

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	LIFESStyle, Prevention and Risk of Acute PaNcreatitIs (LIFESPAN): Protocol of a Multicentre and Multinational Observational Case-Control Study
AUTHORS	Koncz, Balázs; Darvasi, Erika; Erdősi, Dalma; Szentesi, Andrea; Márta, Katalin; Erőss, Bálint; Pécsi, Dániel; Gyöngyi, Zoltán; Girán, János; Farkas, Nelli; Papp, Maria; Fehér, Eszter; Vitális, Zsuzsanna; Janka, Tamás; Vincze, Áron; Izbéki, Ferenc; Dunás-Varga, Veronika; Gajdán, László; Török, Imola; Károly, Sándor; Antal, Judit; Zádori, Noémi; Lerch, Markus; Neoptolemos, John; Sahin-Toth, Miklos; Petersen, Ole; Hegyi, Péter

VERSION 1 – REVIEW

REVIEWER	Vincenzo Neri General Surgery---Department of Medical and Surgical Sciences---- -----University of Foggia-----Italy
REVIEW RETURNED	12-Mar-2019

GENERAL COMMENTS	<p>This manuscript propose an interesting project on the identification of suitable data for recognition of the risk and prevention of acute pancreatitis.</p> <p>The Authors develop a study protocol with the following characteristics: prospective, multicentre and multinational observational case-control study. The Study Protocol has been structured based on the SPIRIT 2013.</p> <p>The Methods reported in the manuscript are complete, accurate and correct.</p> <p>However I have some observations on the project and on the reliability and therefore on the clinical value of the possible, future results. First, in the case group of patients suffered of acute pancreatitis alcohol- induced can be found some uncertainties. In fact there is not unanimous consent on the occurrence of true acute pancreatitis, as inflammatory disease with autodigestion processes of the glande by enzymes inappropriately activated, caused by excessive alcohol consumption. It's more likely that can develop the onset and/or the subsequent acute manifestations of chronic pancreatitis alcohol induced, due to severe tissue inflammation and fibrotic evolution, with abdominal pain, but without impairment of general conditions.</p> <p>More, among the risk factors, analyzed in the protocol study, there are factors with evident connection with possible development of acute pancreatitis such as some dietary factors connected with etiology of biliary lithiasis and acute pancreatitis, or socioeconomic status and lifestyle as alcoholic abuse and chronic pancreatitis. On the contrary for the other factors as dietary habits, socioeconomic status, physical activity, stress, sleeping habits can be very difficult to demonstrate, after the development of this study, the real, positive</p>
-------------------------	---

	connections between these specific factors and occurrence of acute pancreatitis with the reliable clinical value. In summary, in my opinion, the results of the study based on this protocol-study will be able to provide only some general informations.
--	---

REVIEWER	Christiana Kartsonaki University of Oxford, United Kingdom
REVIEW RETURNED	13-Mar-2019

GENERAL COMMENTS	<p>The proposed study is interesting and aiming to examine risk factors for acute pancreatitis. The study design is good, especially the inclusion of several sets of controls which will enable the assessment of various types of bias which may be present in case-control studies. The questionnaire seems extensive and covers several interesting factors that are potentially related to the development of acute pancreatitis.</p> <p>Some comments:</p> <ol style="list-style-type: none"> 1. In the abstract the study is referred to as a 'trial' but it is an observational study. I suggest rewording this to avoid confusion. 2. In the methods and discussion sections the study is referred to as 'prospective', but it appears that individuals will not be followed up prospectively. Please clarify. 3. There are a few minor language errors. 4. Pang et al. (2018, PLoS Medicine) have examined associations of some of the risk factors considered with acute pancreatitis. 5. What about individuals who are eligible for more than one case group (or more than one control group)? For example if a case fulfils the criteria for both alcohol and for gallstones, will they be used in both groups or in only one of them? 6. It would be good if more details on how controls will be match to cases were provided in the methods. For example how finely will they be matched to age and location of residence? 7. How will the matching be taken into account when continuous or binary variables are compared between cases and controls? 8. From how many centres will participants be recruited and will any differences between centres be assessed?
-------------------------	---

VERSION 1 – AUTHOR RESPONSE

Reviewer 2 Comments

1) In the abstract the study is referred to as a 'trial' but it is an observational study. I suggest rewording this to avoid confusion.

