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Impact of red and processed meat and fibre intake on risk of chronic inflammatory diseases: a prospective cohort study on prognostic factors using the Danish "Diet, Cancer and Health" cohort (PROCID-DCH): Protocol for a prospective cohort study of prognostic factors and disease risk.

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Impact of red and processed meat and fibre intake on risk of chronic inflammatory diseases: a prospective cohort study on prognostic factors using the Danish "Diet, Cancer and Health" cohort (PROCID-DCH):

Protocol for a prospective cohort study of prognostic factors and disease risk

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ABSTRACT

Introduction: Chronic inflammatory diseases, CIDs, (Crohn's disease, ulcerative colitis, psoriasis, psoriatic arthritis, rheumatoid arthritis, axial spondyloarthritis, or multiple sclerosis) are diseases of the immune system that have some shared genetic and environmental predisposing factors, but still few studies have investigated the effects of lifestyle on disease risk of several CIDs. The primary aim of this prospective cohort study is to investigate the impact of fibre and red and processed meat on risk of CID, with the perspective that results of this study can contribute in supporting future diet recommendations for effective personalized prevention.

***Methods and analysis*:** The study will use data from 57,053 persons from the prospective Danish cohort study "Diet, Cancer and Health" (DCH) together with National Health Registry data. The follow up period is from December 1993 to May 2018. Questionnaire data on diet and lifestyle were collected at the DCH study entry. The outcome CID is defined as having a diagnosis of one of the CIDs registered in the National Patient Registry (NPR) or, for multiple sclerosis, in the Danish Multiple Sclerosis Registry (DMSR) during follow-up AND being treated with a drug used for the specific disease. The major outcome of the analyses will be to detect variability in risk of any CID and, if power allows, disease risk of each CID diagnosis between persons with different fibre and red and processed meat intake. The outcome will be adjusted for age, sex, BMI, physical activity, alcohol, fermented dairy products, education, smoking status, hormone replacement therapy, and comorbidity.

Trial Registration details: ClinicalTrials.gov identifier: NCT03456206

Keywords: lifestyle; diet; chronic inflammatory diseases; disease risk; fibre; red meat

Ethics and dissemination: The study is approved by the Danish Data Protection Agency (2012-58-0018). The core study is an open register-based cohort study. The study does not need approval from the Ethics committee or Institutional Review Board by Danish law. Study findings will be disseminated through peer-reviewed journals, patient associations and presentations at international conferences.

Strengths and limitations of this study

Strengths:

- The linkage to Danish national registers will ensure almost complete follow-up of the study population, as the Danish registries are considered of high validity and completeness
- The big sample size will enable a sufficient power of the total CID disease group even when taking loss to emigration and competing risk of death into account
- The study includes several chronic inflammatory diseases

Limitations:

- Risk of low specificity of the diagnostic codes and treatment codes as criteria for identifying CID cases
- Prospective studies including younger age groups are necessary to reveal the generalizability of the results

INTRODUCTION

The CIDs can be considered as systemic diseases which primarily affect one organ such as the intestine (inflammatory bowel disease: Crohn's disease (CD) and colitis ulcerosa (UC)), skin (psoriasis (PsO)), joints (rheumatoid arthritis (RA)/axial spondyloarthritis (AxSpA)/psoriatic arthritis (PsA)), or the brain (multiple sclerosis (MS)).

The peak of disease-onset is in the adult phase of life. The diseases have a large impact on the patients and their families' quality of life due to lack of causative treatment, and on the society due to absence from work and on health care economy due to lack of preventative measures.[1-7] The CIDs have a high prevalence, with inflammatory bowel diseases and multiple sclerosis affecting respectively 0.5% and 0.1% of the population in the Western world.[8-12] Studies from across the world have reported prevalence estimates of rheumatoid arthritis and psoriasis ranging from 0.3%–1.0% and 0.7%-3.2% respectively,[2 8 13-15] while the prevalence of psoriatic arthritis is estimated as 0.04-0.25% across countries.[14 16]

The CIDs have some shared genetic[17-21] and environmental (e.g. smoking, gut microbiome) predisposing factors, and causes of the high incidence and prevalence point to such environmental factors.[8 22-37] Therefore, further research of the associations between potential modifiable environmental risk factors and risk of CID is important.

Evidence-based research

A study of inflammatory polyarthritis (including RA) has demonstrated that a high level of red meat consumption is a risk factor for the development of inflammatory polyarthritis.[36 37] A high fibre intake has been associated with low risk of IBD.[24] Furthermore, several studies of the impact of dietary factors on multiple sclerosis point towards an impact of meat preservation such as

smoking or addition of nitrites.[38-41] Studies have also suggested other lifestyle factors such as physical activity,[42-44] BMI,[1 44-46] smoking status,[47-53] and other dietary factors such as alcohol,[1 54-56] dairy products,[35] and glycaemic index[57 58] to be associated with CIDs. Furthermore, studies have shown that the interactions among the microbiota, female sexual hormones, and immunity are associated with the development of autoimmune diseases.[59]

There are many potential mechanisms whereby environment such as diet may affect the immune system (Figure 1). Recently, we provided the hypothesis that intake of high fibre/low red and processed meat may protect against CID.[58] Figure 1 presents a model, proposed in a previous study,[8] whereby a diet high in meat and low in fibres may impact inflammation.

FIGURE 1

Aims and hypotheses

Based on previous evidence, we set out to prospectively identify dietary factors that have an impact on disease risk of CID.

The primary aim of this prospective cohort study is to investigate the impact of fibre and red and processed meat on disease risk outcomes of CID in the DCH cohort. The overall perspectives are that results from this study will be contributing in supporting future diet recommendations for effective personalized prevention of individuals identified to be at high risk.

The main hypothesis is that "the risk of CID will be significantly lower among those with a high fibre/low red and processed meat intake compared to those with a low fibre/high red and processed meat intake." The hypothesis is illustrated in figure 1.

Based on previous research on a shared etiology in CIDs we hypothesize that "the suggested association between high fibre/low red and processed meat intake and risk of developing CID is applicable for each of the CID-diagnoses."

The secondary aim of this prospective cohort study is to investigate whether risk of CID in the DCH cohort is affected by other dietary and lifestyle differences, and therefore to adjust for the potential confounders: age, sex, BMI, physical activity, alcohol intake, intake of fermented dairy products, education after basic school, hormone replacement therapy (HRT), smoking status, and comorbidity.

METHODS AND ANALYSES

Design and setting

This study is an observational study using prospective registry follow up data. We will use the Danish cohort "Diet, Cancer and Health" (DCH), and the follow-up period will be from the date of entry to the DCH cohort (between December 1993 and May 1997) until May 2018.

The DCH Study is an ongoing Danish cohort study designed to investigate the relation between diet, lifestyle, and disease risk.[60] The cohort consists of 57,053 persons, recruited between December 1993 and May 1997. All the subjects (50 to 64 years of age) gave detailed information on diet (food frequency questionnaire) and other lifestyle data. Questionnaire data on diet and lifestyle were collected at study entry.[60] Data from the DCH cohort will be combined with Danish Health registries (the National Patient Registry (NPR), the Danish Civil Registration System (CRS), The Danish National Prescription Registry (DNPR) and the Danish Multiple Sclerosis Registry (DMSR).

Participant characteristics and eligibility criteria

Criteria for inclusion: The population to be studied include participants in the DCH cohort.[60] In short, the criteria for invitation to the DCH cohort were: age between 50 and 64, born in Denmark, and no diagnosis of cancer registered in the Danish Cancer Registry. All persons fulfilling these criteria and living in the areas of Copenhagen and Aarhus were invited.[60]

Criteria for exclusion: Participants registered in NPR with a CID primary diagnosis from a department with relevant area of specialization in the period between 1977 and entry to the DCH cohort will be excluded regardless of whether the person receive medical treatment for CID or not.

