditis in Denmark between 1994 and 2016.

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## Introduction

Several cardiovascular conditions exhibit seasonal periodicity in occurrence, including myocardial infarction [1], stroke [2], and atrial fibrillation [3]. Most often the peaks occur during winter [4]. This periodicity presumably stems from complex interactions among a range of environmental factors, including climatic variables and susceptibility of individuals [4]. Inflammation in the heart is broadly classified as pericarditis, myocarditis, and endocarditis.

These conditions differ in clinical course and underlying etiology. Although an infectious etiology is most frequent in endocarditis, an immunologic origin may be suspected in pericarditis and myocarditis, but overall the diseases share a presumed predominant infectious etiology [5–8].

Pericarditis is an inflammatory disease of the pericardium. Causes of pericarditis vary. Although immunologic mechanisms may be involved, up to 90% of cases remain idiopathic because no added evidence support a generalized immunologic disarray in the individual patient [5,6]. Consequently, it is assumed that most cases of idiopathic pericarditis are triggered by viral infections, including enteroviruses, adenoviruses, herpesviruses, and influenza virus [9]. In developing countries, *Mycobacterium tuberculosis* is the most common cause of pericarditis [9]. Similar to pericarditis, viral infections are the most common cause of myocarditis in developed countries [10]. The incidence rate is largely unknown. Myocarditis

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**Table 1**  
Characteristics (n, %) of patients with pericarditis, myocarditis, and endocarditis, Denmark, 1994–2016

Numbers (%)	Pericarditis	Myocarditis	Endocarditis
All patients	17,203	4141	10,212
Men	11,706 (68.0)	2714 (65.5)	6437 (63.0)
Median age (25th–75th percentiles), y	53 (37–67)	51 (32–70)	69 (55–78)
Age groups, y			
0–29	2726 (15.8)	931 (22.5)	540 (5.3)
30–49	4881 (10.3)	1107 (26.7)	1388 (13.6)
50–69	6313 (36.7)	1045 (25.2)	3510 (34.4)
>70	3283 (19.1)	1058 (25.5)	4774 (46.7)
Charlson Comorbidity Index score			
0	10,441 (60.7)	2425 (58.6)	3737 (36.6)
1	2673 (15.5)	692 (16.7)	1936 (19.0)
2	1918 (11.1)	439 (10.6)	1626 (15.9)
3+	2171 (12.6)	585 (14.1)	2913 (28.5)
Diagnosis in the Danish National Patient Registry			
Primary	13,437 (78.1)	2618 (63.2)	7870 (77.1)
Secondary	3766 (21.9)	1523 (36.8)	2342 (22.9)
Type of pericarditis			
Unclassified pericarditis	11,605 (67.5)	N/A	N/A
Pericardial effusion	3554 (20.7)	N/A	N/A
Infectious pericarditis	1501 (8.7)	N/A	N/A
Underlying autoimmune disease	543 (3.2)	N/A	N/A

N/A = not available.

has a challenging differential diagnosis, including mix-up with myocardial infarction and myocardial injury caused by extracardiac diseases [10].

Endocarditis is a serious condition, and its incidence is increasing [11]. Unlike pericarditis and myocarditis, endocarditis has a predominantly bacterial etiology (most often *Streptococcus* and *Staphylococcus* species) [12].

Knowledge about the seasonal variation of inflammatory diseases of the heart is sparse [13–15]. Because of their predominant infectious etiology, seasonal variation in the occurrence of these conditions is plausible. We therefore examined the seasonal variation in occurrence of pericarditis, myocarditis, and endocarditis from 1994 to 2016.

## Subjects and methods

We identified all inpatients and outpatients with a first-time primary or secondary diagnosis of pericarditis, myocarditis, or endocarditis in the Danish National Patient Registry (DNPR) between January 1, 1994, and December 31, 2016, based on *International Classification of Diseases* (ICD) diagnosis codes [16].

The DNPR [16] is an ongoing population-based administrative registry, which has collected data on dates of all admissions and discharges from nonpsychiatric hospitals since 1977 and on emergency room and outpatient clinic visits since 1995. Each hospital discharge or outpatient visit is recorded in the DNPR with one primary diagnosis and one or more secondary diagnoses coded according to the *Eighth Revision* of the ICD during 1977–1993 and according to the *Tenth Revision* thereafter. Complete and accurate individual-level linkage of all national registries, including the DNPR, is possible using the unique 10-digit identifier assigned to Danish residents by the Danish Civil Registration System by law on birth or immigration.

