National Institute for Health and Care Excellence

Suspected sepsis: recognition, diagnosis and early management

[I] Evidence review for sepsis risk factors

NICE guideline NG253
Evidence reviews underpinning recommendation 1.2.1 and 1.1.4 in the NICE guideline

November 2025

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FINAL

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1 Risk factors for developing sepsis

1.1 Review question

What factors or groups of factors lead to a higher risk of developing sepsis?

1.1.1 Introduction

Identifying people presenting to health care who may be at greater risk of developing sepsis can ensure they receive earlier treatment and help to improve their outcomes. During the update of NICE guideline NG51: Suspected sepsis: recognition, diagnosis and early management (published January 2024) which incorporated the use of the NEWS2 risk stratification tool, stakeholders suggested that the existing recommendations on risk factors in NG51 should be updated in-light of new evidence in this area. This review explores the risk factors for sepsis in this new evidence.

1.1.2 Summary of the protocol

Table 1: Inclusion criteria

Population	Children >28 days, young people and adults presenting to healthcare with possible infection
Association factors	• Clinical conditions including chronic kidney disease and mental health conditions • History of extensive antibiotic exposure • People with spinal injuries • People in long term care • People with multi-morbidities defined in line with NICE guidance NG56 as “presence of 2 or more long-term health conditions” including physical and mental conditions, ongoing conditions, symptom complexes, sensory impairments, alcohol, and substance misuses” Other protected characteristics including: • Race

	• Disability including learning disability and autism • Gender reassignment • Religion or belief • Sex • Sexual orientation • Socioeconomic factors (for example as measured via Index of multiple deprivation quintiles) • Other definable characteristics (including newly arrived migrants [including refugees, asylum seekers and unaccompanied asylum-seeking children, irregular migrants]; people experiencing homelessness; people with low levels of health literacy)
Comparator	People not presenting with the above association factors
Outcomes	• Sepsis diagnosis • Readmission for sepsis • Treatment for suspected sepsis • Multi organ failure • 30-day mortality
Study type	• Systematic reviews of cohort studies • Cohort studies (prospective and retrospective) that have matched or used multivariable regression analysis to adjust for pre-existing comorbidities, age, sex, BMI and ethnicity • Case-control studies that have matched or used multivariable regression analysis to adjust for pre-existing comorbidities, age, sex, BMI and ethnicity

For the full protocol see appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and appendix I.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.3.1 Search methods

The searches for the effectiveness evidence were run on 09 07 2024. The following databases were searched: MEDLINE (Ovid), Embase (Ovid), the Cochrane Database of Systematic Reviews (Wiley), and Epistemonikos. Full search strategies for each database are provided in Appendix B.

A NICE senior information specialist (SIS) conducted the searches. The MEDLINE strategy was quality assured by another NICE SIS. All translated search strategies were peer reviewed to ensure their accuracy. The QA procedures were adapted from the 2015 PRESS Guideline Statement.

1.1.3.2 Protocol deviations

The protocol initially specified systematic reviews of cohort and cohort studies only. During the evidence search a large and highly applicable UK based case-control study that uses real world data was identified. It was agreed to add the case-control study design to the search.

During the evidence sift only one study had matched or adjusted for all five of the confounding variables specified in the review protocol. The decision was made to include studies in a general population that had matched or adjusted for 4 out of 5 variables.

1.1.4 Association evidence

1.1.4.1 Included studies

A systematic search carried out to identify potentially relevant studies found 7867 references (see appendix B for the literature search strategy).

These 7867 references were screened at title and abstract level against the review protocol, with 7793 excluded at this level. 10% of references were screened separately by two reviewers with 97% agreement. Discrepancies were resolved by discussion.

The full texts of 74 systematic reviews of cohort studies, cohort studies and case-control studies were ordered for closer inspection. 2 of these studies met the criteria specified in the review protocol (appendix A). For a summary of the 2 included studies see table 2.

The clinical evidence study selection is presented as a PRISMA diagram in appendix C.

See section 1.1.14 References – included studies for the full references of the included studies.

1.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion are given in appendix G.

1.1.5 Summary of studies included in the association evidence

Table 2: Summary of studies included in the association evidence

Study details	Setting/Location	Population	Association factors	Outcomes predicted (optional)	Risk of bias[2]
Zhong et al 2023 Case-control n=1,570,527	Setting: primary care data was linked to the death data from UK Office for National Statistics, SARS-CoV-2 testing data from Second Generation Surveillance System (SGSS) and hospital secondary care records through the Secondary Uses Services (SUS) Location: UK	Cases - ICD-10 non covid-19 related sepsis diagnosis recorded on hospital admissions record Controls matched on age and sex from general population	Socioeconomic deprivation, ethnicity (white, mixed, Asian, black, other, unknown), chronic respiratory diseases, chronic heart disease, chronic kidney disease (CKD), chronic liver disease, stroke, dementia, other neurological disease, learning disabilities, severe mental illness[1]	Sepsis, Sepsis mortality	Moderate
Liyanarachi 2024 Prospective cohort n= 68,438	Setting: Baseline data from the second and third surveys of the Trøndelag Health Study, HUNT2 (1995–1997) and HUNT3 (2006–2008). Location: Norway	Self-selecting population from Trøndelag in Norway with no exclusions.	CKD as defined by eGFR[1]	Sepsis, Sepsis mortality	Moderate

1. Those listed are relevant to this review
2. CKD = chronic kidney disease
3. eGFR = estimated glomerular filtration rate

See appendix D for full evidence tables

1.1.6 Summary of the association evidence

Interpreting the effectiveness evidence

For mortality outcomes the line of no effect (represented by 1.0 as mortality is a dichotomous outcomes) was used as a clinical decision threshold. The following criteria were used to interpret the effect (column of 'Interpretation of effect' below) in the summary GRADE tables with results divided into 2 groups as follows:

- The evidence showed that there is an effect if the 95% CI does not cross the line of no effect. Where there is an effect, we have stated the direction of the effect.

- The evidence could not differentiate between comparators if the 95% CI crosses the line of no effect. Where this is the case we have stated 'could not differentiate'.

Where default MIDs have been used (0.8 and 1.25) the following criteria were used to interpret the effect (column of 'Interpretation of effect' below) in the summary GRADE tables. The results were divided into 4 groups as follows:

- Where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect. (Where there is an effect, we will state the direction of the effect.)

- Where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence showed there is an effect, but it is less than the defined MID.

- Situations where the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no meaningful difference.

- In all other cases, we state that the evidence could not differentiate between the comparator

Table 3: Odds or hazard of developing sepsis

No of studies	Study design	Cases	Controls	Effect size (odds ratio/Hazard ratio (95% CI)	Absolute effect	Interpretation of effect	Certainty
Index of multiple deprivation (IMD) quintile 1 (most deprived) vs IMD quintile 5 (least deprived)							
1[1]	Case-control	47,575 / 224361	206,509 / 1,346166	Multivariate OR 1.38 (1.36,1.40)	Not estimable[2]	Effect - Increased odds of sepsis	Very low[3]
IMD quintile 2 (most deprived) vs IMD quintile 5 (least deprived)							
1[1]	Case-control	46,030 / 224361	242,459 / 1,346166	Multivariate OR 1.26 (1.23, 1.28)	Not estimable[2]	Effect - Increased odds of sepsis	Very low[4]
IMD quintile 3 (most deprived) vs IMD quintile 5 (least deprived)							
1[1]	Case-control	48,700 / 224361	302,716 / 1,346166	Multivariate OR 1.12 (1.11,1.14)	Not estimable[2]	No meaningful difference	Very low[3]
Chronic Kidney Disease (CKD) stage 3a							
1[1]	Case-control	32315 / 224361	172860 / 1,346166	Multivariate OR 1.24 (1.23, 1.26)	Not estimable[2]	There is an effect but it is less than the defined MID	Very low[4]
CKD stage 3b							

1[1]	Case-control	22825 / 224361	84390 / 1,346166	Multivariate OR 1.70 (1.67, 1.74)	Not estimable[2]	Effect - Increased odds of sepsis	Very low[3]
CKD stage 4							
1[1]	Case-control	10185 / 224361	21980 / 1,346166	Multivariate OR 2.62 (2.55, 2.70)	Not estimable[2]	Effect - Increased odds of sepsis	Very low[3]
CKD stage 5							
1[1]	Case-control	2140 / 224361	1920 / 1,346166	Multivariate OR 6.23 (5.81, 6.69)	Not estimable[2]	Effect - Increased odds of sepsis	Very low[3]
CKD stage 2 Hazard Ratio[6]							
1[5]	Cohort	1685 / 35 618	321 / 23,304	Multi-adjusted HR 0.88 (0.76, 1.02)	Not estimable[2]	Could not differentiate	Very low[4]
CKD stage 3a Hazard Ratio[6]							
1[5]	Cohort	686 / 7816	321 / 23,304	Multi-adjusted HR 0.88 (0.73, 1.07)	Not estimable[2]	Could not differentiate	Very low[4]
CKD stage 3b Hazard Ratio[6]							

1[5]	Cohort	150 / 1556	321 / 23,304	Multi-adjusted HR 1.28 (0.99, 1.66)	Not estimable[2]	Could not differentiate	Very low[4]
CKD stage 4 & 5 Hazard Ratio[6]							
1[5]	Cohort	25 / 144	321 / 23,304	Multi-adjusted HR 2.94 (1.82, 4.75)	Not estimable[2]	Effect - Increased hazard of sepsis	Very low[3]
Potential care home							
1[1]	Case-control	13505 / 223675	30020 / 1344215	Multivariate OR 2.34 (2.28, 2.40)	Not estimable[2]	Effect - Increased odds of sepsis	Very low[3]
Learning disability							
1[1]	Case-control	3135 / 224360	3865 / 1,346165	Multivariate OR 3.53 (3.35, 3.72)	Not estimable[2]	Effect - Increased odds of sepsis	Very low[3]
Severe mental illness							
1[1]	Case-control	6150 / 224360	14700/1,346,165	Multivariate OR 1.96 (1.89, 2.03)	Not estimable[2]	Effect - Increased odds of sepsis	Very low[3]
Alcohol problems							

1[1]	Case-control	25820 / 224360	101065 / 1,346165	Multivariate OR 1.37 (1.35, 1.39)	Not estimable[2]	Effect - Increased odds of sepsis	Very low[3]
Dementia							
1[1]	Case-control	5625 / 224,360	15165 / 1,346165	Multivariate OR 1.42 (1.37,1.47)	Not estimable[2]	Effect - Increased odds of sepsis	Very low[3]
Antibiotic count 1							
1[1]	Case-control	No data[9]	No data[9]	Multivariate OR 1.73 (1.71, 1.76)	Not estimable[2]	Effect - Increased odds of sepsis	Very low[3]
Antibiotic count 2-3							
1[1]	Case-control	No data[9]	No data[9]	Multivariate OR 2.31 (2.28, 2.35)	Not estimable[2]	Effect - Increased odds of sepsis	Very low[3]
Antibiotic count 3 +							
1[1]	Case-control	No data[9]	No data[9]	Multivariate OR 3.36 (3.31, 3.42)	Not estimable[2]	Effect - Increased odds of sepsis	Very low[3]

