Incidence rate of infective endocarditis by socioeconomic position: a Danish nationwide cohort study (2000–2022)

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Summary

Background People with lower socioeconomic positions have a higher risk of cardiac and infectious diseases than those with higher socioeconomic positions. However, how the increasing incidence of infective endocarditis among different socioeconomic groups has played out remains unclear. We therefore aimed to investigate nationwide temporal trends in infective endocarditis incidence rate by socioeconomic position in Denmark.

Methods Using nationwide Danish registries, we investigated infective endocarditis incidence rate (2000–2022). As socioeconomic position indicator, we used affluence level (accounting for household-level income and wealth), dividing the population into low, medium, and high affluence. Average annual percentage changes were computed to evaluate temporal trends. Slope index and relative index of inequality were calculated to obtain inequality gradients.

Findings Per 100,000 person-years, the incidence rate increased from 8.7 in 2000 to 21.2 in 2022 among low; from 7.4 to 14.3 among medium; and from 6.2 to 13.1 among high affluence people. The average annual percentage change was 4.3% among low, 3.5% among medium, and 3.7% among high affluence people. The slope index of inequality increased from 3.8 additional cases per 100,000 person years (95% CI: 0.4–7.3) in 2000 to 12.3 (95% CI: 7.4–17.1) in 2022. The relative index of inequality increased from 1.68 (95% CI: 0.90–2.44) to 2.13 (95% CI: 1.49–2.78).

Interpretation The infective endocarditis incidence rates increased in all affluence levels, with highest rates consistently found in the lowest affluence group, indicating that people with lower socioeconomic positions faced a disproportionately higher risk of infective endocarditis. These findings highlight the need to consider socioeconomic factors when addressing modifiable determinants that may curb the rise in infective endocarditis incidence.

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Keywords: Infective endocarditis; Incidence; Temporal trend; Socioeconomic position

Introduction

Infective endocarditis (IE) is a severe infectious disease with high morbidity and mortality.[1,2] IE typically arises from bacteria spreading haematogenously and adhering to injured endothelium or foreign material.[3] The incidence rate of IE has nearly doubled in recent decades.[4] Concurrently, the at-risk population has shifted from younger patients with rheumatic heart valve disease to older patients with multiple comorbidities and predisposing conditions, such as degenerative heart valve disease, prosthetic heart valves, cardiac implantable electronic devices, or exposure to invasive procedures.[5,6] Overall, patients with lower socioeconomic positions (SEP) have a higher risk of bacteraemia and infectious diseases.[7–9] Cardiac risk factors and diseases are also more prevalent among patients with low SEP than those with high SEP[10]; however, educational inequalities in valvular heart diseases are less pronounced than in conditions such as ischaemic heart disease.[11]

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Translation: For the Danish translation of the abstract see the Supplementary Materials section

Research in context

Evidence before this study

The incidence of infective endocarditis has doubled in recent decades, yet its association with socioeconomic position remains unclear. We reviewed all cohort studies investigating the association between socioeconomic position and incidence of infective endocarditis. On December 04, 2024, we searched MEDLINE, without any date or language restriction, using the terms 'endocarditis', 'socioeconomic', 'educational status', 'income', 'occupation', 'disparity', 'social class', and 'healthcare'. Previous studies suggest that patients with the lowest levels of income and education have an elevated risk of *Staphylococcus aureus* bacteraemia and a similar risk of subsequent infective endocarditis. Patients from deprived areas have also been reported to account for a higher proportion of patients diagnosed with infective endocarditis. However, no studies investigated the overall temporal trends in infective endocarditis incidence rate across individual-level socioeconomic groups.

Added value of this study

This nationwide Danish cohort study provides contemporary evidence that individual-level socioeconomic position is strongly associated with the incidence rate of infective endocarditis. From 2000 to 2022, the incidence rate increased by approximately 4% point annually across all socioeconomic groups. Consequently, the relative inequality remained rather stable. However, due to a higher baseline risk among people with a low socioeconomic position, the absolute inequality increased throughout the study period, reaching 12.3 (95% CI: 7.4–17.1) additional events per 100,000 person-years in 2022.

Implications of all the available evidence

In Denmark, people in low socioeconomic positions face a disproportionately high risk of infective endocarditis, and inequalities have widened in recent decades. These findings highlight the need to consider socioeconomic factors when addressing modifiable determinants that may curb the rise in infective endocarditis incidence. Examining whether similar trends occur in regions with different socioeconomic and healthcare structures is crucial.

Studies investigating the association between SEP and IE risk are sparse. A Danish study showed that patients with the lowest educational level and income levels had an elevated risk of *Staphylococcus aureus* bacteraemia. However, it remained less clear whether the association translated into subsequent IE.[9] A Scottish study demonstrated that patients from the most deprived areas constituted the highest proportion of IE patients; however, SEP was measured by an area-level indicator and presented only as a covariate.[12] Thus, it remains unclear whether IE incidence rate differs across groups of individual-level measured SEP and how the increasing incidence of infective endocarditis has played out among different socioeconomic groups.

We therefore investigated the nationwide temporal trends in IE incidence rate by SEP in Denmark from 2000 to 2022.