Answer: Thank you.

Action: We have made the changes.

2) In the methods and discussion sections the study is referred to as 'prospective', but it

appears that individuals will not be followed up prospectively. Please clarify.
Answer: Relevant data is prospectively collected from patients and controls.

**Action: The text has been expanded in respect to the suggestion.
(Page 6, Line 152-153)**

3) There are a few minor language errors.

Answer: Indeed. Thank you for your awareness.

Action: The manuscript was looked through by a lector, and the corrections are done.

4) Pang et al. (2018, PLoS Medicine) have examined associations of some of the risk factors considered with acute pancreatitis.

Answer: Thank you.

Action: It has been added to the reference list. (Page 17, Line 468-469)

5) What about individuals who are eligible for more than one case group (or more than one control group)? For example if a case fulfils the criteria for both alcohol and for gallstones, will they be used in both groups or in only one of them?
Answer: The individuals who are eligible for more than one case or control group will only be used in the group for the clear cause of AP. For example the case is confirmed as biliary pancreatitis, the patient will be enrolled to the biliary group even though the patient has some alcohol consumption. Unclear etiology will be considered as exclusion criterion. In addition, at the end of the study we will analyze the data with and without these patients.

Action: We updated the manuscript accordingly (please see METHODS/Exclusion criteria). (Page 8, Line 224-225)

6) It would be good if more details on how controls will be matched to cases were provided in the methods. For example how finely will they be matched to age and location of residence?

Answer: Thank you for your question. Age, sex will be matched precisely in each case, location of residence will be considered by the range of population.

Action: We have completed the ms. (Page 8, Line 229-230)

7) How will the matching be taken into account when continuous or binary variables are compared between cases and controls?

Answer: We wish to apply the mixed-effect models for the statistical analysis, where the matched pairs will be used as random subjects.

Action: None.

8) From how many centres will participants be recruited and will any differences between centres be assessed?

Answer: The study will start in four participating centres which are already marked in the manuscript. Since Lifespan is as an open-label study all centers wishing to join are welcome, only a letter of intent is need to be send to the corresponding author via e-mail.

Action: The manuscript is changed accordingly. (Page 15, Line 374-376)

VERSION 2 – REVIEW

REVIEWER	Christiana Kartsonaki University of Oxford, United Kingdom
REVIEW RETURNED	22-Aug-2019

GENERAL COMMENTS	The authors have addressed previous comments. A few follow-up comments: 1. The statistical analysis section is still quite vague and it is not
-------------------------	---

	<p>clear exactly what analyses will be done.</p> <p>2. The authors have responded to how the matching will be taken into account by 'Answer: We wish to apply the mixed-effect models for the statistical analysis, where the matched pairs will be used as random subjects.' and 'Action: None'. This is important and should be part of the statistical analysis section with more details provided.</p> <p>3. The study is still referred to as a 'prospective case-control study' but it seems to me that it is retrospective, in that case/control status has already been observed and is not ascertained during follow-up.</p> <p>4. There are still a few minor language errors.</p>
--	--

VERSION 2 – AUTHOR RESPONSE

Reviewer's Comments:

1) The statistical analysis section is still quite vague and it is not clear exactly what analyses will be done.

Answer: Thank you, we agree with you.

Action: We have clarified and extended the statistical analysis section in the manuscript. (Page: 13-14, Line 338-357)

“Statistical methods: All the collected parameters will be characterized using descriptive statistical method. Depending on the distribution, data will be represented as mean and standard deviation or median with interquartiles range, categorical variables will be given in quantity and percentages.

In order to observe the differences, the endscores and subscale scores of the questionnaires, other parameters such as race, BMI, waist circumference, education, occupation, income and subjective social status will be univariately compared between the AP and the control groups. In case of binary outcomes Chi-square test, in case of continuous variables Variance analysis (ANOVA) or Kruskal- Wallis test with Bonferroni correction will be used provided by the distribution of the data.

