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Direct and indirect effects of socioeconomic status on sepsis risk and mortality: a mediation analysis of the HUNT Study

Running title: Direct and indirect effects of socioeconomic status on sepsis

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Abstract

Background

Socioeconomic status (SES) may influence risk of sepsis and sepsis-related mortality, but to what extent lifestyle and health-related factors mediate this effect is not known.

Methods

The study included 65,227 participants of the population-based HUNT Study in Norway linked with hospital records to identify incident sepsis and sepsis-related deaths. Cox regression estimated hazard ratios of sepsis risk and mortality associated with different indicators of SES, whereas mediation analyses were based on an inverse odds weighting approach.

Results

During ~23 years of follow-up (1.3 million person-years), 4200 sepsis cases and 1277 sepsis-related deaths occurred. Overall, participants with low SES had a consistently increased sepsis risk and sepsis-related mortality using education, occupational class, and financial difficulties as indicators of SES. Smoking and alcohol consumption explained 57% of the sepsis risk related to low education, whereas adding risk factors of cardiovascular disease and chronic diseases to the model increased the explained proportion to 78% and 82%, respectively.

Conclusion

This study shows that SES is inversely associated with sepsis risk and mortality. Approximately eighty percent of the effect of education on sepsis risk was explained by modifiable lifestyle and health-related factors that could be targets for prevention.

Key words

Sepsis, socioeconomic factors, mediation analysis, education, occupations, risk factors.

Key message

What is already known on this topic:

- Socioeconomic status has been inversely associated with sepsis risk and mortality, but population-based studies using individually assessed socioeconomic status are lacking.
- Identification of modifiable mediators between socioeconomic status and sepsis risk can help prevent sepsis.

What this study adds:

- Low socioeconomic status, measured as education, occupation, or financial difficulties, is associated with increased sepsis risk and mortality.
- Modifiable lifestyle and health-related factors explained 80% of the increased sepsis risk associated with low education.
- Promoting improvement in health-related behaviours, particularly among groups with low socioeconomic status, have a large potential for reducing social disparities in sepsis risk

How this study might affect research, practice or policy:

- Causal mediation analyses can identify modifiable factors that can be targets for preventive efforts.

INTRODUCTION

Sepsis is a dysregulated immune response that can arise from any infection and lead to life threatening tissue damage and organ failure.[1] Sepsis affects 48.9 million people globally and accounts for 11 million deaths annually.[2] The reported mortality varies between 26 and 80% and depends on microbe, infection site, and access to timely evidence-based treatment.[3-5] Socioeconomic status (SES), whether measured as education, occupational class or income, has been inversely related to various health conditions, diseases and causes of death.[6] Evidence suggests that the detrimental health effects of low SES are shaped by circumstances throughout life, including in utero and early childhood, living conditions, economic resources, social capital, coping resources and health-related behaviour.[6-8] However, the precise mechanisms relating low SES to higher morbidity and mortality are likely to be heterogeneous and specific to each disease, and may also vary according to national legislations and social support systems.[6] Although Norway has an universal health and welfare system,[9] disparities in health and disease are evident.[10 11] Identifying factors that can mitigate such disparities or their consequences are therefore crucial.

SES has been inversely associated with risk of sepsis,[12 13] sepsis-related mortality[12 14-17] and readmissions due to sepsis.[18] Even studies conducted in countries with an universal welfare system indicate socioeconomic disparities in sepsis and bacteraemia.[19-23] However, these studies have either been conducted on selected data in a clinical setting or only used aggregated data on SES, such as neighbourhood indexes. Mediators of the effect of low SES on risk of sepsis have been suggested, but the existing literature is deficient.[23] Potential mediators of the association between low SES and risk of sepsis are likely to involve known risk factors for sepsis since SES may influence the distribution of these risk factors in a population.[7 24] This include age, obesity, alcoholism, smoking, and a range of chronic diseases such as heart disease, lung disease, diabetes, kidney disease, and cancer.[25]

To our knowledge, no previous study has examined the relation between individual SES and risk of sepsis and sepsis-related mortality in a population-based cohort. Therefore, the main aim was to prospectively examine the effect of individually assessed SES on risk of a first sepsis episode and on sepsis-related mortality in the population-based HUNT study. Secondly, we examined to what extent the effect of SES on sepsis risk is mediated by known risk factors for sepsis.