Methods

Study design and setting

We conducted this population-based cohort study in Denmark. The Danish healthcare system provides tax-supported healthcare to all Danish residents, ensuring universal access to hospitals, private practitioners, and partial reimbursement for prescribed medicines.[13] At birth or immigration, all Danish residents receive a unique Civil Registration Number, enabling unambiguous individual-level data linkage across various registries.[14]

The Danish Civil Registration System was used to enrol Danish residents into the study cohort each study year. This registry holds all changes in vital status and migration status since 1968.[14] First-time IE hospitalisations were identified through the Danish National Patient Registry (DNPR), which has recorded all somatic hospital contact discharges since 1977 and emergency room, outpatient clinic, and psychiatric contacts since 1995.[15] The Income Statistics Registry[16] and the Population Education Register,[17] both issued by Statistics Denmark, provided information on income, wealth, and educational level. A full description of the registries is given in the Supplemental Material.

Socioeconomic position

Inspired by Cairns et al.,[18] we computed an affluence level based on income and wealth (Supplemental Methods). Annually, individuals were assigned an age- and sex-specific rank for income and wealth. The higher rank defined the affluence rank, dividing the population into tertiles using age- and sex-specific cut-offs. This approach yielded three equally sized groups for each age in each study year, enabling fair temporal comparison. We restricted to people aged ≥30 years to ensure that all had the opportunity to establish their household income and wealth, rather than reflecting the affluence of their parents.

Outcomes

Information on first-time IE hospitalisations was obtained from the DNPR. Primary and secondary inpatient diagnoses were used. Only hospital lengths of stays ≥2 weeks or in-hospital mortality prior to 2 weeks were included. This algorithm has a positive predictive value of 90%.[19] Patients with IE prior to January 1 in each study year were excluded. The ICD codes are provided in Table S1.

Covariates

Baseline characteristics were obtained for IE patients. Information on the comorbidities was obtained from the DNPR, considering all preadmission hospital history. From the Danish National Prescription Registry, additional information on redeemed prescriptions for medications to treat hypertension,[20] diabetes mellitus, hypercholesterolaemia, chronic pulmonary disease, mental disorders, alcohol abuse and alcohol-related disorders,[21] and substance abuse[21] was obtained. From the Danish National Health Service Register,[22] information on dentist visits within 1, 3, or 5 years prior to IE was obtained. The specific ICD and ATC codes are provided in Table S1.

Statistical analysis

Patient characteristics were tabulated for patients with IE by affluence level. Categorical variables are shown as counts and percentages. As visual inspections of Q–Q plot and histogram indicated that age-distribution was non-normal, age is presented as median, Q1, and Q3.

The annual IE incidence rate was calculated by dividing the number of first-time IE hospitalisations by the population-at-risk time. To obtain the annual population-at-risk time, all residents in Denmark ≥30 years of age were followed from the index date (*i.e.,* January 1, the date of the 30th birthday, or the date of immigration, whichever came last) until first-time IE hospitalisation, emigration, death, or December 31, whichever came first. Confidence intervals of 95% were calculated assuming an underlying Poisson distribution.

Join point regression analyses were conducted to compute the annual percentage changes (APC) and the average APC (AAPC) in incidence rates for each affluence level.[23] Monte Carlo permutations were used to determine the number of join points. As none were identified, only the AAPC was reported.

To estimate the socioeconomic inequality gradient in IE incidence rate, slope index of inequality (SII) was calculated to measure absolute inequality and relative index of inequality (RII) to measure relative inequality.[24] The SII and RII summarise, in a single number, the best approximation of the expected excess risk from lowest to highest across the entire scale.[24] To calculate SII and RII, each affluence level was first assigned a rank that equals the proportion strictly higher levels constitute of the population plus half of the proportion the given level constitutes of the population. Using hazard models, time-in-study was regressed on the rank using a Cox proportional hazards model to calculate RII and an additive hazard model to calculate SII.[25] To obtain standard errors, a model-robust approach was applied.

