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Keywords:	acute pancreatitis, lifestyle factors, diet, stress, sleeping

LIFEStyle, Prevention and Risk of Acute PaNcreatitis (LIFESPAN): Protocol of a Prospective, Multicentre and Multinational Observational Case-Control Study

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ABSTRACT

Introduction. Acute pancreatitis (AP) is a life-threatening inflammatory disease of the exocrine pancreas which needs acute hospitalization. Despite its importance we have significant lack of knowledge whether the lifestyle factors elevate or decrease the risk of AP or influence the disease outcome. So far no synthetizing study has been carried out examining associations between socio-economic factors, dietary habits, physical activity, chronic stress, sleep quality and AP. Accordingly, LIFESPAN identifies risk factors of acute pancreatitis and helps to prepare preventive recommendations for lifestyle elements.

Methods and analysis. LIFESPAN is a prospective, observational, multicentre international case-control study. Participating subjects will create case and control groups. Study protocol were designed according to the SPIRIT guideline. Patients on the case group (n=1700) have suffered from AP (alcohol-induced, biliary, other (n=500 in each group), hypertriglycieridaemia (HTG=200), the control group subjects have no AP in their medical history. Our study will have three major control groups (n=2200): hospital-based (n=500), population-based (n=500) and etiology-based (n=500 (alcohol) +500 (biliary) +200 (HTG)). All of them will be matched to the case group individually by **gender, age and location of residence**. Aggregately 3900 subjects will be enrolled into the trial. The study participants will complete a complex questionnaire with the help of a clinical research administrator/study nurse. Analysis methods include analysis of the continuous and categorical values.

Ethics and dissemination. The trial has got the relevant ethical approval (54175-2/2018/EKU) and also internationally registered (ISRCTN25940508)

Discussion. LIFESPAN is the first trial, which reveals the associations between socio-economic factors, dietary habits, physical activity, chronic stress, sleep quality and AP. We hope to find associations which will allow for the first time to suggest lifestyle modifications for patients discharged from the hospitals after AP or for those who wish to reduce their risk for AP.

Keywords: acute pancreatitis, lifestyle factors, diet, stress, sleeping.

ARTICLE SUMMARY

LIFESPAN is a prospective, observational, multicentre case-control study aiming to determine negative or positive association between socio-economic factors, dietary habits, physical activity, chronic stress, sleep quality and acute pancreatitis. This trial will provide the first synthetizing results concerning the lifestyle factors of acute pancreatitis with regard to socioeconomic status.

STRENGTHS AND LIMITATION

Strength 1: Innovative results are to be expected concerning that contribution of lifestyle factors to acute pancreatitis is poorly researched and known, therefore evidence based preventive suggestions might be carried out.

Strength 2: LIFESPAN study will include a huge extension of examined patient population because of the three major control groups, all of them will be matched to the case group individually, this will elevate the strength of our study.

Strength 3: The study contains questionnaires only with no additional costs, therefore the study has an excellent cost/benefit ratio.

Limitation 1: The database will mostly consist of patients delivered data.

Limitation 2: The questionnaire requires extensive time which needs plenty of attention from the administrators and subjects as well.

INTRODUCTION

Acute pancreatitis (AP) is a life-threatening inflammatory disease of the exocrine pancreas which needs acute hospitalization. Despite its importance we have significant lack of knowledge concerning the life style factors elevate or decrease the risk of AP or influence the disease outcome. This insufficient information is even more problematic since (i) there is no specific treatment for the disease, therefore prevention would be very important and (ii) 20% of all AP is recurrent so lifestyle suggestions decreasing the risk of an additional attack could be highly efficient.

Genetic and environmental factors play significant role in disease development and outcome. Of course, in most of the cases the genetic background cannot be changed, but the environmental factors. Dietary habits (1), socio-economic status (2), physical activity (3), stress (4) or sleeping habits (5) have been proved to play crucial role in many diseases.

Dietary factors

Association of diet and the risk of diseases is well known in lot of diseases for example in type 2 diabetes mellitus [1, 2] and coronary heart disease [3] and there are ongoing multicenter prospective study about diet and cancer by European Prospective Investigation into Cancer and. Nutrition (EPIC) [4].

Recently a multiethnic cohort study was published about dietary factors that are associated with risk of pancreatitis [5]. Data source was a retrospective multiethnic cohort in Hawaii and Los Angeles (215, 251 adult men and women, respectively, age 45-75 years at baseline, from 1993 to 1996 participants entered the cohort). They used hospitalization claim files (1993-2012) and a self-administered quantitative food frequency questionnaire [6]. The main findings of this study that intakes of saturated fat and cholesterol, and their food sources (red meat, eggs) positively associate with gallstone related AP, intakes of fiber inversely associate with AP, intakes of Vitamin D (mainly milk) inversely associate with gallstone related AP and coffee consumption protect against AP (not related to gallstones).

The association of vegetable, fruit and fish consumption with the non-gallstone acute pancreatitis was examined in a Swedish prospective cohort study [7, 8]. Their conclusion is that vegetable consumption, but not fruit consumption, may play a role in the prevention of non-gallstone-related AP, and the consumption of total fish may be associated with decreased risk of non–gallstone-related AP.

Physical activity

A lot of studies were published about physical activity and public health [9, 10]. Regular exercise offers protection against cardiovascular diseases and Type 2 diabetes mellitus [11]. Until now there are no studies about the association between general physical activity and acute pancreatitis, although there are some surprising case reports about marathon pancreatitis (extreme long distance running results acute pancreatitis) [12].

Socioeconomic status

Socioeconomic status (SES) is strongly associated with risk of disease and mortality [13]. Socioeconomic status includes the economic (measured by income), social (measured by education) and work status (measured by occupation). A clear relationship was also found between socioeconomic deprivation and incidence of AP in a

prospective observational study of AP in the North of England which was largely explained by a higher incidence of alcoholic aetiology [14].

(4) Stress

Chronic stress may also cause disease, either because of molecular changes [15] or because of increasing the probability of smoking, alcohol or drug consumption. Research shows that stress can contribute to the development of major illnesses, such as heart diseases, depression and obesity (www.apa.org), however no information are available concerning the effect of stress on the incidence of AP.

(5) Sleep quality

Currently there are no studies about the association of sleep quality and acute pancreatitis, however several articles claim that sleep deprivation or obstructive sleep apnea is associated with elevated levels of CRP [16, 17], which is the stable marker of inflammation and usually high in AP [18].

In this study our aim is to examine these health affecting individual lifestyle factors that seems to influence the development and outcome.

METHODS

The study has been initiated by the Hungarian Pancreatic Study Group and endorsed by the International Association of Pancreatology and was structured following the SPIRIT 2013 [19].

Design: LIFESPAN is a prospective, observational, multicentre and multinational case-control study. The data collection is based on questionnaires and medical histories. The questionnaires A-F and P (7 questionnaires in the case group, 6 for the control group)about the different fields of the patients' lifestyle will be filled with the help of trained administrators by a one-time meeting. Patients enrolled into the case group have suffered from AP, the control group subjects must have no acute pancreatitis in their medical history.

Trial organization, committees and boards: The coordinator and designer of the LIFESPAN study is the Hungarian Pancreatic Study Group (HPSG-coordinating society, https://tm-centre.org/en/study-groups/hungarian-pancreatic-study-group/). HPSG has been running high quality international, multicentre clinical trials since 2014 [20-24] and has published the relevant guidelines for pancreatic diseases to improve patient care in pancreatology [25-28]

The trial will be supported by four committees:

Steering Committee (SC): The committee will be led by PH (corresponding investigator, gastroenterologist and internal medicine specialist). The members in Szeged (HU) will be: ED (principal investigator); Debrecen (HU): MP (gastroenterologist), ZsV (gastroenterologist), TJ (gastroenterologist); Pécs (HU): ASz (multidisciplinary unit specialist), DE (co-principal investigator), KM (trial management specialist), BE (gastroenterologist), ZGy (public health specialist), JG (public health specialist), ÁV (gastroenterologist); Székesfehérvár (HU): FI (gastroenterologist), LG (gastroenterologist); TarguMures (RO): IT (gastroenterologist). KM is a trial management specialist, whereas ASz leads the multidisciplinary core facility which will assist the scientists to run the study successfully.

International Translational Advisory Board (ITAB): The board will consist of a gastroenterologist (MML), a surgeon and two basic scientists (JN, MST, OHP). The ITAB will continuously monitor the progress of the study and will advise the SC.

Data Monitoring Committee (DMC): DMC will handle all the data and ensure that the data in the eCRF is accurate, complete and legible. Data Management Plan (DMP) will describe the detailed data flow. The Data Manager will validate the data from completed eCRFs, according to a Data Cleaning Plan (DCP). Any missing, implausible or inconsistent recordings in the eCRFs will be referred back to the Investigator using a data query form (DQF), and be documented for each individual subject before clean file status is declared. All changes to eCRFs will be recorded. In case of important protocol modifications DMC will report it to the SC.

Premature termination of the study: Interim analysis will be carried out after half of the presumed number of patients have completed the study. Sample sizes for all questionnaires will be reassessed and modified accordingly. In addition, DMC independently will assess the trial related documents and activities, with the aim of ensuring the respect of subjects' right and to guarantee the plausibility of clinical data.

Sponsor (SP): The sponsor of the study is the Centre for Translational Medicine at the University of Pécs Medical School (coordinating institution and sponsor, www.tm-centre.org).

Study population: All patients diagnosed with AP in participating institutions will be informed concerning the possibility of taking part of the LIFESPAN study.

Case group (1700 cases): Patients in the case assembly will be divided into four groups depending on the causative agents of the AP (alcohol-induced, biliary, hypertriglycieridaemia and other). Taking into consideration the central limit theorem [29] 500 patients will be enrolled in all groups, but the hypertriglycieridaemia-induced group, where due to the low prevalence level, only 200 subjects will be collected. . With the sample size 500, it is thought to be possible to safely analyse the relationship between two variables that contain up to 4 variable values each. Altogether we plan to enrol 1700 individuals as cases. This way, the required number of respondents can be provided for a comparative analysis between the members of the case and control groups as well as for an exploratory study within a given case group.

Control group (2200 cases):

Our study will have three major control groups, all of them will be matched to the case group individually in order to avoid admission rate bias.

(1) Hospital-based control group: we will enrol patients in other clinical departments (e.g. Traumatology Department, Ophthalmic Department, 500 patients); (2) Population-based control group: we will enrol people according to a plan based on gender/age/location of residence ratios in the case group (500 patients); (3) Etiology-based control group: we will enrol people matched to the three etiology-factors of the four case groups (500, 500 and 200, respectively).

Inclusion criteria

The criteria for inclusion in the study in **case groups (A) in general**: (1) patients above 18 years; (2) diagnosed AP on the base of the "2 out of 3" rules of IAP/APA guideline:

(a) upper abdominal pain; (b) serum amylase or lipase >3x upper limit of normal range; (c) characteristic findings on pancreatic imaging; (3) written informed consent form is signed. **According to the ethiology: (A1)** in alcohol etiology group: patients consuming >5 drinks per day or >35 drinks per week for both sexes [= 8.75 units per day; 61.25 units per week] shall be included. Please note that 1 unit of alcohol = 10 mls or 8gr of pure (100%) alcohol [30]; **(A2)** in gallstone etiology group: presence of gallstone (not sludge); **(A3)** in hypertrigliceridaemia etiology group: triglyceride level in blood over 11 mmol/l [31]; **(A4)** in 'other' etiology group: the causative agents do not match either of the first 3 groups, AP is induced by e.g.: ERCP (post-ERCP pancreatitis), virus infection, trauma, medicine (drug induced pancreatitis), congenital anatomical malformation, cystic fibrosis, genetics, gluten sensitive enteropathy etc.

The criteria for inclusion in the study for **control groups (B, C and D) in general**: (1) patients above 18 years; (2) absence of AP at present as well as in the medical history; (3) written informed consent form is signed.

According to the ethiology of the case groups: (B1) in alcohol group: patients consuming >5 drinks per day or >35 drinks per week for both sexes [= 8.75 units per day; 61.25 units per week] shall be included. Please note that 1 unit of alcohol = 10 mls or 8gr of pure (100%) alcohol [30]; **(B2)** in gallstone group: presence of gallstone (not sludge); **(B3)** in hypertrigliceridaemia group: triglyceride level over 11 mmol/l [31]; The criteria for inclusion in the study for **hospital-based control group (C)**: patients are hospitalized for other than internal medicine associated disease, such as hospital admissions in Traumatology or Ophthalmic Department. The criteria for inclusion in the study for **population based control group (D)**: not hospitalized general population.

Exclusion criteria: the criteria for exclusion in all groups: (1) patients do not have reliable information or data; (2) patients may not adhere.

Withdrawal of a subject from the study: According to the ethical regulations individuals are allowed to leave the study at any time without any negative consequences. Patients in the case group will be recruited during their hospital stay. Individuals for the control group are either spread among different units, or not hospitalized at all. In the study the participants in the case and in the control groups will be matched individually and continuously by gender, age and residence. The length of the data collection is 6 years and the data analysis takes another half a year.

Data collection and follow-up: All participant (3900) if meet the inclusion criteria and sign the informed consent form, will be questioned by a clinical research administrator/study nurse who is fully trained before how to fill properly the questionnaires A-F and P. Since trained clinical research administrators will collect information, missing data will be unlikely.

We constructed a complex survey which consists of 7 forms. The forms are based on widely used and validated questionnaires. Data will be collected via printed questionnaires and will be kept in eCRF. In our study we will collect information about the lifestyle of the 1-year period preceding the enrolment (1st part of the questionnaire, e.g. E1). Moreover, we are interested in whether the habits changed in the **last month** just prior to the AP (2nd part of the questionnaire, e.g. E2). Each forms (Form A-F) have sections of a long-time (1 year) and a short-time (1 month) behaviour**,** except Form P. (Table 1, 2)

In **Form A (A1 & A2)** we will collect general information about personal details, current status. The subjective social status will be evaluated with the SES ladder (MacArthur Scale of Subjective Social Status, http://www.macses.ucsf.edu). It is a widespread instrument in large epidemiological European and US studies and found to be significantly associated with health status, independently of objective socioeconomic indicators [32]. (Table 1)

In **Form B (B1 & B2)**, we will collect information about patients' medical history based on Acute Pancreatitis Questionnaire of the registry for pancreatic patients operated by the Hungarian Pancreatic Study Group [33]. This online registry was established for recording data of patients with pancreatic diseases in 2012 (www.tm-centre.org), including details on smoking, alcohol consumption, other risk factors, medical history and the course and outcome of the disease. (Table 1)

In **Form C (C1 & C2),** we will collect data about participants' dietary habits. Food Frequency Questionnaires (FFQs) are commonly used in epidemiological studies to assess the dietary intake of large populations. Their popularity derives from ease of administration, ability to assess dietary intake over a defined period of time and low costs [34]. The DHQII and Diet*Calc Analysis Software is a valid tool to measure dietary habit [35-37] and free to use. It is a very detailed quantitative FFQ with the most general foods and drinks. (Table 1)

In **Form D (D1 & D2)**, we will measure the participants' physical activity (PA) level with a frequently used epidemiology questionnaire namely the International Physical Activity Questionnaire [38]. We will use the long, usual week version (27-item) in the general part of our PA questionnaire. It contents details about the participants' vigorous PA, moderate PA, walking and sitting habits. (Table 1)

In **Form E (E1 & E2)**, we will evaluate the participants' chronic stress level with the Perceived Stress Scale [39]. It is the most widely used psychological instrument for the measuring of chronic stress effect [40-42]. We chose the 10-item version which has high validity and reliability. The time range in the general part is difference from the original questionnaire (last year vs. last month). (Table 1)

In **Form F (F1 & F2)** we will collect data about participants' sleeping habits. We will apply a widely used Pittsburgh Sleep Quality Index, which evaluate the participants' sleeping quality [43]. We skip the 10th questions about bed partner or roommate, because the bed partner will be not at the interview probably and this question does not count in the evaluation. The time range in the general part is also difference from the original questionnaire (last year vs. last month). (Table 1)

In **Form P** we will collect data about patients' acute pancreatitis using the appropriate questions of Acute Pancreatitis Questionnaire (see Form B). (Table 1)

Electronic CRFs will be developed and will be available on www.tm-centre.org.