METHODS

STUDY DESIGN AND POPULATION

We used data from the second and third surveys of the population-based HUNT Study in Norway (HUNT2, 1995-1997 and HUNT3, 2006-2008). All inhabitants aged 20 years or older in the geographical region of Nord-Trøndelag were invited, and 65,237 (69.5%) participated in HUNT2 and 50,807 (54.1%) participated in HUNT3. All participants filled in comprehensive questionnaires on a range of lifestyle and health related factors and met for a clinical examination and blood sampling.[26] More details on sampling procedures and data collection can be found in the following sections. The HUNT Study also contains information of migration and death, and this information is regularly updated from the National Population Register.

Overall, 61,759 participants at HUNT2 had questionnaire-based information on education and could be linked to hospital records on sepsis diagnosis. These constitute the sample for the main analysis on the effect of education, since information on education was not obtained at HUNT3. For the analyses of occupational class, social benefits, and financial difficulties we restricted the sample to those aged <70 years at HUNT2. A total of 54,543 were included in the analysis of social benefits, whereas slightly fewer had information on occupation class (n=39,130) and financial difficulties (n=44,727). To increase the statistical power in the analyses of occupation class, we also conducted additional analyses including 12,150 participants from HUNT3 with data on occupational class. Thus, the total sample for this analysis was 51,280 subjects. Information on social benefits and financial difficulties was not collected at HUNT3.

The study was approved by the Regional Committee for Ethics in Medical Research (reference number 173525).

OUTCOME VARIABLES AND FOLLOW UP

Data from the HUNT Study was linked to hospital records from the Nord-Trøndelag Hospital Trust (i.e., Levanger and Namsos Hospitals) and St. Olavs University Hospital to obtain date of sepsis diagnoses and death for HUNT participants from 1995 throughout 2019. The sepsis diagnosis was defined as either explicit or implicit sepsis based on International Statistical Classification of Diseases and Related Health Problems (ICD) codes, 9th- and 10th edition. Explicit sepsis is a set of codes previously used to define sepsis, whereas implicit sepsis is based on clinically relevant codes of serious infection combined with organ dysfunction coded at the same time. The infection must be coded as the main diagnosis and organ dysfunction as a secondary diagnosis. The codes used in this study is a Norwegian version of the list used by Thompson et al.[27] In the present study, incident sepsis was defined as the first event registered in the hospital records. Sepsis-related mortality was defined as a death where sepsis had occurred within the current or prior calendar month. Participants were followed from date of participation in the HUNT Study until date of sepsis, death, emigration, or end-of follow-up (31st December 2019), whichever occurred first.

SOCIOECONOMIC STATUS

SES was assessed by questionnaire data on education, social benefits, and financial difficulties, whereas information on occupational class was obtained from a structured interview. Highest completed education was self-reported at the HUNT2 survey and categorised as: 1) primary school, 2) vocational high school, 3) academic high school, 4) less than 4 years university, or 5) more than 4 years university. In the mediation analysis, education was re-classified as high (category 1 and 2) or low (category 3 and 4).

Occupation was categorised according to the international Erikson Goldthorpe Portocarero (EGP) social class scheme: Class I, II, III, IV, V + VI, or VII. Class I is considered the highest SES and consist of self-employed higher-grade professionals; Class II is management position in public or private organisation; Class III is professional occupations; Class IV non-professional occupation; Class IV is other self-employed, farmers or fishermen; Class V + VI is skilled manual workers, artisan, supervisor, or manual workers; and class VII is unskilled manual workers or drivers.[11 28] Only participants <70 years were asked about their occupation. In HUNT3 occupation was classified by Standard Classification of Occupations,[29] and converted to the occupational EGP used in HUNT2.

Information on economy was obtained from two questions in HUNT2. First, recipients of social benefits were defined as those who reported sick pay/rehabilitation benefits, retraining benefits, disability pension, family income supplement, unemployment benefits and/or transitional benefits. Second, the question: “During the last year, has it at any time been difficult to meet the costs of food, transportation, housing, and such?" with response options "no, never", "yes, though seldom", "yes, sometimes", or "yes, often" was used to indicate financial difficulties.