The Danish health Registries

We will extract data from the four national registries in those time periods that is possible for each registry; NPR from 1977-2018, CRS from 1977-2018, DNPR from 1994-2018, and DMSR from 1977-2018. An overview of the information obtained from the different registries is presented in **table 1**.

Table 1. Overview of registry information

Variable	Definition	Registry	Time period
CPR	Civil Registration Number	CRS**	1977-2018
ICD-10 code*	International Classification of Diseases	NPR**	1994-2018
ICD-8 code*	International Classification of Diseases	NPR	1977-1993
Medication (ATC code)	Anatomical Therapeutic Chemical classification (ATC) code	DNPR**	1994-2018
Treatment code	Medical treatment classification code	NPR	1994-2018
Department with relevant area of specialization	Neurological department of MS, medical department of IBD, department of rheumatology, department of dermatology)	NPR	1977-2018
ICD-8 and ICD-10 codes for MS	Diagnostic codes for multiple sclerosis	DMSR**	1977-2018

*ICD-8 and ICD-10 codes in the period 1977-1993 will be used to exclude participants with a CID diagnosis before entry to the DCH study
**The Danish Civil Registration System (CRS); National Patient Registry (NPR); Danish National Prescription Registry (DNPR); Danish Multiple Sclerosis Registry (DMSR).

The NPR will be used to identify patients with CID during follow-up and, in addition, patients with CID before study entry. The NPR contains data on all patients admitted to Danish hospitals since 1977. The register covers both inpatient and outpatient records and indicates the main medical reason for diagnostic procedures or treatment (since 1971 according to the eight version and 1994 according to the tenth version of the International Classification of Diseases (ICD-8 and ICD-10)). ICD-8 codes will be used to identify cases diagnosed before entry to the DCH cohort study. Information on the departments with the relevant areas of specialization will be obtained from the NPR and used to identify cases as described in the data analysis section.

The DMSR will be used to identify patients with multiple sclerosis during follow-up, and in addition, patients with multiple sclerosis before study entry.

The DNPR will be used to obtain information on the medical treatment according to the Anatomical Therapeutic Chemical classification (ATC) code, as it is expected that the patients have medication in relation to the diseases.

From the CRS we will extract follow-up information on civil status, death and immigration.

Outcome and exposures

Outcome: In this study, the outcome CID is one of the following diseases; the inflammatory bowel diseases Crohn's disease and ulcerative colitis, psoriasis, psoriatic arthritis, rheumatoid arthritis, axial spondyloarthritis, or multiple sclerosis. This outcome is defined by fulfilling the following two criteria: 1) having the CID disease in NPR (except multiple sclerosis) from a department with relevant area of specialization, or in the DMSR (multiple sclerosis) during the follow-up period AND 2) being treated (irrespective of the number of treatments) with a drug

used for the specific disease, and the treatment being registered either in the DNPR or from a department with relevant area of specialization (criterion 2 will not apply to multiple sclerosis). The outcome CIDs with the associated ICD-8 and ICD-10 codes and the ATC codes in DNPR and treatment codes in the NPR are specified in **table 2**. The date and year of the diagnosis is defined as the date and year of the diagnosis in NPR and/or DMSR.

Table 2. Specification of outcome CIDs with associated diagnostic- and treatment codes

CID	Diagnostic code (NPR)		Medical treatment (DNPR and NPR)	
	ICD-8*	ICD-10	ATC code (DNPR)***	Treatment code (NPR)***
Crohn's disease	563.01, 563.02	K50.0-50.9	L04AA12 L04AB02 L04AA17 L04AB04 L04AB06 L04AB05 L04AA23 L04AA33 A07E	BOHJ18A1 BOHJ18A3 BOHJ18A4 BOHJ18A5 BOHJ26 BOHJ19H4
Ulcerative colitis	563.09, 563.19	K51.0-51.9		
Rheumatoid arthritis	712.19, 712.29, 712.39, 712.59	M05.9, M06.0, M06.9	L04AX01 L04AX03 L04AA13 P01BA02	BWHA115 BLHM2 BWHB83 BOHJ18
Axial spondyloarthritis	712.49	M45.9, M46.1, M46.8+M02.9, M46.8+M07.4, M46.8+M07.5, M46.9		
Psoriatic arthritis	696.09	M09.0, M07.3, M46.8+M07.2		
Psoriasis	696.10, 696.19	L40.0-40.9	D05AX02 D05BB02 D05B L04AA32 L04AB01-02 L04AB04 L04AC05 L04AC10 L04AC13 L04AD01 L04AX03	BNHC0 BOHJ18A1-3 BOHJ18B3 BOHJ18B5
Multiple sclerosis	734.0-9**	G35.9**	Not used	Not used

*ICD-8 codes will be used to exclude participants with a CID diagnosis code before entry to the DCH study.
**ICD-8 and ICD-10 codes for multiple sclerosis will be extracted from the Danish Multiple Sclerosis Registry
***These ATC and treatment codes for CD and UC are used by the Danish National Registry for Biological Therapy in Inflammatory Bowel Disease (BIO-IBD)[61]

Exposure and possible confounders: Information on exposure in this study is defined as high fibre intake and high red and processed meat intake, and also other dietary and lifestyle factors.

In the DCH study, information on diet and lifestyle exposure were collected at enrolment using questionnaires as has been described in details elsewhere.[60] In short, the food-frequency questionnaire (FFQ), diet consumption was assessed in 12 categories of predefined responses, ranking from "never" to "eight times or more per day over the past 12 months". The daily intake was then calculated by FoodCalc.[60] Both intake of dietary fibre and red meat and processed meat were measured as continues variable in g/day. The initially collected data on diet and lifestyle exposure of the DCH cohort is used as the baseline information on exposure in this study.

Information on dietary and lifestyle exposures used for this study is specified in **table 3**. Fibres, red and processed meat are defined based on the classification of the food items in the DCH study,[60] and with inspiration from other studies using dietary data from the DCH cohort.[62-64] Red meat is defined as fresh and minced meat (unprocessed) from beef, veal, pork, and lamb and excluding poultry, fish, or eggs. Red processed meat consists of red meat items that have undergone processing such as smoking, salting or curing. This includes various kinds of sausages, salami, smoked or cooked ham, other cold cuts, bacon and liver pate. Poultry includes chicken and turkey both unprocessed and processed, such as various cold cuts of chicken and turkey. Fish includes all unprocessed and processed fish as well as shellfish. Total meat is defined as the total of red (unprocessed) meat, red processed meat together with poultry and fish.[62-64] Fibres are defined as fibres from fibrous food items from the FFQ.

Information on possible confounders will also be obtained from the questionnaire data at enrolment in relation to sex, age, education after basic school, BMI, physical activity, HRT, comorbidity, smoking status, alcohol intake, and also intake of fermented dairy products. The Charlsons comorbidity index[65] will be used to classify comorbidity among the study participants. ICD-8 and ICD-10 codes from the NPR will be used to calculate the Charlson score, using the updated Charlson comorbidity index.[66]

Table 3. Specification of exposures and overall food groups and lifestyle factors

Variable	Definition (unit)
Diet	
Total energy intake	kJ/day
Total meat	g/day
Red meat	g/day
Red processed meat	g/day
Fish (fresh and processed)	g/day
Poultry (fresh and processed)	g/day
Total dietary fiber intake	g/day
Legumes	g/day
Vegetables	g/day
Fruits	g/day
Cereals	g/day
Dairy products	g/day
Lifestyle factors	
Alcohol intake	units of alcohol/week*
Smoking status	yes/no
Former smoker	
Current smoker	
Never smoker	
MET-score (physical activity)	hours/week
BMI	kg/cm^2
Highest education after basic school	yes/no
Vocational education	
Higher education 1-2 years	

Higher education 3-4 years	
Higher education > 4 years	
Co-morbidity (Charlson comorbidity index)	index score
Hormone replacement therapy (HRT)	yes/no

*One unit of alcohol is defined as 12 grams of pure alcohol

Primary exposure variable: The primary exposure variables will be analyzed in tertiles. Based on the hypothesis that the risk of CID will be lower among those with a high fibre/low red and processed meat intake compared to those with a low fibre/high red and processed meat intake, it is expected that:

- The upper tertile of the sample (33.3% of the total sample), based on the ratio of fibre/meat intake, is associated with lower risk of CID.