ENDPOINTS

Endpoints will be provided by each questions of the questionnaires.

Form A: Age, race, location, body weight, body height, BMI, waist circumference, education, occupation, income, subjective social status (Table 2)

Form B: Alcohol consumption (frequency, amount), smoking (frequency, amount), drug abuse (frequency, amount), diabetes mellitus (type), lipid metabolism disorder (type), any disease of the pancreas, pancreas, disorders in family history, congenital anatomical malformation of the pancreas, other illnesses, medications, diet (Table 2)

Form C: 176 nutrients, dietary constituents and food groups, Carbohydrate constituents, Macronutrients & energy, Fats, fatty acids, & cholesterol, Protein Constituents, Vitamins, Minerals, Carotenoids and Tocopherols, Dietary Constituents from Supplements, Other, Food Pyramid Equivalents, Healthy Eating Index *(HEI-2010) ((0-100): Good: >80, Needs improvement: 51-80, Poor: <51)* (https://www.cnpp.usda.gov/sites/default/files/healthy_eating_index/HEI89-90report.pdf) (Table 2)

Form D: Continuous Scores (MET-minutes/week), Total physical activity (consists of: Total Walking activity (MET-minutes/week), Total Moderate activity (MET-minutes/week), Total Vigorous activity (MET-minutes/week), Average Sitting (min/day)), Categorical Score *(level of PA: Low-This is the lowest level of physical activity. Those individuals who not meet criteria for Categories 2 or 3 are considered to have a 'low' physical activity level, Moderate: 3 or more days of vigorous-intensity activity of at least 20 minutes per day OR 5 or more days of moderate-intensity activity and/or walking of at least 30 minutes per day OR 5 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum Total physical activity of at least 600 MET-minutes/week. High: vigorous-intensity activity on at least 3 days achieving a minimum Total physical activity of at least 1500 MET-minutes/week OR 7 or more days of any combination of walking, moderate-intensity or vigorous-intensity activities achieving a minimum Total physical activity of at least 3000 MET-minutes/week*) (https://sites.google.com/site/theipaq/scoring-protocol) (Table 2)

Form E: Total PSS Score (0-40) (*Categories: Low perceived stress: Scores ranging from 0-13, Moderate perceived stress: Scores ranging from 14-26, High perceived stress: Scores ranging from 27-40.)* (https://das.nh.gov/wellness/Docs/Percieved%20Stress%20Scale.pdf) (Table 2)

Form F: Global PSQI Score (0-21), *(which consists of Subjective sleep quality (0-3): Sleep latency (0-3), Sleep duration (0-3), Habitual sleep efficiency (0-3), Sleep disturbances (0-3), Use of sleeping medication (0-3), Daytime dysfunction (0-3))*, Categories (empirically derived cutoff score*): Score < 5: Good sleepers, Score >5: Poor sleepers* (http://uacc.arizona.edu/sites/default/files/psqi_sleep_questionnaire_1_pg.pdf) (Table 2)

Form P: Mortality, Severity *(mild, moderate, severe*), Complications (*pancreatic, systemic*) (Table 2)

Statistical analysis

Variables: All variables will be identified according to the outcomes mentioned in section 'Endpoints'. They are categorical, continuous and scaled variables. See below:

Form A: Analysis of the continuous and categorical values

Form B: Analysis of the continuous and categorical values

Form C: The Diet*Calc Analysis Program can be evaluated the questionnaire data (https://epi.grants.cancer.gov/dhq2/dietcalc)

Form D: We will use the official scoring protocol to evaluate the survey

(https://sites.google.com/site/theipaq/scoring-protocol)

Form E: The original article contents the evaluation method [39]

Form F: The scoring instruction is described in the original article [43]

Form P: Analysis of the continuous and categorical values [33]

Bias: Deriving from the study design a possible recall bias could occur (patients who have the outcome (cases) are likely to remember the details of negative exposures more clearly than controls). It can be supposed, that it appears randomly, non-differential in the study-groups.

Sample size: The sample size originally was calculated based on the end scores of the four questionnaires (HEI-2010, IPAQ, PSS, PSQI). All calculation were made using a 5% significance level, a power of 80%, a 40% difference between the group means and equal sample size ratio (age, sex and socio-economic-matched control groups). We used the online sample size calculator: http://clincalc.com/Stats/SampleSize.aspx

We achieved the required information e.g. mean and standard deviation from articles (references found after each calculated sample size) or from online databases (HEI scores). In case of two questionnaires (PSQI and PSS) we made the calculation based also on Hungarian and not Hungarian data sources. The required sample sizes for the questionnaires per groups are the following:

- HEI-2010 Score: 195 (National Health and Nutrition Examination Survey, 2011-2012, results in: https://www.cnpp.usda.gov/healthyeatingindex);
- IPAQ Total activity: 155 [44];
- PSS Score: 217 and 13 [45], 23 [46];
- PSQI Score: 231 [47] 187 [48].

Statistical methods: To observe differences between the AP and control groups the end scores and subscale-scores of the questionnaires will be compared. 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 depending on the distribution of the parameters. To obtain interaction between variables multivariable analysis (binary logistic regression or multivariate linear regression) will be performed. To identify possible confounders, subgroup and cluster analysis will be applied. For timed endpoints such as mortality 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 %.

DISCUSSION

This is the first prospective study investigating the associations between socio-economic factors, dietary habits, physical activity, chronic stress, sleep quality and acute pancreatitis. We hope to find both negative and positive associations which will allow for the first time to suggest lifestyle modifications for patients discharged from the hospitals after AP or for those who wish to reduce their risk for AP.

ACKNOWLEDGEMENTS

Centres: The study will start with the following centres (University of Szeged, University of Pécs, University of Debrecen, Szent-György Fejér County Teaching Hospital), however, other centres are welcome to participate in the LIFESPAN study. Completion of the LETTER OF INTENT form will be mandatory for registering the participation of each institution. HPSG will acknowledge receipt of the LETTER OF INTENT form and will contact centres providing them with additional study information.

Each centres must provide the same number of individuals for all the relevant four groups (1 case and 3 controls)

Publication policy: Centres providing more than 40 individuals can provide an author to the authors list. Every additional 20 individuals will give the opportunity to nominate an author.

Dissemination policy: We plan to communicate the results to several members of the healthcare system includining medical doctors, dietitians, nurses, patients etc. We plan to publish the results in a peer-reviewed high quality journal for professionals. In addition, we also plan to publish it for lay readers in order to maximalize the dissemination and benefits of this trial.

Feasibility and earlier experience: The feasibility will be examined by a pilot enrolment of 20 individuals in each groups.

Safety: This is a non-interventional observational clinical trial. Since no unknown drugs/therapy are used in the study no adverse and serious adverse events are expected/interpretable during the trial.

Funding: Center costs (IT, biostatistics, trial organization, etc.) are covered by the University of Pécs Medical School, Momentum Grant of the Hungarian Academy of Sciences (LP2014-10/2014); and Economic Development and Innovation Operative Programme Grant and Highly Cited Publication Grant of the National Research, Development and Innovation Office (GINOP-2.3.2-15-2016-00048 Stay Alive, KH-125678 and EFOP 3.6.2-16-2017-00006 Live Longer), and Translational Medicine Foundation. The study was designed by the SC and ITAB. DMC and SP has not been involved in the design of the study, moreover the SP will have no access to database.

Since no additional treatment is necessary for the study, the general healthcare costs are covered by the National Healthcare System (University of Pécs Medical School).
This study was designed with help of the Centre for Translational Medicine at the University of Pécs. This center is committed to improve patients' life with research activities like registries, observational and interventional trial organizations (https://tm-centre.org).
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Authors' contributions: BK, ED, ZGy, JG, MP, FI, ÁV and PH designed the study. As a member of the ITAB MML, JN, MST and OHP gave advices and will continuously monitor the progress of the study. ZsV, KM, PH, BE, DP, EF, TJ, LG, DE, DVV and IT drafted the manuscript, and ASz, JA, NZ edited the text, ASz, JA, NZ adapted the tables. All authors read and approved the final manuscript.

Competing interests statement: All authors declare any competing interest.

ETHICS AND DISSEMINATION

Trial registration: The trial has been registered at the ISRCTN (25940508).

Ethical approval: Scientific and Research Ethics Committee of the Hungarian Medical Research Council (54175-2/2018/EKU).

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Start of the patient recruitment: In April, 2019.

Planned finish of the study: 30 November 2023

Abbreviations:

AP- acute pancreatitis

CRF – case report form

DMC- Data Monitoring Committee

FFQs - Food Frequency Questionnaires

HEI - Healthy Eating Index

ITAB - International Translational Advisory Board

OR - Odds Ratio

PA - physical activity

PSS - Perceived Stress Scale

PSQI - Pittsburgh Sleep Quality Index

SC – Steering Comittee

SES - socioeconomic status

RR - Relative Risk

RRR - RR Reductions

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Figure legends:

TABLE 1 shows the title and source of the 7 questionnaires willing to use for data collection in LIFESPAN study.

TABLE 2 shows the outputs, values, units and description of the Diet History Questionnaire II, the International Physical Activity Questionnaire, the Percieved Stress Scale (PSS) and the Pittsburgh Sleep Quality Index (PSQI).

SUPPLEMENTUM FIGURE 1. The figure shows the schedule of enrolment and assessments according to the SPIRIT Guideline.

Form	Title	Source
Form A (A1 & A2)	Personal Details, Physical And Socioeconomic Status	National Health and Nutrition Examination Survey (NHANES 2015-16); American Community Survey (ACS); The MacArthurScale of Subjective Social Status
Form B (B1 & B2)	Details From The Medical History	Acute Pancreatitis Questionnaire (Registry for Pancrea Patients by Hungarian Pancreatic Study Group)
Form C (C1 & C2)	Dietary Habits	Diet History Questionnaire, Version 2.0. National Institutes of Health, Epidemiology and Genomics Research Program, National Cancer Institute. 2010.
Form D (D1 & D2)	Physical Activity	International Physical Activity Questionnaire (IPAQ) (long, usual week version)
Form E (E1 & E2)	Stress	Perceived Stress Scale (10-item version)
Form F (F1 & F2)	Sleep Quality	Pittsburgh Sleep Quality Index
Form P	Characteristic Of Acute Pancreatitis (Only For Case Group)	Acute Pancreatitis Questionnaire (see above)

TABLE 1 shows the title and source of the 7 questionnaires willing to use for data collection in LIFESPAN study.

90x59mm (300 x 300 DPI)

Questionnaire	Outputs	Values	Unit	Description
Eating habits: Diet History Questionnaire II (DHQII) past year, with portion size	176 nutrients, dietary constituents, and food groups	varied	varied: mcg, mg, g, kcal, IU, etc.	Food groups Carbohydrate constituents Macronutrients & energy Fats, fatty acids, & cholesterol Protein Constituents Vitamins Minerals Carotenoids and Tocopherols Dietary Constituents from Supplements Other Food Pyramid Equivalents
Physical activity: International Physical Activity Questionnaire (IPAQ) long, last year version	HEI (Healthy Eating Index-2010)	0-100	point	Good: 80-100. Needs Improvement: 51-80. Poor: 0-51.
	Total walking activity	0-	MET-minutes/week OR Kcal/week	
	Total moderate activity	0-	MET-minutes/week OR Kcal/week	
	Total vigorous activity	0-	MET-minutes/week OR Kcal/week	
	Total physical activity	0-	MET-minutes/week OR Kcal/week	
	Sedentary activity	0-	hour and min / day	
	Level of physical activity	Low Moderate High	N/A	Detailed description in the text above
Stress: Perceived Stress Scale (PSS) 10-item version	TOTAL GENERAL PSS SCORE	0-40	point	Low perceived stress: 0-13. Moderate perceived stress: 14-26. High perceived stress: 27-40.
Sleep: Pittsburgh Sleep Quality Index (PSQI)	Component 1: Subjective sleep quality	0-3	point	0-good, 3-bad
	Component 2: Sleep latency	0-3	point	0-good, 3-bad
	Component 3: Sleep duration	0-3	point	0-good, 3-bad
	Component 4: Habitual sleep efficiency	0-3	point	0-good, 3-bad
	Component 5: Sleep disturbances	0-3	point	0-good, 3-bad
	Component 6: Use of sleeping medication	0-3	point	0-good, 3-bad
	Component 7: Daytime dysfunction	0-3	point	0-good, 3-bad
	GLOBAL PSQI SCORE (GENERAL)	0-21	point	Good sleep quality: 0-5. Poor sleep quality: 5-21.

TABLE 2 shows the outputs, values, units and description of the Diet History Questionnaire II, the International Physical Activity Questionnaire, the Percieved Stress Scale (PSS) and the Pittsburgh Sleep Quality Index (PSQI).

44x67mm (300 x 300 DPI)

	STUDY PERIOD		
	Enrolment	Post enrolment	Close-out
TIMEPOINT	*0*	*0*	t_x
ENROLMENT:			
Eligibility screen	X		
Informed consent	X		
QUESTIONNAIRES:		X	
Questionnaire A		X	
Questionnaire B		X	
Questionnaire C		X	
Questionnaire D		X	
Questionnaire E		X	
Questionnaire F		X	
Questionnaire P		X	
DATA ANALYSIS:			X

45x39mm (300 x 300 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3,13
	2b	All items from the World Health Organization Trial Registration Data Set	–
Protocol version	3	Date and version identifier	13
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 12
	5b	Name and contact information for the trial sponsor	7
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	7, 12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	6-7, 12

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-6
	6b	Explanation for choice of comparators	3, 7
Objectives	7	Specific objectives or hypotheses	3-4, 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3-4, 6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	-
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	-
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	-
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	–
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	-
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig 1.