MEDIATORS

All mediators were obtained from HUNT2. Smoking status was categorised as never, former, and current daily smoker based on several smoking related questions. Alcohol use was categorised as <1, 1-7, 8-14, or ≥15 units per 2 weeks. Body mass index (BMI) was calculated as the participants measured weight divided by their height squared (kg/m^2), and classified into six categories as recommended by the World Health Organization: <18.5, 18.5-24.9, 25.0-29.9, 30.0-34.9, 35.0-39.9 or ≥40.0 kg/m^2.[30] Systolic blood pressure was measured by trained nurses, and we used the mean of the second and third measurement. Non-high-density-lipoprotein cholesterol (non-HDL cholesterol) is the difference between total cholesterol and HDL cholesterol. Included chronic diseases are self-reported cardiovascular disease (stroke, angina pectoris, and/or myocardial infarction), lung disease (asthma), diabetes, cancer, and chronic renal disease obtained from standardised measurement of serum creatinine and set as estimated glomerular filtration rate (eGFR) <60 ml/min.

STATISTICAL ANALYSES

We used Cox regression to estimate hazard ratios (HRs) for sepsis and sepsis-related mortality associated with the SES variables. The precision of the estimates was assessed by a 95% confidence interval (CI). The groups with highest SES were used as reference in all analyses, except for occupation where EGP class II was used as reference due to few participants in EGP class I. The analyses of education and occupation were adjusted for age (as timescale) and sex. The analyses of social benefit and financial benefits were controlled for sex, age (as timescale), BMI, smoking and chronic diseases. Multiple imputation by fully conditional specification was used to impute missing data on BMI (666 participants without measures of height or weight) and smoking (1062 participants did not answer the relevant questions). We generated 10 complete datasets and used Cox regression to estimate HRs for sepsis and sepsis-related mortality associated with social benefits and financial difficulties.

The proportional hazards assumption was assessed by log-log plots of survival and test of Schoenfeld residuals. Due to violation of the PH assumptions, potential confounding by sex on occupation was controlled for using the stratified Cox procedure.

We conducted additional analyses to assess the robustness of the results. First, we added HUNT3 participants with occupational information to increase the sample size. Second, there was some evidence of non-proportional hazards related to education when using attained age as the time scale (i.e., suggesting that the effect of education could be underestimated). We therefore repeated the analysis using time on study since HUNT2 as the timescale and controlled for age as a continuous variable (years). Finally, we conducted separate analyses for the association between occupation and risk of sepsis for men and women and examined effect modification by sex. Statistical interaction was assessed by a likelihood-ratio test of a product term of occupation and sex.

To estimate mediation of the association between education and sepsis we used the inverse odds weighting (IOW) approach.[31] IOW estimates the natural direct effect, from education on risk of sepsis, and the natural indirect effect, through three models of mediators, from education on risk of sepsis.[32] Only participants with complete information on all chosen mediators were included in the analysis. The main effect was therefore recalculated in this restricted sample using low or high education as the exposure variable. Instead of analysing single mediators separately we chose to combine several related mediators into three models. The first model includes health-related behaviours: smoking and use of alcohol. The second model adds risk factors of cardiovascular disease: BMI, systolic blood pressure and non-HDL cholesterol. And the third model added chronic diseases: cardiovascular disease, lung disease, diabetes, cancer, and chronic renal disease. Age and sex were controlled for as covariates. CIs for the total effect, the natural direct effect, and the natural indirect effect were obtained from bootstrapping with 1000 replications.[32] The effects are presented as HRs with percentile-based 95% CIs. The proportion mediated was calculated by dividing the natural indirect effect by the total effect.

All statistical analyses were conducted using Stata for MacOS X, version 17.0 (StataCorp LP, College Station, Texas).

RESULTS

In the study population of 65,227 participants, 4200 sepsis cases and 1277 sepsis-related deaths occurred during a median follow up of 23 years (1,294,051 person-years). Baseline characteristics of the HUNT2 study sample are presented in Table 1, stratified by education.

Table 1. Baseline characteristics of the study sample (HUNT2, 1995-97)

	High[a] education	Medium[a] education	Low[a] education
Total number of participants (%)	12,306 (20)	26,769 (43)	22,684 (37)
Age, mean (SD)	42.8 (13.53)	42.9 (15.0)	60.0 (14.83)
Sex, n (%)			
Women	6,525 (53)	12,841 (48)	13,267 (58)
Men	5,781 (47)	13,928 (52)	9,417 (42)