- The lower tertile of the sample (33.3% of the total sample) with respect to intake of red meat and processed meat and the upper tertile of the sample (33.3% of the total sample) with respect to intake of dietary fibres are independently associated with lower risk of CID, and a potential interaction between them may further lower the risk of CID.

Other (exploratory) exposure variables:

- Other dietary and lifestyle factors independently or combined will be analysed, and are presented in table 3.

Statistical analysis plan

The data obtained from this study will be used to investigate our ability to predict risk of CID, based on whether a diet high in fibre and low in red and processed meat is a predictive factor. Furthermore, data on other lifestyle factors and dietary factors obtained from the FFQ will

be used to investigate whether these factors potentially could give risen to confounding of the association between fibre/meat intake and risk of CID.

Descriptive analyses for categorical variables will be presented as frequencies, and differences between CID cases and non-cases will be evaluated by Chi-square test. Continuous variables will be tabulated as medians (with quartiles, Q1 and Q3) and nonparametric tests on the equality of medians will be used to test for differences between groups. P-values below 0.05 will be considered statistically significant. Negative binomial regression will be applied to calculate incidence rates per 1,000 patient years and incidence rate ratios (IRR) between exposures. To investigate the risk of and time to CID-diagnosis the Fine-Gray competing risk regression model will be applied, and thus competing risk of death will be taken into account while handling emigration as censoring and reporting cumulative incidences and sub-hazard ratios (SHR) and the corresponding p-values for CID associated with specified food substitutions. Regressions will be carried out as both crude regression, only including the exposure, and adjusted for age, sex, lifestyle factors and selected comorbidities. Analyses will be conducted using Stata version 15.[67]

If power of each of the disease groups allows, there will be conducted sub-analyses on each of the CID diagnoses separately with the overall aim of testing if the hypothesized association between diet factors and development of CID is applicable for all the CIDs or if some of the CIDs deviate from this association.

Information on the departments with the relevant areas of specialization will be used to evaluate the robustnes of the diagnosis codes from the NPR and to identify the cases as we will only accept cases that have a diagnosis from a relevant department (e.g. department for rhematology, medical department for inflammatory bowel disease). The Danish Multiple Sclerosis

registry is highly validated,[68] and data from the registry will be used to ensure complete follow-up of valid diagnoses of multiple sclerosis.

Power considerations: The age-adjusted (age between 45-69) incidences per 100,000 years of the CIDs in Denmark are 10.1-10.6 for Crohn's disease[69]; 27.5-32.7 for ulcerative colitis[69]; 200-225 for psoriasis[15]; 28-35 for psoriatic arthritis[16]; 4.4-7.5 for multiple sclerosis[70-74]; and 28.1-57.6 for rheumatoid arthritis[75 76]. The incidence of axSpA is low in this age group in Denmark,[77 78] hence the incidence of axSpA in the study population of this study will be considerably low. In the cohort of approximately 57,000 participants and a follow-up period of approximately 20 years, these incidences correspond to an estimate of approximately 2,000 cases of CID in the cohort. To estimate the power of the study we therefore expect approximately 2,000 cases of CID, i.e. an incidence of about 3% and about one third of the cohort in the low risk and two thirds in the high risk exposure. Assuming a fixed follow-up of 20 years and a relevant effect size of 2% CID risk in the low risk exposure compared to 3% in the high risk exposure this would require 11,667 participants to obtain a power of 0.90 in an (unadjusted) Chi-squared-test. Hence with a total cohort size of approximately 57,000, this should ensure a sufficient power even when taking loss to emigration and competing risk of death (resulting in less than 20 years follow-up for some participants) into account.

Strengths and limitations of the study

A strength of this study is that it is not limited to one disease, as it includes several chronic inflammatory diseases. Another strength is that the linkage to Danish Health registries will ensure almost complete follow-up of the study population, as the Danish Health registries are considered the internationally most comprehensive with high validity.[79-82] Furthermore, in this study, we have chosen very restrictive criteria for defining the CID cases by requiring that CID cases fulfill both

diagnostic and treatment criteria, or that the cases were registrered in the DMSR. This approach ensures that a high proportion of the identified cases really had CID. Therefore, some "real" CID cases might not have been identified, hence lowering the sensitivity.[68 83 84]

A possible limitation of this study could have been the validity of the diagnostic codes from the NPR and the treatment codes from the DNPR as criteria for identifying CID cases.[68 83] But, as described in the analysis plan this potential limitation will be sought eliminated by using the information on the hospital departments, and for MS, using the DMSR for identifying MS cases.

The FFQ applied in the present study has been used in the large, European prospective cohort study "The European Prospective Investigation into Cancer and Nutrition" (EPIC),[85 86] and it has been used and evaluated in the Danish population, with results that demonstrate consistency.[87-89] However, the FFQ is not without limitations, with respect to the lack of information on portion sizes[90 91] or to underestimation and overestimation of intake of unhealthy and healthy food.[92] Any imprecision of the FFQ due to standardized portion sizes or incorrect reporting of food intake, will lead to large confidence intervals, which potentially can lead to null results.[8] On the other hand, studies suggest that specification of a standard portion size may not introduce a large error in the estimation of food and nutrient intake.[93] Furthermore, the FFQ has been validated as being appropriate for use in studies that examine relationships between diet and risk of disease.[92]

Another limitation of this study is the validity of the information on exposure as this information is collected at study entry, which potentially can be several years before any outcome appears, and measurement error in the FFQ may occur if the participants change their diet over time. Furthermore, there is a potential risk of recall bias according to the information on exposure, as this information relies on the participants ability to recall their dietary intake. In this study,

however, it is expected that dietary and lifestyle patterns among adults are relatively stable over time, based on other longitudinal studies that showed minimal temporal changes.[94 95]

The MET-score is an accepted standard measure of physical activity.[96] However, the weaknesses of the MET-score include a risk of adding random variation by applying an assumed intensity to include activities. Another weakness of the MET-score is the implicit assumption that the intensity aspect of physical activity is important for development of disease.[96]

The study population in this study is based on a cohort of middle-aged women and men living in urban areas. This could reduce the generalizability of study findings, as the proportion of CID diagnoses could be different for younger or elder persons or persons from rural areas.

The disease groups may be heterogeneous regarding dietary and lifestyle factors. This study may not capture every dietary and lifestyle difference between the disease groups, due to insufficient power of each disease group, as described in the analysis plan. Replication of the results in other well-characterized populations using prospectively sampled dietary data will minimize the risk of potential type 2 errors. Study results should preferably be replicated in cohorts in other countries and other age groups for further evaluation of the robustness of the results.

Project organisation

This registry study is a cross-disciplinary collaboration that includes clinical specialists within neurology, dermatology, rheumatology, inflammatory bowel diseases, prospective cohort study design, and clinical registries.

Perspectives

We anticipate that the PROCID-DCH study will reveal factors of importance, including whether the diet is likely to interfere with the disease risk of CID.

The perspective is that significant results from this study will be sought replicated in other cohorts such as the EPIC-IBD[85] and UK biobank[97] with high-quality prospective lifestyle data. Successful replication indicates the robustness of the findings which is an important step on the road to developing clinical tools for effective personalized prevention of individuals at high risk.

