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Clinical risk factors for pancreatic cancer: protocol for an umbrella review.

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Clinical risk factors for pancreatic cancer: protocol for an umbrella review.

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Keywords: pancreatic cancer; risk factors; umbrella review

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Abstract

Introduction

Identifying cancer earlier can help save lives. An increasingly popular approach to diagnosing cancer earlier is in the development of risk prediction models to be applied to the electronic healthcare record of patients. Development of these models requires systematic and thorough identification of the risk factors that might increase an individual's propensity to develop the disease. This protocol sets out the methods for an umbrella review to identify risk factors that might be included in these models. The example used is pancreatic cancer, a disease with a high percentage of late-stage diagnoses and consequent high mortality.

Methods and analysis

Relevant systematic reviews will be identified through searching of MEDLINE and EMBASE via Ovid and the Science Citation Index Expanded of the Web of Science Core collection. Screening will be performed by two independent reviewers using Covidence software and the results reported as a PRISMA flow diagram. Data from eligible studies will be extracted independently by two reviewers and each systematic review will be graded using defined credibility assessment criteria and the ROBIS tool for assessing risk of bias in systematic reviews. Results will be presented in detail for each paper. Summary results for each risk factor will be discussed in the narrative and summarised using a table, graphical summary and an infographic.

Ethics and dissemination

Ethical approval is not required for this review. Results of the review will be disseminated by publication in a peer reviewed journal and presented at conferences.

PROSPERO registration number: CRD42024526338

Strengths and limitations of this study

- This umbrella review will provide a comprehensive overview of the systematic reviews on individual risk factors for pancreatic cancer.
- Thorough assessment of strength of evidence and quality of included reviews will increase the robustness of the results.
- There will be some overlap of studies used by systematic reviews on the same topic. Clear criteria, using strength of evidence assessments, will be applied to decide on which to include in the final results summary.

Introduction

Pancreatic cancer is increasingly common and its survival universally poor, for example in the UK it is the 10th most common cancer and has a survival rate of only 5% at 5 years (1). This is in part due to most cases being diagnosed at a late stage, when the cancer has spread beyond the pancreas and the prognosis is worse (2).

One hope for improving pancreatic cancer survival is therefore to identify it at an earlier stage, when it hasn't spread and is more treatable. An increasingly popular way of doing this is through using electronic healthcare records to develop models that identify people at current or future high risk of pancreatic cancer (3). Identification of either group can help improve early diagnosis, though the mechanisms for doing so are different. The first, identifying a high risk of undiagnosed current cancer, allows for earlier investigation and potential subsequent earlier diagnosis. The second, identifying people with a high future risk of cancer, means it is possible to initiate screening and/or surveillance as well as implement preventative action. In order to develop either of these model types, it is vital to have an understanding of the key risk factors for pancreatic cancer, as these will form the pool of candidate variables for model development (see box 1 for disambiguation of terms factor, variable and feature).

A systematic review of pancreatic cancer prediction models identified 33 articles describing 38 models predicting the risk of pancreatic cancer (3). Although they summarised which factors were ultimately included in each model, further exploration of the studies behind the models shows no consistent approach to identifying the candidate variables from which the model can be built (3). There are thousands of potential risk factors available in electronic healthcare records and these need to be refined when developing a model, in order to achieve the most accurate prediction (4). There is therefore a significant need for developing a robust process for identifying potential candidate variables from which the final features can be selected. This is usually performed based on subject knowledge and in some cases systematic review followed by statistical or machine learning led selection to define the final variables for inclusion in the model (5).

The candidate variables that can practically be used in these models at present (certainly in the UK setting) are those available to researchers using large databases of coded electronic healthcare records, though in some places this has already been expanded to include free text information using natural language processing capabilities (6). Although research datasets such as UK Biobank may contain information on genetics or novel biomarkers (7), the records used in routine clinical care at present do not.

Given the wealth of literature available on potential risk factors for pancreatic cancer, this study will take the approach of an umbrella review, which systematically identifies and assesses multiple systematic reviews and meta-analyses on a specific topic to provide an overall picture (8,9).