Chronic liver disease							
1[1]	Case-control	7335 / 224,360	15165 / 1,346,165	Multivariate OR 3.06 (2.95, 3.17)	Not estimable[2]	Effect - Increased odds of sepsis	Very low[3]
Stroke							
1[1]	Case-control	27295 / 224360	89545 / 1,346,165	Multivariate OR 1.47 (1.45, 1.50)	Not estimable[2]	Effect - Increased odds of sepsis	Very low[3]
Asplenia							
1[1]	Case-control	1495 / 224360	3010 / 1,346,165	Multivariate OR 1.11 (1.03, 1.19)	Not estimable[2]	No meaningful difference	Very low[3]
Chronic respiratory disease							
1[1]	Case-control	40460 / 224360	126530 / 1,346,165	Multivariate OR 1.44 (1.42,1.47)	Not estimable[2]	Effect - Increased odds of sepsis	Very low[3]
Chronic cardiac disease							
1[1]	Case-control	67290 / 224360	257815 / 1,346,165	Multivariate OR 1.38 (1.37,1.40)	Not estimable[2]	Effect - Increased odds of sepsis	Very low[3]

Other neurological disease							
1[1]	Case-control	11260 / 224360	23795 / 1,346,165	Multivariate OR 2.33 (2.28, 2.39)	Not estimable[2]	Effect - Increased odds of sepsis	Very low[3]
Ethnicity - mixed[8]							
1[1]	Case-control	1430 / 224360	8315 / 1,346,165	Unadjusted OR[7] 0.95 (0.90, 1.01)	0 fewer per 1,000 (from 1 fewer to 0 fewer)	No meaningful difference	Very low[3]
Ethnicity – South Asian[8]							
1[1]	Case-control	9720 / 224360	50250 / 1,346,165	Unadjusted OR[7] 1.08 (1.05, 1.11)	3 more per 1,000 (from 2 more to 4 more)	No meaningful difference	Very low[3]
Ethnicity - Black[8]							
1[1]	Case-control	2975 / 224360	17,465 / 1,346,165	Unadjusted OR[7] 0.96 (0.92, 1.00)	1 fewer per 1,000 (from 1 fewer to 0 fewer)	No meaningful difference	Very low[3]
1 Zhong et al 2023 2 Absolute effect not estimable for adjusted data							

3	Rated down for moderate risk of bias, inconsistency and indirectness
4	Rated down for moderate risk of bias, inconsistency and indirectness and imprecision
5	Liyanarachi 2024
6	Ref/control ‘eGFR >90’
7	Ethnicity OR presented as unadjusted for confounding factors
8	Reference/control ‘white’
9	Event rate data not provided in supplementary paper

IMD = Index of multiple deprivation
CKD = Chronic kidney disease

Table 4: Odds of community acquired sepsis and 30-day mortality

No of studies	Study design	Cases	Controls	Effect size (odds ratio/Hazard ratio (95% CI)	Absolute effect	Interpretation of effect	Certainty
CKD 3a							
1[1]	Case-control	No data[5]	No data[5]	Multivariate OR 0.95 (0.91, 1.00)	Not estimable[2]	No meaningful difference	Very Low[3]
CKD 3b							
1[1]	Case-control	No data[5]	No data[5]	Multivariate OR 1.13 (1.07, 1.19)	Not estimable[2]	Effect - Increased odds of community	Very Low[3]

						acquired sepsis and 30-day mortality	
CKD 4							
1[1]	Case-control	No data[5]	No data[5]	Multivariate OR 1.54 (1.43, 1.65)	Not estimable[2]	Effect - Increased odds of community acquired sepsis and 30-day mortality	Very Low[3]
CKD 5							
1[1]	Case-control	No data[5]	No data[5]	Multivariate OR 1.67 (1.42, 1.96)	Not estimable[2]	Effect - Increased odds of community acquired sepsis and 30 day mortality	Very Low[3]
Severe mental illness							
1[1]	Case-control	No data[5]	No data[5]	Multivariate OR 0.90 (0.81, 1.00)	Not estimable[2]	No meaningful difference	Very Low[3]

1 Zhong et al 2023

2 Absolute effect not estimable for adjusted data

3	Rated down for risk of bias, indirectness and inconsistency
4	Rated down for risk of bias, indirectness, inconsistency and imprecision
5	No data in supplementary paper on event rate

Table 5: CKD/eGFR and hazard of sepsis mortality at 30 days

No of studies	Study design	Cases	Controls[2]	Effect size (odds ratio/Hazard ratio (95% CI)	Absolute effect	Interpretation of effect	Certainty
eGFR 60-89							
1[1]	Cohort	336 / 35,618	33 / 23,304	Multi-adjusted HR 0.75 (0.50, 1.13)	Not estimable[3]	Could not differentiate	Very Low[4]
eGFR 45-59							
1[1]	Cohort	180 / 7816	33 / 23,304	Multi-adjusted HR 0.72 (0.45, 1.16)	Not estimable[3]	Could not differentiate	Very Low[4]
eGFR 30-44							
1[1]	Cohort	51 / 1556	33 / 23,304	Multi-adjusted HR 1.20 (0.68, 2.13)	Not estimable[3]	Could not differentiate	Very Low[4]

eGFR <30							
1[1]	Cohort	13 / 144	33 / 23,304	Multi-adjusted HR 4.10 (1.88, 8.93)	Not estimable[3]	Effect - Increased hazard of sepsis mortality at 30 days	Very Low[5]

1 Liyanarachi 2024
2 Reference/control eGFR >90
3 Absolute effect not estimable for adjusted data
4 Rated down for risk of bias, inconsistency, indirectness and imprecision
5 Rated down for risk of bias, inconsistency, indirectness

See appendix F for full GRADE tables

1.1.7 Economic evidence

Economic evidence was not relevant for this review.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

As this review was about risk factors for developing sepsis, the committee agreed that developing sepsis was the most important outcome, followed by mortality from sepsis.

1.1.12.2 The certainty of the evidence

The committee noted that the certainty of the evidence for all outcomes was rated as very low. Evidence was rated down for risk of bias (large case-control and cohort studies where variation in outcome measurement i.e. sepsis diagnosis can occur, unknown confounders and one study with a self-selecting population leading to potential selection bias), indirectness (studies included some populations excluded from the protocol) and inconsistency (rated down in this domain as evidence came from single study analysis). The committee recognised and discussed the value of these large real world data studies in uncovering populations at risk of developing sepsis. They highlighted that many of the risk factors are linked to one another, but recognised study authors had adjusted for many of the relevant confounding variables.

1.1.12.3 Benefits and harms

The committee discussed the factors that were identified as associated with developing sepsis. They agreed that while it was important for health care practitioners to be aware of these populations at greater risk, that these were not direct risk factors for sepsis but were frequently risk factors for becoming unwell such as with sepsis. They agreed that people with learning difficulties and cognitive impairment may be at greater risk of there being a delay in the recognition of sepsis due to the potential difficulties these people may have in communicating their symptoms and therefore are at greater risk of delayed presentation or not being able to access services. The committee agreed that practitioners should tailor their care

accordingly towards these groups, such as offering face to face consultation where communication might be difficult. In relation to evidence of an association between chronic kidney disease (CKD), chronic liver disease, stroke, asplenia, chronic respiratory disease and other neurological disease, the committee agreed these were all risk factors for being more unwell, not responding to treatment, being more vulnerable to infection and possibly developing sepsis. They noted however that this was true for people with most chronic conditions and adding the specific ones highlighted by the evidence could lead to other presentations being overlooked. They therefore added ‘multimorbidities and severe chronic conditions’ to make practitioners aware that all these presentations represented a risk for developing sepsis.

When considering the evidence around multiple antibiotic prescriptions the committee felt that this could be indicative of treatment failure or antimicrobial resistance, delayed presentation or linked to a chronic comorbidity. They discussed the possibility of adding a recommendation to discuss people on multiple courses of antibiotics, or with a history of repeated courses with a microbiologist. They further discussed the use of the recommendations across primary and secondary care, that people outside of hospital would not have quick access to a microbiologist and that this could become an unwarranted resource burden. They discussed the concerns surrounding possible overdiagnosis and the inappropriate use of antibiotics. Overall, they agreed the importance of raising awareness that people with a history of repeated antibiotic prescriptions could be at greater risk of developing sepsis and therefore added this to the recommendation.

In relation to the evidence on people in a lower deprivation quintile and a significant association with developing sepsis compared with people in higher quintiles, the committee agreed that this was a pattern replicated more broadly across other health care outcomes and that awareness of this is important. Similarly, they noted alcohol problems could also lead to poorer health outcomes and developing sepsis and

therefore added both socioeconomic status and alcohol problems to the recommendation.

The committee discussed the evidence that showed a significant association between people from south Asian backgrounds and developing sepsis. They agreed that this was an important association to highlight but also noted from their own experience that this was true of people from other ethnic backgrounds, and this may not have been demonstrated in the study (the authors had noted some missing data on ethnicity, also ethnicity was not included in the model which had adjusted for comorbidities). They agreed that practitioners should be aware of the possible greater risk for people from ethnic minority backgrounds.

The committee noted that the evidence showed an association between potential care home and developing sepsis. They discussed potential biases related to the definition used for this population in the study they agreed that based on this they couldn't add potential care home to the list of risk factors to be aware of. They noted however that the existing recommendation noted that older people and people who were very frail were at higher risk of developing sepsis and that the care home population would be at least partially covered by this. They agreed this would make the recommendation more usable.

The committee further discussed that as there are many factors that may increase the risk of developing sepsis what would be most useful in practice would be for these to be grouped into key categories to alert clinicians to the overall areas that should be considered. They added examples to these categories noting that with the large number of potential factors involved that this is not an exhaustive list.

1.1.12.4 Cost effectiveness and resource use

Economic evidence was considered not relevant for this review question. The committee discussed those who are at increased risk, and the potential need for increased vigilance. The committee discussed the need to be cautious with the

wording of recommendations due to concerns that increased vigilance could have a resource impact on nurse staff time because in secondary care the majority of patients have at least one of these risk factors. The committee agreed to make a recommendation to be aware of groups at more risk of developing sepsis to limit the potential of overtreatment whilst acknowledging the potential for increased harms in these population groups.

Overall, the committee anticipate these recommendations will lead to improved outcomes because of greater awareness and a better use of healthcare resources as a result of timely care without having a large resource impact.

1.1.12.5 Other factors the committee took into account

The committee wanted to emphasise the action at the start of the recommendation and the context in which it would be enacted; they therefore revised the existing recommendation to include during consultation be aware.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendation 1.2.1.