Dissemination of results to the public and scientifically

Target journals include international journals within internal medicine. In addition to the scientific reporting of results, major findings with translational implications will also be communicated to categories of both health professionals, and targeted stakeholders including public health policymakers, and to the general public through various media and news activities. Intellectual Property Rights (IPRs) to discoveries based upon the outlined research belong to the University of Southern Denmark.

Ethics

This is an open register-based cohort study. The study does not need approval from the local Ethics committee or Institutional Review Board by Danish law. The study was approved by the Danish Data Protection Agency (2012-58-0018).

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Author Contributions:

NFR, KHR and VA wrote the first draft and contributed to the further preparation and final adjustments of the protocol. All authors critically read and accepted the final submitted version.

Conflicts of Interest:

BG declares to have received research funding from Abbvie, Biogen, Pfizer. MLH declares to have received research funding from BMS, MSD, Pfizer, Biogen, Samsung, CellTrion, Lilly, Novartis. All other authors declare no conflict of interest.

FIGURE LEGEND

Figure 1. Hypothesis for effects of diet in relation to development of chronic inflammatory diseases (CID)

Diet (meat[98], fibre[98], animal fat[99], n-3[27] and n-6 polyunsaturated fatty acids, vitamin A[100] and D[101], carotenoids[102], smoking, gluten[103]) may affect the immune system[104 105] either directly or indirectly via e.g. the activity and composition of the gut microbiome.[106 107] The effect of low intake of fiber/high intake of red and processed meat is shown at left: In short, low intake of fibre (which could otherwise serve as a nutrient for the microbes) may lead to the microbial metabolism of mucus and to decrease of the intestinal mucus layer.[58 108 109] A high intake of red and processed meat (containing organic sulphur and sulphate additives) may render the mucus layer penetrable to e.g. bacteria by reducing the disulphide bonds in the mucus network.[8 106 110] Thus, microbes may reach the epithelium[8 111 112] and activate the immune system.[8 113 114] There is some support for such a mechanism in CID[8], including findings of; high amounts of sulphate-reducing bacteria in IBD patients;[8 112 115] association of high fibre intake with low risk of IBD among 170 776 participants from the prospective Nurses' Health Study I (NHSI)[8 24]; and association of high intake of red meat and total protein and risk of developing inflammatory polyarthritis in the population-based prospective cohort of 25 630 participants from the European Prospective Investigation of Cancer in Norfolk (EPIC-Norfolk).[8 36 37]

Note. Figure from "Impact of red and processed meat and fibre intake on treatment outcomes among patients with chronic inflammatory diseases: protocol for a prospective cohort study of prognostic factors and personalised medicine," by Christensen R, Heitmann BL, Andersen KW, et al., *BMJ Open* 2018;8:e018166. doi: 10.1136/bmjopen-2017-018166. Available at: http://bmjopen.bmj.com/content/8/2/e018166. Copyright 2018 by Vibeke Andersen.

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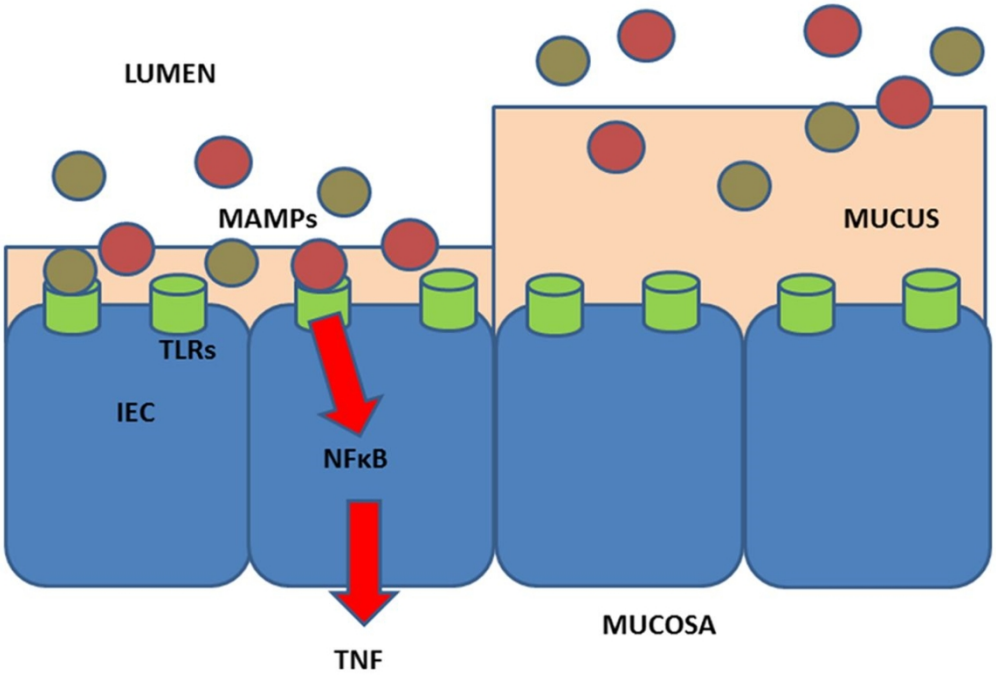

Figure 1. Hypothesis for effects of diet in relation to development of chronic inflammatory diseases (CID) "Diet (meat[98], fibre[98], animal fat[99], n-3[27] and n-6 polyunsaturated fatty acids, vitamin A[100] and D[101], carotenoids[102], smoking, gluten[103]) may affect the immune system[104 105] either directly or indirectly via e.g. the activity and composition of the gut microbiome.[106 107] The effect of low intake of fiber/high intake of red and processed meat is shown at left: In short, low intake of fibre (which could otherwise serve as a nutrient for the microbes) may lead to the microbial metabolism of mucus and to decrease of the intestinal mucus layer.[58 108 109] A high intake of red and processed meat (containing organic sulphur and sulphate additives) may render the mucus layer penetrable to e.g. bacteria by reducing the disulphide bonds in the mucus network.[8 106 110] Thus, microbes may reach the epithelium[8 111 112] and activate the immune system.[8 113 114] There is some support for such a mechanism in CID[8], including findings of; high amounts of sulphate-reducing bacteria in IBD patients;[8 112 115] association of high fibre intake with low risk of IBD among 170 776 participants from the prospective Nurses' Health Study I (NHSI)[8 24]; and association of high intake of red meat and total protein and risk of developing inflammatory polyarthritis in the population-based prospective cohort of 25 630 participants from the European Prospective Investigation of Cancer in Norfolk (EPIC-Norfolk).[8 36 37]Note. Figure from "Impact of red and processed meat and fibre intake on treatment outcomes among patients with chronic inflammatory diseases: protocol for a prospective cohort study of prognostic factors and personalised medicine," by Christensen R, Heitmann BL, Andersen KW, et al., BMJ Open 2018;8:e018166. doi: 10.1136/bmjopen-2017-018166. Available at: http://bmjopen.bmj.com/content/8/2/e018166. Copyright 2018 by Vibeke Andersen.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Impact of red meat, processed meat and fibre intake on risk of late onset chronic inflammatory diseases: a prospective cohort study on prognostic factors using the Danish "Diet, Cancer and Health" cohort (PROCID-DCH): Protocol for a prospective cohort study of prognostic factors and disease risk

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Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Dermatology, Neurology, Nutrition and metabolism, Rheumatology, Epidemiology

Keywords:	lifestyle, diet, chronic inflammatory diseases, disease risk, fibre, red meat

Abbreviated title: Impact of red meat, processed meat and fibre on risk of late onset CID

Impact of red meat, processed meat and fibre intake on risk of late onset chronic inflammatory diseases: a prospective cohort study on prognostic factors using the Danish "Diet, Cancer and Health" cohort (PROCID-DCH):

Protocol for a prospective cohort study of prognostic factors and disease risk

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ABSTRACT

Introduction: Chronic inflammatory diseases, CIDs, (Crohn's disease, ulcerative colitis, psoriasis, psoriatic arthritis, rheumatoid arthritis, and multiple sclerosis) are diseases of the immune system that have some shared genetic and environmental predisposing factors, but still few studies have investigated the effects of lifestyle on disease risk of several CIDs. The primary aim of this prospective cohort study is to investigate the impact of fibre, red meat, and processed meat on risk of late onset CID, with the perspective that results of this study can contribute in supporting future diet recommendations for effective personalized prevention.