The last comprehensive summary review of meta-analytical studies examining risk factors for pancreatic cancer was published nearly ten years ago and since then there have been a significant number of new systematic reviews looking at individual risk factors for pancreatic cancer (10). In addition, the previous review of reviews used a very simplified format for grading the strength of evidence for each association compared to the criteria for credibility assessments used in many umbrella type reviews (10,11). It is therefore timely to repeat and expand this review of reviews, considering the needs of researchers using the findings for the development of risk prediction models using electronic healthcare records.

Objectives

The primary objective of this umbrella review is to identify potential risk factors for pancreatic cancer in adults that are accessible to clinicians and healthcare researchers in the electronic healthcare record. Secondary objectives comprise quantification of the magnitude of the effect and a description of the strength of the evidence for each risk factor.

Box 1: Defining terms: features, factors and variables.

In the literature surrounding risk prediction models, several terms are used interchangeably and can cause confusion. We will therefore clarify how we are using each term for the purposes of this paper.

A dataset is made up of information about an individual, e.g. their age, what medications they take or whether they are smokers. Each piece of information is known as a **variable** and some of these will be of potential relevance to the model and others will not. Those that are identified as potentially relevant are known as the **candidate variables**, from which the **final variables** that will form the basis for the model will be chosen using statistical or machine learning techniques.

Risk factors, sometimes referred to simply as **factors**, are variables that are associated with cancer development. A classic example is smoking. Risk factors affect the prior odds of an individual developing cancer. In this review we are identifying **risk factors** for pancreatic cancer that can be used as **candidate variables** for a risk prediction model.

Features refers to the signs, symptoms or test results that could indicate an undiagnosed cancer is present. These are not being investigated in this paper but will be important for development of models of current undiagnosed cancer risk for symptomatic patients. N.B. The term features is often used in machine leaning literature to refer to variables.

Methods

Design and Registration

This protocol has been developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) (12,13) (see appendix 1). Guidance from the Joanna Briggs Institute, Cochrane collaboration and other published sources on the methodology underpinning systematic and umbrella reviews have been taken into account in its development (8,9,14,15). It has been registered with PROSPERO, registration number CRD42024526338.

Eligibility Criteria

These are based on the PECOS statement (16), see table 1.

Population	Adults over the age of 18 years
Exposure	Any factors which might influence the development of pancreatic cancer and are available in an electronic healthcare record
Comparator	Adults who have not been exposed, or have been differentially exposed, to the factors which might influence the development of pancreatic cancer
Outcome	Diagnosis of pancreatic cancer
Study designs	Systematic reviews and meta-analyses
Setting	Any setting

Table 1. Eligibility criteria for studies to be included in the umbrella review.

Reviews will be eligible for inclusion if they are systematic reviews or meta-analyses of component studies with suitable epidemiological design e.g. cohort or case-control studies, they will not be eligible if theoretical studies or published opinion are their primary source of evidence. Eligible reviews will examine risk factors for pancreatic cancer that could be available in a coded electronic patient healthcare record and will therefore exclude factors that require genome sequencing or use of novel biomarkers. The cancers of interest are primary cancers of the pancreas in adults. Studies solely examining neuroendocrine tumours will be excluded. There will be no geographical or time restriction on the included reviews, but they will be excluded if there is no full text of the completed study available in the English language.

Information sources

Systematic searches will be performed of MEDLINE and EMBASE via Ovid and the Science Citation Index Expanded database on the Web of Science Core Collection. Supplementary searches including forward and backward citation chasing will be performed through Scopus. Grey literature is not being searched as it is very unlikely to be a source of systematic reviews.

Search Strategy

Key search concepts are 'pancreatic cancer', 'risk factors' and 'systematic reviews'. Full details of the exact search terms to be used can be found in appendix 2.

Study Records

Covidence software for managing systematic reviews (https://www.covidence.org/) will be used for screening abstracts and full texts. Two independent reviewers will screen all records retrieved for eligibility. Data from eligible studies will be extracted into preformatted tables by two independent reviewers and compared. Throughout, any disagreement between the two reviewers will be identified and resolved by discussion until consensus is reached and if this is not possible a third reviewer will be consulted. In circumstances where required data is not available then the authors of the original review will be contacted for clarification. If, after a second approach, this is not possible then the review will be included but marked as having missing information.

Data items

Data will be extracted under multiple headings, as shown in table 2.

