

Supplementary materials

Supplement to "Obesity is associated with increased risk of Crohn's disease: Results from the DEFINE-IBD consortium"

Simon S M Chan^{1,2}, Ye Chen³, Kevin Casey³, Ola Olen^{4, 5, 6}, Jonas F Ludvigsson^{7, 8}, Franck Carbonnel^{9, 10}, Bas Oldenburg¹¹, Marc J Gunter¹², Anne Tjønneland^{13, 14}, Olof Grip¹⁵, DEFINE-IBD investigators, Paul Lochhead^{3, 16}, Andrew T Chan^{3, 16}, Alicia Wolk^{17, 18}, Hamed Khalili^{3,16,19}

¹Department of Gastroenterology, Norfolk and Norwich University Hospital NHS Trust, Norwich, NR4 7UY, United Kingdom

²Department of Medicine, Bob Champion Research and Education Building, Norwich Medical School, University of East Anglia, Norwich, NR4 7UQ, United Kingdom

³Clinical and Translational Epidemiology Unit, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

⁴Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

⁵Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden

⁶Department of Paediatric Gastroenterology and Nutrition, Sachs' Children and Youth Hospital, Stockholm, Sweden

⁷Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

⁸Department of Paediatrics, Örebro University Hospital, Örebro, Sweden

⁹Service de Gastroentérologie, Centre hospitalier Universitaire de Bicêtre, Assistance Publique Hôpitaux de Paris, Université Paris Saclay, Le Kremlin Bicêtre, France

¹⁰INSERM U1018, Villejuif, France

¹¹Department of Gastroenterology and Hepatology, University Medical Centre Utrecht, Utrecht, The Netherlands

¹²Section of Nutrition and Metabolism, International Agency for Research on Cancer - WHO, Lyon, France

¹³Danish Cancer Society Research Center, Strandboulevarden 49, Copenhagen, Denmark

¹⁴Department of Public Health, University of Copenhagen, Nørregade 10, Denmark

¹⁵Department of Gastroenterology, Skåne University Hospital, Malmö, Sweden

¹⁶Gastroenterology Unit, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

¹⁷Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

¹⁸Department of Surgical Sciences, Uppsala University, Uppsala, Sweden

¹⁹Broad Institute of MIT and Harvard, Cambridge MA, USA

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SUPPLEMENTARY METHODS

Study populations inclusion criteria

Included studies met the following predefined inclusion criteria *(i)* at least one publication on lifestyle factors and risk of IBD, *(ii)* an assessment of habitual diet, lifestyle (physical activity, smoking status) and anthropometry measurements (height, weight, waist and hip circumference), *(iii)* validation of the assessment methods, *(iv)* confirmation of IBD cases using validated methods. These criteria helped maximize the quality and comparability of the studies in the consortium.

Exposure assessment

In the EPIC cohort height, weight, waist, and hip circumference were measured by the EPIC study personal at recruitment in all centers except for those in France and Oxford where anthropometric measures were self-reported and validated by measuring a limited number of participants. Correlation coefficients between self-reported and measured anthropometric measurements were >0.8 and >0.9 , respectively^{1, 2}. Weight at aged 20 was self-reported by participants at recruitment.

In NHS and NHSII cohorts, participants self-reported weight and height. Waist and hip circumference were self-measured by participants with a tape measure and instructions to measure their own waist circumference at the level of the navel, and hip circumference at the largest circumference around the hips. Self-reported anthropometric measurements were validated among 140 NHS participants by having trained technicians visit these participants with Pearson's correlation coefficients ranging from 0.84 – 0.97 depending on the anthropometric measurement³. Weight at aged 18 years was self-reported by participants at recruitment.

In the COSM and SMC cohorts validated anthropometric measurements for height, weight, waist, and hip circumference were self-reported at recruitment as previously described^{3, 4}. Weight at age 18 years was self-reported at recruitment.

Assessment of covariates

Briefly, dietary data were collected using validated country-specific semi-quantitative food frequency questionnaires (SFFQs) designed to capture local dietary habits in EPIC⁵⁻¹³; a validated 136-item SFFQ in NHS and NHSII^{14, 15}; and a validated 96-item SFFQ in COSM and SMC^{16, 17}. Participants reported average frequency of consumption of each food item in the previous year and portion size. National databases of food composition were then used to calculate standardized total energy, dietary fiber, and dietary fat intake from the questionnaires. Validated physical activity data were collected from the different cohorts using questionnaires that assessed duration and intensity

of leisure and non-leisure activities in the last year¹⁸⁻²². Each activity was assigned a value for metabolic equivalent task (MET) according to established criteria²³ reflecting the intensity of a particular activity. MET hours per week (MET-hr/wk) for each activity were calculated by multiplying the MET score by the participant's reported number of hours of physical activity per week with total physical activity computed as the sum of the MET-hr/wk from all individual activities. Self-reported smoking status at baseline was recorded as current, past, or never.