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	-
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	-
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	-
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	-
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	–
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-8

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7-8
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	7
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	-
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3,13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	7
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	7-8,12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12

	31b	Authorship eligibility guidelines and any intended use of professional writers	12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	attached
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

LIFEStyle, Prevention and Risk of Acute PaNcreatitis (LIFESPAN): Protocol of a Prospective, Multicentre and Multinational Observational Case-Control Study

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LIFEStyle, Prevention and Risk of Acute PaNcreatitis (LIFESPAN): Protocol of a Prospective, Multicentre and Multinational Observational Case-Control Study

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ABSTRACT

Introduction. Acute pancreatitis (AP) is a life-threatening inflammatory disease of the exocrine pancreas which needs acute hospitalization. Despite its importance we have significant lack of knowledge whether the lifestyle factors elevate or decrease the risk of AP or influence the disease outcome. So far no synthetizing study has been carried out examining associations between socio-economic factors, dietary habits, physical activity, chronic stress, sleep quality and AP. Accordingly, LIFESPAN identifies risk factors of acute pancreatitis and helps to prepare preventive recommendations for lifestyle elements.

Methods and analysis. LIFESPAN is a prospective, observational, multicentre international case-control study. Participating subjects will create case and control groups. The study protocol was designed according to the SPIRIT guideline. Patients in the case group (n=1700) have suffered from AP (alcohol-induced, biliary, other (n=500 in each group), hypertriglycieridaemia (HTG=200), the control group subjects have no AP in their medical history. Our study will have three major control groups (n=2200): hospital-based (n=500), population-based (n=500) and etiology-based (n=500 (alcohol) +500 (biliary) +200 (HTG)). All of them will be matched to the case group individually by **gender, age and location of residence**. Aggregately 3900 subjects will be enrolled into the study. The study participants will complete a complex questionnaire with the help of a clinical research administrator/study nurse. Analysis methods include analysis of the continuous and categorical values.

Ethics and dissemination. The study has got the relevant ethical approval (54175-2/2018/EKU) and also internationally registered (ISRCTN25940508)

Keywords: acute pancreatitis, lifestyle factors, diet, stress, sleeping.

STRENGTHS AND LIMITATION

Strength 1: Innovative results are to be expected concerning that contribution of lifestyle factors to acute pancreatitis is poorly researched and known, therefore evidence based preventive suggestions might be carried out.

Strength 2: LIFESPAN study will include a huge extension of examined patient population because of the three major control groups, all of them will be matched to the case group individually, this will elevate the strength of our study.

Strength 3: The study contains questionnaires only with no additional costs, therefore the study has an excellent cost/benefit ratio.

Limitation 1: The database will mostly consist of patients delivered data.

Limitation 2: The questionnaire requires extensive time which needs plenty of attention from the administrators and subjects as well.

INTRODUCTION

Acute pancreatitis (AP) is a life-threatening inflammatory disease of the exocrine pancreas which needs acute hospitalization. Despite its importance we have significant lack of knowledge concerning the life style factors elevate or decrease the risk of AP or influence the disease outcome. This insufficient information is even more problematic since (i) there is no specific treatment for the disease, therefore prevention would be very important and (ii) 20% of all AP is recurrent so lifestyle suggestions decreasing the risk of an additional attack could be highly efficient.

Genetic and environmental factors play significant role in disease development and outcome. Of course, in most of the cases the genetic background can not be changed, but the environmental factors. Dietary habits (1), socio-economic status (2), physical activity (3), stress (4) or sleeping habits (5) have been proved to play crucial role in many diseases.

(1) Dietary factors

Association of diet and the risk of diseases is well known in a lot of diseases for example in type 2 diabetes mellitus [1, 2] and coronary heart disease [3] and there is an ongoing multicenter prospective stud about diet and cancer by the European Prospective Investigation into Cancer and Nutrition (EPIC) [4].

Recently a multiethnic cohort study was published about dietary factors that are associated with risk of pancreatitis [5]. Data source was a retrospective multiethnic cohort in Hawaii and Los Angeles (215, 251 adult men and women, respectively, age 45-75 years at baseline, from 1993 to 1996 participants entered the cohort). They used hospitalization claim files (1993-2012) and a self-administered quantitative food frequency questionnaire [6]. The main findings of this study are that intakes of saturated fat and cholesterol, and their food sources (red meat, eggs) positively associate with gallstone related AP, intakes of fiber inversely associate with AP, intakes of Vitamin D (mainly milk) inversely associate with gallstone related AP and coffee consumption protects against AP (not related to gallstones).

The association of vegetable, fruit and fish consumption with non-gallstone acute pancreatitis was examined in a Swedish prospective cohort study [7, 8]. Their conclusion is that vegetable consumption, but not fruit consumption, may play a role in the prevention of non-gallstone-related AP, and the consumption of total fish may be associated with decreased risk of non–gallstone-related AP.

(2) Physical activity

A lot of studies were published about physical activity and public health [9, 10]. Regular exercise offers protection against cardiovascular diseases and Type 2 diabetes mellitus [11]. So far there are not numerous studies dealing with the association between general physical activity and acute pancreatitis, although there are some surprising case reports about marathon pancreatitis (extreme long distance running results acute pancreatitis) [12]. Results of a prospective cohort study show that there is inverse association between physical activity and risk of acute pancreatitis [13].

(3) Socioeconomic status

Socioeconomic status (SES) is strongly associated with risk of disease and mortality [14]. Socioeconomic status includes the economic (measured by income), social (measured by education) and work status (measured by occupation). A clear relationship was also found between socioeconomic deprivation and incidence of AP in a prospective observational study of AP in the North of England which was largely explained by a higher incidence of alcoholic aetiology [15].

(4) Stress

Chronic stress may also cause disease, either because of molecular changes [16] or because of increasing the probability of smoking, alcohol or drug consumption. Research shows that stress can contribute to the development of major illnesses, such as heart diseases, depression and obesity (www.apa.org), however no informationis available concerning the effect of stress on the incidence of AP.

(5) Sleep quality

Currently there are no studies about the association of sleep quality and acute pancreatitis, however several articles claim that sleep deprivation or obstructive sleep apnea is associated with elevated levels of CRP [17, 18], which is the stable marker of inflammation and usually high in AP [19].

In this study our aim is to examine these health affecting individual lifestyle factors that seem to influence the development and outcome.

METHODS

The study has been initiated by the Hungarian Pancreatic Study Group and endorsed by the International Association of Pancreatology and was structured following the SPIRIT 2013 [20].

Design: LIFESPAN is a prospective, observational, multicentre and multinational case-control study. The data collection is based on questionnaires and medical histories. Relevant data will be prospectively collected from patients and controls. The questionnaires A-F and P (7 questionnaires in the case group, 6 for the control group) about the different fields of the patients' lifestyle will be filled with the help of trained administrators by a one-time meeting. Patients enrolled into the case group have suffered from AP, the control group subjects must not have acute pancreatitis in their medical history.

Study organization, committees and boards: The coordinator and designer of LIFESPAN study is the Hungarian Pancreatic Study Group (HPSG-coordinating society, https://tm-centre.org/en/study-groups/hungarian-pancreatic-study-group/). HPSG has been running high quality international, multicentre clinical trials since 2014 [21-25] and has published the relevant guidelines for pancreatic diseases to improve patient care in pancreatology [26-29]

The study will be supported by four committees:

Steering Committee (SC): The committee will be led by PH (corresponding investigator, gastroenterologist and internal medicine specialist). The members in Szeged (HU) will be: ED (principal investigator); Debrecen (HU): MP (gastroenterologist), ZsV (gastroenterologist), TJ (gastroenterologist); Pécs (HU): ASz (multidisciplinary unit specialist), DE (co-principal investigator), KM (trial management specialist), BE (gastroenterologist), ZGy (public

health specialist), JG (public health specialist), ÁV (gastroenterologist); Székesfehérvár (HU): FI (gastroenterologist), LG (gastroenterologist); Targu Mures (RO): IT (gastroenterologist). KM is a trial management specialist, whereas ASz leads the multidisciplinary core facility which will assist the scientists to run the study successfully.

International Translational Advisory Board (ITAB): The board will consist of a gastroenterologist (MML), a surgeon and two basic scientists (JN, MST, OHP). The ITAB will continuously monitor the progress of the study and will advise the SC.

Data Monitoring Committee (DMC): DMC will handle all the data and ensure that the data in the eCRF is accurate, complete and legible. Data Management Plan (DMP) will describe the detailed data flow. The Data Manager will validate the data from completed eCRFs, according to a Data Cleaning Plan (DCP). Any missing, implausible or inconsistent recordings in the eCRFs will be referred back to the Investigator using a data query form (DQF), and be documented for each individual subject before clean file status is declared. All changes to eCRFs will be recorded. In case of important protocol modifications DMC will report it to the SC.

Premature termination of the study: Interim analysis will be carried out after half of the presumed number of patients have completed the study. Sample sizes for all questionnaires will be reassessed and modified accordingly. In addition, DMC independently will assess the study related documents and activities, with the aim of ensuring the respect of subjects' right and to guarantee the plausibility of clinical data.

Sponsor (SP): The sponsor of the study is the Centre for Translational Medicine at the University of Pécs Medical School (coordinating institution and sponsor, www.tm-centre.org).

Study population: All patients diagnosed with AP in participating institutions will be informed concerning the possibility of taking part of the LIFESPAN study.

Case group (1700 cases): Patients in the case group will be divided into four groups depending on the causative agents of the AP (alcohol-induced, biliary, hypertriglycieridaemia and other). Taking into consideration the central limit theorem [30] 500 patients will be enrolled in all groups, but the hypertriglycieridaemia-induced group, where due to the low prevalence level, only 200 subjects will be collected. With the sample size 500, it is thought to be possible to safely analyse the relationship between two variables that contain up to 4 variable values each. Altogether we plan to enrol 1700 individuals as cases. This way, the required number of respondents can be provided for a comparative analysis between the members of the case and control groups as well as for an exploratory study within a given case group.

Control group (2200 cases):

Our study will have three major control groups, all of them will be matched to the case group individually in order to avoid admission rate bias.

(1) Hospital-based control group: we will enrol patients in other clinical departments (e.g. Traumatology Department, Ophthalmic Department, 500 patients); (2) Population-based control group: we will enrol people according to a plan based on gender/age/location of residence ratios in the case group (500 patients); (3) Etiology-

based control group: we will enrol people matched to the three etiology-factors of the four case groups (500, 500 and 200, respectively).

Inclusion criteria

The criteria for inclusion in the study in **case groups (A) in general**: (1) patients above 18 years; (2) diagnosed AP on the base of the "2 out of 3" rules of IAP/APA guideline:

(a) upper abdominal pain; (b) serum amylase or lipase >3x upper limit of normal range; (c) characteristic findings on pancreatic imaging; (3) written informed consent form is signed. **According to the ethiology: (A1)** in alcohol etiology group: patients consuming >5 drinks per day or >35 drinks per week for both sexes [= 8.75 units per day; 61.25 units per week] shall be included. Please note that 1 unit of alcohol = 10 mls or 8gr of pure (100%) alcohol [31]; **(A2)** in gallstone etiology group: presence of gallstone (not sludge); **(A3)** in hypertrigliceridaemia etiology group: triglyceride level in blood over 11 mmol/l [32]; **(A4)** in 'other' etiology group: the causative agents do not match either of the first 3 groups, AP is induced by e.g.: ERCP (post-ERCP pancreatitis), virus infection, trauma, medicine (drug induced pancreatitis), congenital anatomical malformation, cystic fibrosis, genetics, gluten sensitive enteropathy etc.

The criteria for inclusion in the study for **control groups (B, C and D) in general**: (1) patients above 18 years; (2) absence of AP at present as well as in the medical history; (3) signed written informed consent form.

According to the ethiology of the case groups: (B1) in alcohol group: patients consuming >5 drinks per day or >35 drinks per week for both sexes [= 8.75 units per day; 61.25 units per week] shall be included. Please note that 1 unit of alcohol = 10 mls or 8gr of pure (100%) alcohol [31]; **(B2)** in gallstone group: presence of gallstone (not sludge); **(B3)** in hypertrigliceridaemia group: triglyceride level over 11 mmol/l [32]; The criteria for inclusion in the study for **hospital-based control group (C)**: patients are hospitalized for other than internal medicine associated disease, such as hospital admissions in Traumatology or Ophthalmic Department. The criterion for inclusion in the study for **population based control group (D)**: not hospitalized general population.

Exclusion criteria: the criteria for exclusion in all groups: (1) patients do not have reliable information or data; (2) patients may not adhere; (3) unclear etiology.

Withdrawal of a subject from the study: According to the ethical regulations individuals are allowed to leave the study at any time without any negative consequences. Patients in the case group will be recruited during their hospital stay. Individuals for the control group are either spread among different units, or not hospitalized at all. In the study the participants in the case and in the control groups will be matched individually and continuously by gender, age and residence. Age, sex will be matched precisely in each case, location of residence will be considered by the range of population. The length of the data collection is 6 years and the data analysis takes another half a year.

Data collection and follow-up: Each participant (3900) if meets the inclusion criteria and signs the informed consent form, will be questioned by a clinical research administrator/study nurse who is fully trained before how to fill properly the questionnaires A-F and P. Since trained clinical research administrators will collect information, missing data will be unlikely. *The schedule of enrolment and assessments will be carried out according to the SPIRIT Guideline).*

In **Form A (A1 & A2)** we will collect general information about personal details, current status. The subjective social status will be evaluated with the SES ladder (MacArthur Scale of Subjective Social Status, http://www.macses.ucsf.edu). It is a widespread instrument in large epidemiological European and US studies and found to be significantly associated with health status, independently of objective socioeconomic indicators [33]. (Table 1)

TABLE 1 shows the title and source of the 7 questionnaires willing to use for data collection in LIFESPAN study.