***Methods and analysis*:** The study will use data from 57,053 persons from the prospective Danish cohort study "Diet, Cancer and Health" together with National Health Registry data. The follow-up period is from December 1993 to May 2018. Questionnaire data on diet and lifestyle were collected at entry to the "Diet, Cancer and Health" study. The outcome CID is defined as having a diagnosis of one of the CIDs registered in the National Patient Registry or, for multiple sclerosis, in the Danish Multiple Sclerosis Registry during follow-up AND being treated with a drug used for the specific disease. The major outcome of the analyses will be to detect variability in risk of late onset of any CID and, if power allows, disease risk of late onset of each CID diagnosis between persons with different fibre and red meat, and processed meat intake. The outcome will be adjusted for age, sex, BMI, physical activity, energy, alcohol, fermented dairy products, education, smoking status, hormone replacement therapy, and comorbidity.

Ethics and dissemination: The study is approved by the Danish Data Protection Agency (2012-58-0018). The core study is an open register-based cohort study. The study does not need approval

from the Ethics committee or Institutional Review Board by Danish law. Study findings will be disseminated through peer-reviewed journals, patient associations and presentations at international conferences.

Keywords: lifestyle; diet; chronic inflammatory diseases; disease risk; fibre; red meat

Strengths and limitations of this study

Strengths:

- The linkage to Danish national registers will ensure almost complete follow-up of the study population, as the Danish registries are considered of high validity and completeness
- The big sample size will enable a sufficient power of the total late onset CID disease group even when taking loss to emigration and competing risk of death into account
- The study includes several chronic inflammatory diseases

Limitations:

- Risk of low specificity of the diagnostic codes and treatment codes as criteria for identifying late onset CID cases
- Prospective studies including younger age groups are necessary to reveal the generalizability of the results

Trial Registration details: ClinicalTrials.gov identifier: NCT03456206

INTRODUCTION

The CIDs can be considered as systemic diseases which primarily affect one organ such as the intestine (inflammatory bowel disease (IBD): Crohn's disease (CD) and colitis ulcerosa (UC)), skin (psoriasis (PsO)), joints (rheumatoid arthritis (RA) and psoriatic arthritis (PsA)), or the brain (multiple sclerosis (MS)).

The peak of disease-onset is in the adult phase of life. The diseases have a large impact on the patients and their families' quality of life due to lack of causative treatment, and on the society due to absence from work and on health care economy due to lack of preventative measures.[1-7] The CIDs have a high prevalence, with IBD and MS affecting respectively 0.5% and 0.1% of the population in the Western world.[8-12] Studies from across the world have reported prevalence estimates of RA and PsO ranging from 0.3%–1.0% and 0.7%-3.2% respectively,[2 8 13-15] while the prevalence of PsA is estimated as 0.04-0.25% across countries.[14 16] Furthermore, one-third of RA patients are diagnosed at >60 years of age[17] and the incidence of late-onset IBD and MS have been reported to increase.[18 19]

The CIDs have some shared genetic[20-24] and environmental (e.g. smoking, gut microbiome) predisposing factors, and causes of the high incidence and prevalence point to such environmental factors.[8 25-40] Therefore, further research of the associations between potential modifiable environmental risk factors and risk of CID is important.

Evidence-based research

It has been demonstrated that a high level of red meat consumption is a risk factor for the development of inflammatory polyarthritis (including RA).[39 40] A high fibre intake has been associated with low risk of IBD.[27] Furthermore, several studies of the impact of dietary factors on MS point towards an impact of meat preservation such as smoking or addition of nitrites.[41-44]

Studies have also suggested other lifestyle factors such as physical activity,[45-47] body mass index (BMI),[1 47-49] smoking status,[50-56] and other dietary factors such as alcohol,[1 57-59] dairy products,[38] and glycaemic index[60 61] to be associated with CIDs. Furthermore, studies have shown that the interactions among the microbiota, female sexual hormones, and immunity are associated with the development of autoimmune diseases.[62]

There are many potential mechanisms whereby environment such as diet may affect the immune system (Figure 1). Recently, we provided the hypothesis that intake of high fibre/low red and processed meat may protect against CID.[61] Figure 1 presents a model, proposed in a previous study,[8] whereby a diet high in meat and low in fibres may impact inflammation.

FIGURE 1

Aims and hypotheses

Based on previous evidence, we set out to prospectively identify dietary factors that have an impact on disease risk of late onset CID.

The primary aim of this prospective cohort study is to investigate the impact of fibre, red meat, and processed meat on disease risk outcomes of late onset CID in the "Diet, Cancer and Health" (DCH) cohort. The overall perspectives are that results from this study will be contributing in supporting future diet recommendations for effective personalized prevention of individuals identified to be at high risk.

The main hypothesis is that "the risk of late onset CID will be significantly lower among those with a high fibre/low red meat, and processed meat intake compared to those with a low fibre/high red meat and processed meat intake." The hypothesis is illustrated in figure 1.

Based on previous research on a shared etiology in CIDs we hypothesize that "the suggested association between high fibre/low red meat, and processed meat intake and risk of developing CID is applicable for each of the CID diagnoses."

The secondary aim of this prospective cohort study is to investigate whether risk of late onset CID in the DCH cohort is affected by other dietary and lifestyle differences, and therefore to adjust for the potential confounders: age, sex, BMI, physical activity, energy, alcohol intake, intake of fermented dairy products, education after basic school, hormone replacement therapy (HRT), smoking status, and comorbidity.

METHODS AND ANALYSES

Design and setting

This study is an observational study using prospective registry follow-up data. We will use the Danish cohort "Diet, Cancer and Health", and the follow-up period will be from the date of entry in the DCH cohort (between December 1993 and May 1997) until May 2018.

The DCH Study is an ongoing Danish cohort study designed to investigate the relation between diet, lifestyle, and disease risk.[63] The cohort consists of 57,053 persons, recruited between December 1993 and May 1997. All the subjects (50 to 64 years of age) gave detailed information on diet (food frequency questionnaire (FFQ)) and other lifestyle data. Questionnaire data on diet and lifestyle were collected at study entry.[63] Data from the DCH cohort will be combined with Danish Health registries (the National Patient Registry (NPR), the Danish Civil Registration System (CRS), The Danish National Prescription Registry (DNPR) and the Danish Multiple Sclerosis Registry (DMSR).

Participant characteristics and eligibility criteria

Criteria for inclusion: The population to be studied include participants in the DCH cohort.[63] In short, the criteria for invitation to the DCH cohort were: age between 50 and 64, born in Denmark, and no diagnosis of cancer registered in the Danish Cancer Registry. All persons fulfilling these criteria and living in the areas of Copenhagen and Aarhus were invited.[63]

Criteria for exclusion: Participants registered in NPR or DMSR with a CID primary diagnosis from a department with relevant area of specialization in the period between 1977 and entry to the DCH cohort will be excluded regardless of whether the person receive medical treatment for CID or not.

The Danish health Registries

We will extract data from the four national registries in those time periods that is possible for each registry; NPR from 1977-2018, CRS from 1977-2018, DNPR from 1994-2018, and DMSR from 1977-2018. An overview of the information obtained from the different registries is presented in **table 1**.