	Affluence level		
	Low	Medium	High
	n (%)	n (%)	n (%)
Total	4135 (100)	3117 (100)	2890 (100)
Median age, in years (Q1;Q3)	70 (58;78)	73 (64;80)	74 (65;81)
Age group			
30–54 years	814 (20)	372 (12)	291 (10)
55–69 years	1240 (30)	863 (28)	744 (26)
70–84 years	1727 (42)	1508 (48)	1445 (50)
≥85 years	354 (8.6)	374 (12)	410 (14)
Sex, male	2759 (67)	2043 (66)	1990 (69)
Calendar period			
2000–2004	571 (14)	434 (14)	379 (13)
2005–2009	660 (16)	594 (19)	555 (19)
2010–2014	950 (23)	669 (21)	620 (21)
2015–2018	896 (22)	694 (22)	648 (22)
2019–2022	1058 (26)	726 (23)	688 (24)
Educational level			
Low	1978 (48)	1118 (36)	539 (19)
Medium	1686 (41)	1461 (47)	1226 (42)
High	238 (5.8)	376 (12)	960 (33)
Unknown	233 (5.6)	162 (5.2)	165 (5.7)
Cohabitation status			
Cohabiting	1808 (44)	1868 (60)	1845 (64)
Living alone	2327 (56)	1249 (40)	1045 (36)
Comorbidities			
Myocardial infarction	577 (14)	413 (13)	300 (10)
Congestive heart failure	958 (23)	722 (23)	599 (21)
Cardiomyopathy	194 (4.7)	129 (4.1)	124 (4.3)
Atrial fibrillation or flutter	1104 (27)	941 (30)	848 (29)
Congenital heart disease	109 (2.6)	67 (2.1)	93 (3.2)
Valvular heart disease	1276 (31)	1156 (37)	1094 (38)
Prosthetic heart valve	633 (15)	583 (19)	554 (19)
Cardiac implantable electronic device	638 (15)	446 (14)	428 (15)
Hypertension	2356 (57)	1790 (57)	1582 (55)
Stroke	647 (16)	477 (15)	423 (15)
Dementia	107 (2.6)	81 (2.6)	62 (2.1)
Parkinson's disease	27 (0.7)	25 (0.8)	24 (0.8)
Diabetes	1153 (28)	685 (22)	484 (17)
Hypercholesterolaemia	1744 (42)	1302 (42)	1121 (39)
Venous thromboembolism	301 (7.3)	198 (6.4)	170 (5.9)
Chronic pulmonary disease	1150 (28)	715 (23)	550 (19)
Chronic kidney disease	671 (16)	399 (13)	296 (10)
Dialysis	326 (7.9)	177 (5.7)	131 (4.5)
Liver disease	393 (9.5)	165 (5.3)	93 (3.2)
Cancer	721 (17)	621 (20)	658 (23)
Neurotic, stress-related, and somatoform disorders	711 (17)	403 (13)	311 (11)
Mood disorders	1017 (25)	597 (19)	470 (16)
Schizophrenia and related disorders	356 (8.6)	126 (4.0)	86 (3.0)
Alcohol abuse and alcohol-related disorders	670 (16)	241 (7.7)	166 (5.7)
Substance abuse	273 (6.6)	59 (1.9)	17 (0.6)
Dentist visit			
Within 1 year	1768 (43)	1913 (61)	2107 (73)
Within 3 years	2325 (56)	2246 (72)	2404 (83)
Within 5 years	2615 (63)	2374 (76)	2485 (86)

(Table 1 continues on next page)

	Affluence level		
	Low	Medium	High
	n (%)	n (%)	n (%)
(Continued from previous page)			
Preadmission medication use			
Beta blockers	1591 (38)	1229 (39)	1046 (36)
ACE inhibitors	1219 (29)	944 (30)	837 (29)
Angiotensin–II–receptor blockers	741 (18)	611 (20)	582 (20)
Lipid-lowering drugs	1603 (39)	1216 (39)	1042 (36)
Antiplatelet drugs	1566 (38)	1174 (38)	1001 (35)
Anticoagulant drugs	1177 (28)	983 (32)	921 (32)
Glucocorticoids, systemic	592 (14)	509 (16)	380 (13)
Anxiolytics	505 (12)	333 (11)	273 (9.4)
Antidepressants	919 (22)	562 (18)	431 (15)
Antipsychotics	311 (7.5)	114 (3.7)	82 (2.8)

Abbreviation: ACE, angiotensin-converting-enzyme.

Table 1: **Characteristics of patients with first-time infective endocarditis hospitalisation by affluence level in Denmark, 2000–2022.**

Additional analyses

We conducted the following stratified analyses and sensitivity analyses:

(1) We stratified the main analysis by age groups (30–54, 55–69, 70–84, and ≥85 years) and sex.
(2) We investigated the IE incidence rate among people 18–29 years of age, using the educational level of the highest educated parent as SEP indicator.
(3) Since May 2019, Danish guidelines have stated that patients can be discharged to continued peroral treatment after ≥10 days of intravenous antibiotics (or ≥7 days after cardiac surgery) if the infection is under control and caused by certain microorganisms.[26] Therefore, our requirement of a ≥14-day admission length could have resulted in decreasing numbers of IE cases after 2019. We therefore changed the admission length criteria to ≥14 days prior to 2019 and ≥10 days thereafter.
(4) We investigated different SEP indicators encompassing household income, household wealth, and educational level. To avoid including people born prior to 1921, for whom data on educational level were limited, the study period was confined to 2010–2022 and restricted to individuals 30–89 years of age, when educational level was used as SEP indicator.
(5) To investigate whether inequality was driven solely by differences in prevalence of strong IE risk factors, we repeated the analysis after excluding people with a prosthetic heart valve or a complex congenital heart disease prior to the index date in each study year.[27] A similar approach was applied to people with a history of substance abuse.
(6) We examined the impact of dividing the population into quartiles instead of tertiles. Moreover, to investigate the association between IE incidence and affluence as a continuous variable, we used a Cox proportional hazards model with restricted cubic splines. The model examined the association between affluence rank (stabilised to range evenly from 0 to 1) and the hazard of IE incidence. The hazard rate at an affluence rank of 0.5 was used as the reference. Hazard ratios with 95% confidence intervals were plotted. For the latter analysis, data from the calendar year 2022 were used.
(7) To investigate the temporal change in patient characteristics, we tabulated the baseline characteristics by each affluence level and the following calendar years: 2000–2006, 2007–2014, and 2015–2022.