Form	TITLE	SOURCE
Form A (A1 & A2)	PERSONAL DETAILS, PHYSICAL AND SOCIOECONOMIC STATUS	National Health and Nutrition Examination Survey (NHANES 2015-16); American Community Survey (ACS); The MacArthur Scale of Subjective Social Status
Form B (B1 & B2)	DETAILS FROM THE MEDICAL HISTORY	Acute Pancreatitis Questionnaire (Registry for Pancreatic Patients by Hungarian Pancreatic Study Group)
Form C (C1 & C2)	DIETARY HABITS	Diet History Questionnaire, Version 2.0. National Institutes of Health, Epidemiology and Genomics Research Program, National Cancer Institute. 2010.
Form D (D1 & D2)	PHYSICAL ACTIVITY	International Physical Activity Questionnaire (IPAQ) (long, usual week version)
Form E (E1 & E2)	STRESS	Percieved Stress Scale (10-item version)
Form F (F1 & F2)	SLEEP QUALITY	Pittsburgh Sleep Quality Index
Form P	CHARACTERISTIC OF ACUTE PANCREATITIS (ONLY FOR CASE GROUP)	Acute Pancreatitis Questionnaire (see above)

In **Form B (B1 & B2)**, we will collect information about patients‘ medical history based on Acute Pancreatitis Questionnaire of the registry for pancreatic patients operated by the Hungarian Pancreatic Study Group [34]. This online registry was established for recording data of patients with pancreatic diseases in 2012 (www.tm-centre.org), including details on smoking, alcohol consumption, other risk factors, medical history and the course and outcome of the disease. (Table 1)

In **Form C (C1 & C2),** we will collect data about participants’ dietary habits. Food Frequency Questionnaires (FFQs) are commonly used in epidemiological studies to assess the dietary intake of large populations. Their popularity derives from ease of administration, ability to assess dietary intake over a defined period of time and low costs [35]. The DHQII and Diet*Calc Analysis Software is a valid tool to measure dietary habits [36-38] and free to use. It is a very detailed quantitative FFQ with the most general foods and drinks. (Table 1)

In **Form D (D1 & D2)**, we will measure the participants' physical activity (PA) level with a frequently used epidemiology questionnaire namely the International Physical Activity Questionnaire [39]. We will use the long, usual week version (27-item) in the general part of our PA questionnaire. It contents details about the participants' vigorous PA, moderate PA, walking and sitting habits. (Table 1)

In **Form E (E1 & E2)**, we will evaluate the participants' chronic stress level with the Perceived Stress Scale [40]. It is the most widely used psychological instrument for the measuring of chronic stress effect [41-43]. We chose the 10-item version which has high validity and reliability. The time range in the general part is different from the original questionnaire (last year vs. last month). (Table 1)

In **Form F (F1 & F2)** we will collect data about participants' sleeping habits. We will apply the widely used Pittsburgh Sleep Quality Index, which evaluates the participants' sleeping quality [44]. We skip the 10th question about bed partner or roommate, because the bed partner will not be at the interview probably and this question does not count in the evaluation. The time range in the general part is also different from the original questionnaire (last year vs. last month). (Table 1)

In **Form P** we will collect data about patients' acute pancreatitis using the appropriate questions of Acute Pancreatitis Questionnaire (see Form B). (Table 1)

Electronic CRFs will be developed and will be available on www.tm-centre.org.

Patient and Public Involvement: 10 individuals were involved in he testing procedure of the in order to optimize the feasibility.

ENDPOINTS

Endpoints will be provided by each question of the questionnaires.

Form A: Age, race, location, body weight, body height, BMI, waist circumference, education, occupation, income, subjective social status (Table 2)

TABLE 2 shows the outputs, values, units and description of the Diet History Questionnaire II, the International Physical Activity Questionnaire, the Percieved Stress Scale (PSS) and the Pittsburgh Sleep Quality Index (PSQI).

Questionnaire	Outputs	Values	Unit	Description
Eating habits: Diet History Questionnaire II (DHQII) past year, with portion size	176 nutrients, dietary constituents, and food groups	varied	varied: • mcg, • mg, • g, • kcal, • IU, etc.	Food groups: • Carbohydrate constituents • Macronutrients & energy • Fats, fatty acids, & cholesterol • Protein Constituents • Vitamins • Minerals • Carotenoids and Tocopherols • Dietary Constituents from Supplements • Other • Food Pyramid Equivalents

	HEI (Healthy Eating Index-2010)	0-100	point	Good: 80-100. Needs Improvement: 51-80. Poor: 0-51.
Physical activity: International Physical Activity Questionnaire (IPAQ) long, last year version	Total walking activity	0-	MET-minutes/week OR Kcal/week	
	Total moderate activity	0-	MET-minutes/week OR Kcal/week	
	Total vigorous activity	0-	MET-minutes/week OR Kcal/week	
	Total physical activity	0-	MET-minutes/week OR Kcal/week	
	Sedentary activity	0-	hour and min / day	
	Level of physical activity	Low Moderate High	N/A	Detailed description in the text above
Stress: Percieved Stress Scale (PSS) 10-item version	TOTAL GENERAL PSS SCORE	0-40	point	Low perceived stress: 0-13. Moderate perceived stress: 14-26. High perceived stress: 27-40.
Sleep: Pittsburgh Sleep Quality Index (PSQI)	Component 1: Subjective sleep quality	0-3	point	0-good, 3-bad
	Component 2: Sleep latency	0-3	point	0-good, 3-bad
	Component 3: Sleep duration	0-3	point	0-good, 3-bad
	Component 4: Habitual sleep efficiency	0-3	point	0-good, 3-bad
	Component 5: Sleep disturbances	0-3	point	0-good, 3-bad
	Component 6: Use of sleeping medication	0-3	point	0-good, 3-bad
	Component 7: Daytime dysfunction	0-3	point	0-good, 3-bad
	GLOBAL PSQI SCORE (GENERAL)	0-21	point	Good sleep quality : 0-5. Poor sleep quality: 5-21.

Form B: Alcohol consumption (frequency, amount), smoking (frequency, amount), drug abuse (frequency, amount), diabetes mellitus (type), lipid metabolism disorder (type), any disease of the pancreas, pancreas, disorders in family history, congenital anatomical malformation of the pancreas, other illnesses, medications, diet (Table 2)

Form C: 176 nutrients, dietary constituents and food groups, Carbohydrate constituents, Macronutrients & energy, Fats, fatty acids, & cholesterol, Protein Constituents, Vitamins, Minerals, Carotenoids and Tocopherols, Dietary Constituents from Supplements, Other, Food Pyramid Equivalents, Healthy Eating Index *(HEI-2010) ((0-100): Good: >80, Needs improvement: 51-80, Poor: <51)*
(https://www.cnpp.usda.gov/sites/default/files/healthy_eating_index/HEI89-90report.pdf) (Table 2)

Form D: Continuous Scores (MET-minutes/week), Total physical activity (consists of: Total Walking activity (MET-minutes/week), Total Moderate activity (MET-minutes/week), Total Vigorous activity (MET-minutes/week), Average Sitting (min/day)), Categorical Score *(level of PA: Low-This is the lowest level of physical activity. Those individuals who do not meet criteria for Categories 2 or 3 are considered to have a 'low' physical activity level, Moderate: 3 or more days of vigorous-intensity activity of at least 20 minutes per day OR 5 or more days of moderate-intensity activity and/or walking of at least 30 minutes per day OR 5 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum Total physical activity of at least 600 MET-minutes/week. High: vigorous-intensity activity on at least 3 days achieving a minimum Total physical activity of at least 1500 MET-minutes/week OR 7 or more days of any combination of walking, moderate-intensity or vigorous-intensity activities achieving a minimum Total physical activity of at least 3000 MET-minutes/week*)
(https://sites.google.com/site/theipaq/scoring-protocol) (Table 2)

Form E: Total PSS Score (0-40) (*Categories: Low perceived stress: Scores ranging from 0-13, Moderate perceived stress: Scores ranging from 14-26, High perceived stress: Scores ranging from 27-40.)*
(https://das.nh.gov/wellness/Docs/Percieved%20Stress%20Scale.pdf) (Table 2)

Form F: Global PSQI Score (0-21), *(which consists of Subjective sleep quality (0-3): Sleep latency (0-3), Sleep duration (0-3), Habitual sleep efficiency (0-3), Sleep disturbances (0-3), Use of sleeping medication (0-3), Daytime dysfunction (0-3))*, Categories (empirically derived cutoff score*): Score < 5: Good sleepers, Score >5: Poor sleepers*
(http://uacc.arizona.edu/sites/default/files/psqi_sleep_questionnaire_1_pg.pdf) (Table 2)

Form P: Mortality, Severity *(mild, moderate, severe*), Complications (*pancreatic, systemic*) (Table 2)

Statistical analysis

Variables: All variables will be identified according to the outcomes mentioned in section 'Endpoints'. They are categorical, continuous and scaled variables. See below:

Form A: Analysis of the continuous and categorical values
Form B: Analysis of the continuous and categorical values
Form C: The Diet*Calc Analysis Program can be evaluated the questionnaire data
(https://epi.grants.cancer.gov/dhq2/dietcalc)
Form D: We will use the official scoring protocol to evaluate the survey
(https://sites.google.com/site/theipaq/scoring-protocol)
Form E: The original article contents the evaluation method [40]

Form F: The scoring instruction is described in the original article [44]

Form P: Analysis of the continuous and categorical values [34]

Bias: Deriving from the study design a possible recall bias could occur (patients who have the outcome (cases) are likely to remember the details of negative exposures more clearly than controls). It can be supposed, that it appears randomly, non-differential in the study-groups.

Sample size: The sample size was originally calculated based on the end scores of the four questionnaires (HEI-2010, IPAQ, PSS, PSQI). All calculations were made using a 5% significance level, a power of 80%, a 40% difference between the group means and equal sample size ratio (age, sex and socio-economic-matched control groups). We used the online sample size calculator: http://clincalc.com/Stats/SampleSize.aspx

We achieved the required information e.g. mean and standard deviation from articles (references found after each calculated sample size) or from online databases (HEI scores). In case of two questionnaires (PSQI and PSS) we made the calculation based also on Hungarian and not Hungarian data sources. The required sample sizes for the questionnaires per groups are the following:

- HEI-2010 Score: 195 (National Health and Nutrition Examination Survey, 2011-2012, results in: https://www.cnpp.usda.gov/healthyeatingindex);
- IPAQ Total activity: 155 [45];
- PSS Score: 217 and 13 [46], 23 [47];
- PSQI Score: 231 [48] 187 [49].

Statistical methods: To observe differences between the AP and control groups the end scores and subscale-scores of the questionnaires will be compared. 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 depending on the distribution of the parameters. To obtain interaction between variables multivariable analysis (binary logistic regression or multivariate linear regression) will be performed. To identify possible confounders, subgroup and cluster analysis will be applied. For timed endpoints such as mortality 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 %.

DISCUSSION

This is the first study prospectively collecting patients-reported data investigating the associations between socio-economic factors, dietary habits, physical activity, chronic stress, sleep quality and acute pancreatitis. We hope to find both negative and positive associations which will allow for the first time to suggest lifestyle modifications for patients discharged from the hospitals after AP or for those who wish to reduce their risk for AP.

ACKNOWLEDGEMENTS

We would like to say thank you for all the interviewed individuals for providing useful information on personal experience concerning acute pancreatitis, inquiring about lifestyle elements, hereby contributing to designing the study and constructing the questionnaires.

Centres: The study will start with the following centres (University of Szeged, University of Pécs, University of Debrecen, Szent-György Fejér County Teaching Hospital), however, other centres are welcome to participate in the LIFESPAN as an open label study. Completion of the LETTER OF INTENT form will be mandatory for registering the participation of each institution. HPSG will acknowledge receipt of the LETTER OF INTENT form and will contact centres providing them with additional study information.

Each centre must provide the same number of individuals for all the relevant four groups (1 case and 3 controls).

Publication policy: Centres providing more than 40 individuals can provide an author to the authors list. Every additional 20 individuals will give the opportunity to nominate an author.

Dissemination policy: We plan to communicate the results to several members of the healthcare system including medical doctors, dietitians, nurses, patients etc. We plan to publish the results in a peer-reviewed high quality journal for professionals. In addition, we also plan to publish it for lay readers in order to maximalize the dissemination and benefits of this study.

Feasibility and earlier experience: The feasibility will be examined by a pilot enrolment of 20 individuals in each group.

Safety: This is a non-interventional observational clinical study. Since no unknown drugs/therapy are used in the study no adverse and serious adverse events are expected/interpretable during the study.

Funding: Center costs (IT, biostatistics, study organization, etc.) are covered by the University of Pécs Medical School, Momentum Grant of the Hungarian Academy of Sciences (LP2014-10/2014); and Economic Development and Innovation Operative Programme Grant and Highly Cited Publication Grant of the National Research, Development and Innovation Office (GINOP-2.3.2-15-2016-00048 Stay Alive, KH-125678 and EFOP 3.6.2-16-2017-00006 Live Longer), and Translational Medicine Foundation. The study was designed by the SC and ITAB. DMC and SP has not been involved in the design of the study, moreover the SP will have no access to database.

Since no additional treatment is necessary for the study, the general healthcare costs are covered by the National Healthcare System (University of Pécs Medical School).

This study was designed with help of the Centre for Translational Medicine at the University of Pécs. This center is committed to improve patients' life with research activities like registries, observational and interventional study organizations (https://tm-centre.org).

For joining centres, the additional local costs have to be covered by the centre. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Authors' contributions: BK, ED, ZGy, JG, NF, MP, FI, ÁV and PH designed the study. As a member of the ITAB MML, JN, MST and OHP gave advices and will continuously monitor the progress of the study. ZsV, KM, PH, BE, DP, EF, TJ, LG, DE, DVV and IT drafted the manuscript, and ASz, JA, NZ edited the text, ASz, JA, NZ adapted the tables. All authors read and approved the final manuscript.

Competing interests statement: All authors declare any competing interest.

ETHICS AND DISSEMINATION

The study has been registered at the ISRCTN (25940508) and received he relevant ethical approval from the Scientific and Research Ethics Committee of the Hungarian Medical Research Council under the reference number of 54175-2/2018/EKU. After obtaining the final conclusions we will publish the data to the medical community and will also disseminate our results via open access.

Protocol Version: V1.0 08.01.2019.
Start of the patient recruitment: In April, 2019.
Planned finish of the study: 30 November 2023

Abbreviations:
AP- acute pancreatitis
CRF – case report form
DMC- Data Monitoring Committee
FFQs - Food Frequency Questionnaires
HEI - Healthy Eating Index
ITAB - International Translational Advisory Board
OR - Odds Ratio
PA - physical activity
PSS - Perceived Stress Scale
PSQI - Pittsburgh Sleep Quality Index
SC – Steering Comittee
SES - socioeconomic status
RR - Relative Risk
RRR - RR Reductions

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Figure legends:

TABLE 1 shows the title and source of the 7 questionnaires willing to use for data collection in LIFESPAN study.

TABLE 2 shows the outputs, values, units and description of the Diet History Questionnaire II, the International Physical Activity Questionnaire, the Percieved Stress Scale (PSS) and the Pittsburgh Sleep Quality Index (PSQI).

SUPPLEMENTUM FIGURE 1. The figure shows the schedule of enrolment and assessments according to the SPIRIT Guideline.

	STUDY PERIOD		
	Enrolment	Post enrolment	Close-out
TIMEPOINT	*0*	*0*	t_x
ENROLMENT:			
Eligibility screen	X		
Informed consent	X		
QUESTIONNAIRES:		X	
Questionnaire A		X	
Questionnaire B		X	
Questionnaire C		X	
Questionnaire D		X	
Questionnaire E		X	
Questionnaire F		X	
Questionnaire P		X	
DATA ANALYSIS:			X

45x39mm (300 x 300 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3,13
	2b	All items from the World Health Organization Trial Registration Data Set	–
Protocol version	3	Date and version identifier	13
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 12
	5b	Name and contact information for the trial sponsor	7
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	7, 12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	6-7, 12

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-6
	6b	Explanation for choice of comparators	3, 7
Objectives	7	Specific objectives or hypotheses	3-4, 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3-4, 6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	-
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	-
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	-
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	–
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	-
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig 1.