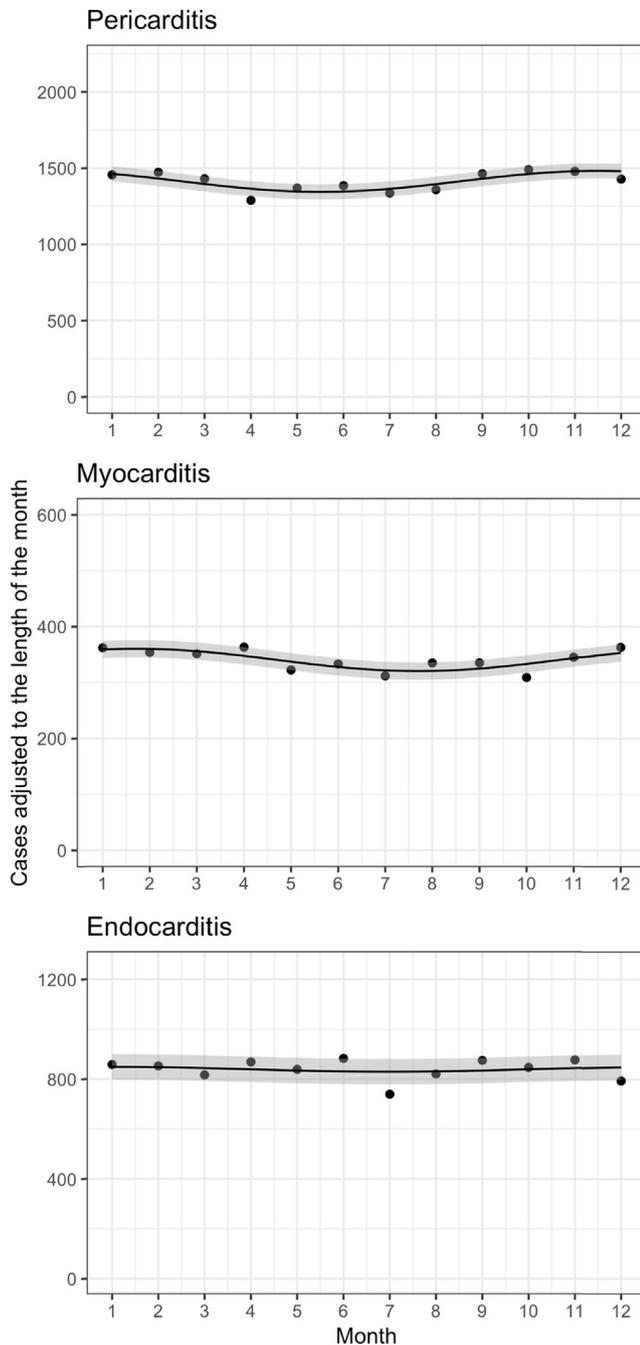
We obtained data from the Civil Registration System and DNPR on the distribution of sex, age, comorbidities, type of diagnosis, and type of pericarditis among affected patients. To assess seasonal variation in these conditions during the study period, we performed two separate analyses. First, we identified all cases of pericarditis, myocarditis, and endocarditis during the study period on a monthly basis. To adjust for varying length of month, we multiplied each monthly count by 30 and divided the result by the

length of the month. Applying Edwards' model [17], we computed the peak-to-trough ratio of the summed adjusted monthly frequency of cases based on a sine curve fitted to the 12 adjusted monthly frequencies. This model assumes that the expected values for the monthly frequencies follow a sine curve with a single annual cycle. The magnitude of the peak-to-trough ratio measures the intensity of seasonal variation in occurrence, analogous to a risk ratio that contrasts risks for the month of peak occurrence versus the trough month. By definition, the peak-to-trough ratio cannot be less than 1.0, a value obtained only in the extreme case of identical risks for all months in a yearly cycle. The ratio increases above 1.0 with increasing intensity of seasonal variation [18]. We implemented this model using Episheet [19], in which the data entered included monthly cases as well as the size of the population for the given month, allowing us to calculate an incidence proportion. To examine temporal trends, we tabulated yearly counts, populations at risk, and incidence proportions over time.