All analyses were conducted using RStudio version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics, approvals, and registration

According to Danish law, ethical approval and informed consent are not required for registry-based studies. The study was reported to the Danish Data Protection Agency through institutional registration at Aarhus University (serial number 3220).

Role of the funding source

None of the funding organisations had any role in the design and conduct of the study; in the collection, management, and analysis of the data; or in the preparation, review, and approval of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit.

Results

During the study period from 2000 through 2022, we identified an annual average of 3,641,263 people ≥30 years of age residing in Denmark with no history of IE. On average, the affluence level was missing for 16,673 (0.5%) people. By definition, each affluence level comprised 33% of the cohort.

Patient characteristics

Table 1 presents patient characteristics by affluence level. Patients with low affluence were younger than those with medium and high affluence (median age: 70 *vs.* 73 *vs.* 74 years). Sex and calendar-year distributions were similar across affluence levels. Patients with low affluence had lower educational levels and were more often living alone than medium and high affluence patients. Dental visits within 5 years prior to IE diagnosis were less frequent in low (63%) compared to medium (76%) and high (86%) affluence patients. Cardiovascular disease prevalence was similar, but valvular heart disease and prosthetic valve implantation were slightly less frequent in low-affluence patients. Low affluence was associated with higher frequencies of diabetes, chronic pulmonary and kidney disease, dialysis, liver disease, mental disorders, alcohol- and substance-related disorders. Preadmission medication use varied only slightly.

Temporal trends in incidence rate by affluence level

We identified in total 10,142 IE events over 81,692,491 person-years of follow-up. Per 100,000 person-years, the incidence rate increased from 8.7 in 2000 to 21.2 in 2022 for those with low affluence, from 7.4 to 14.3 for those with medium affluence, and from 6.2 to 13.1 for those with high affluence (Fig. 1). The AAPC was 4.3% (95% CI: 3.7%–5.1%) for those with low affluence, 3.5% (95% CI: 2.6%–4.5%) for those with medium affluence, and 3.7% (95% CI: 2.7%–4.9%) for those with high affluence.

Per 100,000 person-years, SII increased from 3.8 additional cases (95% CI: 0.4–7.3) in 2000 to a peak of 14.3 additional cases (95% CI: 9.4–19.1) in 2019 and subsequently declined to 12.3 (95% CI: 7.4–17.1) in 2022 (Fig. 2). The RII increased from 1.68 (95% CI: 0.90–2.44) in 2000 to a peak of 2.84 (95% CI: 1.80–3.88) in 2011 and subsequently declined to 2.13 (95% CI: 1.49–2.78) in 2022 (Fig. 2).

Additional results

(1) The age-stratified analysis showed that IE incidence was highest in the oldest age groups and increased over time for all affluence levels, except for stable trends in age group 30–54 years (Fig. 3). Incidence was highest in low-affluence patients, especially in age groups 30–54, 55–69, and 70–84 years. Males had a higher incidence than females, with rates rising over time for both sexes. Low affluence was associated with the highest incidence in both sexes (Fig. 4).

(2) When we investigated individuals 18–29 years of age and used the educational level of the parent with the highest educational level as a proxy for SEP, we did not observe a clear pattern of differences in the IE incidence rate; however, the