1.1.14 References – included studies

1.1.14.1 Association evidence:

Liyanarachi, Kristin Vardheim, Mohus, Randi Marie, Rogne, Tormod et al. (2024) Chronic kidney disease and risk of bloodstream infections and sepsis: a 17-year follow-up of the population-based Trondelag Health Study in Norway. Infection

Zhong, Xiaomin, Ashiru-Oredope, Diane, Pate, Alexander et al. (2023) Clinical and health inequality risk factors for non-COVID-related sepsis during the global COVID-19 pandemic: a national case-control and cohort study. EClinicalMedicine 66: 102321

Appendices

Appendix A – Review protocols

Review protocol for the identification of factors associated with a higher risk of developing sepsis

ID	Field	Content
0.	PROSPERO registration number	N/A – not registered
1.	Review title	Identification of factors associated with an increased risk of developing sepsis
2.	Review question	What factors or groups of factors lead to a higher risk of developing sepsis?
3.	Objective	To determine which factors are associated with an increased risk of developing sepsis
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • 2010 • English Language • Human studies • Conference abstracts excluded Other searches: • Reference searching

		The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Suspected sepsis
6.	Population	Inclusion: • Children >28 days, young people and adults presenting to healthcare with possible infection Exclusion: • No exclusions

7.	Index prognostic factors	• Clinical conditions including chronic kidney disease and mental health conditions
		• History of extensive antibiotic exposure
		• People with spinal injuries
		• People in long term care
		• People with multi-morbidities defined in line with NICE guidance NG56 as “presence of 2 or more long-term health conditions” including physical and mental conditions, ongoing conditions, symptom complexes, sensory impairments, alcohol, and substance misuses”
		• Other protected characteristics including:
		  ○ Race
		  ○ Disability including learning disability and autism
		  ○ Gender reassignment
		  ○ Religion or belief
		  ○ Sex
		  ○ Sexual orientation
		• Socioeconomic factors (for example as measured via Index of multiple deprivation quintiles)

		• Other definable characteristics (including newly arrived migrants [including refugees, asylum seekers and unaccompanied asylum-seeking children, irregular migrants]; people experiencing homelessness; people with low levels of health literacy)
8.	Comparator prognostic factors	• People not presenting with the index prognostic factors
9.	Types of study to be included	• Systematic reviews of cohort studies • Cohort studies (prospective and retrospective) that have used multivariable regression analysis to adjust for pre-existing comorbidities, age, sex, BMI and ethnicity
10.	Other exclusion criteria	• All other study types • Dissertations, letters, opinion pieces and other non-empirical evidence • Non-English language studies • Non-OECD studies
11.	Context	The early recognition and prompt treatment of sepsis can prevent progression to septic shock and increase the chances of survival. Identifying sepsis can be challenging as the clinical presentation is variable and depends on several factors including the underlying cause and individual person characteristics. The current NG51 guideline has recommendations on 'When to suspect sepsis' and 'People who are most vulnerable to sepsis' which outlines population groups who may be at higher risk of developing sepsis (including those with learning disabilities or autism, the very young, older people, immunocompromised people, people who

		are pregnant or have recently been pregnant). At consultation for a previous update in November 2023, a stakeholder outlined a UK-based case-control and cohort study (Zhong et al 2023). The study highlighted the association between a diagnosis for sepsis and risk factors including socioeconomic deprivation, having a learning disability and cancer. This review protocol seeks to investigate this further to understand which risk factors are associated with a diagnosis for sepsis and update recommendations to inform people with sepsis, their families and carers, and healthcare professionals working in primary, secondary and tertiary care of these factors to support recognition, diagnosis and early management of suspected sepsis.
12.	Primary outcomes (critical outcomes)	• Sepsis diagnosis • Readmission for sepsis • Treatment for suspected sepsis • Multi organ failure • 30-day mortality
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

		The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow. Where appropriate, this review will make use of the priority screening functionality within the EPPI-reviewer software. At least 50% of the data set will be screened and we will stop screening after that if we screen more than 250 records without an include
15.	Risk of bias (quality) assessment	Risk of bias of individual studies will be assessed using the preferred checklist as described in Developing NICE guidelines: the manual: • PROBAST checklist for prognostic studies • QUIPS checklist for simple association studies for particular prognostic factors or variables and their associations with a prognosis • ROBIS checklist for systematic reviews
16.	Strategy for data synthesis	**Approach to meta-analysis** Where possible, meta-analyses will be conducted to combine the results of quantitative studies for each outcome. Where appropriate, hazard ratios will be pooled using the generic inverse-variance method. Adjusted odds ratios, hazard ratios and risk ratios from multivariate models will only be pooled if the same set of factors are used across multiple studies and if the same thresholds to measure factors were used across studies. Fixed- and random-effects models (der Simonian and Laird) will be fitted for all outcomes, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be deemed to be inappropriate if

		one or both of the following conditions are met: Significant between-study heterogeneity in methodology, population, intervention, or comparator was identified by the reviewer in advance of data analysis. The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$. In any meta-analyses where some (but not all) of the data comes from studies at high risk of bias, a sensitivity analysis will be conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses will be reported. Similarly, in any meta-analyses where some (but not all) of the data comes from indirect studies, a sensitivity analysis will be conducted, excluding those studies from the analysis. **Approach to GRADE** A modified approach will be applied using the GRADE framework. Data from cohort studies will be initially rated as high quality, with the quality of the evidence for each outcome then downgraded or not from this initial point.
17.	Analysis of sub-groups	None.
18.	Type and method of review	☐ Intervention ☐ Diagnostic ☒ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	June 2024

22.	Anticipated completion date	TBC		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** Centre for guidelines – Guideline Development Team B **5b Named contact e-mail** sepsisupdate@nice.org.uk **5e Organisational affiliation of the review**		

		National Institute for Health and Care Excellence (NICE) and Guideline Development Team B
25.	Review team members	From the Centre for Guidelines: • Guideline lead: Emma McFarlane • Senior technical analyst: James Jagroo • Technical analyst: Anthony Gildea • Health Economist: Lindsay Claxton • Information specialist: Lynda Ayiku
26.	Funding sources/sponsor	This systematic review is being completed by the Centre for guidelines – Guideline Development Team B which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: TBC
29.	Other registration details	N/A
30.	Reference/URL for published protocol	TBC

31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Sepsis, Risk factors, Prognosis
33.	Details of existing review of same topic by same authors	This is a new review question that will update Sepsis: recognition, diagnosis and early management NG51
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	N/A
36.	Details of final publication	www.nice.org.uk

Appendix B – Literature search strategies

Background and development

Search design and peer review

A NICE Senior Information Specialist (SIS) conducted the literature searches for the evidence review. The searches were run on 09 07 2024.

This search report is compliant with the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

The MEDLINE strategies below were quality assured (QA) by a trained NICE SIS. All translated search strategies were peer reviewed by another SIS to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

The principal search strategies were developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess "low-probability" matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The search terms for the sepsis population from '(A) Evidence reviews for stratifying risk of severe illness or death from sepsis' in NG51 (Jan 2024) were used to inform the population terms for the search strategy.

Search limits and other restrictions

Formats

Limits were applied in adherence to standard NICE practice and the review protocol to exclude:

- Animal studies

- Conference abstracts and posters
- Registry entries for ongoing clinical trials or those that contain no results
- Papers not published in the English language.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from:

> Dickersin K, Scherer R & Lefebvre C. (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Date limits

A date limit of 2010 to the current day was applied, as stated in the review protocol.

Search filters and classifiers

Systematic reviews filters:

Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. BMC Medical Research Methodology, 12(1), 51.

- In MEDLINE, the standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.
- In Embase, the standard NICE modifications were used: pubmed.tw added to line medline.tw.

Case controlled studies and cohort studies terms:

Terms for case-control and cohort studies were adapted from the observational studies filters. The terms used for observational studies are standard NICE practice that have been developed in house.

Geographic search filters:

The OECD countries filters were used without modification:

Ayiku, L., Hudson, T., Williams, C., Levay, P., & Jacob, C. (2021). The NICE OECD countries' geographic search filters: Part 2 - Validation of the MEDLINE and Embase (Ovid) filters. *Journal of the Medical Library Association*, 109(4), 583–589

Key decisions

The review protocol listed several conditions and populations as risk factors for sepsis. However, it was not possible to add such a wide variety of different groups to the search strategy and so they were not added. Instead, general terms for the concept of 'risk factors' were used in the search strategy.

The approach of the search strategy aimed to retrieve case-control studies, cohort studies, and systematic reviews about risk factors for sepsis. Due to the large result numbers (20,000), terms for outcomes and terms for readmission/ICU admission were added to the search strategy to identify the most relevant results.

It is acknowledged that running such a specific search has risks because some relevant papers could be missed. However, due to the large search results involved, a pragmatic search approach that balanced sensitivity and precision was required.

Searches

Database results

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
Cochrane Database of Systematic Reviews (CDSR)	9th July 2024	Wiley	Issue 6 of 12, June 2024	140
Embase	9th July 2024	Ovid	Embase <1974 to 2024 July 08>	5401
Epistemonikos	9th July 2024	Epistemonikos	Searched 9th July 2024	723
MEDLINE ALL	9th July 2024	Ovid	Ovid MEDLINE(R) ALL <1946 to July 08, 2024>	6307

Search strategy history

Database name: MEDLINE ALL

Searches
1 exp *sepsis/ (105990)
2 sepsis.ti,ab. (125274)
3 *blood-borne pathogens/ (1560)
4 (blood* adj2 (pathogen* or poison*)).ti,ab. (3478)
5 (septicaemi* or septicemi*).ti,ab. (22608)
6 ((septic or cryptic) adj2 shock).ti,ab. (28623)
7 (pyaemi* or pyemi* or pyohemi*).ti,ab. (260)
8 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab. (74620)
9 or/1-8 (260714)
10 exp *risk factors/ (2389)
11 (risk* adj1 (factor* or indicat* or assess* or sign* or symptom* or evaluat* or analy* or measur* or scor* or relativ* or associat* or inciden* or increas* or high* or heighten* or sever* or more or most or large* or predict* or prognos* or likel* or population* or condition* or disorder* or patient* or inpatient*)).tw. (1776322)

Searches
12 correlat*.tw. (2386669)
13 or/10-12 (3986850)
14 9 and 13 (49028)
15 exp *Hospitalization/ (102654)
16 (hospital* or inhospital*).tw. (1723628)
17 exp *Intensive Care Units/ (46110)
18 exp *Critical Care/ (38801)
19 (icu or itu or hdu).tw. (92063)
20 high dependency.tw. (1815)
21 ((intensive* or critical* or emergenc*) adj3 (care* or ill* or therap* or treat*)).tw. (363358)
22 or/15-21 (2006843)
23 14 and 22 (21719)
24 *case-control studies/ (1390)
25 ((case adj2 (control* or base* or referrent* or referent* or compar* or compeer*)) or controls).tw. (1138348)
26 *Comparative Study.pt. (1920880)
27 ((compar* or control*) adj2 (study or studies or trial* or group*)).tw. (1747654)
28 or/24-27 (4162160)
29 23 and 28 (4816)
30 exp *Cohort Studies/ (4802)
31 (cohort adj (study or studies)).tw. (357248)
32 cohort analy$.tw. (13272)
33 (follow up adj (study or studies)).tw. (58469)
34 longitudinal.tw. (349423)
35 prospective.tw. (763638)
36 retrospective.tw. (823579)
37 or/30-36 (1983588)
38 (multivaria* or multi-varia* or regression* or variable* or ratio*).tw. (3832003)
39 37 and 38 (643510)
40 23 and 39 (5523)
41 *Patient Readmission/ (11266)
42 (readmi* or re-admi* or rehospitali* or re-hospitali*).tw. (64755)
43 ((return* or repeat*) adj2 hospitali*).tw. (1440)
44 *Multiple Organ Failure/ (6097)
45 ((organ* or multiorgan*) adj3 (fail* or disease* or dysfunct* or dys-funct* or malfunct* or shutdown* or shut-down*)).tw. (80787)
46 mods.tw. (2502)
47 exp *Mortality/ (72497)
48 (mortalit* or fatal* or death* or dead* or dying* or die or dies).tw. (2167825)
49 (health* adj3 quality of life).tw. (81599)