To examine potential interactions in subgroups, we performed stratified seasonal analyses by sex, age groups (0–29, 30–49, 50–69, and >70+ years), Charlson Comorbidity Index scores (0, 1, 2, and >3), type of diagnosis (primary and secondary), and type of pericarditis (unclassified pericarditis, pericardial effusion, infectious pericarditis, and underlying autoimmune disease).

Because the peak-to-trough ratio is always 1.0 or greater, variability of monthly frequencies even in the absence of any seasonality will give estimates of the ratio greater than 1.0 [20]. Conversely, if there is a cyclic pattern, random variation will tend to obscure it, diminishing the peak-to-trough ratio. To assess this effect of randomness in these data, we performed a plasmode simulation analysis [21], randomly reassigning the summarized monthly frequencies to the array of monthly slots in Episheet and then estimating the peak-to-trough ratio. We repeated this process 1000 times and computed the mean of all simulations.

All figures were constructed using R, version 3.3.3 (R Project for Statistical Computing, Vienna, Austria). The plasmode simulation analyses were conducted using SAS, version 9.4 (SAS Institute Inc., Cary, NC). The ICD codes used in the study are listed in eTables 1 and 2. According to Danish legislation, informed consent and approval from an ethics committee are not required for registry-based studies. The study was approved by the Danish Data Protection Agency (record number: 2016-051-000001, rec. no. 818).



**Fig. 1.** Summarized cases of pericarditis, myocarditis, and endocarditis within each calendar month during 1994–2016, adjusted for the length of the month with a fitted sine curve and 95% confidence band.

## Results

Our study included 31,556 patients with a diagnosis of first-time pericarditis (54.5%), myocarditis (13.1%), or endocarditis (32.4%). Of these, 733 patients (2%) had a simultaneous diagnosis of pericarditis and myocarditis. Men constituted the majority of the study population for all three conditions. The median age (25th–75th percentiles) was 53 years (37–67 years) for pericarditis, 51 years (32–70 years) for myocarditis, and 69 years (55–78 years) for endocarditis. A higher proportion of patients with endocarditis had a Charlson Comorbidity Index score of greater than 3 than patients with pericarditis and myocarditis. Unclassified pericarditis accounted for most cases of pericarditis (67.5%; [Table 1](#)).

[Figure 1](#) shows summarized monthly cases, adjusted for length of month. The crude peak-to-trough ratios of these case summaries were 1.10 (95% confidence interval [CI], 1.05–1.14) for pericarditis, 1.11 (95% CI, 1.02–1.21) for myocarditis, and 1.01 (95% CI, 1.00–1.07) for endocarditis ([Table 2](#)). Peak months of summarized cases occurred in October for pericarditis, in April and December for myocarditis, and in June for endocarditis, whereas trough months occurred in April for pericarditis, in October for myocarditis, and in July for endocarditis. Of the three conditions, only pericarditis followed a typical seasonal pattern, with the peak followed by a trough after approximately 6 months. For myocarditis and endocarditis, the trough and peak months were only two months and one month apart, respectively. However, across individual years in the study period, the time of peak varied substantially for all three conditions ([eTable 3](#)). Incidence proportions increased by 47% (from 10.5 cases per 100,000 population in 1994 to 15.4 cases per 100,000 population in 2016) for pericarditis, by 47% (from 3.3 cases per 100,000 population in 1994 to 4.8 cases per 100,000 population in 2016) for myocarditis, and by 88% (from 5.3 cases per 100,000 population in 1994 to 9.9 cases per 100,000 population in 2016) for endocarditis ([eTable 4](#)).

In subgroups, crude peak-to-trough ratios were largely consistent with ratios estimated for overall groups ([Table 2](#)).

In comparison with these observed values, the simulated mean peak-to-trough ratios after randomly assigning monthly frequencies within each year were 1.04 (95% CI, 1.00–1.09) for pericarditis, 1.04 (95% CI, 1.00–1.13) for myocarditis, and 1.04 (95% CI, 1.00–1.10) for endocarditis.

## Discussion

In this population-based study using Danish registries, we observed no biologically meaningful seasonal variation in occurrence of pericarditis, myocarditis, and endocarditis between 1994 and 2016, after consideration of bias in peak-to-trough ratios stemming from random variation.