Column heading	Explanation
Risk factor	NB. if a review explores more than one risk factor it will be included multiple times in the extraction, once for each factor.
Reference	To include lead author, year, DOI
Type of review	e.g. pooled/meta-analysis
Number/type of studies	e.g. cohort/case-control
Number of cases/controls	Across the whole review/meta-analysis
Population characteristics	e.g. location, sex
Strata	Difference between exposed and comparator populations e.g. 5 unit increase in BMI or BMI above or below 30
Effect size metric	e.g. relative risk/odds ratio/hazard ratio
Summary effect size (95%CI)	As per the study findings
P value for summary effect estimate	As per the study findings
Measure of heterogeneity	e.g. I^2, as per the study findings
Grading of strength of evidence	Based on criteria for credibility of assessment (see below)
Notes	Any extra notes from the extractor on the review

Table 2. Data extraction fields for each eligible review

Most data will be extracted directly from the identified reviews but grading the strength of evidence and quality of the reviews will be completed separately as part of the process.

Grading strength of evidence for each association

There is no consensus on the best method for grading strength of evidence in an umbrella review. In a scoping review of what has been used previously, only half of studies assessed certainty of the evidence and within those studies the most commonly used criteria was credibility assessment (80%), followed by the GRADE approach (14%) (11).

Credibility assessment criteria were similar between studies but the levels at which they met a threshold varied slightly depending on the study (11). We have used the most commonly occurring criteria and thresholds, as identified in table S6 of Sadoyu et al. (11) and recommended in Fusar-Poli et al (17), as the basis for our credibility assessment criteria, see table 3.

Given the primary aim of this review is the identification of *potential* risk factors, we will not be deriving 95% prediction intervals, evidence of small-study effects or evidence of excess significance bias in order to assess publication and other biases within the component studies of a systematic review, nor including them in our credibility assessment criteria.

Measure	**Threshold**			
	Convincing	**Highly suggestive**	**Suggestive**	**Weak**
Number of cases	>1000 cases	>1000 cases	>1000 cases	
P-value	$p < 10^{-6}$	$p < 10^{-6}$	$p < 10^{-3}$	$p < 0.05$
Heterogeneity	$I^2 < 50\%$	-	-	-
Largest study with statistically significant effect	Largest study nominally significant ($p < 0.05$)	-	-	-

Table 3. Credibility assessment criteria for this study, derived from findings of Sadoyu et al. (11).

Assessing methodological quality of reviews

For the type of reviews included in this study, the best available method for assessing quality is the ROBIS tool which includes four key domains: study eligibility criteria, identification and selection of studies, data collection and study appraisal and synthesis and findings (18,19). This will be completed for each included study and summary shown in the final detailed results table.

Other data considerations

Comparing the effect sizes

Effect size is a measure of the strength of the relationship between the risk factor and the development of the disease. Effect size is the main quantitative outcome of interest for this study and it is important that effect sizes can be compared between risk factors (17). Although not all studies use the same measures to report their effect size, we can treat the likely reported measures of relative risk, hazard ratios, odds ratios and incidence rate ratios as approximately equal because the event rate for pancreatic cancer is typically less than 10% (17,20).

Multiple reviews on the same risk factor

There are likely to be multiple reviews on the same risk factor and there is no consensus on how to deal with overlapping reviews (14,21). In the previous review of reviews of the topic in 2015, the authors averaged the risk estimates reported in all available meta-analyses and pooled analyses (10). However, this leads to a risk of including multiple component studies more than once, as they occur repeatedly in each review. Given the aim of that study was simply to *identify* potential risk factors, overlap of included studies did not matter. However, there remains the issue of the strength of the evidence in each study and the risk of the results of smaller high-quality analyses being diluted by large poor-quality studies. To avoid this we will use an alternative, common approach to overlapping studies, which is to select the single largest, most recent or highest quality meta-analysis or systematic review to represent the relationship between the exposure and outcome (21). Our priority is to identify robust relationships and we therefore propose that, in the event of multiple reviews of the same risk factor, once data has been extracted for each study, we will select the study with the highest strength of evidence according to our credibility assessment criteria grading (see previous section). If there is more than one review with 'convincing' evidence, we will select from them the review with the best quality according to the ROBIS assessment. If this still results in more than one study we will select that with the largest pooled number of participants.

Outcomes and prioritisation

The main outcome will be a list of risk factors for pancreatic cancer that can be defined in coded electronic healthcare records. Additional outcomes will be the strength of the effect of the risk factor and the strength of the evidence for the effect, according to the criteria described above.