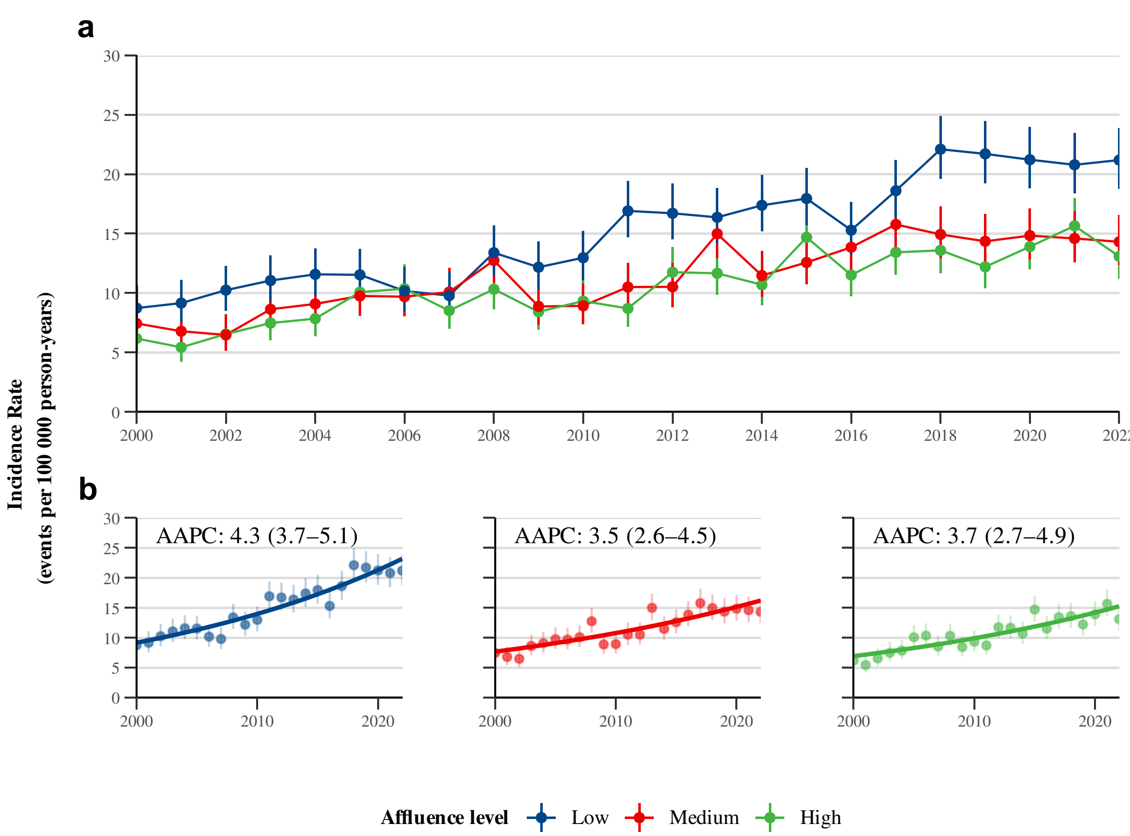

Fig. 1: Incidence rate of infective endocarditis per 100,000 person-years among people ≥30 years of age by affluence level in Denmark, 2000–2022. a) Point ranges represent the observed incidence rates and 95% confidence interval. Point ranges are connected by the solid line. b) Point ranges represent the observed incidence rates and 95 confidence interval. The solid lines represent the modelled incidence rates obtained from Join point regression analyses. Average annual percentage changes are provided as text labels. Abbreviation: AAPC, average annual percentage change.

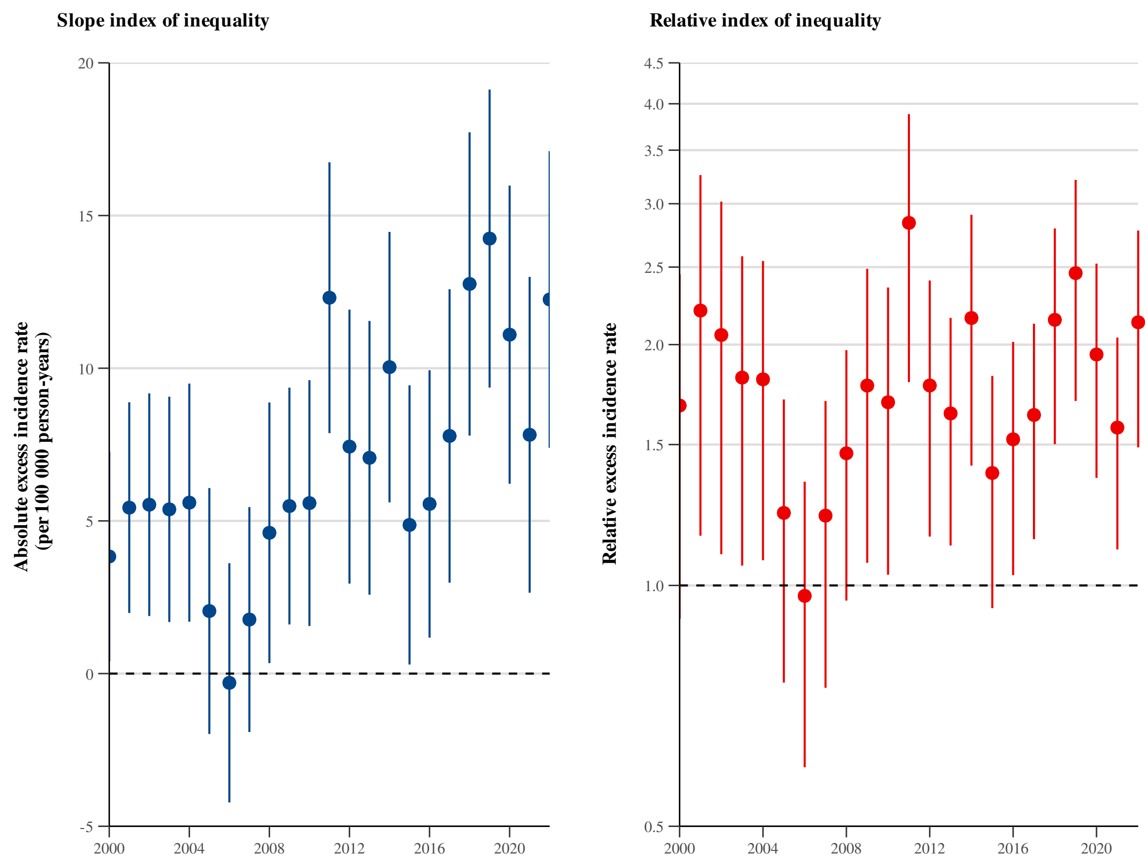

Fig. 2: Slope index of inequality and relative index of inequality of the infective endocarditis incidence rate among people ≥30 years of age across affluence levels. Denmark, 2000–2022.