Occupation, EGP classes, n (%)			
Class I	2,355 (19)	1,134 (4)	302 (1)
Class II	5,124 (42)	1,601 (6)	277 (1)
Class III	901 (7)	5,114 (19)	2,317 (10)
Class IV	482 (4)	3,799 (14)	2,856 (13)
Class V + VI	208 (2)	3,580 (13)	1,217 (5)
Class VII	243 (2)	3,347 (13)	3,610 (16)
Missing	2,993 (24)	8,194 (31)	12,105 (53)
Receiving social benefits, n (%)			
No	10,815 (88)	20,834 (78)	11,891 (52)
Yes	976 (8)	4,181 (16)	4,259 (19)
Missing	515 (4)	1,754 (7)	6,536 (29)
Financial difficulties last year, n (%)			
No, never	7,731 (63)	13,418 (50)	9,101 (40)
Yes, though seldom	1,409 (11)	3,746 (14)	1,722 (8)
Yes, sometimes	713 (6)	2,480 (9)	1,599 (7)
Yes, often	243 (2)	919 (3)	648 (3)
Missing	2,210 (18)	6,206 (23)	9,614 (42)
Smoking, n (%)			
Current	2,257 (18)	8,463 (32)	7,029 (31)
Former	2,978 (24)	7,015 (26)	6,607 (29)
Never	6,898 (56)	10,918 (41)	8,532 (38)
Alcohol (units per 2 weeks), n (%)			
<1	3,168 (26)	7,770 (29)	11,926 (53)
1-7	6,732 (55)	14,112 (53)	7,907 (35)
8-14	1,748 (14)	3,346 (12)	1,416 (6)
≥15	530 (4)	1,030 (4)	363 (2)
BMI (kg/m^2), mean (SD)	25.5 (3.7)	26.0 (3.9)	27.1 (4.3)
Systolic blood pressure (mmHg), mean (SD)	129.8 (17.2)	133.0 (18.5)	145.8 (23.5)
Non-HDL cholesterol (mmol/L), mean (SD)	4.1 (1.2)	4.3 (1.2)	5.0 (1.3)
Past medical history, n (%)			
Lung disease	954 (8)	2,326 (9)	2,187 (10)
Cardiovascular disease	357 (3)	1,206 (5)	3,082 (14)
Diabetes	176 (1)	466 (2)	1,110 (5)
Cancer	340 (3)	524 (3)	1,187 (6)
Chronic kidney disease	228 (2)	539 (2)	1,757 (8)

Abbreviations: SD = standard deviation, EGP = Erikson Goldthorpe Portocarero, BMI = body mass index, HDL = high density lipoprotein.

[a]Education defined as high (completed university), medium (completed high school) and low (completed primary school).

Overall, low SES was associated with an increased risk of sepsis (Table 2). Compared with the reference group of ≥4 years of university education, the HRs for persons with vocational high school and primary school were 1.30 (95% CI: 1.12-1.51) and 1.40 (95% CI: 1.21-1.63), respectively. The HRs associated with EGP social class V + VI (skilled manual workers, artisan, supervisor, or manual workers) and VII (unskilled manual workers) were 1.21 (95% CI: 1.02-1.44) and 1.38 (95% CI: 1.18-1.60), respectively, compared to social class II (management positions in public or private organisation). Participants receiving social benefits had a HR of 1.43 (95% CI: 1.32-1.54) compared to the participants receiving no social benefits, whereas the HRs were 1.30 (95% CI: 1.14-1.48) for those who sometimes had financial difficulties and 1.69 (95% CI: 1.40-2.03) for those who often had financial difficulties.

Expanding the sample size by including HUNT3 participants to the analysis of occupation gave largely similar results as described above, but with somewhat higher precision (Supplementary Table S1). The HRs were 1.18 (95% CI: 1.00-1.39) for participants in EGP social class V + VI and 1.35 (1.17-1.56) for class VII, compared to class II. In Supplementary Table S2, the HR comparing primary school to ≥4 years of university education was somewhat attenuated when age was included as the timescale (HR: 1.19, 95% CI: 1.03-1.39).

Analyses stratified by sex (Supplementary Tables S3 and S4) suggest somewhat stronger effect of occupational class in men than in women, where men in EGP social class VII had a HR for sepsis of 1.64 (95% CI: 1.32-2.04), whereas women in the same class had a HR of 1.13 (95% CI: 0.91-1.41), both compared to social class II. Men in EGP social class V + VI had a HR for sepsis of 1.29 (95% CI: 1.03-1.60), while the HR for women was 1.41 (95% CI: 0.95-2.09), both compared to class II. This was also supported by the interaction test (P=0.053).