Data synthesis

In this umbrella review, quantitative synthesis will not be performed, instead summary results for each risk factor will be presented in a table (see table 4 for key headings) and discussed in the

narrative. A graphical summary will be developed from the key results to show direction and magnitude of reported effect sizes and a simple infographic grouping the factors by section e.g. demographic, lifestyle, medical history.

Column heading	Explanation
Risk factor	Description of factor
Degree of association	Measured by relative risk in largest study of good quality
Strength of evidence	As per credibility assessment criteria above

Table 4. Summary results table plan (results of the main selected study on each factor)

Ethics

Ethical approval is not required to perform this review.

Patient and Public Involvement

The patient and public involvement team, already recruited to the overarching study, will contribute to discussions around the findings of this umbrella review in a designated session. Their thoughts will be integrated into the final write up of the study.

Dissemination

Results of the study will be published in a peer reviewed journal and presented at academic conferences. All collected data will be made available as appendices to the published paper.

Data statement

All data generated will be available as appendices to the final published study report.

Footnotes

Author contributions: SM and GA designed the study and developed the search strategy. SM and GD will implement the search strategy, screen retrieved studies for eligibility, extract data from eligible studies, conduct the quality assessment and perform the analysis. GA or SP will act as a third reviewer as needed. The protocol was written SM and approved by SM, GD, SP, GA, FW and RN.

Funding statement: This work was supported by a doctoral fellowship for primary care clinicians awarded to SM by Wellcome, grant number PMHG1A4.

Competing interests statement: There are no competing interests to be declared.

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Appendix 1.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	13
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	16
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8, 9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	N/A
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	N/A
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9,10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Appendix 2: Specific search terms by database and platform

MEDLINE via Ovid

1 (pancrea* neoplasm* or (pancrea* adj3 carcinoma*) or (Cancer adj3 pancrea*) or (Malignan* adj3 pancrea*) or (Pancrea* adj3 carcinogenesis) or (Pancrea* adj3 tumo?r)).af. or Pancreatic neoplasms.sh.

2 (risk factor* or health correlate* or population* at risk or precipitating factor* or sociodemographic factor* or protective factor* or epidemiologic* factor* or epidemiologic* determinant* or relative risk).ti,ab,mp. or Risk Factors.sh. or Protective factors.sh. or Epidemiologic factors.sh.

3 (systematic review* or umbrella review* or meta?analys* or meta regression or meta analys* or medline or pubmed).ti,ab,mp. or meta-analysis.sh. or systematic review.sh.

4 1 and 2 and 3

EMBASE via Ovid

1 (pancrea* neoplasm* or (pancrea* adj3 carcinoma*) or (Cancer adj3 pancrea*) or (Malignan* adj3 pancrea*) or (Pancrea* adj3 carcinogenesis) or (Pancrea* adj3 tumo?r)).af. or Pancreas cancer.ec. or Pancreas carcinoma.ec.

2 (risk factor* or health correlate* or population* at risk or precipitating factor* or sociodemographic factor* or protective factor* or epidemiologic* factor* or epidemiologic* determinant* or relative risk).ti,ab,mp. or risk factor.ec. or protection.ec.

3 (systematic review* or umbrella review* or meta?analys* or meta regression or meta analys* or medline or pubmed). ti,ab,mp. or Meta analysis.ec. or Systematic review.ec.

4 1 and 2 and 3

Science Citation Index Expanded on Web of Science Core Collection

1: (((((TS=(pancrea* neoplasm*)) OR TS=(pancrea* NEAR/3 carcinoma*)) OR TS=(Cancer NEAR/3 pancrea*)) OR TS=(Malignan* NEAR/3 pancrea*)) OR TS=(Pancrea* NEAR/3 carcinogenesis)) OR TS=(Pancrea* NEAR/3 tumo$r)

2: (((((((TS=(risk factor*)) OR TS=(health correlate*)) OR TS=(population* at risk)) OR TS=(Precipitating factor*)) OR TS=(Sociodemographic factor*)) OR TS=(Protective factor*)) OR TS=(Epidemiologic* factor*)) OR TS=(Epidemiologic* determinant*)) OR TS=(Relative risk)