Searches
50 (hql or hqol or hrqol).tw. (24784)
51 ((sepsis* or septic*) adj1 (diagnos* or confirm* or therap* or treat* or manag*)).tw. (5460)
52 or/41-51 (2345871)
53 40 and 52 (4207)
54 29 or 53 (8208)
55 afghanistan/ or africa/ or africa, northern/ or africa, central/ or africa, eastern/ or "africa south of the sahara"/ or africa, southern/ or africa, western/ or albania/ or algeria/ or andorra/ or angola/ or "antigua and barbuda"/ or argentina/ or armenia/ or azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or "bosnia and herzegovina"/ or botswana/ or brazil/ or brunei/ or bulgaria/ or burkina faso/ or burundi/ or cabo verde/ or cambodia/ or cameroon/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cote d'ivoire/ or croatia/ or cuba/ or "democratic republic of the congo"/ or cyprus/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or egypt/ or el salvador/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or fiji/ or gabon/ or gambia/ or "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or independent state of samoa/ or exp india/ or indian ocean islands/ or indochina/ or indonesia/ or iran/ or iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libya/ or madagascar/ or malaysia/ or malawi/ or mali/ or malta/ or mauritania/ or mauritius/ or mekong valley/ or melanesia/ or micronesia/ or monaco/ or mongolia/ or montenegro/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nepal/ or nicaragua/ or niger/ or nigeria/ or oman/ or pakistan/ or palau/ or exp panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or qatar/ or "republic of belarus"/ or "republic of north macedonia"/ or romania/ or exp russia/ or rwanda/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or "sao tome and principe"/ or saudi arabia/ or serbia/ or sierra leone/ or senegal/ or seychelles/ or singapore/ or somalia/ or south africa/ or south sudan/ or sri lanka/ or sudan/ or suriname/ or syria/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or uganda/ or ukraine/ or united arab emirates/ or uruguay/ or uzbekistan/ or vanuatu/ or venezuela/ or vietnam/ or west indies/ or yemen/ or zambia/ or zimbabwe/ (1354670)
56 "organisation for economic co-operation and development"/ (611)
57 australasia/ or exp australia/ or austria/ or baltic states/ or belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or exp denmark/ or estonia/ or europe/ or finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or exp japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or portugal/ or exp "republic of korea"/ or "scandinavian and nordic countries"/ or slovakia/ or slovenia/ or spain/ or sweden/ or switzerland/ or turkey/ or exp united kingdom/ or exp united states/ (3570545)
58 european union/ (18074)
59 developed countries/ (21581)
60 or/56-59 (3586952)
61 55 not 60 (1263457)
62 54 not 61 (7285)
63 (MEDLINE or pubmed).tw. (365701)
64 systematic review.tw. (307547)

Searches
65 systematic review.pt. (265653)
66 meta-analysis.pt. (203753)
67 intervention$.ti. (217118)
68 or/63-67 (758013)
69 14 and 68 (1971)
70 62 or 69 (8831)
71 limit 70 to yr="2010 -Current" (6797)
72 animals/ not humans/ (5204358)
73 71 not 72 (6745)
74 limit 73 to english language (6364)
75 limit 74 to (letter or historical article or comment or editorial or news or case reports) (57)
76 74 not 75 (6307)

Database name: Embase

Searches
1 exp *sepsis/ (124228)
2 sepsis.ti,ab. (196129)
3 *bloodborne bacterium/ (804)
4 (blood* adj2 (pathogen* or poison*)).ti,ab. (4537)
5 (septicaemi* or septicemi*).ti,ab. (26594)
6 ((septic or cryptic) adj2 shock).ti,ab. (46972)
7 (pyaemi* or pyemi* or pyohemi*).ti,ab. (136)
8 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab. (103709)
9 or/1-8 (364233)
10 exp *risk factor/ (141706)
11 (risk* adj1 (factor* or indicat* or assess* or sign* or symptom* or evaluat* or analy* or measur* or scor* or relativ* or associat* or inciden* or increas* or high* or heighten* or sever* or more or most or large* or predict* or prognos* or likel* or population* or condition* or disorder* or patient* or inpatient*)).tw. (2630728)
12 correlat*.tw. (3153324)
13 or/10-12 (5516130)
14 9 and 13 (79783)
15 *hospitalization/ (49051)
16 (hospital* or inhospital*).tw. (2698198)
17 exp *intensive care unit/ (65176)
18 exp *intensive care/ (294746)
19 (icu or itu or hdu).tw. (183967)
20 *high dependency unit/ (116)
21 (icu or itu or hdu).tw. (183967)

Searches
22 high dependency.tw. (3416)
23 ((intensive* or critical* or emergenc*) adj3 (care* or ill* or therap* or treat*)).tw. (535769)
24 or/15-22 (3014813)
25 14 and 24 (34473)
26 exp *controlled study/ (31025)
27 ((case adj2 (control* or base* or referrent* or referent* or compar* or compeer*)) or controls).tw. (1585901)
28 ((compar* or control*) adj2 (study or studies or trial* or group*)).tw. (2441866)
29 or/26-28 (3584843)
30 25 and 29 (5302)
31 *Cohort analysis/ (49105)
32 *cross-sectional study/ (14735)
33 cohort analy$.tw. (21402)
34 *Longitudinal study/ (9371)
35 *Retrospective study/ (40402)
36 *Prospective study/ (43590)
37 (Cohort adj (study or studies)).tw. (513797)
38 (follow up adj (study or studies)).tw. (76547)
39 longitudinal.tw. (472177)
40 (cross sectional adj (study or studies)).tw. (378604)
41 prospective.tw. (1169573)
42 retrospective.tw. (1364339)
43 or/31-42 (3363652)
44 (multivaria* or multi-varia* or regression* or variable* or ratio*).tw. (5186677)
45 43 and 44 (1146475)
46 25 and 45 (8653)
47 *hospital readmission/ (19726)
48 (readmi* or re-admi* or rehospitali* or re-hospitali*).tw. (119418)
49 ((return* or repeat*) adj2 hospitali*).tw. (2616)
50 exp multiple organ failure/ (55986)
51 ((organ* or multiorgan*) adj3 (fail* or disease* or dysfunct* or dys-funct* or malfunct* or shutdown* or shut-down*)).tw. (124488)
52 mods.tw. (3896)
53 exp *mortality/ (210908)
54 (mortalit* or fatal* or death* or dead* or dying* or die or dies).tw. (3078871)
55 (health* adj3 quality of life).tw. (118549)
56 (hql or hqol or hrqol).tw. (40092)
57 ((sepsis* or septic*) adj1 (diagnos* or confirm* or therap* or treat* or manag*)).tw. (8193)
58 or/47-57 (3365904)
59 46 and 58 (6708)

Searches
60 30 or 59 (11056)
61 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ (1783983)
62 exp "organisation for economic co-operation and development"/ (3029)
63 exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or exp mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or switzerland/ or "Turkey (republic)"/ or exp united kingdom/ or exp united states/ or western europe/ (3893650)
64 european union/ (32367)
65 developed country/ (36362)
66 or/62-65 (3928559)
67 61 not 66 (1624254)
68 60 not 67 (9840)
69 (MEDLINE or pubmed).tw. (452367)
70 exp systematic review/ or systematic review.tw. (562611)
71 meta-analysis/ (321228)
72 intervention$.ti. (284704)
73 or/69-72 (1054313)

Searches
74 14 and 73 (2880)
75 68 or 74 (12229)
76 limit 75 to english language (11683)
77 nonhuman/ not human/ (5479113)
78 76 not 77 (11592)
79 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (5987819)
80 78 not 79 (6756)
81 limit 80 to yr="2010 -Current" (5401)

Database name: Cochrane Database of Systematic Reviews (CDSR)

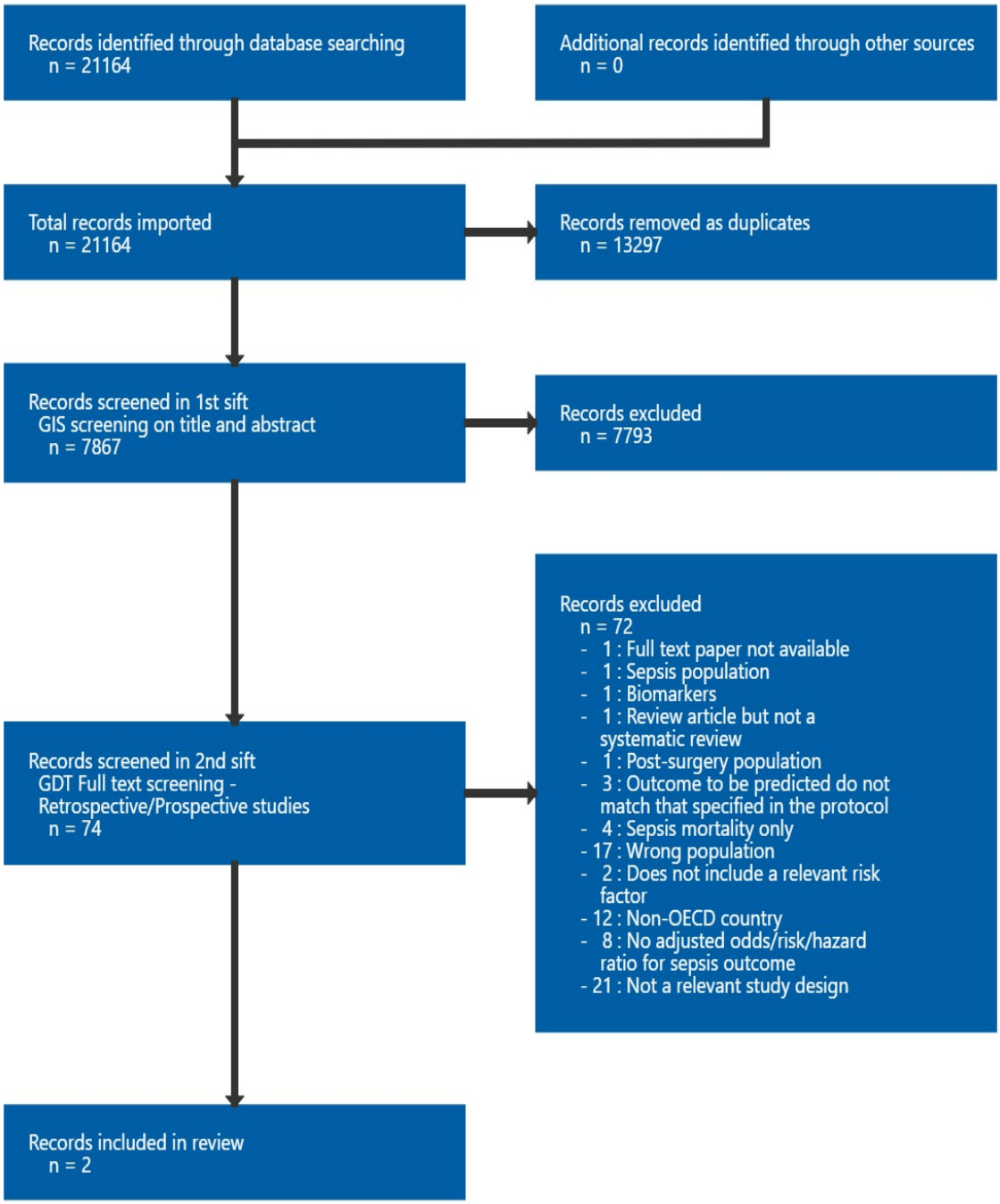
Searches
#1 MeSH descriptor: [Sepsis] explode all trees 6523
#2 sepsis:ti,ab,kw 14305
#3 MeSH descriptor: [Blood-Borne Pathogens] this term only 38
#4 (blood* near/2 (pathogen* or poison*)):ti,ab,kw 382
#5 (septicaemi* or septicemi*):ti,ab,kw 1055
#6 ((septic or cryptic) near/2 shock):ti,ab,kw 4088
#7 (pyaemi* or pyemi* or pyohemi*):ti,ab,kw 7
#8 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*):ti,ab,kw 6828
#9 {or #1-#8} 23448
#10 MeSH descriptor: [Risk Factors] explode all trees 38250
#11 (risk* near/1 (factor* or indicat* or assess* or sign* or symptom* or evaluat* or analy* or measur* or scor* or relativ* or associat* or inciden* or increas* or high* or heighten* or sever* or more or most or large* or predict* or prognos* or likel* or population* or condition* or disorder* or patient* or inpatient* or in-patient*)):ti,ab,kw 201628
#12 correlat*:ti,ab,kw 104950
#13 {or #10-#12} 294254
#14 #9 and #13 with Cochrane Library publication date Between Jan 2010 and Jun 2024 4062 = 140 results