Table 1. Overview of registry information

Variable	Definition	Registry	Time period
CPR	Civil Registration Number	CRS	1977-2018
ICD-10 code*	International Classification of Diseases	NPR	1994-2018
ICD-8 code*	International Classification of Diseases	NPR	1977-1993
Medication (ATC code)	Anatomical Therapeutic Chemical classification (ATC) code	DNPR	1994-2018
Treatment code	Medical treatment classification code	NPR	1994-2018
Department with relevant area of specialization	Medical and gastroenterological department (IBD), medical and rheumatological department (RA, PsA), Medical and dermatological department (PsA, PsO)	NPR	1977-2018
ICD-8 and ICD-10 codes for MS	Diagnostic codes for multiple sclerosis	DMSR	1977-2018

*ICD-8 and ICD-10 codes in the period 1977-1997 will be used to define CID diagnosis
Abbreviations: The Danish Civil Registration System (CRS); National Patient Registry (NPR); Danish National Prescription Registry (DNPR); Danish Multiple Sclerosis Registry (DMSR).

The NPR will be used to identify patients with CID during follow-up and, in addition, patients with CID before study entry. The NPR contains data on all patients admitted to Danish hospitals since 1977. The register covers both inpatient and outpatient records and indicates the main medical reason for diagnostic procedures or treatment (since 1971 according to the eight version and 1994 according to the tenth version of the International Classification of Diseases (ICD-8 and ICD-10)). ICD-8 and ICD-10 codes will be used to identify cases diagnosed before entry to the DCH cohort study. Information on the departments with the relevant areas of specialization will be obtained from the NPR and used to identify cases as described in the data analysis section.

The DMSR will be used to identify patients with MS during follow-up, and in addition, patients with MS before study entry.

The DNPR will be used to obtain information on the medical treatment according to the Anatomical Therapeutic Chemical classification (ATC) code.

From the CRS we will extract follow-up information on civil status, death and immigration.

Data will be linked by the unique identification number assigned to all residents in Denmark at birth or first immigration which provides a unique opportunity to link information about diagnoses, medications, etc. at the individual level.

Outcome and exposures

Outcome: In this study, the outcome *late onset CID* is defined as one of the following diseases; CD, UC, PsO, PsA, RA, or MS. This outcome is defined by fulfilling the following two criteria: 1) having the CID disease in NPR (except MS) from a department with relevant area of specialization,

or in the DMSR (MS) during the follow-up period AND 2) being treated (irrespective of the number of treatments) with a drug used for the specific disease, and the treatment being registered either in the DNPR or from a department with relevant area of specialization (criterion 2 will not apply to MS). The outcome late onset CIDs with the associated ICD-8 and ICD-10 codes and the ATC codes in DNPR and treatment codes in the NPR are specified in **table 2**. The date and year of the diagnosis is defined as the date and year of the diagnosis in NPR and/or DMSR. If a patient has several CID diseases, only time to the first diagnosis will be included in the analyses.

Table 2. Specification of outcome CIDs with associated diagnostic- and treatment codes

Chronic Inflammatory Disease (CID)	Diagnostic code (NPR)		Medical treatment (DNPR and NPR)		Depart. with relevant area of specialization
	ICD-8*	ICD-10	ATC code (DNPR)***	Treatment code (NPR)***	
Crohn's disease (CD)	563.01, 563.02	K50.0-50.9	L04AB02 L04AB04 L04AB06 L04AB05 L04AA33 L04AX01 L04AX03 L01BB02 A07E	BOHJ18A1 BOHJ18A3 BOHJ18A4 BOHJ18A5 BOHJ26 BOHJ19H4	Gastroenterology, Internal Medicine
Ulcerative colitis (UC)	563.09, 563.19	K51.0-51.9			Gastroenterology, Internal Medicine
Chronic polyarthritis, including RA	712.19, 712.29, 712.39, 712.59	M05.9, M06.0	L04AX01 L04AX03 L04AA13 P01BA02	BWHA115 BLHM2 BWHB83 BOHJ18	Rheumatology, Internal Medicine
Psoriatic arthritis (PsA)	696.09	M09.0, M07.3, M46.8+M07.2			Rheumatology, Internal Medicine
Psoriasis (PsO)	696.10, 696.19	L40.0-40.9	D05AX02 D05BB02 D05B L04AA32 L04AB01-02 L04AB04 L04AC05 L04AC10 L04AC13 L04AD01 L04AX03	BWHA115 BOHJ20 BNHC BOHJ18A1-3 BOHJ18B3 BOHJ18B5	Dermatology, Internal Medicine
Multiple sclerosis (MS)	734.0-9**	G35.9**	Not used	Not used	Danish Multiple Sclerosis Registry

*ICD-8 and ICD-10 codes will be used to define participants with a CID diagnosis.
**ICD-8 and ICD-10 codes for MS will be extracted from the Danish Multiple Sclerosis Registry (DMSR)
***These ATC and treatment codes for CD and UC are used by the Danish National Registry for Biological Therapy in Inflammatory Bowel Disease (BIO-IBD)[64]

Exposure and possible confounders: Information on exposure in this study is defined as high fibre intake and high red meat, and processed meat intake, and also other dietary and lifestyle factors.

In the DCH study, information on diet and lifestyle exposure were collected at enrollment using questionnaires as has been described in details elsewhere.[63] In short, in the FFQ diet consumption was assessed in 12 categories of predefined responses, ranking from "never" to "eight times or more per day over the past 12 months". The daily intake was then calculated by FoodCalc.[63] Both intake of dietary fibre and red meat and processed meat were measured as continues variable in g/day. The initially collected data on diet and lifestyle exposure of the DCH cohort is used as the baseline information on exposure in this study.

Information on dietary and lifestyle exposures used for this study is specified in **table 3**. Fibres, red meat, and processed meat are defined based on the classification of the food items in the DCH study,[63] and with inspiration from other studies using dietary data from the DCH cohort.[65-67] Red meat is defined as fresh and minced meat (unprocessed) from beef, veal, pork, and lamb and excluding poultry, fish, and eggs. Processed meat consists of red meat, poultry and fish items that have undergone processing such as smoking, salting or curing. This includes various kinds of sausages, salami, smoked or cooked ham, poultry or fish, other cold cuts, bacon and liver pate. Poultry includes chicken and turkey both unprocessed and processed, such as various cold cuts of chicken and turkey. Fish includes all unprocessed and processed fish as well as shellfish. Total meat is defined as the total of red (unprocessed) meat, red processed meat together with poultry and fish.[65-67] Fibres are defined as fibres from fibrous food items from the FFQ.

Information on possible confounders will also be obtained from the questionnaire data at enrollment in relation to sex, age, education after basic school, BMI, physical activity, energy, HRT, comorbidity, smoking status, alcohol intake, and also intake of fermented dairy products. The Charlsons comorbidity index[68] will be used to classify comorbidity among the study participants. ICD-8 and ICD-10 codes from the NPR will be used to calculate the Charlson score, using the updated Charlson comorbidity index.[69]

Table 3. Specification of exposures and overall food groups and lifestyle factors

Variable	Definition (unit)
Diet	
Total energy intake	kJ/day
Total meat	g/day
Red meat	g/day
Red, processed meat	g/day
Fish (fresh and processed)	g/day
Poultry (fresh and processed)	g/day
Total dietary fibre intake	g/day
Legumes	g/day
Vegetables	g/day
Fruits	g/day
Cereals	g/day
Dairy products	g/day
Lifestyle factors	
Alcohol intake	units of alcohol/week*
Smoking status	yes/no
Former smoker	
Current smoker	
Never smoker	
MET-score (physical activity)	hours/week
Body Mass Index (BMI)	kg/cm^2
Highest education after basic school	yes/no
Vocational education	
Higher education 1-2 years	

Higher education 3-4 years	
Higher education > 4 years	
Co-morbidity (Charlson comorbidity index)	index score
Hormone replacement therapy (HRT)	yes/no

*One unit of alcohol is defined as 12 grams of pure alcohol

Primary exposure variable: The primary exposure variables will be analyzed in tertiles. Based on the hypothesis that the risk of CID and late onset CID will be lower among those with a high fibre/low red meat, and processed meat intake compared to those with a low fibre/high red meat, and processed meat intake, it is expected that:

- The upper tertile of the sample (33.3% of the total sample), based on the ratio of fibre/meat intake, is associated with lower risk of CID and late onset CID.