3: ((((((((TS=(systematic review*)) OR TS=(umbrella review*)) OR TS=(Meta-analys*)) OR TS=(Meta regression)) OR TS=(Meta analys*)) OR TS=(Metaanalys*)) OR TS=(Medline*)) OR TS=(Pubmed*))

4: #1 AND #2 AND #3

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Secondary Subject Heading:	General practice / Family practice, Oncology, Public health
Keywords:	Risk Factors, Epidemiology < ONCOLOGY, Systematic Review

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Abstract

Introduction

Identifying cancer earlier can help save lives. An increasingly popular approach to diagnosing cancer earlier is in the development of risk prediction models to be applied to the electronic healthcare record of patients. Development of these models requires systematic and thorough identification of the risk factors that might increase an individual's propensity to develop the disease. This protocol sets out the methods for an umbrella review to identify risk factors that might be included in these models. The example used is pancreatic cancer, a disease with a high percentage of late-stage diagnoses and consequent high mortality.

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PROSPERO registration number: CRD42024526338

Strengths and limitations of this study

- Using umbrella review methodology will provide a comprehensive overview of the systematic reviews and meta-analyses on individual clinical risk factors for pancreatic cancer.
- Thorough assessment of strength of evidence and quality of included reviews will increase the robustness of the results.
- There will be some overlap of studies used by systematic reviews on the same topic. This will be mitigated by using strength of evidence assessments, to decide which studies to include in the final results summary.

Introduction

Pancreatic cancer is increasingly common and its survival universally poor, for example in the UK it is the 10th most common cancer and has a survival rate of only 5% at 5 years [1]. This is in part due to most cases being diagnosed at a late stage, when the cancer has spread beyond the pancreas and the prognosis is worse [2].

One hope for improving pancreatic cancer survival is therefore to identify it at an earlier stage, when it hasn't spread and is more treatable. An increasingly popular way of doing this is through using electronic healthcare records to develop models that identify people at current or future high risk of pancreatic cancer [3]. Identification of either group can help improve early diagnosis, though the mechanisms for doing so are different. The first, identifying a high risk of undiagnosed current cancer, allows for earlier investigation and potential subsequent earlier diagnosis. The second, identifying people with a high future risk of cancer, means it is possible to initiate screening and/or surveillance as well as implement preventative action. In order to develop either of these model types, it is vital to have an understanding of the key risk factors for pancreatic cancer, as these will form the pool of candidate variables for model development (see box 1 for disambiguation of terms factor, variable and feature).

A systematic review of pancreatic cancer prediction models identified 33 articles describing 38 models predicting the risk of pancreatic cancer [3]. Although they summarised which factors were ultimately included in each model, further exploration of the studies behind the models shows no consistent approach to identifying the candidate variables from which the model can be built [3]. There are thousands of potential risk factors available in electronic healthcare records and these need to be refined when developing a model, in order to achieve the most accurate prediction [4]. There is therefore a significant need for developing a robust process for identifying potential candidate variables from which the final features can be selected. This is usually performed based on subject knowledge and in some cases systematic review followed by statistical or machine learning led selection to define the final variables for inclusion in the model [5].

The candidate variables that can practically be used in these models at present (certainly in the UK setting) are those available to researchers using large databases of coded electronic healthcare records, though in some places this has already been expanded to include free text information using natural language processing capabilities [6]. Although research datasets such as UK Biobank may contain information on genetics or novel biomarkers [7], the records used in routine clinical care at present do not. In addition to this, there is limited access in routine healthcare data to

information on diet and these factors have already been explored in recent comprehensive reviews [8,9].

Given the wealth of literature available on potential risk factors for pancreatic cancer, this study will take the approach of an umbrella review, which systematically identifies and assesses multiple systematic reviews and meta-analyses on a specific topic to provide an overall picture [10,11].

The last comprehensive summary review of meta-analytical studies examining clinical risk factors for pancreatic cancer was published nearly ten years ago and since then there have been a significant number of new systematic reviews looking at individual risk factors for pancreatic cancer [12]. In addition, the previous review of reviews used a very simplified format for grading the strength of evidence for each association compared to the criteria for credibility assessments used in many umbrella type reviews [12,13]. It is therefore timely to repeat and expand this review of reviews, considering the needs of researchers using the findings for the development of risk prediction models using electronic healthcare records.