Database name: Epistemonikos

Searches
(title:((sepsis OR systemic inflammatory response syndrome* OR sirs OR septi* OR crypti* OR pyaemi* OR pyemi* OR pyohemi* OR bacteremi* OR bacteraemi* OR fungemi* OR fungaemi* OR parasitemi* OR parasitaemi* OR viremi* OR viraemi*)) OR abstract:((sepsis OR systemic inflammatory response syndrome* OR sirs OR septi* OR crypti* OR pyaemi* OR pyemi* OR pyohemi* OR bacteremi* OR bacteraemi* OR fungemi* OR fungaemi* OR parasitemi* OR parasitaemi* OR viremi* OR viraemi*))) AND (title:(risk* AND (factor* OR indicat* OR assess* OR sign* OR symptom* OR evaluat* OR analy* OR measur* OR scor* OR relativ* OR inciden* OR increas* OR high* OR heighten* OR sever* OR more OR most OR large* OR predict* OR prognos* OR likel* OR population* OR condition* OR disorder*

Searches
OR patient* OR inpatient* OR "in-patient*") OR correlat*) OR abstract:(risk* AND (factor* OR indicat* OR assess* OR sign* OR symptom* OR evaluat* OR analy* OR measur* OR scor* OR relativ* OR inciden* OR increas* OR high* OR heighten* OR sever* OR more OR most OR large* OR predict* OR prognos* OR likel* OR population* OR condition* OR disorder* OR patient* OR inpatient* OR "in-patient*") OR correlat*)) = 723 results (limited to 2010-2024, systematic reviews)

Appendix C – Association evidence study selection



Appendix D –Association evidence

Liyanarachi, 2024

Bibliographic Reference	Liyanarachi, Kristin Vardheim; Mohus, Randi Marie; Rogne, Tormod; Gustad, Lise Tuset; Asvold, Bjorn Olav; Romundstad, Solfrid; Solligard, Erik; Hallan, Stein; Damas, Jan Kristian; Chronic kidney disease and risk of bloodstream infections and sepsis: a 17-year follow-up of the population-based Trondelag Health Study in Norway.; Infection; 2024

Study Characteristics

Study design	Prospective cohort study
Study details	Study location Norway Study setting General population - baseline data from the second and third surveys of the Trøndelag Health Study, HUNT2 (1995–1997) and HUNT3 (2006–2008). Study dates From the day of first inclusion (1995) until February 2017. The follow-up time was up to 22.8 years (median 17.4 years).

	Sources of funding Open access funding provided by NTNU Norwegian University of Science and Technology (incl St. Olavs Hospital - Trondheim University Hospital). This work was supported by Samarbeidsorganet Helse Midt-Norge, NTNU (Norwegian University of Science and Technology) (Trondheim, Norway).
Inclusion criteria	Criteria X None - self-selecting sample taken from the general population
Exclusion criteria	Criteria 1 None - self-selecting sample taken from the general population
Number of participants and recruitment methods	n=68,438 . 'Baseline data from the second and third surveys of the Trøndelag Health Study, HUNT2 (1995–1997) and HUNT3 (2006–2008), in which a total of 79,393 subjects participated (69.5% and 54.1% of the invited population for HUNT2 and HUNT3, respectively)'
Length of follow-up	22.8 years (median 17.4)
Loss to follow up	n=79,393 participated in the health surveys however the 'total population' the authors have data for is n=68,438. The

	reasons for this are unclear though possibly related to participants who had a blood sample taken
Outcome(s) of interest	Blood Stream Infection (BSI), mortality and sepsis
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	CKD according to eGFR status: eGFR>90, eGFR 60-89, eGFR 45-59, eGFR 30-44, eGFR <30
Covariates adjusted for in the multivariable regression modelling	Age (at beginning of period), sex, diabetes, cardiovascular disease, smoking status, SBP, and BMI

Population characteristics

Study-level characteristics

Characteristic	**Study (N = 68438)**
% Female Custom value	53%
Mean age (SD) Mean (SD)	47.7 (16.6)

Characteristic	Study (N = 68438)
BMI (kg/m²) Mean (SD)	26.4 (4.2)
Current smoker Custom value	27.4%
Former smoker Custom value	27.2%
Diabetes Custom value	3%
Myocardial infarction Custom value	2.7%
Mobility impairment Custom value	34.2%

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Although it has a large sample size, this is a self-selecting sample which the authors themselves point out could create selection bias meaning high risk groups could be underrepresented)*
Study Attrition	Study Attrition Summary	Moderate risk of bias *(No details provided by study authors on difference between sample respondents and study population. The study website confirms that 65,000 had a blood sample taken which likely accounts for most of the reason given blood sample is required for eGFR calculation, however we cannot be sure the reason for no blood sample is not associated with a key characteristic.)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Although setting for clinical examination not described, assessments used for eGFR calculation are objective and authors point out that data for the county comes from two hospitals)*

Section	Question	Answer
Outcome Measurement	Outcome Measurement Summary	Moderate risk of bias *(Sepsis classification and diagnosis is difficult; the authors had to retrospectively come to a diagnosis based on other ICD codes because the unreliability of the WHO one. This may have resulted in some misclassification)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Ethnicity not adjusted for (with no baseline data on ethnicity). Different exposure groups (eGFR groupings) not matched for in study design though appropriate regression analysis done on key variables)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(appropriate regression analysis and well presented)*
Overall risk of bias and directness	Risk of Bias	Moderate *(Outcome measurement reliant on authors retrospectively diagnosing sepsis through different ICD codes which may lead to misclassification. No adjustment in cox regression analysis for ethnicity or description of this as a baseline variable in the paper.)*

Section	Question	Answer
Overall risk of bias and directness	Directness	Partially applicable *(Percentage of people with diabetes (immunosuppressed which was an exclusion from this review protocol) increases to 19% at the lowest eGFR level)*

Zhong, 2023

Bibliographic Reference	Zhong, Xiaomin; Ashiru-Oredope, Diane; Pate, Alexander; Martin, Glen P; Sharma, Anita; Dark, Paul; Felton, Tim; Lake, Claire; MacKenna, Brian; Mehrkar, Amir; Bacon, Sebastian C J; Massey, Jon; Inglesby, Peter; Goldacre, Ben; Hand, Kieran; Bladon, Sian; Cunningham, Neil; Gilham, Ellie; Brown, Colin S; Mirfenderesky, Mariyam; Palin, Victoria; van Staa, Tjeerd Pieter; Clinical and health inequality risk factors for non-COVID-related sepsis during the global COVID-19 pandemic: a national case-control and cohort study.; EClinicalMedicine; 2023; vol. 66; 102321

Study Characteristics

Study design	Case–control studies
Study details	Study location UK

	Study setting Hospital/secondary care Study dates January 1, 2019 and June 31, 2022, Sources of funding This study was supported by funding from the UK Health Security Agency, NIHR Manchester Biomedical Research Centre (NIHR203308), Health Data Research UK (Better prescribing in frail elderly people with polypharmacy: learning from practice and nudging prescribers into better practice-BetterRx) and by National Institute for Health Research
Inclusion criteria	ICD-10 sepsis diagnosis Non-covid-19 related sepsis The non-COVID-19 sepsis cohort was defined as a sepsis diagnosis without a COVID-19 infection record from primary or secondary care six weeks before/after index date
Exclusion criteria	Criteria 1 Patients were excluded if they were not registered at a primary care practice for at least one-year prior to the index date Criteria 2

	Cases without a record of index of multiple deprivation (IMD) or region recorded were excluded.
Number of participants and recruitment methods	Cases - 'Patients diagnosed with sepsis were identified using ICD-10 codes from the hospital admissions record based on existing study codelists.' n=224361 Controls - 'Every six months, we selected and extracted potential controls. We extracted patients who did not have a diagnosis of sepsis from 15 days prior to the start date up to 15 days after the end date. (The start date and end date were the cut-off dates for each six-month period.)' n=1346166
Length of follow-up	Retrospective
Loss to follow up	Retrospective
Outcome(s) of interest	Sepsis in community, sepsis in hospital and all-cause mortality following sepsis diagnosis
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Primary: Socioeconomic deprivation, region, ethnicity (white, mixed, Asian, black, other, unknown), and body mass index (BMI), Secondary: high blood pressure or diagnosed hypertension, chronic respiratory diseases (excluding asthma), asthma (classified based on with or without recent use of oral steroids), chronic heart disease, diabetes (classified based on the most recent HbA1c measurement within the 15 months before the index date), cancer (non-

	haematological and haematological), chronic kidney disease (CKD) or renal replacement therapy(RRT) (classified based on estimated glomerular filtration rates of ≥60 [absent],
Covariates adjusted for in the multivariable regression modelling	Model 1, the specific COVID-19 time periods were assumed to be a moderator variable All comorbidities from primary and secondary set of predictors (above) – population already matched on age and sex

Population characteristics

Arm-level characteristics

Characteristic	**Sepsis in community or hospital (N = 224361)**	**Controls (N = 1346166)**
% Female Custom value	48.6%	48.6%
Mean age (SD) Mean (SD)	69.6 (19.3)	69.6 (19.3)
IMD Quintile 1 (most deprived) Custom value	21.2%	15.4%