To date, literature on seasonal variation in occurrence of inflammatory conditions in and around the heart is sparse [[13–15](#)]. An Israeli study of 175 patients with acute idiopathic pericarditis conducted between 2010 and 2015 reported presence of a seasonal pattern with a distinct winter peak [[13](#)]. However, this study also reported that recurrent cases did not follow such a seasonal pattern. A study conducted in Brazil, which included 84 patients with idiopathic or other pericarditis over a 3-year period (1999–2001), reported a fall peak in occurrence [[14](#)]. A study in the United States included a total of 60 patients with endocarditis treated in a university hospital over a 9-year period (1993–2001) [[15](#)]. It reported a fall/winter predominance in cases. Small study sizes and crude comparisons of individual calendar months may have led to the somewhat inconsistent results [[13–15](#)]. None of the previous studies included data on the seasonal variation of myocarditis occurrence.

In the present study, peaks varied considerably between individual years for all three conditions. As well, only pericarditis followed a typical seasonal pattern. As noted earlier, random error will tend to obscure an existing seasonal pattern, but in the absence of any seasonal variation, it will bias results away from the null value of the peak-to-trough ratio. The inconsistency of the timing of peak across years and the magnitude of the simulated mean peak-to-trough ratios indicate that randomness is a sufficient explanation for the small degree of seasonality observed in the data. The increase in incidence proportions during the study period is likely attributed to improved diagnostics and did not affect measures of seasonal variation [[9](#)].

**Table 2**  
Crude peak-to-trough ratios of summarized monthly cases during 1994–2016

Crude peak-to-trough ratios	Pericarditis	Myocarditis	Endocarditis
All patients	1.10 (1.05–1.14)	1.11 (1.02–1.21)	1.01 (1.00–1.07)
Men	1.10 (1.05–1.16)	1.09 (1.00–1.21)	1.01 (1.00–1.08)
Women	1.08 (1.00–1.16)	1.15 (1.00–1.34)	1.05 (1.00–1.15)
Age groups, y			
0–29	1.06 (1.00–1.17)	1.05 (1.00–1.27)	1.05 (1.00–1.34)
30–49	1.09 (1.01–1.19)	1.07 (1.00–1.27)	1.03 (1.00–1.20)
50–69	1.05 (1.00–1.13)	1.15 (1.00–1.37)	1.02 (1.00–1.12)
>70	1.19 (1.08–1.31)	1.23 (1.03–1.46)	1.03 (1.00–1.11)
Charlson Comorbidity Index score			
0	1.06 (1.00–1.12)	1.13 (1.01–1.27)	1.07 (1.00–1.17)
1	1.12 (1.01–1.25)	1.15 (1.00–1.43)	1.00 (1.00–1.14)
2	1.29 (1.13–1.47)	1.27 (1.00–1.67)	1.08 (1.00–1.24)
>3	1.06 (1.00–1.20)	1.09 (1.00–1.37)	1.01 (1.00–1.11)
Diagnosis in the Danish National Patient Registry			
Primary	1.10 (1.05–1.15)	1.12 (1.00–1.24)	1.01 (1.00–1.07)
Secondary	1.12 (1.02–1.23)	1.08 (1.00–1.24)	1.13 (1.01–1.27)
Type of pericarditis			
Unclassified pericarditis	1.07 (1.02–1.13)	N/A	N/A
Pericardial effusion	1.12 (1.02–1.23)	N/A	N/A
Infectious pericarditis	1.21 (1.05–1.40)	N/A	N/A
Underlying autoimmune disease	1.02 (1.00–1.30)	N/A	N/A

N/A = not available.

Values are represented in peak-to-trough ratios (confidence interval).

Our study has limitations. Our results are contingent on the validity of the diagnoses in the DNPR. Although previous studies found high positive predictive values for diagnoses of first-time pericarditis (92%), lower values were found for diagnoses of endocarditis (82%) and myocarditis (64%) in the DNPR [22]. In addition, we detected few myocarditis events, which lowered the precision of estimates. None of these limitations has a systematic seasonal element, but any of them could dilute or offset a real seasonal pattern. Study strengths include a long observation period and a population-based design within a uniform health care system, reducing the potential for selection biases arising from selective inclusion of insurance plans, specific hospitals, ethnicities, regions, or socioeconomic levels.

Our study was conducted in Denmark, which has a temperate climate. Annual climatic cycles can affect seasonal variation in a variety of ways, including cyclic appearance of pathogens [18]. Consequently, our findings may not apply to other populations with distinct climates.

## Conclusion

In this analysis of seasonal patterns in occurrence of pericarditis, myocarditis, and endocarditis, we found no meaningful seasonal variation.

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## Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.annepidem.2019.07.005>.

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