Table 2. Hazard ratio (HR) for sepsis associated with indicators of socioeconomic status (SES) in HUNT2 (1995-97)

SES variables	No. of person-years	No. of sepsis cases	Rate per 10 000 person-years	Adjusted[a] HR	95% CI
Education					
University, 4 years or more	103,305	197	19	1.00	Reference
University, less than 4 years	167,440	278	17	1.07	(0.89-1.28)
High school, academic	130,776	141	11	1.07	(0.87-1.33)
High school, vocational	444,669	1136	26	1.30	(1.12-1.51)
Primary school	399,514	2082	52	1.40	(1.21-1.63)
Occupation (EGP classes)[b]					
I	82,874	234	28	1.08	(0.90-1.29)
II	157,884	267	17	1.00	Reference
III	186,687	389	21	1.16	(0.99-1.36)
IV	155,874	526	34	1.17	(1.01-1.36)
V + VI	110,529	284	26	1.21	(1.02-1.44)
VII	159,704	443	28	1.38	(1.18-1.60)
Social benefit[c]					
No	978,112	2195	22	1.00	Reference
Yes	202,528	901	44	1.43	(1.32-1.54)
Financial difficulties last year[d]					
No, never	669,206	1829	27	1.00	Reference
Yes, though seldom	155,177	315	20	1.26	(1.11-1.42)
Yes, sometimes	107,146	265	25	1.30	(1.14-1.48)
Yes, often	40,063	123	31	1.69	(1.40-2.03)

Abbreviations: CI = confidence interval, EGP = Erikson Goldthorpe Portocarero.

[a]Education is adjusted for age (years) and sex (men, women), and time on study is used as timescale. Occupation is adjusted for age (as timescale) and stratified by sex (men, women). Social benefit and financial difficulties last year are adjusted for age (as timescale), sex (men, women), BMI (kg/m^2), smoking (current, former, never), and chronic diseases (cardiovascular disease, lung disease, diabetes, cancer, chronic kidney disease).

[b,c,d]Only among participants aged <70 years.

The total effect, natural direct effect, and natural indirect effect of low versus high education on risk of sepsis are presented in Table 3. The HR for sepsis in persons with low compared to high education was 1.28 (95% CI: 1.13-1.46) in the restricted sample with information on all possible mediators. Health-related behaviours explained 57% of the total effect between education and risk of sepsis. Adding risk factors of cardiovascular disease increased this proportion to 78%, whereas health behaviours, risk factors of cardiovascular disease and chronic diseases combined explained 82%.

Table 3. Hazard ratios (HRs) for total, direct and indirect effects of education on risk of sepsis from inverse odds weighted mediation analyses

Mediating variables and mediating effects	HR (95% CI)
Mediation by health-related behaviour	
Total effect	1.28 (1.13-1.46)
Natural direct effect (NDE)	1.11 (0.98-1.27)
Natural indirect effect (NIE)	1.15 (1.11-1.20)
Proportion mediated	57 %
Mediation by health-related behaviour and risk factors of cardiovascular disease	
Total effect	1.28 (1.13-1.46)
Natural direct effect (NDE)	1.06 (0.92-1.20)
Natural indirect effect (NIE)	1.22 (1.17-1.28)
Proportion mediated	78 %
Mediation by health-related behaviour, risk factors of cardiovascular disease and chronic diseases	
Total effect	1.28 (1.13-1.46)
Natural direct effect (NDE)	1.05 (0.92-1.19)
Natural indirect effect (NIE)	1.23 (1.18-1.29)
Proportion mediated	82 %

Abbreviations: CI = confidence interval.

Overall, the analyses of sepsis-related mortality gave largely similar HRs as those observed for sepsis risk (Table 4). Educational attainment at the level of vocational high school and primary school was associated with HRs of 1.20 (95% CI: 0.88-1.64) and 1.32 (95% CI: 0.98-1.79), respectively, compared to ≥4 years of university education. Those receiving social benefits and those who often had financial difficulties had HRs of 1.51 (95% CI: 1.29-1.76) and 1.53 (95% CI: 1.02-2.30) compared to not receiving social benefits/having financial difficulties, respectively. The association between EGP social classes and sepsis-related mortality were somewhat stronger than for sepsis risk, where those on class V + VI and class VII had HRs of 1.58 (95% CI: 1.11-2.24) and 1.63 (95% CI: 1.18-2.25), respectively, compared to social class II.