Characteristic	Sepsis in community or hospital (N = 224361)	Controls (N = 1346166)
IMD Quintile 5 (least deprived) Custom value	16.8%	21.7%
White Custom value	97.8%	87%
Black Custom value	1.3%	1.3%
South Asian Custom value	4.3%	3.7%
Smoker current Custom value	13.9%	9.6%
Smoker former Custom value	50.6%	46.6%
BMI 40+ (kg/m2) Custom value	5.1%	2.3%
BMI 35–39.9 (kg/m2)	6.5%	4.7%

Characteristic	Sepsis in community or hospital (N = 224361)	Controls (N = 1346166)
Custom value		
BMI 30-34.9 (kg/m2) Custom value	14.5%	13.8%

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Study Attrition	Outcome and prognostic factor information on those lost to follow-up	Yes *(No loss to follow up - retrospective data)*
Study Attrition	Study Attrition Summary	Low risk of bias *(retrospective study design)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Moderate risk of bias *(Some missing data and likely variation in practice in how some variables are recorded)*

Section	Question	Answer
Outcome Measurement	Outcome Measurement Summary	Moderate risk of bias *(Retrospective data reliant on sepsis diagnoses from ICD codes and variable practice across the country may lead to misclassification; sepsis diagnosis criteria may differ)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Variables were well defined with authors taking account of them in regression analysis and matching- including at different timepoints etc, however residual confounding can occur with the type of analysis and variation in the measurement of confounders could have occurred due to the wide geographical spread of the data and variation in practice)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis well presented with all confounders described in paper and supplementary materials and how missing data was accounted for)*
Overall risk of bias and directness	Risk of Bias	Moderate *(Measurement of prognostic, confounding and outcome variables at moderate risk of bias due to variation in practice and different settings across a wide geographical location that these can occur, although authors have designed the*

Section	Question	Answer
		study well and used appropriate statistical analysis to address confounding factors)
Overall risk of bias and directness	Directness	Partially applicable *(Although a large representative UK sample, 9.1% of cases and 2.3% of controls have an immunosuppressive condition (exclusion from the protocol due to recommendation in NG51 already highlighting this population as at increased risk of developing sepsis). Also a proportion of people with diabetes and cancer who may also be immunosuppressed.)*

Appendix E – Forest plots

No meta-analysis undertaken

Appendix F – GRADE tables

Odds or hazard of developing sepsis

No of studies	Study design	Cases	Controls	Effect size (odds ratio/Hazard ratio (95% CI)	Absolute effect	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
IMD quintile 1 (most deprived) vs IMD quintile 5 (least deprived)										
1[1]	Case-control	47,575 / 224361	206,509 / 1,346166	Multivariate OR 1.38 (1.36,1.40)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very low
IMD quintile 2 (most deprived) vs IMD quintile 5 (least deprived)										
1[1]	Case-control	46,030 / 224361	242,459 / 1,346166	Multivariate OR 1.26 (1.23, 1.28)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Serious[7]	Very low
IMD quintile 3 (most deprived) vs IMD quintile 5 (least deprived)										
1[1]	Case-control	48,700 / 224361	302,716 / 1,346166	Multivariate OR 1.12 (1.11,1.14)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very low

CKD stage 3a										
1[1]	Case-control	32315 / 224361	172860 / 1,346166	Multivariate OR 1.24 (1.23, 1.26)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Serious[7]	Very low
CKD stage 3b										
1[1]	Case-control	22825 / 224361	84390 / 1,346166	Multivariate OR 1.70 (1.67, 1.74)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very low
CKD stage 4										
1[1]	Case-control	10185 / 224361	21980 / 1,346166	Multivariate OR 2.62 (2.55, 2.70)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very low
CKD stage 5										
1[1]	Case-control	2140 / 224361	1920 / 1,346166	Multivariate OR 6.23 (5.81, 6.69)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very low
CKD stage 2 Hazard Ratio[6]										
1[5]	Cohort	1685 / 35 618	321 / 23,304	Multi-adjusted HR 0.88 (0.76, 1.02)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Serious[7]	Very low

CKD stage 3a Hazard Ratio[6]										
1[5]	Cohort	686 / 7816	321 / 23,304	Multi-adjusted HR 0.88 (0.73, 1.07)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Serious[7]	Very low
CKD stage 3b Hazard Ratio[6]										
1[5]	Cohort	150 / 1556	321 / 23,304	Multi-adjusted HR 1.28 (0.99, 1.66)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Serious[7]	Very low
CKD stage 4 & 5 Hazard Ratio[6]										
1[5]	Cohort	25 / 144	321 / 23,304	Multi-adjusted HR 2.94 (1.82, 4.75)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very low
Potential care home										
1[1]	Case-control	13505 / 223675	30020 / 1344215	Multivariate OR 2.34 (2.28, 2.40)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very low

Learning disability										
1[1]	Case-control	3135 / 224360	3865 / 1,346165	Multivariate OR 3.53 (3.35, 3.72)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very low
Severe mental illness										
1[1]	Case-control	6150 / 224360	14700/1,346,165	Multivariate OR 1.96 (1.89, 2.03)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very low
Alcohol problems										
1[1]	Case-control	25820 / 224360	101065 / 1,346165	Multivariate OR 1.37 (1.35, 1.39)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very low
Dementia										
1[1]	Case-control	5625 / 224,360	15165 / 1,346165	Multivariate OR 1.42 (1.37,1.47)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very low
Antibiotic count 1										
1[1]	Case-control	No data	No data	Multivariate OR 1.73 (1.71, 1.76)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very low

Antibiotic count 2-3										
1[1]	Case-control	No data	No data	Multivariate OR 2.31 (2.28, 2.35)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very low
Antibiotic count 3 +										
1[1]	Case-control	No data	No data	Multivariate OR 3.36 (3.31, 3.42)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very low
Chronic liver disease										
1[1]	Case-control	7335 / 224,360	15165 / 1,346,165	Multivariate OR 3.06 (2.95, 3.17)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very low
Stroke										
1[1]	Case-control	27295 / 224360	89545 / 1,346,165	Multivariate OR 1.47 (1.45, 1.50)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very low
Asplenia										
1[1]	Case-control	1495 / 224360	3010 / 1,346,165	Multivariate OR 1.11 (1.03, 1.19)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very low

Chronic respiratory disease										
1[1]	Case-control	40460 / 224360	126530 / 1,346,165	Multivariate OR 1.44 (1.42,1.47)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very low
Chronic cardiac disease										
1[1]	Case-control	67290 / 224360	257815 / 1,346,165	Multivariate OR 1.38 (1.37,1.40)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very low
Other neurological disease										
1[1]	Case-control	11260 / 224360	23795 / 1,346,165	Multivariate OR 2.33 (2.28, 2.39)	Not estimable[8]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very low
Ethnicity - mixed[10]										
1[1]	Case-control	1430 / 224360	8315 / 1,346,165	Unadjusted OR[9] 0.95 (0.90, 1.01	0 fewer per 1,000 (from 1 fewer to 0 fewer)	Serious[2]	Serious[3]	Serious[4]	Not serious	Very low
Ethnicity – South Asian[10]										

1[1]	Case-control	9720 / 224360	50250 / 1,346,165	Unadjusted OR[9] 1.08 (1.05, 1.11)	3 more per 1,000 (from 2 more to 4 more)	Serious[2]	Serious[3]	Serious[4]	Not serious	Very low
Ethnicity - Black[10]										
1[1]	Case-control	2975 / 224360	17,465 / 1,346,165	Unadjusted OR[9] 0.96 (0.92, 1.00	1 fewer per 1,000 (from 1 fewer to 0 fewer)	Serious[2]	Serious[3]	Serious[4]	Not serious	Very low

1 Zhong et al 2023
2 Rated down once for moderate risk of bias
3 Evidence from single study rated down once as per agreed guidelines methodology
4 Rated as partially applicable due to some immunocompromised in population
5 Liyanarachi 2024
6 Ref/control ‘eGFR >90’
7 Confidence interval crosses one end of the default MID (0.8-1.25)
8 Absolute effect not estimable for adjusted data
9 Ethnicity OR presented as unadjusted for confounding factors by authors
10 Reference/control ‘white’

Odds of community acquired sepsis and 30-day mortality

No of studies	Study design	Cases	Controls	Effect size (odds ratio/Hazard ratio (95% CI)	Absolute effect	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
CKD 3a										
1[1]	Case-control	No data	No data	Multivariate OR 0.95 (0.91, 1.00)	Not estimable[5]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very Low
CKD 3b										
1[1]	Case-control	No data	No data	Multivariate OR 1.13 (1.07, 1.19)	Not estimable[5]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very Low
CKD 4										
1[1]	Case-control	No data	No data	Multivariate OR 1.54 (1.43, 1.65)	Not estimable[5]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very Low
CKD 5										
1[1]	Case-control	No data	No data	Multivariate OR 1.67 (1.42, 1.96)	Not estimable[5]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very Low

Severe mental illness										
1[1]	Case-control	No data	No data	Multivariate OR 0.90 (0.81, 1.00)	Not estimable[5]	Serious[2]	Serious[3]	Serious[4]	Not serious	Very Low

1 Zhong et al 2023
2 Rated down once for moderate risk of bias
3 Evidence from single study rated down once as per agreed guidelines methodology
4 Rated as partially applicable due to some immunocompromised in population
5 Absolute effect not estimable for adjusted data

CKD/eGFR and hazard of sepsis mortality at 30 days

No of studies	Study design	Cases	Controls[2]	Effect size (odds ratio/Hazard ratio (95% CI)	Absolute effect	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
eGFR 60-89										
1[1]	Cohort	336 / 35,618	33 / 23,304	Multi-adjusted HR 0.75 (0.50, 1.13)	Not estimable[3]	Serious[4]	Serious[5]	Serious[6]	Serious[7]	Very Low

eGFR 45-59										
1[1]	Cohort	180 / 7816	33 / 23,304	Multi-adjusted HR 0.72 (0.45, 1.16)	Not estimable[3]	Serious[4]	Serious[5]	Serious[6]	Serious[7]	Very Low
eGFR 30-44										
1[1]	Cohort	51 / 1556	33 / 23,304	Multi-adjusted HR 1.20 (0.68, 2.13)	Not estimable[3]	Serious[4]	Serious[5]	Serious[6]	Very serious[8]	Very Low
eGFR <30										
1[1]	Cohort	13 / 144	33 / 23,304	Multi-adjusted HR (4.10 (1.88, 8.93)	Not estimable[3]	Serious[4]	Serious[5]	Serious[6]	Not serious	Very Low

1 Liyanarachi 2024
2 Reference/control eGFR >90
3 Absolute effect not estimable for adjusted data
4 Rated down once for moderate risk of bias
5 Evidence from single study rated down once as per agreed guidelines methodology
6 Rated as partially applicable due to some immunocompromised in population
7 Confidence interval crosses one end of the default MID (0.8-1.25)
8 Confidence interval crosses both ends of the default MID (0.8-1.25)