incidence rates were often based on very few events, thus hindering any firm conclusions from being drawn (Figure S1);

(3) After the IE algorithm was changed to require only ≥10 days of hospitalisation for patients admitted after January 1, 2019, the incidence rate increased slightly in the years 2019–2022 but did so uniformly across all affluence levels (Figure S2);

(4) When household income level and household wealth level were used separately as SEP indicators, we observed no major differences in comparison with using the affluence level (Figure S3). When using educational level as SEP indicator, we observed the same trend of increasing incidence rate across all educational levels; however, the difference in IE incidence rate across educational level throughout the study period was expectedly greater than the differences across affluence level (Figure S3);

(5) After excluding people with complex congenital cardiac disease or prosthetic heart valve implantation, the incidence rate decreased for all affluence levels, but those with low affluence continued to have the highest incidence rates (Figure S4). Excluding people with a diagnosis of substance abuse did not change the overall observed differences in IE incidence rate across affluence levels (Figure S5).

(6) Dividing the population into quartiles instead of tertiles did not change the overall trend of rising IE incidence over time across all affluence levels (Figure S6). Incidence remained highest in low-affluence groups. Medium-low affluence had higher rates than medium–high and high groups. The SII and RII based on quartiles closely matched those from tertiles (Figure S7). Modelling IE hazard as a continuous non-linear function of affluence rank confirmed an inverse association across the entire affluence range (Figure S8).

(7) Across all affluence levels, the prevalence of the following characteristics increased in prevalence over time: median age, educational level, atrial fibrillation, valvular heart disease, prosthetic heart valve implantation, CIED implantation, hypertension, stroke, diabetes, hypercholesterolaemia, kidney disease, and cancer (Table S2).

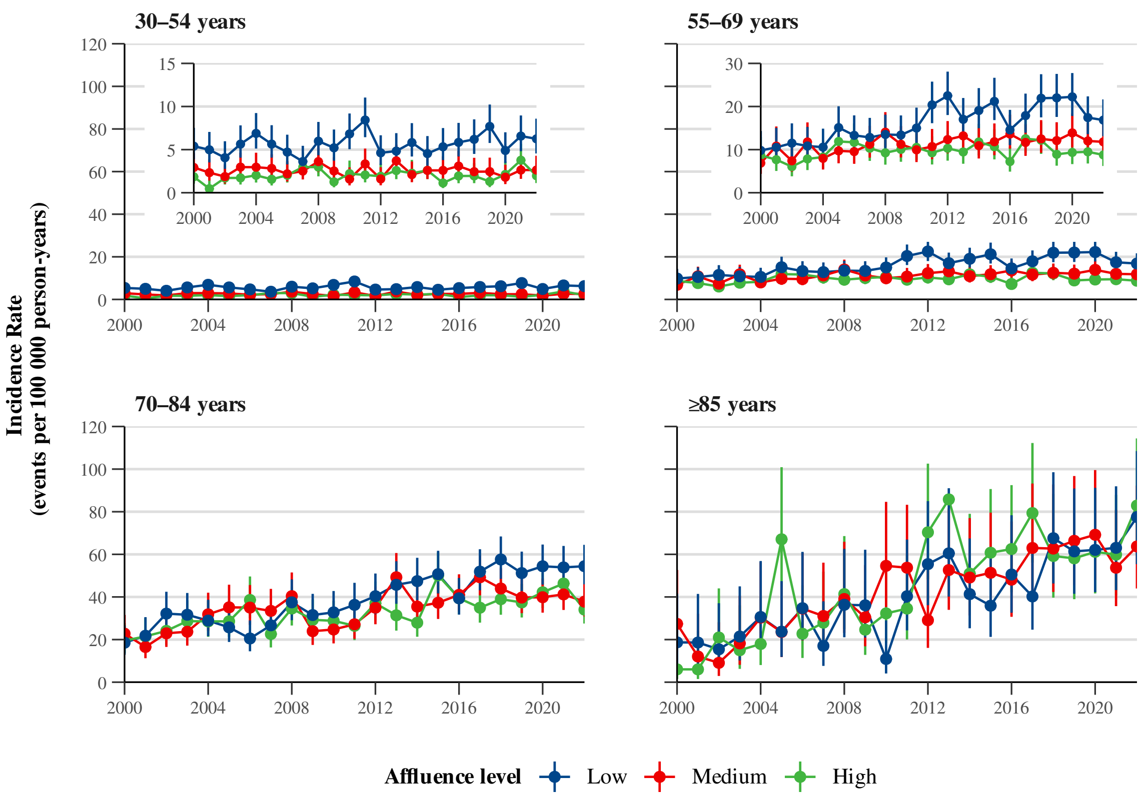

Fig. 3: Incidence rate of infective endocarditis per 100,000 person-years among people ≥30 years of age by affluence level and age group in Denmark, 2000–2022.

Discussion

The IE incidence rate increased across all affluence levels between 2000 and 2022. Throughout the study period, people with low affluence had the highest IE incidence rate. The relative increase in incidence was slightly higher among those with low affluence compared to those with medium and high affluence. Consequently, the relative inequality gradient remained rather stable, while the absolute inequality gradient widened. These findings were largely consistent across age groups, sex, and different SEP indicators and could not be explained by differences in the proportion of people defined at high risk of IE (complex congenital heart disease, prosthetic heart valve, and substance abuse).