- The lower tertile of the sample (33.3% of the total sample) with respect to intake of red meat and processed meat and the upper tertile of the sample (33.3% of the total sample) with respect to intake of dietary fibres are independently associated with lower risk of CID and late onset CID, and a potential interaction between them may further lower the risk of CID and late onset CID.

Other (exploratory) exposure variables:

- Other dietary and lifestyle factors independently or combined will be analysed, and are presented in table 3.

Statistical analysis plan

The data obtained from this study will be used to investigate our ability to predict risk of late onset CID, based on whether a diet high in fibre and low in red meat, and processed meat is a

predictive factor. Furthermore, data on other lifestyle factors and dietary factors obtained from the FFQ will be used to investigate whether these factors potentially could give risen to confounding of the association between fibre/meat intake and risk of late onset CID.

Descriptive analyses for categorical variables will be presented as frequencies, and differences between late onset CID cases and non-cases will be evaluated by Chi-square test. Continuous variables will be tabulated as medians (with quartiles, Q1 and Q3) and nonparametric tests on the equality of medians will be used to test for differences between groups. P-values below 0.05 will be considered statistically significant. Negative binomial regression will be applied to calculate incidence rates per 1,000 patient years and incidence rate ratios (IRR) between exposures. To investigate the risk of and time to CID diagnosis the Fine-Gray competing risk regression model will be applied, and thus competing risk of death will be taken into account while handling emigration as censoring and reporting cumulative incidences and sub-hazard ratios (SHR) and the corresponding p-values for late onset CID associated with specified food substitutions. Regressions will be carried out as both crude regressions, only including the exposure, and adjusted for age, sex, lifestyle factors and selected comorbidities. Sensitivity analyses of the outcome variable and use of medication will be carried out.

Logistic regression will be conducted to examining the association between fibre/meat intake and already being diagnosed with a CID diagnose. Analyses will be conducted using Stata version 15.[70]

If power of each of the disease groups allows, there will be conducted sub-analyses on each of the late onset CID diagnoses separately with the overall aim of testing if the hypothesized association between diet factors and development of late onset CID is applicable for all the late

onset CIDs or if some of the late onset CIDs deviate from this association. Moreover, analyses omitting MS from the overall definition of CID, will be performed.

Information on the departments with the relevant areas of specialization will be used to evaluate the robustnes of the diagnosis codes from the NPR and to identify the cases as we will only accept cases that have a diagnosis from a relevant department. The DMSR is highly validated,[71] and data from the registry will be used to ensure complete follow-up of valid diagnoses of MS.

Power considerations, late onset CID: The age-adjusted (age between 45-69) incidences per 100,000 years of the CIDs in Denmark are 10.1-10.6 for CD[72]; 27.5-32.7 for UC[72]; 200-225 for PsO[15]; 28-35 for PsA[16]; 4.4-7.5 for MS[19 73-76]; and 28.1-57.6 for RA[77 78]. In the cohort of approximately 57,000 participants and a follow-up period of approximately 20 years, these incidences correspond to an estimate of approximately 2,000 cases of CID in the cohort. To estimate the power of the study we therefore expect approximately 2,000 cases of CID, i.e. an incidence of about 3% and about one third of the cohort in the low risk and two thirds in the high risk exposure. Assuming a fixed follow-up of 20 years and a relevant effect size of 2% CID risk in the low risk exposure compared to 3% in the high risk exposure this would require 11,667 participants to obtain a power of 0.90 in an (unadjusted) Chi-squared-test. Hence with a total cohort size of approximately 57,000, this should ensure a sufficient power even when taking loss to emigration and competing risk of death (resulting in less than 20 years follow-up for some participants) into account.

Patient and Public Involvement

This study is register based and there will be no patients or public involvement in the study.

Strengths and limitations of the study

A strength of this study is that it is not limited to one disease, as it includes several CIDs. Another strength is that the linkage to Danish Health registries will ensure almost complete follow-up of the study population, as the Danish Health registries are considered the internationally most comprehensive with high validity.[79-82] Furthermore, in this study, we have chosen very restrictive criteria for defining the late onset CID cases by requiring that cases fulfill both diagnostic and treatment criteria, or that the cases were registrered in the DMSR. This approach ensures that a high proportion of the identified cases really had late onset CID. Therefore, some "real" CID cases might not have been identified, hence lowering the sensitivity.[71 83 84]

A possible limitation of this study could have been the validity of the diagnostic codes from the NPR and the treatment codes from the DNPR as criteria for identifying late onset CID cases.[71 83] But, as described in the analysis plan this potential limitation will be sought eliminated by using the information on the hospital departments, and for MS, using the DMSR for identifying MS cases. In addition, usually dietary habits do not change much during life. Therefore, the exposure time to the diet is long in 50+ age group and a possible impact of diet is possibly located much earlier in life. Therefore, we have included an analysis among those who at entry to the DCH cohort already had a CID diagnosis to examine if their low/high intake of dietary fibre, red meat and processed meat is associated with having CID. We are well aware that such an analysis might be impacted by bias by indication and that the results should be interpreted with this in mind.

The FFQ applied in the present study has been used in the large, European prospective cohort study "The European Prospective Investigation into Cancer and Nutrition" (EPIC),[85 86] and it has been used and evaluated in the Danish population, with results that demonstrate consistency.[87-89] However, the FFQ is not without limitations, with respect to the lack of

information on portion sizes[90 91] or to underestimation and overestimation of intake of unhealthy and healthy food.[92] Any imprecision of the FFQ due to standardized portion sizes or incorrect reporting of food intake, will lead to large confidence intervals, which potentially can lead to null results.[8] On the other hand, studies suggest that specification of a standard portion size may not introduce a large error in the estimation of food and nutrient intake.[93] Furthermore, the FFQ has been validated as being appropriate for use in studies that examine relationships between diet and risk of disease.[92]

Another limitation of this study is the validity of the information on exposure as this information is collected at study entry, which potentially can be several years before any outcome appears, and measurement error in the FFQ may occur if the participants change their diet over time. Furthermore, there is a potential risk of recall bias according to the information on exposure, as this information relies on the participants' ability to recall their dietary intake. In this study, however, it is expected that dietary and lifestyle patterns among adults are relatively stable over time, based on other longitudinal studies that showed minimal temporal changes.[94 95]

The MET-score is an accepted standard measure of physical activity.[96] However, the weaknesses of the MET-score include a risk of adding random variation by applying an assumed intensity to include activities. Another weakness of the MET-score is the implicit assumption that the intensity aspect of physical activity is important for development of disease.[96]

The study population in this study is based on a cohort of middle-aged women and men living in urban areas. This could reduce the generalizability of study findings, as the incidence of CID diagnoses could be different for younger persons and persons from rural areas.

The disease groups may be heterogeneous regarding dietary and lifestyle factors. This study may not capture every dietary and lifestyle difference between the disease groups, due to

insufficient power of each disease group, as described in the analysis plan. Replication of the results in other well-characterized populations using prospectively sampled dietary data will minimize the risk of potential type 2 errors. Study results should preferably be replicated in cohorts in other countries and other age groups for further evaluation of the robustness of the results.

Project organisation

This registry study is a cross-disciplinary collaboration that includes clinical specialists within neurology, dermatology, rheumatology, inflammatory bowel diseases, prospective cohort study design, and clinical registries.