Multivariable analysis will be applied to identify lifestyle factors that influence the risk of developing AP. To detect these factors binary logistic regression and multivariate mixed-effect linear regression will be performed where the matched pairs will be handled as random subjects.

The case groups and control groups will be matched by the next three criteria: age, gender and location. During the match, 2 controls will belong to each patient (case), the match-tolerance will be set for age: +/- 5 years, gender: exact, location of residence: situated in the same country and +/- 15% of the population.

In spite of indentifying a possiblie correlation between lifestyle, other parameters and etiology, cluster analysis will be applied.

The effect of the parameters on survival the Kaplan-Meier survival analysis followed by multivariable Cox proportional hazards model will be used. We will calculate Odds Ratio (OR), Relative Risk (RR) and RR Reductions (RRR) with corresponding 95 % confidence intervals. All statistical analysis will be handled with a significance level of 5 %.”

2) The authors have responded to how the matching will be taken into account by 'Answer: We wish to apply the mixed-effect models for the statistical analysis, where the matched pairs will be used as random subjects.' and 'Action: None'. This is important and should be part of the statistical analysis section with more details provided.

Answer: Indeed.

Action: Now it is the part of the statistical analysis.
 (Page: 13-14, Line 338-357)

3) The study is still referred to as a 'prospective case-control study' but it seems to me that it is retrospective, in that case/control status has already been observed and is not ascertained during follow-up.

Answer: Thank you for your comment. We consider LIFESPAN as a prospective study, because the information obtained from the control and the case group is pre-defined, the study is registered before data collection and data are collected in a timely manner during a personal interview. In addition, the actual medical condition of the case group is monitored in the hospital. The data are collected during the episode of AP and not after it. The data collection is referred in the ward and the course of the disease/severity are also monitored. However, we have to agree with you that regarding the control group questions and some of the case group questions relate to lifestyle habits or events that have already occurred in the past.

Action: None.

4) There are still a few minor language errors.

Answer: We totally agree with you, thank you.

Action: The errors are corrected.

VERSION 3 – REVIEW

REVIEWER	Christiana Kartsonaki University of Oxford
REVIEW RETURNED	11-Oct-2019

GENERAL COMMENTS	<p>1. The statistical analysis section has been improved but there are still a few issues:</p> <ul style="list-style-type: none"> - 'All the collected parameters' should be 'All the collected variables'. - 'In spite of indentifying a possiblie correlation between lifestyle, other parameters and etiology, cluster analysis will be applied.' This is unclear. What will be clustered and why? - Cox proportional hazards models to not estimate odds ratios, but hazard ratios. Will the survival analysis be done among cases? <p>2. Logistic regression should also account for the matching.</p> <p>3. Although there may be a prospective component (e.g. following cases up for survival or other outcomes), the main part of the study is not prospective because the outcome is not ascertained during follow-up but individuals are selected based on their status as a case or control.</p>
-------------------------	---

VERSION 3 – AUTHOR RESPONSE

Reviewer's Comments

*1) The statistical analysis section has been improved but there are still a few issues:
 - 'All the collected parameters' should be 'All the collected variables'.
 - 'In spite of indentifying a possiblie correlation between lifestyle, other parameters and etiology, cluster analysis will be applied.' This is unclear. What will be clustered and why?*

- Cox proportional hazards models to not estimate odds ratios, but hazard ratios. Will the survival analysis be done among cases?

Answer: Thank you for your comment.

Action: The statistical section has been modified in the manuscript according to that.
(page 13, "Statistical methods" part)

2) Logistic regression should also account for the matching.

Answer: We agree with you.

Action: The required changes have been made to the statistical analysis.

3) Although there may be a prospective component (e.g. following cases up for survival or other outcomes), the main part of the study is not prospective because the outcome is not ascertained during follow-up but individuals are selected based on their status as a case or control.

Answer: You have right.

Action: Corrected.