Data from the Global Burden of Disease studies demonstrated an increase in the disability-adjusted life years lost due to IE from 1990 through 2021, with rising inequality.[28] Although national parameters rather than individual-level measures were used as SEP indicators. A Danish cohort study investigated the incidence rate of *S. aureus* bacteraemia and the subsequent rate of IE by educational level and showed a higher rate of bacteraemia with each incremental decrease in educational level.[9] Among those with bacteraemia, educational level did, however, not appear to influence the subsequent progression to IE, except for the lowest educated group where the point estimate suggested a higher rate than that for the highest educated group (incidence rate ratio: 1.20; 95% CI: 0.79–1.81). These results suggest that a higher rate of bacteraemia with typical endocarditis bacteria among those with low affluence compared with those with higher affluence may be the main driver of inequality. In a Scottish study reporting on the incidence rate and outcomes of IE,[12] the baseline characteristics included the Scottish Index of Multiple Deprivation, an area-level SEP indicator encompassing information on multiple domains. In agreement with our findings, the most deprived individuals constituted a higher proportion of patients with IE than the least deprived individuals throughout the study period (1990–2014).

The mechanisms underlying the inequality in IE incidence rate remain speculative. We did not find evidence supporting that inequality was driven solely by differences across affluence levels in strong IE risk factors, *i.e.*, complex congenital cardiac disease, prosthetic heart valves, or substance abuse. Importantly, we lacked available information on the microbiological aspects of IE, such as the causative microorganism, the

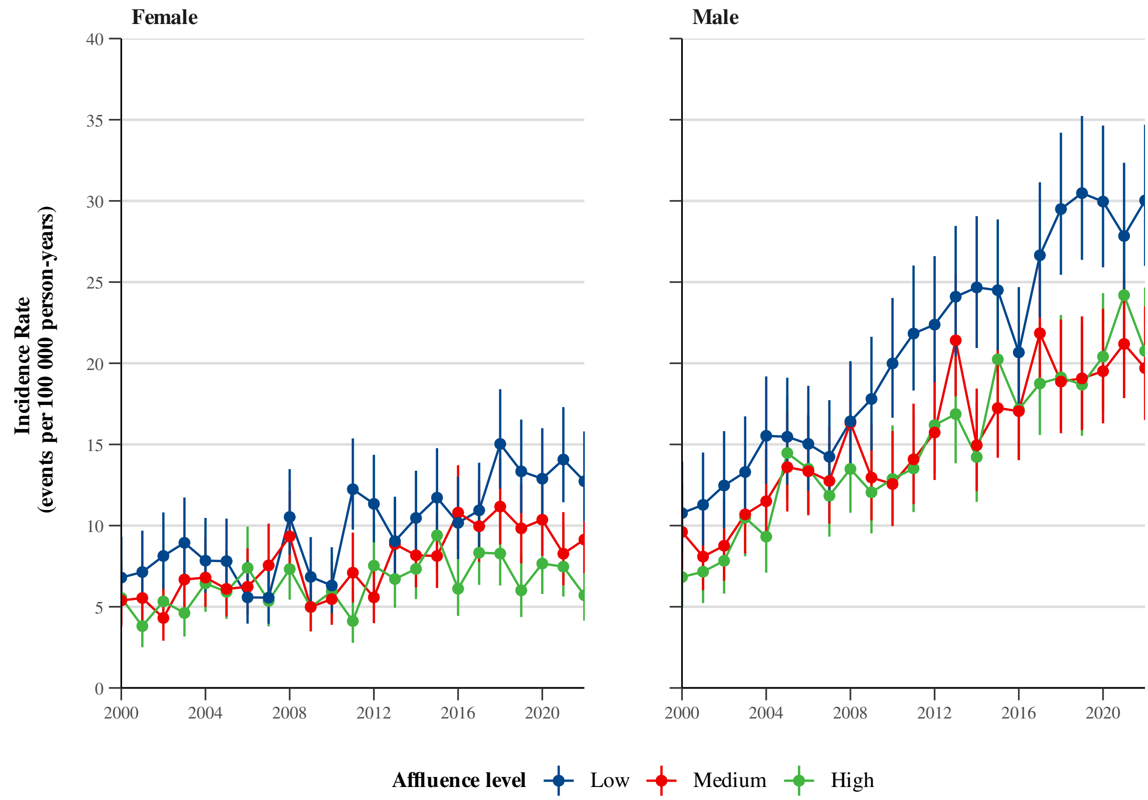

Fig. 4: Incidence rate of infective endocarditis per 100,000 person-years among people ≥30 years of age by affluence level and sex in Denmark, 2000–2022.

route of entry (*e.g.*, dental focus, invasive procedures, or intravenous drug use), and the site of infection. However, a lower frequency of dental visits within 5 years prior to IE diagnosis (used as an indicator of dental status) and a higher frequency of dialysis among those with low affluence may have indicated a contribution from these routes of entry. Additional detailed clinical information could aid in clarifying the drivers of the elevated IE risk among those with the lowest affluence level. Further studies are thus highly warranted to identify underlying modifiable social determinants of health that may curb the rise in IE incidence, particularly among disadvantaged socioeconomic groups.