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	-
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	-
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	-
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	-
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	–
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-8

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7-8
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	7
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	-
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3,13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	7
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	7-8,12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12

	31b	Authorship eligibility guidelines and any intended use of professional writers	12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	attached
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

LIFEStyle, Prevention and Risk of Acute PaNcreatitis (LIFESPAN): Protocol of a Prospective, Multicentre and Multinational Observational Case-Control Study

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Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	acute pancreatitis, lifestyle factors, diet, stress, sleeping

LIFEStyle, Prevention and Risk of Acute PaNcreatitis (LIFESPAN): Protocol of a Prospective, Multicentre and Multinational Observational Case-Control Study

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ABSTRACT

Introduction. Acute pancreatitis (AP) is a life-threatening inflammatory disease of the exocrine pancreas which needs acute hospitalization. Despite its importance we have significant lack of knowledge whether the lifestyle factors elevate or decrease the risk of AP or influence the disease outcome. So far no synthetizing study has been carried out examining associations between socio-economic factors, dietary habits, physical activity, chronic stress, sleep quality and AP. Accordingly, LIFESPAN identifies risk factors of acute pancreatitis and helps to prepare preventive recommendations for lifestyle elements.

Methods and analysis. LIFESPAN is a prospective, observational, multicenter international case-control study. Participating subjects will create case and control groups. The study protocol was designed according to the SPIRIT guideline. Patients in the case group (n=1700) have suffered from AP (alcohol-induced, biliary, other (n=500 in each group), hypertriglyceridemia (HTG=200), the control group subjects have no AP in their medical history. Our study will have three major control groups (n=2200): hospital-based (n=500), population-based (n=500) and etiology-based (n=500 (alcohol) +500 (biliary) +200 (HTG)). All of them will be matched to the case group individually by **gender, age and location of residence**. Aggregately 3900 subjects will be enrolled into the study. The study participants will complete a complex questionnaire with the help of a clinical research administrator/study nurse. Analysis methods include analysis of the continuous and categorical values.

Ethics and dissemination. The study has got the relevant ethical approval (54175-2/2018/EKU) and also internationally registered (ISRCTN25940508)

Keywords: acute pancreatitis, lifestyle factors, diet, stress, sleeping.

STRENGTHS AND LIMITATION

Strength 1: Innovative results are to be expected concerning that contribution of lifestyle factors to acute pancreatitis is poorly researched and known, therefore evidence based preventive suggestions might be carried out.

Strength 2: LIFESPAN study will include a huge extension of examined patient population because of the three major control groups, all of them will be matched to the case group individually, this will elevate the strength of our study.

Strength 3: The study contains questionnaires only with no additional costs, therefore the study has an excellent cost/benefit ratio.

Limitation 1: The database will mostly consist of patients delivered data.

Limitation 2: The questionnaire requires extensive time which needs plenty of attention from the administrators and subjects as well.

INTRODUCTION

Acute pancreatitis (AP) is a life-threatening inflammatory disease of the exocrine pancreas which needs acute hospitalization. Despite its importance, we have significant lack of knowledge concerning the lifestyle factors elevate or decrease the risk of AP or influence the disease outcome. This insufficient information is even more problematic since (i) there is no specific treatment for the disease, therefore prevention would be very important and (ii) 20% of all AP is recurrent so lifestyle suggestions decreasing the risk of an additional attack could be highly efficient.

Genetic and environmental factors play significant role in disease development and outcome. Of course, in most of the cases the genetic background can not be changed, but the environmental factors. Dietary habits (1), socio-economic status (2), physical activity (3), stress (4) or sleeping habits (5) have been proved to play crucial role in many diseases.

(1) Dietary factors

Association of diet and the risk of diseases is well known in a lot of diseases for example in type 2 diabetes mellitus [1, 2] and coronary heart disease [3] and there is an ongoing multicenter prospective study about diet and cancer by the European Prospective Investigation into Cancer and Nutrition (EPIC) [4].

Recently a multiethnic cohort study was published about dietary factors that are associated with risk of pancreatitis [5]. Data source was a retrospective multiethnic cohort in Hawaii and Los Angeles (215, 251 adult men and women, respectively, age 45-75 years at baseline, from 1993 to 1996 participants entered the cohort). They used hospitalization claim files (1993-2012) and a self-administered quantitative food frequency questionnaire [6]. The main findings of this study are that intakes of saturated fat and cholesterol, and their food sources (red meat, eggs) positively associate with gallstone related AP, intakes of fiber inversely associate with AP, intakes of Vitamin D (mainly milk) inversely associate with gallstone related AP and coffee consumption protects against AP (not related to gallstones).

The association of vegetable, fruit and fish consumption with non-gallstone acute pancreatitis was examined in a Swedish prospective cohort study [7, 8]. Their conclusion is that vegetable consumption, but not fruit consumption, may play a role in the prevention of non-gallstone-related AP, and the consumption of total fish may be associated with decreased risk of non–gallstone-related AP.

(2) Physical activity

A lot of studies were published about physical activity and public health [9, 10]. Regular exercise offers protection against cardiovascular diseases and Type 2 diabetes mellitus [11]. So far there are not numerous studies dealing with the association between general physical activity and acute pancreatitis, although there are some surprising case reports about marathon pancreatitis (extreme long distance running results acute pancreatitis) [12]. Results of a prospective cohort study show that there is inverse association between physical activity and risk of acute pancreatitis [13].

(3) Socioeconomic status

Socioeconomic status (SES) is strongly associated with risk of disease and mortality [14]. Socioeconomic status includes the economic (measured by income), social (measured by education) and work status (measured by occupation). A clear relationship was also found between socioeconomic deprivation and incidence of AP in a prospective observational study of AP in the North of England which was largely explained by a higher incidence of alcoholic etiology [15].

(4) Stress

Chronic stress may also cause disease, either because of molecular changes [16] or because of increasing the probability of smoking, alcohol or drug consumption. Research shows that stress can contribute to the development of major illnesses, such as heart diseases, depression and obesity (www.apa.org), however no information is available concerning the effect of stress on the incidence of AP.

(5) Sleep quality

Currently there are no studies about the association of sleep quality and acute pancreatitis, however several articles claim that sleep deprivation or obstructive sleep apnea is associated with elevated levels of CRP [17, 18], which is the stable marker of inflammation and usually high in AP [19].

In this study our aim is to examine these health affecting individual lifestyle factors that seem to influence the development and outcome.

METHODS

The study has been initiated by the Hungarian Pancreatic Study Group and endorsed by the International Association of Pancreatology and was structured following the SPIRIT 2013 [20].

Design: LIFESPAN is a prospective, observational, multicentre and multinational case-control study. The data collection is based on questionnaires and medical histories. Relevant data will be prospectively collected from patients and controls. The questionnaires A-F and P (7 questionnaires in the case group, 6 for the control group) about the different fields of the patients' lifestyle will be filled with the help of trained administrators by a one-time meeting. Patients enrolled into the case group have suffered from AP, the control group subjects must not have acute pancreatitis in their medical history.

Study organization, committees and boards: The coordinator and designer of LIFESPAN study is the Hungarian Pancreatic Study Group (HPSG-coordinating society, https://tm-centre.org/en/study-groups/hungarian-pancreatic-study-group/). HPSG has been running high quality international, multicentre clinical trials since 2014 [21-25] and has published the relevant guidelines for pancreatic diseases to improve patient care in pancreatology [26-29]

The study will be supported by four committees:

Steering Committee (SC): The committee will be led by PH (corresponding investigator, gastroenterologist and internal medicine specialist). The members in Szeged (HU) will be: ED (principal investigator); Debrecen (HU): MP (gastroenterologist), ZsV (gastroenterologist), TJ (gastroenterologist); Pécs (HU): ASz (multidisciplinary unit specialist), DE (co-principal investigator), KM (trial management specialist), BE (gastroenterologist), ZGy (public

health specialist), JG (public health specialist), ÁV (gastroenterologist); Székesfehérvár (HU): FI (gastroenterologist), LG (gastroenterologist); Targu Mures (RO): IT (gastroenterologist). KM is a trial management specialist, whereas ASz leads the multidisciplinary core facility which will assist the scientists to run the study successfully.

International Translational Advisory Board (ITAB): The board will consist of a gastroenterologist (MML), a surgeon and two basic scientists (JN, MST, OHP). The ITAB will continuously monitor the progress of the study and will advise the SC.

Data Monitoring Committee (DMC): DMC will handle all the data and ensure that the data in the eCRF is accurate, complete and legible. Data Management Plan (DMP) will describe the detailed data flow. The Data Manager will validate the data from completed eCRFs, according to a Data Cleaning Plan (DCP). Any missing, implausible or inconsistent recordings in the eCRFs will be referred back to the Investigator using a data query form (DQF), and be documented for each individual subject before clean file status is declared. All changes to eCRFs will be recorded. In case of important protocol modifications DMC will report it to the SC.

Premature termination of the study: Interim analysis will be carried out after half of the presumed number of patients have completed the study. Sample sizes for all questionnaires will be reassessed and modified accordingly. In addition, DMC independently will assess the study related documents and activities, with the aim of ensuring the respect of subjects' right and to guarantee the plausibility of clinical data.

Sponsor (SP): The sponsor of the study is the Centre for Translational Medicine at the University of Pécs Medical School (coordinating institution and sponsor, www.tm-centre.org).

Study population: All patients diagnosed with AP in participating institutions will be informed concerning the possibility of taking part of the LIFESPAN study.

Case group (1700 cases): Patients in the case group will be divided into four groups depending on the causative agents of the AP (alcohol-induced, biliary, hypertriglycieridemia and other). Taking into consideration the central limit theorem [30] 500 patients will be enrolled in all groups, but the hypertriglyceridemia-induced group, where due to the low prevalence level, only 200 subjects will be collected. With the sample size 500, it is thought to be possible to safely analyse the relationship between two variables that contain up to 4 variable values each. Altogether we plan to enroll 1700 individuals as cases. This way, the required number of respondents can be provided for a comparative analysis between the members of the case and control groups as well as for an exploratory study within a given case group.

Control group (2200 cases):

Our study will have three major control groups, all of them will be matched to the case group individually in order to avoid admission rate bias.

(1) Hospital-based control group: we will enroll patients in other clinical departments (e.g. Traumatology Department, Ophthalmic Department, 500 patients); (2) Population-based control group: we will enroll people according to a plan based on gender/age/location of residence ratios in the case group (500 patients); (3) Etiology-

based control group: we will enroll people matched to the three etiology-factors of the four case groups (500, 500 and 200, respectively).

Inclusion criteria

The criteria for inclusion in the study in **case groups (A) in general**: (1) patients above 18 years; (2) diagnosed AP on the base of the "2 out of 3" rules of IAP/APA guideline:

(a) upper abdominal pain; (b) serum amylase or lipase >3x upper limit of normal range; (c) characteristic findings on pancreatic imaging; (3) written informed consent form is signed. **According to the etiology: (A1)** in alcohol etiology group: patients consuming >5 drinks per day or >35 drinks per week for both sexes [= 8.75 units per day; 61.25 units per week] shall be included. Please note that 1 unit of alcohol = 10 mls or 8gr of pure (100%) alcohol [31]; **(A2)** in gallstone etiology group: presence of gallstone (not sludge); **(A3)** in hypertrigliceridaemia etiology group: triglyceride level in blood over 11 mmol/l [32]; **(A4)** in 'other' etiology group: the causative agents do not match either of the first 3 groups, AP is induced by e.g.: ERCP (post-ERCP pancreatitis), virus infection, trauma, medicine (drug induced pancreatitis), congenital anatomical malformation, cystic fibrosis, genetics, gluten sensitive enteropathy etc.

The criteria for inclusion in the study for **control groups (B, C and D) in general**: (1) patients above 18 years; (2) absence of AP at present as well as in the medical history; (3) signed written informed consent form.

According to the etiology of the case groups: (B1) in alcohol group: patients consuming >5 drinks per day or >35 drinks per week for both sexes [= 8.75 units per day; 61.25 units per week] shall be included. Please note that 1 unit of alcohol = 10 mls or 8gr of pure (100%) alcohol [31]; **(B2)** in gallstone group: presence of gallstone (not sludge); **(B3)** in hypertrigliceridaemia group: triglyceride level over 11 mmol/l [32]; The criteria for inclusion in the study for **hospital-based control group (C)**: patients are hospitalized for other than internal medicine associated disease, such as hospital admissions in Traumatology or Ophthalmic Department. The criterion for inclusion in the study for **population based control group (D)**: not hospitalized general population.

Exclusion criteria: the criteria for exclusion in all groups: (1) patients do not have reliable information or data; (2) patients may not adhere; (3) unclear etiology.

Withdrawal of a subject from the study: According to the ethical regulations individuals are allowed to leave the study at any time without any negative consequences. Patients in the case group will be recruited during their hospital stay. Individuals for the control group are either spread among different units, or not hospitalized at all. In the study the participants in the case and in the control groups will be matched individually and continuously by gender, age and residence. Age, sex will be matched precisely in each case, location of residence will be considered by the range of population. The length of the data collection is 6 years and the data analysis takes another half a year.

Data collection and follow-up: Each participant (3900) if meets the inclusion criteria and signs the informed consent form, will be questioned by a clinical research administrator/study nurse who is fully trained before how to fill properly the questionnaires A-F and P. Since trained clinical research administrators will collect information, missing data will be unlikely. *The schedule of enrolment and assessments will be carried out according to the SPIRIT Guideline* (Supplementary figure 1).

In **Form A (A1 & A2)** we will collect general information about personal details, current status. The subjective social status will be evaluated with the SES ladder (MacArthur Scale of Subjective Social Status, http://www.macses.ucsf.edu). It is a widespread instrument in large epidemiological European and US studies and found to be significantly associated with health status, independently of objective socioeconomic indicators [33]. (Table 1)

TABLE 1 shows the title and source of the 7 questionnaires willing to use for data collection in LIFESPAN study.