Expanding the samples size with HUNT3 participants in the analyses of occupational class gave similar results as the main analysis (Supplementary Table S5). The HRs in EGP social class V + VI and VII were 1.62 (95% CI: 1.15-2.29) and 1.72 (95% CI: 1.25-2.36), respectively.

Table 4. Hazard ratio (HR) for sepsis-related mortality associated with indicators of socioeconomic status (SES) in HUNT2 (1995-97)

SES variables	No. of person-years	No. of mortality cases	Rate per 10 000 person-years	Adjusted[a] HR	95% CI
Education					
University, 4 years or more	104,125	46	4	1.00	Reference
University, less than 4 years	168,553	71	4	1.19	(0.82-1.73)
High school, academic	131,458	27	2	0.98	(0.61-1.57)
High school, vocational	449,404	277	6	1.20	(0.88-1.64)
Primary school	406,388	680	17	1.32	(0.98-1.79)
Occupation (EGP classes)[b]					
I	83,785	51	6	1.02	(0.69-1.51)
II	159,139	54	3	1.00	Reference
III	188,411	91	5	1.31	(0.93-1.84)
IV	157,919	121	8	1.13	(0.81-1.56)
V + VI	111,506	85	8	1.58	(1.11-2.24)
VII	161,556	116	7	1.63	(1.18-2.25)
Social benefit[c]					
No	986,796	538	5	1.00	Reference
Yes	206,271	245	12	1.51	(1.29-1.76)
Financial difficulties last year[d]					
No, never	676,545	468	7	1.00	Reference
Yes, though seldom	156,488	67	4	1.21	(0.93-1.56)
Yes, sometimes	108,385	63	6	1.32	(1.02-1.73)
Yes, often	40,510	25	6	1.53	(1.02-2.30)

Abbreviations: CI = confidence interval, EGP = Erikson Goldthorpe Portocarero.

[a]Education and occupation is adjusted for age (as timescale) and sex (men, women). Social benefit and financial difficulties last year are adjusted for age (as timescale), sex (men, women), BMI (kg/m^2), smoking (current, former, never), and chronic diseases (cardiovascular disease, lung disease, diabetes, cancer, chronic kidney disease).

[b,c,d]Only among participants aged <70 years.

DISCUSSION

This large population-based study shows that low SES, determined by either educational attainment, occupational class and financial difficulties, is associated with a 40 to 70 percent increased risk of sepsis and sepsis-related mortality compared to high SES. The increased risk of sepsis among participants with low education was to a large extent mediated by established and modifiable risk factors for sepsis that could provide targets for preventive efforts.

These results are in line with a case-control study where persons in the lowest third of education had a two-times higher odds of sepsis and the lowest third of personal annual income had nearly three times higher odds of bacteraemia compared to the highest third.[23] Another study used group-level SES and reported a higher risk of sepsis among participants living in Sepsis Belt and Sepsis Cluster. The Sepsis Belt and Sepsis Cluster were identified as regions with higher rates of sepsis-related mortality. The association between living in given regions and higher odds of sepsis tended to be mediated by a higher level of poverty.[13]

To our knowledge, there are no previous population-based studies on sepsis-related mortality. However, studies have reported reduced survival of sepsis in patients residing in neighbourhoods with the lowest income,[17] and that sepsis patients in the lowest third of education and income had increased 30-day mortality compared to the highest third.[22] Moreover, an ICU cohort reported an increased 30-day mortality in the group with lowest education compared to the highest groups.[21]

Moreover, this is the first study to perform causal mediation analysis to explain the association between low SES and increased risk of sepsis. The IOW approach enables analysing multiple mediators at once, both continuous and categorical, and are robust to mediator-outcome confounding.[32] Smoking and use of alcohol mediated over half of the effect of low education on risk of sepsis. Cigarette smoking is associated with increased susceptibility to several bacterial infections. Several mechanisms have been suggested to increase the risk of bacterial infections: Tobacco induces physiological and structural changes in the human body, it can interact with bacteria and increase their virulence, and it also leads to a dysregulation of both the innate and adaptive immune system.[33] Moderate and high alcohol consumption can influence the function of several immune cells and lead to diminished immune responses.[34] Risk factors of cardiovascular disease, systolic blood pressure, non-HDL cholesterol and BMI, combined with health behaviours explained more than three quarters of the effect of education on sepsis. HDL cholesterol is a protective factor of sepsis as it can suppress inflammatory responses, induce reparation of damaged endothelium and prevent activation of thrombosis.[35] An unhealthy diet and physical inactivity raises the levels of total cholesterol and increases the amount of non-HDL cholesterol. Obesity and diabetes leads to a persistent dysregulation of the immune system. This results in chronic low-grade inflammation and a shift to a pro-inflammatory state.[36] Mediation by lifestyle and health-related factors was only assessed for sepsis risk and not for sepsis-related mortality. It is likely that other factors could mediate mortality rates, since these are partly determined by the prognosis of sepsis.[37]