The overall rise in IE incidence is likely driven by multiple factors. These include advancements in imaging and microbiological diagnostics, an ageing population, and increasing exposure to healthcare-related risk factors, such as prosthetic heart valve implantation, cardiac implantable electronic device implantation, invasive procedures, and hospitalisations.[5] The similar proportionate increase in IE incidence across socioeconomic groups may thus partly reflect equitable healthcare access. Paradoxically, this equitable healthcare access may have contributed to the widening absolute inequality, given the higher baseline IE risk in lower socioeconomic groups.

The peak in absolute inequality in IE incidence rate in 2019, followed by a decline from 2020 to 2022, raises the question about any impact of the COVID-19 pandemic. Potentially, the pandemic and ensuing intensified hygienic precautions and populational-level restrictions decreased the incidence rate among those with low and medium affluence levels, while the rates among those with high affluence remained unaffected. However, the incidence rate peaked already in 2018 among those with low affluence and primarily showed regular variations among those with medium affluence from 2016 and onwards. Additionally, a Danish study revealed no difference in the overall IE incidence rate when comparing 2020 with 2018/2019.[29] Any impact of the COVID-19 pandemic is thus not convincingly clear.

Several limitations must be acknowledged when interpreting the validity of our findings. Because of the population-based and nationwide design in a country with universal health care and the possibility of having virtually complete follow-up, selection of specific groups and loss to follow-up were minor concerns.

We used the affluence level as the main indicator of SEP, but acknowledge that other commonly used indicators, *e.g.,* educational level, could have been preferred. However, using educational level in examining temporal trends has shortcomings: The main concern relates to the overall increase in educational attainment at the population level throughout the study period (Figure S9). The group of people with a low educational level thus were likely to represent an increasingly homogeneous and disadvantaged group with poor health status and health literacy. Accordingly, we may have observed increasing inequality across educational levels over time because of this aspect alone.[30] However, the SII and RII would have taken these dynamics into account, to a certain extent. In addition, educational level was available for only a few people born prior to 1921, thus confining the length of the study period if inclusion of people of high age were warranted. On the contrary, educational level has several advantages, *e.g.,* providing a relatively simple measure that also captures characteristics such as knowledge, skills, health literacy, and prestige, and being established early in adult life, thus minimising the risk of reverse causation. Importantly, however, the overall conclusion did not change when different indicators were used.

Given that a record of IE in the DNPR has a positive predictive value of 90%,[19] some misclassifications were likely but probably independent of affluence level. Identifying people with substance abuse using diagnosis codes and redeemed prescriptions has not been validated but is inherently prone to misclassification since people with substance abuse may not have a hospital record of substance abuse or receive medications; Likewise, some people may have a history of substance abuse without such exposure causing the IE.

The additional analyses in which people with strong risk factors for IE were removed may be acceptable because affluence level was based on income and wealth value in the prior 3 years; hence the IE risk factors may have confounded rather than mediated the association between affluence level and IE. On the other hand, because the affluence level could also be considered a proxy for a person's overall adult-life SEP, some risk factors (particularly degenerative heart valve disease leading to prosthetic heart valve implantation) could be considered mediators. Hence, a restriction-based analysis could be problematic because some of the effects of affluence level on IE were removed when excluding mediators.

The socioeconomic and healthcare contexts in Denmark may differ from other countries, so our findings should be transported beyond the Nordic countries with caution.

In conclusion, the IE incidence rate increased in all affluence levels between 2000 and 2022, with the lowest affluence group consistently exhibiting the highest rates. While the relative inequality remained rather stable, the absolute inequality widened throughout the study period. Our study reinforces the importance of socioeconomic factors in determining health risks.

Contributors

SKM, MS, HEB, and HTS had the study idea. All authors contributed to the design of the study. HTS acquired the data. HTS and SKM verified the data and had access to raw data. SKM carried out the statistical analyses. SKM wrote the initial draft. All authors contributed to the discussion and interpretation of the results, which secured the intellectual content of the manuscript. All authors accepted the final version for submission.

Data sharing statement

The supporting individual-level data used for this study are not publicly available but can be obtained by application to the Danish Health Data Authority.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used Microsoft Copilot, powered by GPT-4 and Grammarly in order to improve readability and language. After using this service, the authors reviewed and edited the content as needed and takes full responsibility for the content of this publication.

Declaration of interests

SKM, MS, KKS, HEB, and HTS report that the Department of Clinical Epidemiology, Aarhus University, receives funding for other studies in the form of institutional research grants to (and administered by) Aarhus University. The Department of Clinical Epidemiology, Aarhus University, confirms that none of these studies have any relation to the present study. HEB reports participation in a Data Safety Monitoring Board for to the following studies: Danish CRT Study DSMB (NCT03280862); Comparison of Eligible TAVI-valves DSMB (NCT04443023); and Intravascular Ultrasound Guidance for Complex High-risk Indicated Procedures DSMB (NCT04854070).

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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.2025.101267.

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