Form	TITLE	SOURCE
Form A (A1 & A2)	PERSONAL DETAILS, PHYSICAL AND SOCIOECONOMIC STATUS	National Health and Nutrition Examination Survey (NHANES 2015-16); American Community Survey (ACS); The MacArthur Scale of Subjective Social Status
Form B (B1 & B2)	DETAILS FROM THE MEDICAL HISTORY	Acute Pancreatitis Questionnaire (Registry for Pancreatic Patients by Hungarian Pancreatic Study Group)
Form C (C1 & C2)	DIETARY HABITS	Diet History Questionnaire, Version 2.0. National Institutes of Health, Epidemiology and Genomics Research Program, National Cancer Institute. 2010.
Form D (D1 & D2)	PHYSICAL ACTIVITY	International Physical Activity Questionnaire (IPAQ) (long, usual week version)
Form E (E1 & E2)	STRESS	Percieved Stress Scale (10-item version)
Form F (F1 & F2)	SLEEP QUALITY	Pittsburgh Sleep Quality Index
Form P	CHARACTERISTIC OF ACUTE PANCREATITIS (ONLY FOR CASE GROUP)	Acute Pancreatitis Questionnaire (see above)

In **Form B (B1 & B2)**, we will collect information about patients‘ medical history based on Acute Pancreatitis Questionnaire of the registry for pancreatic patients operated by the Hungarian Pancreatic Study Group [34]. This online registry was established for recording data of patients with pancreatic diseases in 2012 (www.tm-centre.org), including details on smoking, alcohol consumption, other risk factors, medical history and the course and outcome of the disease. (Table 1)

In **Form C (C1 & C2),** we will collect data about participants’ dietary habits. Food Frequency Questionnaires (FFQs) are commonly used in epidemiological studies to assess the dietary intake of large populations. Their popularity derives from ease of administration, ability to assess dietary intake over a defined period of time and low costs [35]. The DHQII and Diet*Calc Analysis Software is a valid tool to measure dietary habits [36-38] and free to use. It is a very detailed quantitative FFQ with the most general foods and drinks. (Table 1)

In **Form D (D1 & D2)**, we will measure the participants' physical activity (PA) level with a frequently used epidemiology questionnaire namely the International Physical Activity Questionnaire [39]. We will use the long, usual week version (27-item) in the general part of our PA questionnaire. It contents details about the participants' vigorous PA, moderate PA, walking and sitting habits. (Table 1)

In **Form E (E1 & E2)**, we will evaluate the participants' chronic stress level with the Perceived Stress Scale [40]. It is the most widely used psychological instrument for the measuring of chronic stress effect [41-43]. We chose the 10-item version which has high validity and reliability. The time range in the general part is different from the original questionnaire (last year vs. last month). (Table 1)

In **Form F (F1 & F2)** we will collect data about participants' sleeping habits. We will apply the widely used Pittsburgh Sleep Quality Index, which evaluates the participants' sleeping quality [44]. We skip the 10th question about bed partner or roommate, because the bed partner will not be at the interview probably and this question does not count in the evaluation. The time range in the general part is also different from the original questionnaire (last year vs. last month). (Table 1)

In **Form P** we will collect data about patients' acute pancreatitis using the appropriate questions of Acute Pancreatitis Questionnaire (see Form B). (Table 1)

Electronic CRFs will be developed and will be available on www.tm-centre.org.

Patient and Public Involvement: 10 individuals were involved in the testing procedure of the study in order to optimize the feasibility.

ENDPOINTS

Endpoints will be provided by each question of the questionnaires.

Form A: Age, race, location, body weight, body height, BMI, waist circumference, education, occupation, income, subjective social status.

TABLE 2 shows the outputs, values, units and description of the Diet History Questionnaire II, the International Physical Activity Questionnaire, the Perceived Stress Scale (PSS) and the Pittsburgh Sleep Quality Index (PSQI).

Questionnaire	Outputs	Values	Unit	Description
Eating habits: Diet History Questionnaire II (DHQII) past year, with portion size	176 nutrients, dietary constituents, and food groups	varied	varied: • mcg, • mg, • g, • kcal, • IU, etc.	Food groups: • Carbohydrate constituents • Macronutrients & energy • Fats, fatty acids, & cholesterol • Protein Constituents • Vitamins • Minerals • Carotenoids and Tocopherols • Dietary Constituents from Supplements • Other • Food Pyramid Equivalents

	HEI (Healthy Eating Index-2010)	0-100	point	Good: 80-100. Needs Improvement: 51-80. Poor: 0-51.
Physical activity: International Physical Activity Questionnaire (IPAQ) long, last year version	Total walking activity	0-	MET-minutes/week OR Kcal/week	
	Total moderate activity	0-	MET-minutes/week OR Kcal/week	
	Total vigorous activity	0-	MET-minutes/week OR Kcal/week	
	Total physical activity	0-	MET-minutes/week OR Kcal/week	
	Sedentary activity	0-	hour and min / day	
	Level of physical activity	Low Moderate High	N/A	Detailed description in the text above
Stress: Percieved Stress Scale (PSS) 10-item version	TOTAL GENERAL PSS SCORE	0-40	point	Low perceived stress: 0-13. Moderate perceived stress: 14-26. High perceived stress: 27-40.
Sleep: Pittsburgh Sleep Quality Index (PSQI)	Component 1: Subjective sleep quality	0-3	point	0-good, 3-bad
	Component 2: Sleep latency	0-3	point	0-good, 3-bad
	Component 3: Sleep duration	0-3	point	0-good, 3-bad
	Component 4: Habitual sleep efficiency	0-3	point	0-good, 3-bad
	Component 5: Sleep disturbances	0-3	point	0-good, 3-bad
	Component 6: Use of sleeping medication	0-3	point	0-good, 3-bad
	Component 7: Daytime dysfunction	0-3	point	0-good, 3-bad
	GLOBAL PSQI SCORE (GENERAL)	0-21	point	Good sleep quality : 0-5. Poor sleep quality: 5-21.

Form B: Alcohol consumption (frequency, amount), smoking (frequency, amount), drug abuse (frequency, amount), diabetes mellitus (type), lipid metabolism disorder (type), any disease of the pancreas, pancreas, disorders in family history, congenital anatomical malformation of the pancreas, other illnesses, medications, diet.

Form C: 176 nutrients, dietary constituents and food groups, Carbohydrate constituents, Macronutrients & energy, Fats, fatty acids, & cholesterol, Protein Constituents, Vitamins, Minerals, Carotenoids and Tocopherols, Dietary Constituents from Supplements, Other, Food Pyramid Equivalents, Healthy Eating Index *(HEI-2010) ((0-100): Good: >80, Needs improvement: 51-80, Poor: <51)*
(https://www.cnpp.usda.gov/sites/default/files/healthy_eating_index/HEI89-90report.pdf) (Table 2)

Form D: Continuous Scores (MET-minutes/week), Total physical activity (consists of: Total Walking activity (MET-minutes/week), Total Moderate activity (MET-minutes/week), Total Vigorous activity (MET-minutes/week), Average Sitting (min/day)), Categorical Score *(level of PA: Low-This is the lowest level of physical activity. Those individuals who do not meet criteria for Categories 2 or 3 are considered to have a 'low' physical activity level, Moderate: 3 or more days of vigorous-intensity activity of at least 20 minutes per day OR 5 or more days of moderate-intensity activity and/or walking of at least 30 minutes per day OR 5 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum Total physical activity of at least 600 MET-minutes/week. High: vigorous-intensity activity on at least 3 days achieving a minimum Total physical activity of at least 1500 MET-minutes/week OR 7 or more days of any combination of walking, moderate-intensity or vigorous-intensity activities achieving a minimum Total physical activity of at least 3000 MET-minutes/week*)
(https://sites.google.com/site/theipaq/scoring-protocol) (Table 2)

Form E: Total PSS Score (0-40) (*Categories: Low perceived stress: Scores ranging from 0-13, Moderate perceived stress: Scores ranging from 14-26, High perceived stress: Scores ranging from 27-40.)*
(https://das.nh.gov/wellness/Docs/Percieved%20Stress%20Scale.pdf) (Table 2)

Form F: Global PSQI Score (0-21), *(which consists of Subjective sleep quality (0-3): Sleep latency (0-3), Sleep duration (0-3), Habitual sleep efficiency (0-3), Sleep disturbances (0-3), Use of sleeping medication (0-3), Daytime dysfunction (0-3))*, Categories (empirically derived cutoff score*): Score < 5: Good sleepers, Score >5: Poor sleepers*
(http://uacc.arizona.edu/sites/default/files/psqi_sleep_questionnaire_1_pg.pdf) (Table 2)

Form P: Mortality, Severity *(mild, moderate, severe*), Complications (*pancreatic, systemic*).

Statistical analysis

Variables: All variables will be identified according to the outcomes mentioned in section 'Endpoints'. They are categorical, continuous and scaled variables. See below:

Form A: Analysis of the continuous and categorical values
Form B: Analysis of the continuous and categorical values
Form C: The Diet*Calc Analysis Program can be evaluated the questionnaire data
(https://epi.grants.cancer.gov/dhq2/dietcalc)
Form D: We will use the official scoring protocol to evaluate the survey
(https://sites.google.com/site/theipaq/scoring-protocol)
Form E: The original article contents the evaluation method [40]

Form F: The scoring instruction is described in the original article [44]

Form P: Analysis of the continuous and categorical values [34]

Bias: Deriving from the study design a possible recall bias could occur (patients who have the outcome (cases) are likely to remember the details of negative exposures more clearly than controls). It can be supposed, that it appears randomly, non-differential in the study-groups.

Sample size: The sample size was originally calculated based on the end scores of the four questionnaires (HEI-2010, IPAQ, PSS, PSQI). All calculations were made using a 5% significance level, a power of 80%, a 40% difference between the group means and equal sample size ratio (age, sex and socio-economic-matched control groups). We used the online sample size calculator: http://clincalc.com/Stats/SampleSize.aspx

We achieved the required information e.g. mean and standard deviation from articles (references found after each calculated sample size) or from online databases (HEI scores). In case of two questionnaires (PSQI and PSS) we made the calculation based also on Hungarian and not Hungarian data sources. The required sample sizes for the questionnaires per groups are the following:

- HEI-2010 Score: 195 (National Health and Nutrition Examination Survey, 2011-2012, results in: https://www.cnpp.usda.gov/healthyeatingindex);
- IPAQ Total activity: 155 [45];
- PSS Score: 217 and 13 [46], 23 [47];
- PSQI Score: 231 [48] 187 [49].

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 indentifing 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 %.

DISCUSSION

This is the first study prospectively collecting patients-reported data investigating the associations between socio-economic factors, dietary habits, physical activity, chronic stress, sleep quality and acute pancreatitis. We hope to find both negative and positive associations which will allow for the first time to suggest lifestyle modifications for patients discharged from the hospitals after AP or for those who wish to reduce their risk for AP.

ACKNOWLEDGEMENTS

We would like to say thank you for all the interviewed individuals for providing useful information on personal experience concerning acute pancreatitis, inquiring about lifestyle elements, hereby contributing to designing the study and constructing the questionnaires.

Centres: The study will start with the following centres (University of Szeged, University of Pécs, University of Debrecen, Szent-György Fejér County Teaching Hospital), however, other centres are welcome to participate in the LIFESPAN as an open label study. Completion of the LETTER OF INTENT form will be mandatory for registering the participation of each institution. HPSG will acknowledge receipt of the LETTER OF INTENT form and will contact centres providing them with additional study information.

Each centre must provide the same number of individuals for all the relevant four groups (1 case and 3 controls).

Publication policy: Centres providing more than 40 individuals can provide an author to the authors list. Every additional 20 individuals will give the opportunity to nominate an author.

Dissemination policy: We plan to communicate the results to several members of the healthcare system including medical doctors, dietitians, nurses, patients etc. We plan to publish the results in a peer-reviewed high quality journal for professionals. In addition, we also plan to publish it for lay readers in order to maximize the dissemination and benefits of this study.

Feasibility and earlier experience: The feasibility will be examined by a pilot enrolment of 20 individuals in each group.

Safety: This is a non-interventional observational clinical study. Since no unknown drugs/therapy are used in the study no adverse and serious adverse events are expected/interpretable during the study.

Funding: Center costs (IT, biostatistics, study organization, etc.) are covered by the University of Pécs Medical School, Momentum Grant of the Hungarian Academy of Sciences (LP2014-10/2014); and Economic Development and Innovation Operative Programme Grant and Highly Cited Publication Grant of the National Research, Development and Innovation Office (GINOP-2.3.2-15-2016-00048 Stay Alive, KH-125678 and EFOP 3.6.2-16-2017-00006 Live Longer), and Translational Medicine Foundation. The study was designed by the SC and ITAB. DMC and SP has not been involved in the design of the study, moreover the SP will have no access to database.

Since no additional treatment is necessary for the study, the general healthcare costs are covered by the National Healthcare System (University of Pécs Medical School).

This study was designed with help of the Centre for Translational Medicine at the University of Pécs. This center is committed to improve patients' life with research activities like registries, observational and interventional study organizations (https://tm-centre.org).

For joining centres, the additional local costs have to be covered by the centre. This research received no specific grant from any funding agency in the public, commercial or not-for-profit organizations.

Authors' contributions: BK, ED, ZGy, JG, NF, MP, FI, ÁV and PH designed the study. As a member of the ITAB MML, JN, MST and OHP gave advices and will continuously monitor the progress of the study. ZsV, KM, PH, BE, DP, EF, TJ, LG, DE, DVV and IT drafted the manuscript, and ASz, JA, NZ edited the text, ASz, JA, NZ adapted the tables. All authors read and approved the final manuscript.

Competing interests statement: All authors declare any competing interest.

ETHICS AND DISSEMINATION

The study has been registered at the ISRCTN (25940508) and received the relevant ethical approval from the Scientific and Research Ethics Committee of the Hungarian Medical Research Council under the reference number of 54175-2/2018/EKU. After obtaining the final conclusions we will publish the data to the medical community and will also disseminate our results via open access.

Protocol Version: V1.0 08.01.2019.
Start of the patient recruitment: In April, 2019.
Planned finish of the study: 30 November 2023

Abbreviations:
AP- acute pancreatitis
CRF – case report form
DMC- Data Monitoring Committee
FFQs - Food Frequency Questionnaires
HEI - Healthy Eating Index
ITAB - International Translational Advisory Board
OR - Odds Ratio
PA - physical activity
PSS - Perceived Stress Scale
PSQI - Pittsburgh Sleep Quality Index
SC – Steering Comittee
SES - socioeconomic status
RR - Relative Risk
RRR - RR Reductions

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Figure legends:

TABLE 1 shows the title and source of the 7 questionnaires willing to use for data collection in LIFESPAN study.

TABLE 2 shows the outputs, values, units and description of the Diet History Questionnaire II, the International Physical Activity Questionnaire, the Perceived Stress Scale (PSS) and the Pittsburgh Sleep Quality Index (PSQI).

SUPPLEMENTUM FIGURE 1. The figure shows the schedule of enrolment and assessments according to the SPIRIT Guideline.

	STUDY PERIOD		
	Enrolment	Post enrolment	Close-out
TIMEPOINT	*0*	*0*	t_x
ENROLMENT:			
Eligibility screen	X		
Informed consent	X		
QUESTIONNAIRES:		X	
Questionnaire A		X	
Questionnaire B		X	
Questionnaire C		X	
Questionnaire D		X	
Questionnaire E		X	
Questionnaire F		X	
Questionnaire P		X	
DATA ANALYSIS:			X

45x39mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3,13
	2b	All items from the World Health Organization Trial Registration Data Set	–
Protocol version	3	Date and version identifier	13
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 12
	5b	Name and contact information for the trial sponsor	7
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	7, 12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	6-7, 12

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-6
	6b	Explanation for choice of comparators	3, 7
Objectives	7	Specific objectives or hypotheses	3-4, 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3-4, 6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	-
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	-
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	-
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	–
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	-
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig 1.