Appendix G – Excluded studies

Excluded studies

Study	Reason for exclusion
Ahiawodzi, Peter D, Kelly, Kimberly, Massengill, Alyssa et al. (2018) Risk factors for sepsis morbidity in a rural hospital population: A case-control study. American journal of infection control 46(9): 1041-1046	- Wrong population *Specific to populations in rural hospitals and not clear what was adjusted for in regression analysis*
Ahmed, Haroon, Farewell, Daniel, Francis, Nick A et al. (2018) Risk of adverse outcomes following urinary tract infection in older people with renal impairment: Retrospective cohort study using linked health record data. PLoS medicine 15(9): e1002652	- Not a relevant study design *Not enough variables adjusted or matched for as per the review protocol*
Amrein, Karin, Zajic, Paul, Schnedl, Christian et al. (2014) Vitamin D status and its association with season, hospital and sepsis mortality in critical illness. Critical care (London, England) 18(2): r47	- Sepsis population *Sepsis mortality reported only - cannot answer review question of people at risk of developing sepsis*
Bassetti, M., Vena, A., Meroi, M. et al. (2020) Factors associated with the development of septic shock in patients with candidemia: A post hoc analysis from two prospective cohorts. Critical Care 24(1): 117	- Wrong population *Risk factors in a candidemia population only. Did not adjust for enough of the specified confounding factors in the protocol*
Bladon, Sian, Ashiru-Oredope, Diane, Cunningham, Neil et al. (2024) Rapid systematic review on risks and outcomes of sepsis: the influence of risk factors associated with health inequalities. International journal for equity in health 23(1): 34	- Not a relevant study design *Narrative review with no meta-analysis*
Brunetti, Enrico, Presta, Roberto, Rinaldi, Gianluca et al. (2023) Predictors of In-Hospital Mortality in Older Inpatients with Suspected Infection. Journal of the American Medical Directors Association 24(12): 1868-1873	- Sepsis mortality only *Risk of sepsis mortality only, not risk of developing sepsis. Biomarkers not risk factors*

Study	Reason for exclusion
Cerceo, Elizabeth, Rachoin, Jean-Sebastien, Gaughan, John et al. (2021) Association of gender, age, and race on renal outcomes and mortality in patients with severe sepsis and septic shock. Journal of critical care 61: 52-56	- Outcome to be predicted do not match that specified in the protocol *AKI outcomes in sepsis patients only*
Chen, Shaoqiu, Gao, Zitong, Hu, Ling et al. (2022) Association of Septic Shock with Mortality in Hospitalized COVID-19 Patients in Wuhan, China. Advances in virology 2022: 3178283	- Biomarkers *Biomarkers reported - not risk factors from protocol* - Non-OECD country
de Haan, Kim, Groeneveld, A B Johan, de Geus, Hilde R H et al. (2014) Vitamin D deficiency as a risk factor for infection, sepsis and mortality in the critically ill: systematic review and meta-analysis. Critical care (London, England) 18(6): 660	- No adjusted odds/risk/hazard ratio for sepsis outcome *Raw data used for RR in analysis - no adjustment for confounders*
Failla, Kim Reina and Connelly, Cynthia D (2017) Systematic Review of Gender Differences in Sepsis Management and Outcomes. Journal of nursing scholarship : an official publication of Sigma Theta Tau International Honor Society of Nursing 49(3): 312-324	- Not a relevant study design *Narrative review with no meta analysis*
Fathi, Mohammad; Markazi-Moghaddam, Nader; Ramezankhani, Azra (2019) A systematic review on risk factors associated with sepsis in patients admitted to intensive care units. Australian critical care : official journal of the Confederation of Australian Critical Care Nurses 32(2): 155-164	- Not a relevant study design *Qualitative review with no meta-analysis*
Feng, QiPing, Wei, Wei-Qi, Chaugai, Sandip et al. (2019) Association Between Low-Density Lipoprotein Cholesterol Levels and Risk for Sepsis Among Patients Admitted to the Hospital With Infection. JAMA network open 2(1): e187223	- Not a relevant study design *Haven't adjusted for enough of the confounding factors as specified in the protocol*
Galiatsatos, Panagis, Sun, Junfeng, Welsh, Judith et al. (2019) Health Disparities and Sepsis: a Systematic Review and Meta-Analysis on the Influence of Race on Sepsis-Related Mortality. Journal of racial and ethnic health disparities 6(5): 900-908	- Sepsis mortality only *Does not have data on risk of developing sepsis*

Study	Reason for exclusion
He, Mingyi, Cao, Tao, Wang, Jing et al. (2021) Vitamin D deficiency relation to sepsis, paediatric risk of mortality III score, need for ventilation support, length of hospital stay, and duration of mechanical ventilation in critically ill children: A meta-analysis. International journal of clinical practice 75(4): e13908	- Non-OECD country *Studies in meta-analysis non-OECD* - No adjusted odds/risk/hazard ratio for sepsis outcome *Raw data used to form OR - not included in a regression analysis*
Henriksen, Daniel Pilsgaard, Pottegard, Anton, Laursen, Christian B et al. (2015) Risk factors for hospitalization due to community-acquired sepsis - a population-based case-control study. PloS one 10(4): e0124838	- Not a relevant study design *Did not adjust for enough of the variables specified in the review protocol*
Hsiao, Chih-Yen, Chen, Tsung-Hsien, Lee, Yi-Chien et al. (2020) Risk factors for uroseptic shock in hospitalized patients aged over 80 years with urinary tract infection. Annals of translational medicine 8(7): 477	- Non-OECD country
Hsiao, Chih-Yen, Yang, Huang-Yu, Chang, Chih-Hsiang et al. (2015) Risk Factors for Development of Septic Shock in Patients with Urinary Tract Infection. BioMed research international 2015: 717094	- Non-OECD country
Jang, Sukbin, Jeon, Minji, Mun, Seok Jun et al. (2024) Clinical characteristics and risk factors for septic shock in patients with pyometra: A retrospective multicenter cohort study. Journal of infection and public health 17(5): 862-867	- Wrong population *Pyometra population specifically*
Jiang, Wei, Song, Lin, Zhang, Yaosheng et al. (2024) The influence of gender on the epidemiology of and outcome from sepsis associated acute kidney injury in ICU: a retrospective propensity-matched cohort study. European journal of medical research 29(1): 56	- Outcome to be predicted do not match that specified in the protocol *Sepsis AKI outcome not sepsis specifically - participants recruited already had sepsis*
Jin, W.-W., Song, D.-L., Gao, X. et al. (2021) Analysis of risk factors affecting the prognosis of septic shock and clinical intervention. Journal of Biological	- Full text paper not available *Unable to find paper; likely a non-OECD country*

Study	Reason for exclusion
Regulators and Homeostatic Agents 35(1): 295-301	
Johnson, Amy L, Ratnasekera, Isanka U, Irvine, Katharine M et al. (2021) Bacteraemia, sepsis and antibiotic resistance in Australian patients with cirrhosis: a population-based study. BMJ open gastroenterology 8(1)	- Wrong population *cirrhosis specific population* - Not a relevant study design *Has not adjusted for enough confounding factors as specified in protocol*
Kaye, Alexander J, Patel, Shivani J, Meyers, Sarah R et al. (2022) Outcomes of Inflammatory Bowel Disease in Hospitalized Patients With Generalized Anxiety Disorder. Cureus 14(8): e27656	- Wrong population *IBD population specifically*
Khamnuan, Patcharin, Chongruksut, Wilaiwan, Jearwattanakanok, Kijja et al. (2015) Clinical predictors for severe sepsis in patients with necrotizing fasciitis: an observational cohort study in northern Thailand. Infection and drug resistance 8: 207-16	- Non-OECD country
Kisat, Mehreen, Villegas, Cassandra V, Onguti, Sharon et al. (2013) Predictors of sepsis in moderately severely injured patients: an analysis of the National Trauma Data Bank. Surgical infections 14(1): 62-8	- Wrong population *Specifically a severely injured/trauma population only*
Kumar, Anand, Teslova, Tatiana, Taub, Erin et al. (2021) Comorbid Diabetes in Inflammatory Bowel Disease Predicts Adverse Disease-Related Outcomes and Infectious Complications. Digestive diseases and sciences 66(6): 2005-2013	- Wrong population *Risk factors specifically in an IBD population*
Lai, Hongyin, Mubashir, Talha, Shiwalkar, Nimisha et al. (2022) Association of pre-admission opioid abuse and/or dependence on major complications in traumatic brain injury (TBI) patients. Journal of clinical anesthesia 79: 110719	- Non-OECD country
Lai, T.-S., Wang, C.-Y., Pan, S.-C. et al. (2013) Risk of developing severe sepsis after acute kidney injury: A population-based cohort study. Critical Care 17(5): r231	- Non-OECD country

Study	Reason for exclusion
Lee, David Uihwan, Fan, Greg Hongyuan, Ahern, Ryan Richard et al. (2021) The effect of malnutrition on the infectious outcomes of hospitalized patients with cirrhosis: analysis of the 2011-2017 hospital data. European journal of gastroenterology & hepatology 32(2): 269-278	- Wrong population *Cirrhosis population specifically and didn't adjust for enough confounding factors as specified in the review protocol*
Liang, C.-M., Hsu, C.-N., Tai, W.-C. et al. (2016) Risk factors influencing the outcome of peptic ulcer bleeding in chronic kidney disease after initial endoscopic hemostasis A nationwide cohort study. Medicine (United States) 95(36): e4795	- No adjusted odds/risk/hazard ratio for sepsis outcome
Lichte, Philipp, Kobbe, Philipp, Almahmoud, Khalid et al. (2015) Post-traumatic thrombo-embolic complications in polytrauma patients. International orthopaedics 39(5): 947-54	- No adjusted odds/risk/hazard ratio for sepsis outcome
Lima, E.M., Cid, P.A., Beck, D.S. et al. (2020) Predictive factors for sepsis by carbapenem resistant Gram-negative bacilli in adult critical patients in Rio de Janeiro: A case-case-control design in a prospective cohort study. Antimicrobial Resistance and Infection Control 9(1): 132	- Not a relevant study design *Case-control but both cases and controls have sepsis*
Lindstrom, Ann-Charlotte, Eriksson, Mikael, Martensson, Johan et al. (2021) Nationwide case-control study of risk factors and outcomes for community-acquired sepsis. Scientific reports 11(1): 15118	- Not a relevant study design *Study does not adjust for enough confounding factors as specified in the review protocol*
Liu, Michael A, Bakow, Brianna R, Hsu, Tzu-Chun et al. (2021) Temporal Trends in Sepsis Incidence and Mortality in Patients With Cancer in the US Population. American journal of critical care : an official publication, American Association of Critical-Care Nurses 30(4): e71-e79	- Not a relevant study design *Study does not adjust for enough confounding factors listed in the protocol*
Luders, Florian, Bunzemeier, Holger, Engelbertz, Christiane et al. (2016) CKD and Acute and Long-Term Outcome of Patients with Peripheral Artery Disease and Critical Limb Ischemia. Clinical journal of	- No adjusted odds/risk/hazard ratio for sepsis outcome