Outcome ascertainment

EPIC participants following recruitment were monitored to identify those who developed a new diagnosis of either CD or UC. The identification methods used included: local and national inflammatory bowel disease registries, follow-up questionnaires, pathology databases and hospital in-patient records. All the medical notes of potential cases were reviewed by physicians to confirm the diagnoses and to obtain information on both the confirmatory investigations used and the extent of the disease from endoscopic, radiological, and surgical records. Participants who developed indeterminate or microscopic colitis were excluded.

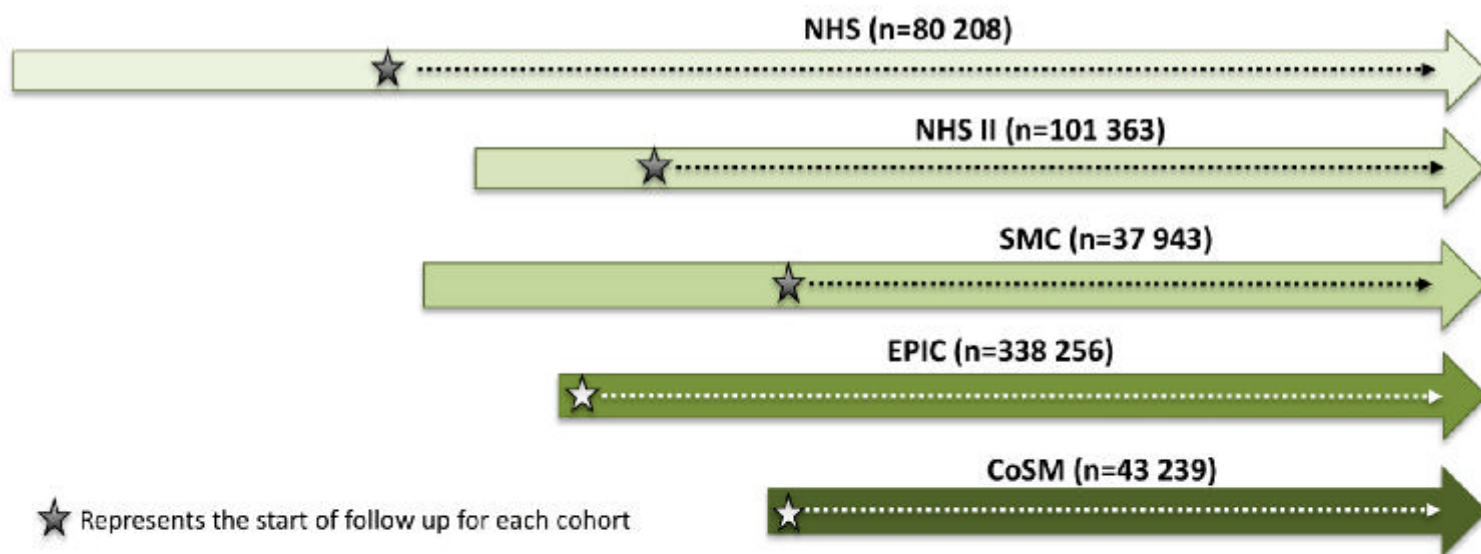
The NHS I and NHS II specifically asked participants about diagnoses of CD and UC on biennial questionnaires. When a diagnosis was reported on any biennial questionnaire, a supplementary questionnaire and related medical records were requested and reviewed by two gastroenterologists blinded to exposure information. Participants who subsequently denied the diagnosis on the supplementary questionnaire or permission to review their records were excluded. Data were extracted on diagnostic tests, histopathology, anatomical location of disease and disease behaviour. Standardised criteria were used: UC diagnosis was based on a typical clinical presentation ≥ 4 weeks and endoscopic or surgical pathological specimen consistent with UC (e.g. evidence of chronicity); CD diagnosis was based on a typical clinical history for ≥ 4 weeks and endoscopy or radiological evaluation demonstrating small-bowel findings, or surgical findings consistent with CD combined with pathology suggesting transmural inflammation or granuloma contributed to a diagnosis of CD. Disagreements were resolved through consensus.

Incident cases of CD and UC were ascertained through linkage of SMC and CoSM participants to the Swedish Patient Register and were defined by at least two inpatient or outpatient encounters with a primary or secondary diagnosis (for UC ICD9: '556' or ICD10: 'K51'; for CD ICD9: 555 or ICD10: K50) following the return of baseline questionnaires in 1997 in both cohorts. Use of International Classification of Diseases (ICD) coding for identifying a number of chronic diseases, including IBD, in the inpatient component of the Swedish Patient Register has a positive predictive value of 85%–95%.