Perspectives

We anticipate that the PROCID-DCH study will reveal factors of importance, including whether the diet is likely to interfere with the disease risk of late onset CID.

The perspective is that significant results from this study will be sought replicated in other cohorts such as the EPIC-IBD[85] and UK biobank[97] with high-quality prospective lifestyle data. Successful replication indicates the robustness of the findings which is an important step on the road to developing clinical tools for effective personalized prevention of individuals at high risk.

Dissemination of results to the public and scientifically

Target journals include international journals within internal medicine. In addition to the scientific reporting of results, major findings with translational implications will also be communicated to categories of both health professionals, and targeted stakeholders including public health

policymakers, and to the general public through various media and news activities. Intellectual Property Rights (IPRs) to discoveries based upon the outlined research belong to the University of Southern Denmark.

Ethics

This is an open register-based cohort study. The study does not need approval from the local Ethics committee or Institutional Review Board by Danish law. The study was approved by the Danish Data Protection Agency (2012-58-0018).

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Author Contributions:

VA conceived of the presented idea and achieved funding. AT (diet and environmental factors, epidemiology) designed the cohort, collected the data and made the data available for the present project. NFR, KHR, MS and VA wrote the first draft and contributed to the further preparation and final adjustments of the protocol. According to their respective specialization, all other authors, ES (multiple sclerosis), MLH (rheumatology), BG (rheumatology) and AB (psoriasis) contributed to the project. All authors discussed the results and contributed to the final manuscript.

Conflicts of Interest:

BG declares to have received research funding from Abbvie, Biogen, Pfizer. MLH declares to have received research funding from BMS, MSD, Pfizer, Biogen, Samsung, CellTrion, Lilly, Novartis. AB

has participated in development of educational material for Biogen. All other authors declare no conflict of interest.

FIGURE LEGEND

Figure 1. Hypothesis for effects of diet in relation to development of chronic inflammatory diseases (CIDs)

Diet (meat[98], fibre[98], animal fat[99], n-3[30] and n-6 polyunsaturated fatty acids, vitamin A[100] and D[101], carotenoids[102], smoking, gluten[103]) may affect the immune system[104 105] either directly or indirectly via e.g. the activity and composition of the gut microbiome.[106 107] The effect of low intake of fibre/high intake of red and processed meat is shown at left: In short, low intake of fibre (which could otherwise serve as a nutrient for the microbes) may lead to the microbial metabolism of mucus and to decrease of the intestinal mucus layer.[61 108 109] A high intake of red and processed meat may render the mucus layer penetrable to e.g. bacteria by reducing the disulphide bonds in the mucus network.[8 106 110] Thus, microbes may reach the epithelium[8 111 112] and activate the immune system.[8 113 114] There is some support for such a mechanism in chronic inflammatory diseases (CID)[8], including findings of; high amounts of sulphate-reducing bacteria in inflammatory bowel disease (IBD) patients;[8 112 115] association of high fibre intake with low risk of IBD among 170 776 participants from the prospective Nurses' Health Study I[8 27]; and association of high intake of red meat and total protein and risk of developing inflammatory polyarthritis in the population-based prospective cohort of 25 630 participants from the European Prospective Investigation of Cancer in Norfolk.[8 39 40]

Note. Figure from "Impact of red and processed meat and fibre intake on treatment outcomes among patients with chronic inflammatory diseases: protocol for a prospective cohort study of prognostic factors and personalised medicine," by Christensen R, Heitmann BL, Andersen KW, et al., *BMJ Open* 2018;8:e018166. doi: 10.1136/bmjopen-2017-018166. Available at: http://bmjopen.bmj.com/content/8/2/e018166. Copyright 2018 by Vibeke Andersen.

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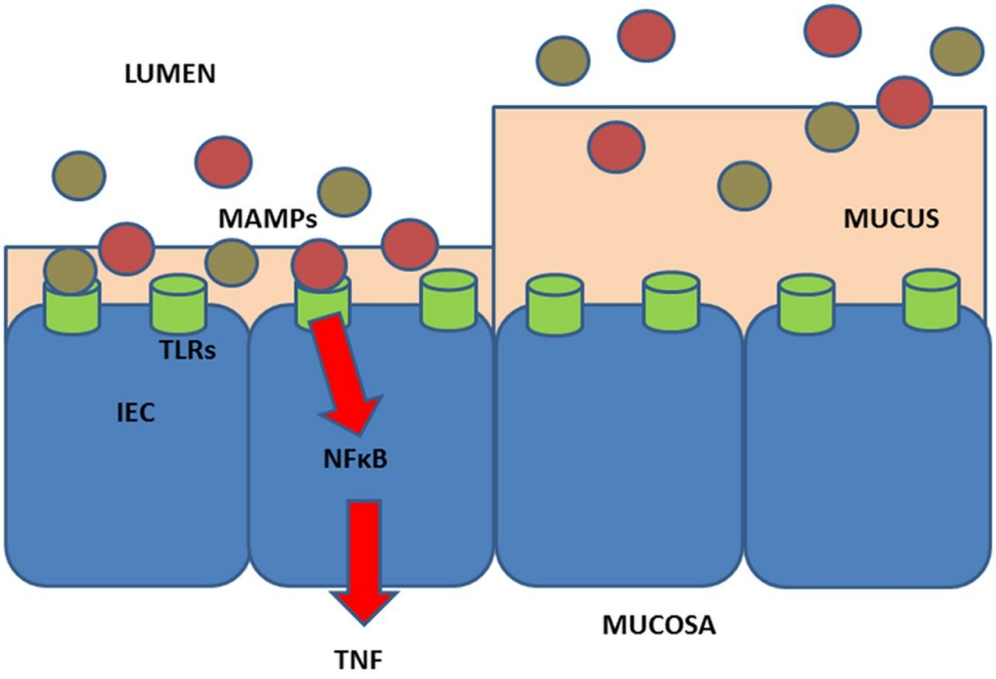

Figure 1. Hypothesis for effects of diet in relation to development of chronic inflammatory diseases (CIDs) "Diet (meat98, fibre98, animal fat99, n-330 and n-6 polyunsaturated fatty acids, vitamin A100 and D101, carotenoids102, smoking, gluten103) may affect the immune system104 105 either directly or indirectly via e.g. the activity and composition of the gut microbiome.106 107 The effect of low intake of fiber/high intake of red and processed meat is shown at left: In short, low intake of fibre (which could otherwise serve as a nutrient for the microbes) may lead to the microbial metabolism of mucus and to decrease of the intestinal mucus layer.61 108 109 A high intake of red and processed meat may render the mucus layer penetrable to e.g. bacteria by reducing the disulphide bonds in the mucus network.8 106 110 Thus, microbes may reach the epithelium8 111 112 and activate the immune system.8 113 114 There is some support for such a mechanism in chronic inflammatory diseases (CIDs)8, including findings of; high amounts of sulphate-reducing bacteria in inflammatory bowel disease (IBD) patients;8 112 115 association of high fibre intake with low risk of IBD among 170 776 participants from the prospective Nurses' Health Study I8 27; and association of high intake of red meat and total protein and risk of developing inflammatory polyarthritis in the population-based prospective cohort of 25 630 participants from the European Prospective Investigation of Cancer in Norfolk.8 39 40""Note. Figure from "Impact of red and processed meat and fibre intake on treatment outcomes among patients with chronic inflammatory diseases: protocol for a prospective cohort study of prognostic factors and personalised medicine," by Christensen R, Heitmann BL, Andersen KW, et al., BMJ Open 2018;8:e018166. doi: 10.1136/bmjopen-2017-018166. Available at: http://bmjopen.bmj.com/content/8/2/e018166. Copyright 2018 by Vibeke Andersen.

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