Objectives

The primary objective of this umbrella review is to identify potential risk factors for pancreatic cancer in adults that are accessible to clinicians and healthcare researchers in the electronic

Box 1: Defining terms: features, factors and variables.

In the literature surrounding risk prediction models, several terms are used interchangeably and can cause confusion. We will therefore clarify how we are using each term for the purposes of this paper.

A dataset is made up of information about an individual, e.g. their age, what medications they take or whether they are smokers. Each piece of information is known as a **variable** and some of these will be of potential relevance to the model and others will not. Those that are identified as potentially relevant are known as the **candidate variables**, from which the **final variables** that will form the basis for the model will be chosen using statistical or machine learning techniques.

Risk factors, sometimes referred to simply as **factors**, are variables that are associated with cancer development. A classic example is smoking. Risk factors affect the prior odds of an individual developing cancer. In this review we are identifying **risk factors** for pancreatic cancer that can be used as **candidate variables** for a risk prediction model.

Features refers to the signs, symptoms or test results that could indicate an undiagnosed cancer is present. These are not being investigated in this paper but will be important for development of models of current undiagnosed cancer risk for symptomatic patients. N.B. The term features is often used in machine leaning literature to refer to variables.

healthcare record. Secondary objectives comprise quantification of the magnitude of the effect and a description of the strength of the evidence for each risk factor.

Methods

Design and Registration

This protocol has been developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) [14,15] (see appendix 1). Guidance from the Joanna Briggs Institute, Cochrane collaboration and other published sources on the methodology underpinning systematic and umbrella reviews have been taken into account in its development [10,11,16,17]. It has been registered with PROSPERO, registration number CRD42024526338.

Eligibility Criteria

These are based on the PECOS statement [18], see table 1.

Population	Adults over the age of 18 years
Exposure	Any factors which might influence the development of pancreatic cancer and are available in an electronic healthcare record
Comparator	Adults who have not been exposed, or have been differentially exposed, to the factors which might influence the development of pancreatic cancer
Outcome	Diagnosis of pancreatic cancer
Study designs	Systematic reviews and meta-analyses
Setting	Any setting

Table 1. Eligibility criteria for studies to be included in the umbrella review.

Reviews will be eligible for inclusion if they are systematic reviews or meta-analyses of component studies with suitable epidemiological design e.g. cohort or case-control studies, they will not be eligible if theoretical studies or published opinion are their primary source of evidence. Eligible reviews will examine risk factors for pancreatic cancer that could be available in a coded electronic patient healthcare record and will therefore exclude factors that require genome sequencing or use of novel biomarkers. The cancers of interest are primary cancers of the pancreas in adults. Studies solely examining neuroendocrine tumours will be excluded. There will be no geographical or time restriction on the included reviews, but they will be excluded if there is no full text of the completed study available in the English language.

Information sources

Systematic searches will be performed of MEDLINE and EMBASE via Ovid and the Science Citation Index Expanded database on the Web of Science Core Collection. Supplementary searches including forward and backward citation chasing will be performed through Scopus. The Cochrane database has not been included as their focus is on interventional rather than observational studies. Grey literature is not being searched as it is very unlikely to be a source of systematic reviews.

Search Strategy

Key search concepts are 'pancreatic cancer', 'risk factors' and 'systematic reviews'. Full details of the exact search terms to be used can be found in appendix 2.

Study Records

Covidence software for managing systematic reviews (https://www.covidence.org/) will be used for screening abstracts and full texts. Two independent reviewers will screen all records retrieved for eligibility. Data from eligible studies will be extracted into preformatted tables by two independent reviewers and compared. Throughout, any disagreement between the two reviewers will be identified and resolved by discussion until consensus is reached and if this is not possible a third reviewer will be consulted. In circumstances where required data is not available then the authors of the original review will be contacted for clarification. If, after a second approach, this is not possible then the review will be included but marked as having missing information.

Data items

Data will be extracted under multiple headings, as shown in table 2.