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	-
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	-
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	-
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	-
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	–
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-8

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7-8
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	7
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	-
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3,13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	7
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	7-8,12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12

	31b	Authorship eligibility guidelines and any intended use of professional writers	12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	attached
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

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LIFEStyle, Prevention and Risk of Acute PaNcreatitis (LIFESPAN): Protocol of a Multicentre and Multinational Observational Case-Control Study

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Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	acute pancreatitis, lifestyle factors, diet, stress, sleeping

LIFEStyle, Prevention and Risk of Acute PaNcreatitis (LIFESPAN): Protocol of a Multicentre and Multinational Observational Case-Control Study

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ABSTRACT

Introduction. Acute pancreatitis (AP) is a life-threatening inflammatory disease of the exocrine pancreas which needs acute hospitalization. Despite its importance we have significant lack of knowledge whether the lifestyle factors elevate or decrease the risk of AP or influence the disease outcome. So far no synthetizing study has been carried out examining associations between socio-economic factors, dietary habits, physical activity, chronic stress, sleep quality and AP. Accordingly, LIFESPAN identifies risk factors of acute pancreatitis and helps to prepare preventive recommendations for lifestyle elements.

Methods and analysis. LIFESPAN is an observational, multicenter international case-control study. Participating subjects will create case and control groups. The study protocol was designed according to the SPIRIT guideline. Patients in the case group (n=1700) have suffered from AP (alcohol-induced, biliary, other (n=500 in each group), hypertriglyceridemia (HTG=200), the control group subjects have no AP in their medical history. Our study will have three major control groups (n=2200): hospital-based (n=500), population-based (n=500) and etiology-based (n=500 (alcohol) +500 (biliary) +200 (HTG)). All of them will be matched to the case group individually by **gender, age and location of residence**. Aggregately 3900 subjects will be enrolled into the study. The study participants will complete a complex questionnaire with the help of a clinical research administrator/study nurse. Analysis methods include analysis of the continuous and categorical values.

Ethics and dissemination. The study has got the relevant ethical approval (54175-2/2018/EKU) and also internationally registered (ISRCTN25940508)

Keywords: acute pancreatitis, lifestyle factors, diet, stress, sleeping.

STRENGTHS AND LIMITATION

Strength 1: Innovative results are to be expected concerning that contribution of lifestyle factors to acute pancreatitis is poorly researched and known, therefore evidence based preventive suggestions might be carried out.

Strength 2: LIFESPAN study will include a huge extension of examined patient population because of the three major control groups, all of them will be matched to the case group individually, this will elevate the strength of our study.

Strength 3: The study contains questionnaires only with no additional costs, therefore the study has an excellent cost/benefit ratio.

Limitation 1: The database will mostly consist of patients delivered data.

Limitation 2: The questionnaire requires extensive time which needs plenty of attention from the administrators and subjects as well.

INTRODUCTION

Acute pancreatitis (AP) is a life-threatening inflammatory disease of the exocrine pancreas which needs acute hospitalization. Despite its importance, we have significant lack of knowledge concerning the lifestyle factors elevate or decrease the risk of AP or influence the disease outcome. This insufficient information is even more problematic since (i) there is no specific treatment for the disease, therefore prevention would be very important and (ii) 20% of all AP is recurrent so lifestyle suggestions decreasing the risk of an additional attack could be highly efficient.

Genetic and environmental factors play significant role in disease development and outcome. Of course, in most of the cases the genetic background can not be changed, but the environmental factors. Dietary habits (1), socio-economic status (2), physical activity (3), stress (4) or sleeping habits (5) have been proved to play crucial role in many diseases.

(1) Dietary factors

Association of diet and the risk of diseases is well known in a lot of diseases for example in type 2 diabetes mellitus [1, 2] and coronary heart disease [3] and there is an ongoing multicenter prospective study about diet and cancer by the European Prospective Investigation into Cancer and Nutrition (EPIC) [4].

Recently a multiethnic cohort study was published about dietary factors that are associated with risk of pancreatitis [5]. Data source was a retrospective multiethnic cohort in Hawaii and Los Angeles (215, 251 adult men and women, respectively, age 45-75 years at baseline, from 1993 to 1996 participants entered the cohort). They used hospitalization claim files (1993-2012) and a self-administered quantitative food frequency questionnaire [6]. The main findings of this study are that intakes of saturated fat and cholesterol, and their food sources (red meat, eggs) positively associate with gallstone related AP, intakes of fiber inversely associate with AP, intakes of Vitamin D (mainly milk) inversely associate with gallstone related AP and coffee consumption protects against AP (not related to gallstones).

The association of vegetable, fruit and fish consumption with non-gallstone acute pancreatitis was examined in a Swedish prospective cohort study [7, 8]. Their conclusion is that vegetable consumption, but not fruit consumption, may play a role in the prevention of non-gallstone-related AP, and the consumption of total fish may be associated with decreased risk of non–gallstone-related AP.

(2) Physical activity

A lot of studies were published about physical activity and public health [9, 10]. Regular exercise offers protection against cardiovascular diseases and Type 2 diabetes mellitus [11]. So far there are not numerous studies dealing with the association between general physical activity and acute pancreatitis, although there are some surprising case reports about marathon pancreatitis (extreme long distance running results acute pancreatitis) [12]. Results of a prospective cohort study show that there is inverse association between physical activity and risk of acute pancreatitis [13].

(3) Socioeconomic status

Socioeconomic status (SES) is strongly associated with risk of disease and mortality [14]. Socioeconomic status includes the economic (measured by income), social (measured by education) and work status (measured by occupation). A clear relationship was also found between socioeconomic deprivation and incidence of AP in a prospective observational study of AP in the North of England which was largely explained by a higher incidence of alcoholic etiology [15].

(4) Stress

Chronic stress may also cause disease, either because of molecular changes [16] or because of increasing the probability of smoking, alcohol or drug consumption. Research shows that stress can contribute to the development of major illnesses, such as heart diseases, depression and obesity (www.apa.org), however no information is available concerning the effect of stress on the incidence of AP.

(5) Sleep quality

Currently there are no studies about the association of sleep quality and acute pancreatitis, however several articles claim that sleep deprivation or obstructive sleep apnea is associated with elevated levels of CRP [17, 18], which is the stable marker of inflammation and usually high in AP [19].

In this study our aim is to examine these health affecting individual lifestyle factors that seem to influence the development and outcome.

METHODS

The study has been initiated by the Hungarian Pancreatic Study Group and endorsed by the International Association of Pancreatology and was structured following the SPIRIT 2013 [20].

Design: LIFESPAN is an observational, multicentre and multinational case-control study. The data collection is based on questionnaires and medical histories. Relevant data will be prospectively collected from patients and controls. The questionnaires A-F and P (7 questionnaires in the case group, 6 for the control group) about the different fields of the patients' lifestyle will be filled with the help of trained administrators by a one-time meeting. Patients enrolled into the case group have suffered from AP, the control group subjects must not have acute pancreatitis in their medical history.

Study organization, committees and boards: The coordinator and designer of LIFESPAN study is the Hungarian Pancreatic Study Group (HPSG-coordinating society, https://tm-centre.org/en/study-groups/hungarian-pancreatic-study-group/). HPSG has been running high quality international, multicentre clinical trials since 2014 [21-25] and has published the relevant guidelines for pancreatic diseases to improve patient care in pancreatology [26-29]

The study will be supported by four committees:

Steering Committee (SC): The committee will be led by PH (corresponding investigator, gastroenterologist and internal medicine specialist). The members in Szeged (HU) will be: ED (principal investigator); Debrecen (HU): MP (gastroenterologist), ZsV (gastroenterologist), TJ (gastroenterologist); Pécs (HU): ASz (multidisciplinary unit specialist), DE (co-principal investigator), KM (trial management specialist), BE (gastroenterologist), ZGy (public

health specialist), JG (public health specialist), ÁV (gastroenterologist); Székesfehérvár (HU): FI (gastroenterologist), LG (gastroenterologist); Targu Mures (RO): IT (gastroenterologist). KM is a trial management specialist, whereas ASz leads the multidisciplinary core facility which will assist the scientists to run the study successfully.

International Translational Advisory Board (ITAB): The board will consist of a gastroenterologist (MML), a surgeon and two basic scientists (JN, MST, OHP). The ITAB will continuously monitor the progress of the study and will advise the SC.

Data Monitoring Committee (DMC): DMC will handle all the data and ensure that the data in the eCRF is accurate, complete and legible. Data Management Plan (DMP) will describe the detailed data flow. The Data Manager will validate the data from completed eCRFs, according to a Data Cleaning Plan (DCP). Any missing, implausible or inconsistent recordings in the eCRFs will be referred back to the Investigator using a data query form (DQF), and be documented for each individual subject before clean file status is declared. All changes to eCRFs will be recorded. In case of important protocol modifications DMC will report it to the SC.

Premature termination of the study: Interim analysis will be carried out after half of the presumed number of patients have completed the study. Sample sizes for all questionnaires will be reassessed and modified accordingly. In addition, DMC independently will assess the study related documents and activities, with the aim of ensuring the respect of subjects' right and to guarantee the plausibility of clinical data.

Sponsor (SP): The sponsor of the study is the Centre for Translational Medicine at the University of Pécs Medical School (coordinating institution and sponsor, www.tm-centre.org).

Study population: All patients diagnosed with AP in participating institutions will be informed concerning the possibility of taking part of the LIFESPAN study.

Case group (1700 cases): Patients in the case group will be divided into four groups depending on the causative agents of the AP (alcohol-induced, biliary, hypertriglycieridemia and other). Taking into consideration the central limit theorem [30] 500 patients will be enrolled in all groups, but the hypertriglyceridemia-induced group, where due to the low prevalence level, only 200 subjects will be collected. With the sample size 500, it is thought to be possible to safely analyse the relationship between two variables that contain up to 4 variable values each. Altogether we plan to enroll 1700 individuals as cases. This way, the required number of respondents can be provided for a comparative analysis between the members of the case and control groups as well as for an exploratory study within a given case group.

Control group (2200 cases):

Our study will have three major control groups, all of them will be matched to the case group individually in order to avoid admission rate bias.

(1) Hospital-based control group: we will enroll patients in other clinical departments (e.g. Traumatology Department, Ophthalmic Department, 500 patients); (2) Population-based control group: we will enroll people according to a plan based on gender/age/location of residence ratios in the case group (500 patients); (3) Etiology-

based control group: we will enroll people matched to the three etiology-factors of the four case groups (500, 500 and 200, respectively).

Inclusion criteria

The criteria for inclusion in the study in **case groups (A) in general**: (1) patients above 18 years; (2) diagnosed AP on the base of the "2 out of 3" rules of IAP/APA guideline:

(a) upper abdominal pain; (b) serum amylase or lipase >3x upper limit of normal range; (c) characteristic findings on pancreatic imaging; (3) written informed consent form is signed. **According to the etiology: (A1)** in alcohol etiology group: patients consuming >5 drinks per day or >35 drinks per week for both sexes [= 8.75 units per day; 61.25 units per week] shall be included. Please note that 1 unit of alcohol = 10 mls or 8gr of pure (100%) alcohol [31]; **(A2)** in gallstone etiology group: presence of gallstone (not sludge); **(A3)** in hypertrigliceridaemia etiology group: triglyceride level in blood over 11 mmol/l [32]; **(A4)** in 'other' etiology group: the causative agents do not match either of the first 3 groups, AP is induced by e.g.: ERCP (post-ERCP pancreatitis), virus infection, trauma, medicine (drug induced pancreatitis), congenital anatomical malformation, cystic fibrosis, genetics, gluten sensitive enteropathy etc.

The criteria for inclusion in the study for **control groups (B, C and D) in general**: (1) patients above 18 years; (2) absence of AP at present as well as in the medical history; (3) signed written informed consent form.

According to the etiology of the case groups: (B1) in alcohol group: patients consuming >5 drinks per day or >35 drinks per week for both sexes [= 8.75 units per day; 61.25 units per week] shall be included. Please note that 1 unit of alcohol = 10 mls or 8gr of pure (100%) alcohol [31]; **(B2)** in gallstone group: presence of gallstone (not sludge); **(B3)** in hypertrigliceridaemia group: triglyceride level over 11 mmol/l [32]; The criteria for inclusion in the study for **hospital-based control group (C)**: patients are hospitalized for other than internal medicine associated disease, such as hospital admissions in Traumatology or Ophthalmic Department. The criterion for inclusion in the study for **population based control group (D)**: not hospitalized general population.

Exclusion criteria: the criteria for exclusion in all groups: (1) patients do not have reliable information or data; (2) patients may not adhere; (3) unclear etiology.

Withdrawal of a subject from the study: According to the ethical regulations individuals are allowed to leave the study at any time without any negative consequences. Patients in the case group will be recruited during their hospital stay. Individuals for the control group are either spread among different units, or not hospitalized at all. In the study the participants in the case and in the control groups will be matched individually and continuously by gender, age and residence. Age, sex will be matched precisely in each case, location of residence will be considered by the range of population. The length of the data collection is 6 years and the data analysis takes another half a year.

Data collection and follow-up: Each participant (3900) if meets the inclusion criteria and signs the informed consent form, will be questioned by a clinical research administrator/study nurse who is fully trained before how to fill properly the questionnaires A-F and P. Since trained clinical research administrators will collect information, missing data will be unlikely. *The schedule of enrolment and assessments will be carried out according to the SPIRIT Guideline* (Supplementary figure 1).

In **Form A (A1 & A2)** we will collect general information about personal details, current status. The subjective social status will be evaluated with the SES ladder (MacArthur Scale of Subjective Social Status, http://www.macses.ucsf.edu). It is a widespread instrument in large epidemiological European and US studies and found to be significantly associated with health status, independently of objective socioeconomic indicators [33]. (Table 1)

TABLE 1 shows the title and source of the 7 questionnaires willing to use for data collection in LIFESPAN study.