Study	Reason for exclusion
the American Society of Nephrology : CJASN 11(2): 216-22	
Lui, Aiden K, Lin, Fangyi, Uddin, Anaz et al. (2023) A double-hit: End-stage renal disease patients suffer worse outcomes in intracerebral hemorrhage. Brain circulation 9(3): 172-177	- No adjusted odds/risk/hazard ratio for sepsis outcome
M, Kiran Kumar, Das, Sarthak, Biswal, Niranjan et al. (2020) Vitamin D Status at Admission and Its Association With Mortality in Children Admitted to the Pediatric Intensive Care Unit. Cureus 12(6): e8413	- Non-OECD country
Ma, Zhaohui, Jiang, Zeping, Li, Huiping et al. (2024) Prevalence, early predictors, and outcomes of sepsis in neurocritical illnesses: A prospective cohort study. American journal of infection control 52(7): 827-833	- Non-OECD country
Mathew, Anna G, Kaye, Alexander J, Patel, Shivani J et al. (2023) Outcomes of Gastroparesis in Hospitalized Patients With Generalized Anxiety Disorder. Cureus 15(3): e35832	- Wrong population *gastroparesis population specifically*
McDonald, H.I., Thomas, S.L., Millett, E.R.C. et al. (2015) CKD and the risk of acute, community-acquired infections among older people with diabetes mellitus: A retrospective cohort study using electronic health records. American Journal of Kidney Diseases 66(1): 60-68	- No adjusted odds/risk/hazard ratio for sepsis outcome
Minejima, Emi and Wong-Beringer, Annie (2021) Impact of Socioeconomic Status and Race on Sepsis Epidemiology and Outcomes. The journal of applied laboratory medicine 6(1): 194-209	- Review article but not a systematic review *narrative*
Mweene, M.D., Richards, G.A., Paget, G. et al. (2022) Risk factors and outcomes of sepsis-associated acute kidney injury in intensive care units in Johannesburg, South Africa. South African Medical Journal 112(12): 919-923	- Outcome to be predicted do not match that specified in the protocol *Two groups both have sepsis - sepsis AKI vs sepsis non AKI - risk factors are for sepsis AKI specifically*

Study	Reason for exclusion
Naderpour, Z., Momeni, M., Vahidi, E. et al. (2019) Procalcitonin and d-dimer for predicting 28-day-mortality rate and sepsis severity based on sofa score; a cross-sectional study. Bulletin of Emergency and Trauma 7(4): 361-365	- Not a relevant study design *and wrong risk factors*
Naseem, Khadija, Sohail, Abdullah, Quang Nguyen, Vu et al. (2023) Predictors of Hospital-related Outcomes of COVID-19 Infection in Patients With Inflammatory Bowel Disease in the Early Pandemic Phase: A Nationwide Inpatient Database Survey. Inflammatory bowel diseases	- Wrong population *risk factors in an IBD or IBD and Covid population only*
Nilsson, Niklas Harry, Bendix, Marie, Ohlund, Louise et al. (2021) Increased Risks of Death and Hospitalization in Influenza/Pneumonia and Sepsis for Individuals Affected by Psychotic Disorders, Bipolar Disorders, and Single Manic Episodes: A Retrospective Cross-Sectional Study. Journal of clinical medicine 10(19)	- Not a relevant study design *No regression analysis done*
O'Brien, James M Jr, Lu, Bo, Ali, Naeem A et al. (2011) Insurance type and sepsis-associated hospitalizations and sepsis-associated mortality among US adults: a retrospective cohort study. Critical care (London, England) 15(3): r130	- Does not include a relevant risk factor
Onwuneme, Chike, Carroll, Aoife, Doherty, Dermot et al. (2015) Inadequate vitamin D levels are associated with culture positive sepsis and poor outcomes in paediatric intensive care. Acta paediatrica (Oslo, Norway : 1992) 104(10): e433-8	- No adjusted odds/risk/hazard ratio for sepsis outcome
Oud, Lavi and Garza, John (2022) Impact of history of mental disorders on short-term mortality among hospitalized patients with sepsis: A population-based cohort study. PloS one 17(3): e0265240	- Not a relevant study design *Cross-sectional*
Page-Wilson, Gabrielle, Arakawa, Rachel, Nemeth, Samantha et al. (2021) Obesity is independently associated with septic shock, renal complications, and mortality in a	- Wrong population *Covid-19 population specifically*

Study	Reason for exclusion
multiracial patient cohort hospitalized with COVID-19. PloS one 16(8): e0255811	
Peach, Brian C, Garvan, Gerard J, Garvan, Cynthia S et al. (2016) Risk Factors for Urosepsis in Older Adults: A Systematic Review. Gerontology & geriatric medicine 2: 2333721416638980	- Not a relevant study design *Narrative review only*
Pericas, Juan M, Hernandez-Meneses, Marta, Munoz, Patricia et al. (2021) Outcomes and Risk Factors of Septic Shock in Patients With Infective Endocarditis: A Prospective Cohort Study. Open forum infectious diseases 8(6): ofab119	- Wrong population *Infective endocarditis (IE) population specifically*
Reid, Alice L, Bailey, Michael, Harwood, Matire et al. (2022) Outcomes for Maori and European patients admitted to New Zealand intensive care units between 2009 and 2018. The New Zealand medical journal 135(1550): 26-46	- Sepsis mortality only *Results not presented for sepsis but for risk of mortality in total. Population also not applicable to UK context*
Ruiz-Mesa, Juan D, Marquez-Gomez, Ignacio, Sena, Gabriel et al. (2017) Factors associated with severe sepsis or septic shock in complicated pyelonephritis. Medicine 96(43): e8371	- Not a relevant study design *Does not adjust for enough of the confounding factors specified in the review protocol*
Sakr, Yasser, Elia, Cristina, Mascia, Luciana et al. (2013) The influence of gender on the epidemiology of and outcome from severe sepsis. Critical care (London, England) 17(2): r50	- Sepsis mortality only *Does not answer review question re risk of developing sepsis*
Sozio, Emanuela, Bertini, Alessio, Bertolino, Giacomo et al. (2021) Recognition in Emergency Department of Septic Patients at Higher Risk of Death: Beware of Patients without Fever. Medicina (Kaunas, Lithuania) 57(6)	- Wrong population *10% had catheters, 5% trauma. 3.7% had surgery undergone surgery, and 9% were immunocompromised and results don't disaggregate or account for this.*
Storm, L, Schnegelsberg, A, Mackenhauer, J et al. (2018) Socioeconomic status and risk of intensive care unit admission with sepsis. Acta anaesthesiologica Scandinavica 62(7): 983-992	- Not a relevant study design *Did not adjust for enough confounders as specified in the protocol*

Study	Reason for exclusion
Su, Chih-Min, Kung, Chia-Te, Chen, Fu-Cheng et al. (2018) Manifestations and Outcomes of Patients with Parkinson's Disease and Serious Infection in the Emergency Department. BioMed research international 2018: 6014896	- Non-OECD country
Su, Guo-Yun, Fan, Chao-Nan, Fang, Bo-Liang et al. (2022) Comparison between hospital- and community-acquired septic shock in children: a single-center retrospective cohort study. World journal of pediatrics : WJP 18(11): 734-745	- Non-OECD country
Suh, Jin Woong; Kim, Min Ja; Kim, Jong Hun (2021) Risk factors of septic shock development and thirty-day mortality with a predictive model in adult candidemia patients in intensive care units. Infectious diseases (London, England) 53(12): 908-919	- Wrong population *Candidemia population specifically can only tell us about risk in that population, not relative risk of sepsis from being in that population*
Tan, Debbie, Wiseman, Taneal, Betihavas, Vasiliki et al. (2021) Patient, provider, and system factors that contribute to health care-associated infection and sepsis development in patients after a traumatic injury: An integrative review. Australian critical care : official journal of the Confederation of Australian Critical Care Nurses 34(3): 269-277	- Not a relevant study design *Review with no meta-analysis*
Taskin, Gurhan, Sekerci, Cagri Akin, Tanidir, Yiloren et al. (2021) The Significance of Asymptomatic Kidney Stones as a Predictive Factor for Sepsis in Critically Ill Older Adults. Puerto Rico health sciences journal 40(1): 33-37	- Not a relevant study design *No multivariable regression analysis*
Trong, T.N., Thao, D.T., Thu, V.P.M. et al. (2021) Septic shock outcome and factors associated with mortality in the intensive care unit in Vietnam. Journal of the Medical Association of Thailand 104(8): 1249-1254	- Not a relevant study design *Cross-sectional design*
Upala, Sikarin; Sanguankeo, Anawin; Permpalung, Nitipong (2015) Significant association between vitamin D deficiency	- Not a relevant study design *Contains cross-sectional designs in quantitative analysis*

Study	Reason for exclusion
and sepsis: a systematic review and meta-analysis. BMC anesthesiology 15: 84	
Vardar, Ufuk, Ilelaboye, Ayodeji, Murthi, Mukunthan et al. (2023) Racial Disparities in Patients With COVID-19 Infection: A National Inpatient Sample Analysis. Cureus 15(2): e35039	- Wrong population *Risk factors in a covid population specifically*
Vazquez Guillamet, M Cristina, Dodda, Sai, Liu, Lei et al. (2022) Race Does Not Impact Sepsis Outcomes When Considering Socioeconomic Factors in Multilevel Modeling. Critical care medicine 50(3): 410-417	- Does not include a relevant risk factor - Not a relevant study design
Videholm, Samuel, Kostenniemi, Urban, Lind, Torbjorn et al. (2021) Perinatal factors and hospitalisations for severe childhood infections: a population-based cohort study in Sweden. BMJ open 11(10): e054083	- No adjusted odds/risk/hazard ratio for sepsis outcome
Wang, Sheng-Fen, Lai, Po-Liang, Liu, Hsiang-Fu et al. (2021) Risk Factors of Coexisting Septic Spondylitis and Arthritis: A Case-Control Study in a Tertiary Referral Hospital. Journal of clinical medicine 10(22)	- Post-surgery population – exclusion in protocol
Wang, Yongjie, Li, Xiaolu, Yu, Yanyan et al. (2023) Risk factors for sepsis in patients with colorectal cancer complicated with gastrointestinal perforation and its impact on prognosis. Journal of gastrointestinal oncology 14(2): 806-814	- Does not include a relevant risk factor
Weissman, Simcha, Pandol, Stephen J, Ghaffar, Umar et al. (2023) Impact of sex and comorbid diabetes on hospitalization outcomes in acute pancreatitis: A large United States population-based study. AIMS public health 10(1): 105-115	- Wrong population *acute pancreatitis specific population*
Yamamichi, Fukashi, Shigemura, Katsumi, Kitagawa, Koichi et al. (2018) Comparison between non-septic and septic cases in stone-related obstructive acute pyelonephritis and risk factors for septic shock: A multi-center retrospective study. Journal of infection and chemotherapy :	- Wrong population *Obstructive acute pyelonephritis (APN) population only*

Study	Reason for exclusion
official journal of the Japan Society of Chemotherapy 24(11): 902-906	
Zaid, Yahia, Rajeh, Abbas, Hosseini Teshnizi, Saeed et al. (2019) Epidemiologic features and risk factors of sepsis in ischemic stroke patients admitted to intensive care: A prospective cohort study. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia 69: 245-249	- Non-OECD country
Zhou, Q., Shen, Q., Chen, X. et al. (2024) Identifying depression's genetic role as a precursor to sepsis and increased mortality risk: Comprehensive insights from mendelian randomization analysis. PLoS ONE 19(5may): e0300275	- Not a relevant study design
Zhou, W., Mao, S., Wu, L. et al. (2018) Association between Vitamin D status and sepsis. Clinical Laboratory 64(4): 451-460	- Non-OECD country *Non-OECD countries included in quantitative analysis*

Appendix H– Research recommendations – full details

No research recommendations were developed based on this review