Lifestyle and health-related behaviours differ among socioeconomic groups. Low SES is associated with less personal control and limited ability to influence future outcomes, which leads to a more present-oriented behaviour, a behaviour that prioritises present over future needs.[38 39] This disinvestment in the future is considered an appropriate response to structural and ecological factors within the given context. Evolutionary theorethical models of extrinsic mortality and ageing suggest that extrinsic mortality risk will lead to disinvestment in future health outcomes and models of feedback and feedforward processes implies that positive feedback loops can amplify initital small differences into large disparities.[39 40] In addition, behavioural responses can be affected by differences in how rewards are perceived and motivation, social norms and automatic and unconscious decitions.[39]

This study adds to the literature of socioeconomic disparities in health both in an international and national perspective. Although social and economic differences are smaller in Norway than in many other countirs,[9] socioeconomic disparities are observed in both behavioural factors, diseases risk and mortality.[10 11] The differences in the prevalence of smoking between educational groups are among the largest in Europe, and the same applies to differences in mortality.[41 42]

This study have identified several modifiable lifestyle and health-related factors that can be targeted for intervention. Interventions should preferably be implemented at a population-level,[43] but special attention could be directed towards low SES groups to ensure adherence. Strategies to reduce socioeconomic disparities directly include interventions targeted at parental support programs in early childhood and access to education; community developments that favours healthy changes in physical activity and nutrition; and employment and living environment.[44]

Important strengths of our study include the population-based design, long follow-up through hospital registries, and use of individual-based information on SES. Also, we were able to assess if modifiable risk factors for sepsis can explain some of the observed socioeconomic disparities in sepsis risk. Blood sampling, clinical examination and information on health behaviours and chronic diseases made causal mediation analyses possible. All these are factors that may contribute to the internal validity of the results, and thus increase the external validity.[45] Some limitations should also be considered. First, the definition of sepsis is based on implicit and explicit sepsis that may represent a heterogenous diagnosis. Norwegian guidelines for coding advice clinicians to use the explicit sepsis codes when the focus of the infection is unknown.[46] The use of only explicit sepsis to define sepsis leads to an underestimation,[47] while combining explicit and implicit sepsis as presented by Rudd et al. may be too broad and result in overestimation.[48] Additionally, coding practice may have changed during the follow-up period. Second, sepsis severity could not be studied since data on number of organ dysfunctions among those classified as explicit sepsis was not available in the hospital records. Nevertheless, we believe the analyses of sepsis mortality to some extent reflect the risk of more severe sepsis, and there was suggestive evidence that low occupational class was more strongly associated with sepsis-related mortality than sepsis risk. Third, SES was measured only once and could have changed during the follow-up period, and we did not have information on income, which can be a useful measure of SES. On the other hand, education as an indicator of SES is easy to measure, it often has fewer missing data than reports on income, and it is largely unaffected by diseases with onset in adult life. On the contrary, diseases in childhood could have affected both educational attainment and sepsis risk. A final limitation is the possibility for birth cohort effects as there might be an over-representation of older cohorts in the group with low education due to improved educational levels over time.[49]

In this study we found that low SES, measured as education, occupation, receiving social benefits and having financial difficulties, is associated with sepsis and sepsis-related mortality. Approximately 80% of the association between low education and risk of sepsis was explained by health-related behaviours, risk factors of cardiovascular disease and chronic diseases. Interventions towards increasing the standards of living in low socioeconomic groups and improve health-related behaviours may contribute to the prevention of sepsis and sepsis-related deaths.

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COMPETING INTERESTS

All authors declare that they have no conflicts of interest.

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DATA AND MATERIAL AVAILABILITY

HUNT data cannot be made available in open repositories due to privacy regulations, but data can be reproduced and made available upon approval of applications to the HUNT Research Center, the Nord-Trøndelag Hospital Trust, and St. Olavs Hospital.

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