Column heading	**Explanation**
Risk factor	NB. if a review explores more than one risk factor it will be included multiple times in the extraction, once for each factor.
Reference	To include lead author, year, DOI
Type of review	e.g. pooled/meta-analysis
Number/type of studies	e.g. cohort/case-control
Number of cases/controls	Across the whole review/meta-analysis
Population characteristics	e.g. location, sex
Strata	Difference between exposed and comparator populations e.g. 5 unit increase in BMI or BMI above or below 30
Effect size metric	e.g. relative risk/odds ratio/hazard ratio
Summary effect size (95%CI)	As per the study findings
P value for summary effect estimate	As per the study findings
Measure of heterogeneity	e.g. I^2, as per the study findings

Grading of strength of evidence	Based on criteria for credibility of assessment (see below)
Notes	Any extra notes from the extractor on the review

Table 2. Data extraction fields for each eligible review

Most data will be extracted directly from the identified reviews but grading the strength of evidence and quality of the reviews will be completed separately as part of the process.

Grading strength of evidence for each association

There is no consensus on the best method for grading strength of evidence in an umbrella review. In a scoping review of what has been used previously, only half of studies assessed certainty of the evidence and within those studies the most commonly used criteria was credibility assessment (80%), followed by the GRADE approach (14%) [13].

Credibility assessment criteria were similar between studies but the levels at which they met a threshold varied slightly depending on the study [13]. We have used the most commonly occurring criteria and thresholds, as identified in Sadoyu et al. [13] and recommended in Fusar-Poli et al [19], as the basis for our credibility assessment criteria, see table 3.

Given the primary aim of this review is the identification of *potential* risk factors, we will not be deriving 95% prediction intervals, evidence of small-study effects or evidence of excess significance bias in order to assess publication and other biases within the component studies of a systematic review, nor including them in our credibility assessment criteria.

Measure	**Threshold**			
	Convincing	**Highly suggestive**	**Suggestive**	**Weak**
Number of cases	>1000 cases	>1000 cases	>1000 cases	
P-value	$p < 10^{-6}$	$p < 10^{-6}$	$p < 10^{-3}$	$p < 0.05$
Heterogeneity	$I^2 < 50\%$	-	-	-
Largest study with statistically significant effect	Largest study nominally significant ($p < 0.05$)	-	-	-

Table 3. Credibility assessment criteria for this study, derived from findings of Sadoyu et al. [13].

Assessing methodological quality of reviews

For the type of reviews included in this study, the best available method for assessing quality is the ROBIS tool which includes four key domains: study eligibility criteria, identification and selection of studies, data collection and study appraisal and synthesis and findings [20,21]. This tool was chosen

as it has been shown to perform better in the assessment of meta-analyses which we anticipate will form the majority of our included papers [22]. The ROBIS tool will be completed for each included study and summary shown in the final detailed results table.

Other data considerations

Comparing the effect sizes

Effect size is a measure of the strength of the relationship between the risk factor and the development of the disease. Effect size is the main quantitative outcome of interest for this study and it is important that effect sizes can be compared between risk factors [19]. Although not all studies use the same measures to report their effect size, we can treat the likely reported measures of relative risk, hazard ratios, odds ratios and incidence rate ratios as approximately equal because the event rate for pancreatic cancer is typically less than 10% [19,23].

Multiple reviews on the same risk factor

There are likely to be multiple reviews on the same risk factor and there is no consensus on how to deal with overlapping reviews [16,24]. In the previous review of reviews of the topic in 2015, the authors averaged the risk estimates reported in all available meta-analyses and pooled analyses [12]. However, this leads to a risk of including multiple component studies more than once, as they occur repeatedly in each review. Given the aim of that study was simply to *identify* potential risk factors, overlap of included studies did not matter. However, there remains the issue of the strength of the evidence in each study and the risk of the results of smaller high-quality analyses being diluted by large poor-quality studies. To avoid this we will use an alternative, common approach to overlapping studies, which is to select the single largest, most recent or highest quality meta-analysis or systematic review to represent the relationship between the exposure and outcome [24]. Our priority is to identify robust relationships and we therefore propose that, in the event of multiple reviews of the same risk factor, once data has been extracted for each study, we will select the study with the highest strength of evidence according to our credibility assessment criteria grading (see previous section). If there is more than one review with 'convincing' evidence, we will select from them the review with the best quality according to the ROBIS assessment. If this still results in more than one study we will select that with the largest pooled number of participants.

Outcomes and prioritisation

The main outcome will be a list of risk factors for pancreatic cancer that can be defined in coded electronic healthcare records. Additional outcomes will be the strength of the effect of the risk factor and the strength of the evidence for the effect, according to the criteria described above.