Form	TITLE	SOURCE
Form A (A1 & A2)	PERSONAL DETAILS, PHYSICAL AND SOCIOECONOMIC STATUS	National Health and Nutrition Examination Survey (NHANES 2015-16); American Community Survey (ACS); The MacArthur Scale of Subjective Social Status
Form B (B1 & B2)	DETAILS FROM THE MEDICAL HISTORY	Acute Pancreatitis Questionnaire (Registry for Pancreatic Patients by Hungarian Pancreatic Study Group)
Form C (C1 & C2)	DIETARY HABITS	Diet History Questionnaire, Version 2.0. National Institutes of Health, Epidemiology and Genomics Research Program, National Cancer Institute. 2010.
Form D (D1 & D2)	PHYSICAL ACTIVITY	International Physical Activity Questionnaire (IPAQ) (long, usual week version)
Form E (E1 & E2)	STRESS	Percieved Stress Scale (10-item version)
Form F (F1 & F2)	SLEEP QUALITY	Pittsburgh Sleep Quality Index
Form P	CHARACTERISTIC OF ACUTE PANCREATITIS (ONLY FOR CASE GROUP)	Acute Pancreatitis Questionnaire (see above)

In **Form B (B1 & B2)**, we will collect information about patients‘ medical history based on Acute Pancreatitis Questionnaire of the registry for pancreatic patients operated by the Hungarian Pancreatic Study Group [34]. This online registry was established for recording data of patients with pancreatic diseases in 2012 (www.tm-centre.org), including details on smoking, alcohol consumption, other risk factors, medical history and the course and outcome of the disease. (Table 1)

In **Form C (C1 & C2),** we will collect data about participants’ dietary habits. Food Frequency Questionnaires (FFQs) are commonly used in epidemiological studies to assess the dietary intake of large populations. Their popularity derives from ease of administration, ability to assess dietary intake over a defined period of time and low costs [35]. The DHQII and Diet*Calc Analysis Software is a valid tool to measure dietary habits [36-38] and free to use. It is a very detailed quantitative FFQ with the most general foods and drinks. (Table 1)

In **Form D (D1 & D2)**, we will measure the participants' physical activity (PA) level with a frequently used epidemiology questionnaire namely the International Physical Activity Questionnaire [39]. We will use the long, usual week version (27-item) in the general part of our PA questionnaire. It contents details about the participants' vigorous PA, moderate PA, walking and sitting habits. (Table 1)

In **Form E (E1 & E2)**, we will evaluate the participants' chronic stress level with the Perceived Stress Scale [40]. It is the most widely used psychological instrument for the measuring of chronic stress effect [41-43]. We chose the 10-item version which has high validity and reliability. The time range in the general part is different from the original questionnaire (last year vs. last month). (Table 1)

In **Form F (F1 & F2)** we will collect data about participants' sleeping habits. We will apply the widely used Pittsburgh Sleep Quality Index, which evaluates the participants' sleeping quality [44]. We skip the 10th question about bed partner or roommate, because the bed partner will not be at the interview probably and this question does not count in the evaluation. The time range in the general part is also different from the original questionnaire (last year vs. last month). (Table 1)

In **Form P** we will collect data about patients' acute pancreatitis using the appropriate questions of Acute Pancreatitis Questionnaire (see Form B). (Table 1)

Electronic CRFs will be developed and will be available on www.tm-centre.org.

Patient and Public Involvement: 10 individuals were involved in the testing procedure of the study in order to optimize the feasibility.

ENDPOINTS

Endpoints will be provided by each question of the questionnaires.

Form A: Age, race, location, body weight, body height, BMI, waist circumference, education, occupation, income, subjective social status.

TABLE 2 shows the outputs, values, units and description of the Diet History Questionnaire II, the International Physical Activity Questionnaire, the Perceived Stress Scale (PSS) and the Pittsburgh Sleep Quality Index (PSQI).

Questionnaire	Outputs	Values	Unit	Description
Eating habits: Diet History Questionnaire II (DHQII) past year, with portion size	176 nutrients, dietary constituents, and food groups	varied	varied: • mcg, • mg, • g, • kcal, • IU, etc.	Food groups: • Carbohydrate constituents • Macronutrients & energy • Fats, fatty acids, & cholesterol • Protein Constituents • Vitamins • Minerals • Carotenoids and Tocopherols • Dietary Constituents from Supplements • Other • Food Pyramid Equivalents

	HEI (Healthy Eating Index-2010)	0-100	point	Good: 80-100. Needs Improvement: 51-80. Poor: 0-51.
Physical activity: International Physical Activity Questionnaire (IPAQ) long, last year version	Total walking activity	0-	MET-minutes/week OR Kcal/week	
	Total moderate activity	0-	MET-minutes/week OR Kcal/week	
	Total vigorous activity	0-	MET-minutes/week OR Kcal/week	
	Total physical activity	0-	MET-minutes/week OR Kcal/week	
	Sedentary activity	0-	hour and min / day	
	Level of physical activity	Low Moderate High	N/A	Detailed description in the text above
Stress: Percieved Stress Scale (PSS) 10-item version	TOTAL GENERAL PSS SCORE	0-40	point	Low perceived stress: 0-13. Moderate perceived stress: 14-26. High perceived stress: 27-40.
Sleep: Pittsburgh Sleep Quality Index (PSQI)	Component 1: Subjective sleep quality	0-3	point	0-good, 3-bad
	Component 2: Sleep latency	0-3	point	0-good, 3-bad
	Component 3: Sleep duration	0-3	point	0-good, 3-bad
	Component 4: Habitual sleep efficiency	0-3	point	0-good, 3-bad
	Component 5: Sleep disturbances	0-3	point	0-good, 3-bad
	Component 6: Use of sleeping medication	0-3	point	0-good, 3-bad
	Component 7: Daytime dysfunction	0-3	point	0-good, 3-bad
	GLOBAL PSQI SCORE (GENERAL)	0-21	point	Good sleep quality : 0-5. Poor sleep quality: 5-21.

Form B: Alcohol consumption (frequency, amount), smoking (frequency, amount), drug abuse (frequency, amount), diabetes mellitus (type), lipid metabolism disorder (type), any disease of the pancreas, pancreas, disorders in family history, congenital anatomical malformation of the pancreas, other illnesses, medications, diet.

Form C: 176 nutrients, dietary constituents and food groups, Carbohydrate constituents, Macronutrients & energy, Fats, fatty acids, & cholesterol, Protein Constituents, Vitamins, Minerals, Carotenoids and Tocopherols, Dietary Constituents from Supplements, Other, Food Pyramid Equivalents, Healthy Eating Index *(HEI-2010) ((0-100): Good: >80, Needs improvement: 51-80, Poor: <51)*
(https://www.cnpp.usda.gov/sites/default/files/healthy_eating_index/HEI89-90report.pdf) (Table 2)

Form D: Continuous Scores (MET-minutes/week), Total physical activity (consists of: Total Walking activity (MET-minutes/week), Total Moderate activity (MET-minutes/week), Total Vigorous activity (MET-minutes/week), Average Sitting (min/day)), Categorical Score *(level of PA: Low-This is the lowest level of physical activity. Those individuals who do not meet criteria for Categories 2 or 3 are considered to have a 'low' physical activity level, Moderate: 3 or more days of vigorous-intensity activity of at least 20 minutes per day OR 5 or more days of moderate-intensity activity and/or walking of at least 30 minutes per day OR 5 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum Total physical activity of at least 600 MET-minutes/week. High: vigorous-intensity activity on at least 3 days achieving a minimum Total physical activity of at least 1500 MET-minutes/week OR 7 or more days of any combination of walking, moderate-intensity or vigorous-intensity activities achieving a minimum Total physical activity of at least 3000 MET-minutes/week*)
(https://sites.google.com/site/theipaq/scoring-protocol) (Table 2)

Form E: Total PSS Score (0-40) (*Categories: Low perceived stress: Scores ranging from 0-13, Moderate perceived stress: Scores ranging from 14-26, High perceived stress: Scores ranging from 27-40.)*
(https://das.nh.gov/wellness/Docs/Percieved%20Stress%20Scale.pdf) (Table 2)

Form F: Global PSQI Score (0-21), *(which consists of Subjective sleep quality (0-3): Sleep latency (0-3), Sleep duration (0-3), Habitual sleep efficiency (0-3), Sleep disturbances (0-3), Use of sleeping medication (0-3), Daytime dysfunction (0-3))*, Categories (empirically derived cutoff score*): Score < 5: Good sleepers, Score >5: Poor sleepers*
(http://uacc.arizona.edu/sites/default/files/psqi_sleep_questionnaire_1_pg.pdf) (Table 2)

Form P: Mortality, Severity *(mild, moderate, severe*), Complications (*pancreatic, systemic*).

Statistical analysis

Variables: All variables will be identified according to the outcomes mentioned in section 'Endpoints'. They are categorical, continuous and scaled variables. See below:

Form A: Analysis of the continuous and categorical values
Form B: Analysis of the continuous and categorical values
Form C: The Diet*Calc Analysis Program can be evaluated the questionnaire data
(https://epi.grants.cancer.gov/dhq2/dietcalc)
Form D: We will use the official scoring protocol to evaluate the survey
(https://sites.google.com/site/theipaq/scoring-protocol)
Form E: The original article contents the evaluation method [40]

Form F: The scoring instruction is described in the original article [44]

Form P: Analysis of the continuous and categorical values [34]

Bias: Deriving from the study design a possible recall bias could occur (patients who have the outcome (cases) are likely to remember the details of negative exposures more clearly than controls). It can be supposed, that it appears randomly, non-differential in the study-groups.

Sample size: The sample size was originally calculated based on the end scores of the four questionnaires (HEI-2010, IPAQ, PSS, PSQI). All calculations were made using a 5% significance level, a power of 80%, a 40% difference between the group means and equal sample size ratio (age, sex and socio-economic-matched control groups). We used the online sample size calculator: http://clincalc.com/Stats/SampleSize.aspx

We achieved the required information e.g. mean and standard deviation from articles (references found after each calculated sample size) or from online databases (HEI scores). In case of two questionnaires (PSQI and PSS) we made the calculation based also on Hungarian and not Hungarian data sources. The required sample sizes for the questionnaires per groups are the following:

- HEI-2010 Score: 195 (National Health and Nutrition Examination Survey, 2011-2012, results in: https://www.cnpp.usda.gov/healthyeatingindex);
- IPAQ Total activity: 155 [45];
- PSS Score: 217 and 13 [46], 23 [47];
- PSQI Score: 231 [48] 187 [49].

Statistical methods: All the collected variables 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 conditional 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 by for age: +/- 5 years, gender: exact, location of residence: situated in the same country and +/- 15% of the population.

In order to identify possible patients' outcomes (e.g. severity of AP or mortality), the end scores of the questionnaires (DHQII, IPAQ, PSS, PSQI), the variables from the FormA and B will be used in hierarchical cluster analysis using Ward's method and the squared Euclidean distance.

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

DISCUSSION

This is the first study in which the relevant patient reported retrospective data will be collected in a prospective manner, and the associations between socio-economic factors, dietary habits, physical activity, chronic stress, sleep quality and acute pancreatitis will be investigated. We hope to find both negative and positive associations which will allow for the first time to suggest lifestyle modifications for patients discharged from the hospitals after AP or for those who wish to reduce their risk for AP.

ACKNOWLEDGEMENTS

We would like to say thank you for all the interviewed individuals for providing useful information on personal experience concerning acute pancreatitis, inquiring about lifestyle elements, hereby contributing to designing the study and constructing the questionnaires.

Centres: The study will start with the following centres (University of Szeged, University of Pécs, University of Debrecen, Szent-György Fejér County Teaching Hospital), however, other centres are welcome to participate in the LIFESPAN as an open label study. Completion of the LETTER OF INTENT form will be mandatory for registering the participation of each institution. HPSG will acknowledge receipt of the LETTER OF INTENT form and will contact centres providing them with additional study information.

Each centre must provide the same number of individuals for all the relevant four groups (1 case and 3 controls).

Publication policy: Centres providing more than 40 individuals can provide an author to the authors list. Every additional 20 individuals will give the opportunity to nominate an author.

Dissemination policy: We plan to communicate the results to several members of the healthcare system including medical doctors, dietitians, nurses, patients etc. We plan to publish the results in a peer-reviewed high quality journal for professionals. In addition, we also plan to publish it for lay readers in order to maximize the dissemination and benefits of this study.

Feasibility and earlier experience: The feasibility will be examined by a pilot enrolment of 20 individuals in each group.

Safety: This is a non-interventional observational clinical study. Since no unknown drugs/therapy are used in the study no adverse and serious adverse events are expected/interpretable during the study.

Funding: Center costs (IT, biostatistics, study organization, etc.) are covered by the University of Pécs Medical School, Momentum Grant of the Hungarian Academy of Sciences (LP2014-10/2014); and Economic Development and Innovation Operative Programme Grant and Highly Cited Publication Grant of the National Research, Development and Innovation Office (GINOP-2.3.2-15-2016-00048 Stay Alive, KH-125678 and EFOP 3.6.2-16-2017-00006 Live Longer), and Translational Medicine Foundation. The study was designed by the SC and ITAB. DMC and SP has not been involved in the design of the study, moreover the SP will have no access to database.

Since no additional treatment is necessary for the study, the general healthcare costs are covered by the National Healthcare System (University of Pécs Medical School).

This study was designed with help of the Centre for Translational Medicine at the University of Pécs. This center is committed to improve patients' life with research activities like registries, observational and interventional study organizations (https://tm-centre.org).

For joining centres, the additional local costs have to be covered by the centre. This research received no specific grant from any funding agency in the public, commercial or not-for-profit organizations.

Authors' contributions: BK, ED, ZGy, JG, NF, MP, FI, ÁV and PH designed the study. As a member of the ITAB MML, JN, MST and OHP gave advices and will continuously monitor the progress of the study. ZsV, KM, PH, BE, DP, EF, TJ, LG, DE, DVV, SK and IT drafted the manuscript, and ASz, JA, NZ edited the text, ASz, JA, NZ adapted the tables. All authors read and approved the final manuscript.

Competing interests statement: All authors declare any competing interest.

ETHICS AND DISSEMINATION

The study has been registered at the ISRCTN (25940508) and received the relevant ethical approval from the Scientific and Research Ethics Committee of the Hungarian Medical Research Council under the reference number of 54175-2/2018/EKU. After obtaining the final conclusions we will publish the data to the medical community and will also disseminate our results via open access.

Protocol Version: V1.0 08.01.2019.
Start of the patient recruitment: In April, 2019.
Planned finish of the study: 30 November 2023

Abbreviations:
AP- acute pancreatitis
CRF – case report form
DMC- Data Monitoring Committee
FFQs - Food Frequency Questionnaires
HEI - Healthy Eating Index
ITAB - International Translational Advisory Board
OR - Odds Ratio
PA - physical activity
PSS - Perceived Stress Scale
PSQI - Pittsburgh Sleep Quality Index
SC – Steering Comittee
SES - socioeconomic status
RR - Relative Risk
RRR - RR Reductions

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Figure legends:

TABLE 1 shows the title and source of the 7 questionnaires willing to use for data collection in LIFESPAN study.

TABLE 2 shows the outputs, values, units and description of the Diet History Questionnaire II, the International Physical Activity Questionnaire, the Perceived Stress Scale (PSS) and the Pittsburgh Sleep Quality Index (PSQI).

SUPPLEMENTUM FIGURE 1. The figure shows the schedule of enrolment and assessments according to the SPIRIT Guideline.

	STUDY PERIOD		
	Enrolment	Post enrolment	Close-out
TIMEPOINT	*0*	*0*	t_x
ENROLMENT:			
Eligibility screen	X		
Informed consent	X		
QUESTIONNAIRES:		X	
Questionnaire A		X	
Questionnaire B		X	
Questionnaire C		X	
Questionnaire D		X	
Questionnaire E		X	
Questionnaire F		X	
Questionnaire P		X	
DATA ANALYSIS:			X

45x39mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3,13
	2b	All items from the World Health Organization Trial Registration Data Set	–
Protocol version	3	Date and version identifier	13
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 12
	5b	Name and contact information for the trial sponsor	7
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	7, 12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	6-7, 12

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-6
	6b	Explanation for choice of comparators	3, 7
Objectives	7	Specific objectives or hypotheses	3-4, 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3-4, 6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	-
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	-
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	-
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	–
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	-
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig 1.

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	-
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	-
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	-
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	-
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	–
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-8

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7-8
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	7
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	-
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3,13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	7
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	7-8,12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12

	31b	Authorship eligibility guidelines and any intended use of professional writers	12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	attached
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.