In addition, in a recent validation study designed specifically for IBD, using both inpatient and outpatient components of the Swedish Patient Register, the positive predictive values using our aforementioned definitions for CD, UC and IBD cases were 81%, 90% and 93% respectively.

SUPPLEMENTARY FIGURES

Figure 1: An overview of the study populations in the DEFINe-IBD consortium



1976 78 80 82 84 86 88 90 92 94 96 98 00 02 04 06 08 10 12 14 16 18					
Cohort	Country	Calendar period; median follow up (years)	Age, years (median)	CD ^Δ	UC ^Δ
EPIC*	8 European countries	1991 – 2009 (14)	18 – 98 (53)	125	336
NHS	USA	1986 – 2016 (29)	39 – 67 (54)	152	161
NHSII	USA	1993 – 2017(24)	28 – 48 (39)	144	197
COSM	Sweden	1997 – 2019 (11)	45 – 79 (60)	86	226
SMC	Sweden	1997 – 2019 (22)	48 – 83 (62)	56	127
Total				563	1047

Abbreviations: Cohort of Swedish Men (CoSM), European prospective cohort into cancer and nutrition (EPIC), Nurses' Health Study (NHS), Swedish Mammography Cohort (SMC). *Excludes Asturias, Greece, Naples, Norway, Umeå, and Varse. Δ Represent number of cases after exclusion.

SUPPLEMENTARY TABLES

Supplementary Table 1: Design of Cohorts in Pooled Analyses	
Cohort	Description
European prospective investigation into cancer and nutrition (EPIC)	Prospective cohort study of 521 000 participants from 10 western European countries [¶] recruited between 1991 – 1998. The EPIC-IBD cohort is a sub-cohort of EPIC consisting of all centres from Denmark, France, Germany, Italy*, Netherlands, Spain‡, Sweden¥ and the United Kingdom.
Nurses Health Study (NHS)	Prospective cohort study of 121 700 female registered nurses between the ages of 30 and 55 years from 11 most populous states ^Δ in the U.S. initially established in 1976.
Nurses Health Study II (NHSII)	Prospective cohort study of 116 430 female registered nurses between the ages of 25 and 42 years from 14 states [†] in the U.S. initially established in 1989.
Cohort of Swedish Men (CoSM)	Population-based prospective cohort study of 50,000 middle-aged and older men (born between 1918-1952) established in the counties of Västmanland and Örebro, Sweden in the fall of 1997.
Swedish Mammography Cohort (SMC)	Population-based prospective cohort study of 66,651 middle-aged and older women (born between 1918-1948) established between 1987 and 1990 in Uppsala County, Sweden. All women who lived in Uppsala County born and were eligible for mammography screening programme invited to participate.

¶ The European counties included were France, Italy, Spain, United Kingdom, the Netherlands, Greece, Germany, Sweden, Denmark, and Norway. *Excludes Varse and Naples, ‡Excludes Astruias, ¥Excludes Umeå. Δ The original states included: California, Connecticut, Florida, Maryland, Massachusetts, Michigan, New Jersey, New York, Ohio, Pennsylvania, and Texas. † The states included: California, Connecticut, Indiana, Iowa, Kentucky, Massachusetts, Michigan, Missouri, New York, North Carolina, Ohio, Pennsylvania, South Carolina, and Texas.

Supplementary Table 2: Risk of Crohn's disease and ulcerative colitis according to weight change from early to middle adulthood*					
	Change in weight from early to middle adulthood				P _{trend}
	Weight loss >2.5kg	-2.5 kg ≤ Weight change <2.5kg	2.5 kg ≤ Weight gain <10kg	Weight gain ≥10kg	
Crohn's disease					
Pooled age and sex adjusted HR (95% CI)	1.00(0.65 – 1.53)	1.00	0.96 (0.72 – 1.29)	0.99 (0.74 – 1.32)	0.92
Pooled MV-adjusted HR (95% CI) ^Δ	0.89 (0.57 – 1.40)	1.00	1.00 (0.74 – 1.35)	1.03 (0.76 – 1.38)	0.45
Ulcerative colitis					
Pooled age and sex adjusted HR (95% CI)	0.81 (0.58 – 1.12)	1.00	0.94 (0.75 – 1.18)	0.85 (0.69 – 1.06)	0.22
Pooled MV-adjusted HR (95% CI) ^Δ	0.72 (0.53 – 0.98)	1.00	0.95 (0.75 – 1.20)	0.83 (0.67 – 1.04)	0.19

*Abbreviations: Confidence interval (CI), multi-variable (MV), hazard ratio (HR), *P* values for all categories of weight change for pooled analyses = 0%.

^Δ Models adjusted for age at baseline (continuous), sex, weight in early adulthood (continuous), height (continuous), smoking status (never/former/current), physical activity (Quartiles), energy intake (continuous), dietary fibre (continuous) for CD only, dietary fat (continuous) for UC only.

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