Data synthesis

In this umbrella review, quantitative synthesis will not be performed, instead summary results for each risk factor will be presented in a table (see table 4 for key headings) and discussed in the

narrative. A graphical summary will be developed from the key results to show direction and magnitude of reported effect sizes and a simple infographic grouping the factors by section e.g. demographic, lifestyle, medical history.

Column heading	Explanation
Risk factor	Description of factor
Degree of association	Measured by relative risk in largest study of good quality
Strength of evidence	As per credibility assessment criteria above

Table 4. Summary results table plan (results of the main selected study on each factor)

Patient and Public Involvement

The patient and public involvement team, already recruited to the overarching study, will contribute to discussions around the findings of this umbrella review in a designated session. Their thoughts will be integrated into the final write up of the study.

Ethics and Dissemination

Ethical approval is not required to perform this review.

Results of the study will be published in a peer reviewed journal and presented at academic conferences. All collected data will be made available as appendices to the published paper.

Data statement

All data generated will be available as appendices to the final published study report.

Footnotes

Author contributions: SM and GA designed the study and developed the search strategy. SM and GD will implement the search strategy, screen retrieved studies for eligibility, extract data from eligible studies, conduct the quality assessment and perform the analysis. GA or SP will act as a third reviewer as needed. The protocol was written SM and approved by SM, GD, SP, GA, FW and RN. SM is the guarantor for the article.

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Appendix 2: Specific search terms by database and platform

MEDLINE via Ovid

1 (pancrea* neoplasm* or (pancrea* adj3 carcinoma*) or (Cancer adj3 pancrea*) or (Malignan* adj3 pancrea*) or (Pancrea* adj3 carcinogenesis) or (Pancrea* adj3 tumo?r)).af. or Pancreatic neoplasms.sh.

2 (risk factor* or health correlate* or population* at risk or precipitating factor* or sociodemographic factor* or protective factor* or epidemiologic* factor* or epidemiologic* determinant* or relative risk).ti,ab,mp. or Risk Factors.sh. or Protective factors.sh. or Epidemiologic factors.sh.

3 (systematic review* or umbrella review* or meta?analys* or meta regression or meta analys* or medline or pubmed).ti,ab,mp. or meta-analysis.sh. or systematic review.sh.

4 1 and 2 and 3

EMBASE via Ovid

1 (pancrea* neoplasm* or (pancrea* adj3 carcinoma*) or (Cancer adj3 pancrea*) or (Malignan* adj3 pancrea*) or (Pancrea* adj3 carcinogenesis) or (Pancrea* adj3 tumo?r)).af. or Pancreas cancer.ec. or Pancreas carcinoma.ec.

2 (risk factor* or health correlate* or population* at risk or precipitating factor* or sociodemographic factor* or protective factor* or epidemiologic* factor* or epidemiologic* determinant* or relative risk).ti,ab,mp. or risk factor.ec. or protection.ec.

3 (systematic review* or umbrella review* or meta?analys* or meta regression or meta analys* or medline or pubmed). ti,ab,mp. or Meta analysis.ec. or Systematic review.ec.

4 1 and 2 and 3

Science Citation Index Expanded on Web of Science Core Collection

1: (((((TS=(pancrea* neoplasm*)) OR TS=(pancrea* NEAR/3 carcinoma*)) OR TS=(Cancer NEAR/3 pancrea*)) OR TS=(Malignan* NEAR/3 pancrea*)) OR TS=(Pancrea* NEAR/3 carcinogenesis)) OR TS=(Pancrea* NEAR/3 tumo$r)

2: (((((((TS=(risk factor*)) OR TS=(health correlate*)) OR TS=(population* at risk)) OR TS=(Precipitating factor*)) OR TS=(Sociodemographic factor*)) OR TS=(Protective factor*)) OR TS=(Epidemiologic* factor*)) OR TS=(Epidemiologic* determinant*)) OR TS=(Relative risk)

3: ((((((((TS=(systematic review*)) OR TS=(umbrella review*)) OR TS=(Meta-analys*)) OR TS=(Meta regression)) OR TS=(Meta analys*)) OR TS=(Metaanalys*)) OR TS=(Medline*)) OR TS=(Pubmed*))

4: #1 AND #2 AND #3