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Stress resilience and the risk of inflammatory bowel disease

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Title page

Manuscript title: Stress resilience and the risk of inflammatory bowel disease

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ABSTRACT

Objective: To determine if low psychosocial stress resilience in adolescence (increasing chronic stress arousal throughout life) is associated with an increased inflammatory bowel disease (IBD) risk in adulthood. Subclinical Crohn's disease (CD) and ulcerative colitis (UC) can exist over many years and we hypothesise that psychosocial stress may result in conversion to symptomatic disease through its pro-inflammatory or barrier function effects.

Design: National register-based cohort study of men followed from late adolescence to middle age.

Setting: A general population cohort of men in Sweden.

Participants: Swedish population-based registers provided information on all men born between 1952 and 1956 who underwent mandatory Swedish military conscription assessment (n=239,591). Men with any gastrointestinal diagnoses (except appendicitis) prior to follow-up were excluded.

Primary outcome measures: An inpatient or outpatient diagnosis of Crohn's disease or ulcerative colitis recorded in the Swedish Patient Register (1970-2009).

Results: A total of 938 men received a diagnosis of CD and 1,799 UC. Lower stress resilience in adolescence was associated with increased IBD risk, with unadjusted hazard ratios (95% confidence intervals) of 1.54 (1.26-1.88) and 1.24 (1.08-1.42), for CD and UC, respectively. After adjustment for potential confounding factors, including markers of subclinical disease activity in adolescence they are 1.39 (1.13-1.71) and 1.19 (1.03-1.37).

Conclusions: Lower stress resilience may increase the risk of a diagnosis of IBD in adulthood, possibly through an influence on inflammation or barrier function.

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Strengths and limitations of this study

- This study used a prospectively collected measure of stress resilience in adolescence to examine the association of it (thus examining susceptibility to stress) with the risk of subsequent Crohn's disease and ulcerative colitis in adulthood.
- Stress resilience was measured before typical IBD onset age, and potential effects of prodromal disease activity in adolescence were taken into account in the analysis.
- Although some data suggest that stress resilience is stable over time, a potential disadvantage is that this study only measured it at one point in time.
- As we examined only stress resilience and not stressful exposures, we may have underestimated the magnitude of associations between stress resilience and IBD.
- The study did not have a measure of smoking and while this could be a pathway relevant to CD, it cannot explain the increased risk of UC.
- The results are based on men up to middle age and may not be applicable to older ages or to women.

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INTRODUCTION

The aetiology of inflammatory bowel disease (IBD) - Crohn's disease (CD) and ulcerative colitis (UC) - is believed to involve an interaction between genetic and environmental factors that results in an atypical immune response to gut microbiota.[1-3] Genetic factors are clearly important in the aetiology,[1 4] but the importance of environmental factors are signalled by temporal trends in incidence.[5] It appears that exposures in early life are potentially relevant to bowel colonisation and homeostasis,[6] such as infections and antibiotic therapy,[7] are particularly important in determining lifetime IBD risk suggesting a long and silent natural history[8] as frank disease onset occurs in adulthood.[9] Acute appendicitis before age 20 years has been linked consistently with a reduced risk of UC,[10 11] and it has been suggested recently this may be due to genetic factors influencing risk of both appendicitis and UC risk.[11] Some exposures in adulthood may be risks,[5] but the best documented risk is cigarette smoking, which is associated with an increased risk of CD, but a reduced risk of UC.[5]

Psychosocial stress may increase inflammation, including through sympathetic nervous system influences,[12] and as subclinical low-grade inflammation related to IBD can exist over many years,[8] it is possible that stress may result in conversion to symptomatic IBD. Inflammation can increase permeability and compromise the integrity of the gastrointestinal mucosal barrier thus stress may promote passage over the epithelial barrier of bacterial pathogens and activate mucosal immune responses.[13]

Studies of psychosocial stress and IBD exacerbations have generated inconsistent results.[14-17] Low levels of stress and better coping strategies are associated with reduced risk of both CD and UC relapses in prospective studies[14 15] but not life events.[16 17] Psychosocial stress was associated with an increased risk of CD but not UC in a prospective cohort study[18] but not in other studies.[19 20] To our knowledge, no previous study has considered individual variation in stress susceptibility – a potentially important determinant of chronic stress arousal.[21] Here we use Swedish register data to examine the association of stress resilience in adolescence with CD and UC risk in subsequent adulthood.

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MATERIALS AND METHODS

Study population

The study population, and measures have been described in detail elsewhere.[22 23] Briefly, the participants were males born during 1952-1956. Most men were 18-19 years of age when they attended compulsory Swedish military conscription assessments during 1969-1976. The follow-up period for CD and UC was from four years after the conscription assessment (to reduce the possibility of reverse causation, such that symptomatic disease reduced stress resilience), until diagnosis, migration, death, or end of the study, 31st December 2009 (to a maximum age of 57 years).

The entire cohort comprised 284,198 males. Exclusions were for female sex, uncertain vital status or personal number, emigration or death before follow-up (n=5,504). We also excluded men who were assessed before 17 years of age, did not undertake part of the conscription assessments or had missing data (n=35,101). Additionally, cohort members were excluded if they had any gastrointestinal diagnoses (except appendicitis), including IBD, at the conscription assessment including when recorded in the Patient Register prior to follow-up (n=4,002). In total 44,607 (15.7 %) men were excluded.

Data sources and measures

Socioeconomic and demographic data

Parental socioeconomic index (SEI) during childhood was obtained using the Population and Housing Census in 1960. We classified parental occupation into business owners/managers, farm owner/managers, manual workers, agricultural workers, office workers, and other. Data on date of birth, sex, region of residence, vital status (dead or alive) and migration were obtained from the Total Population Register.

The Swedish Military Service Conscription Register

Military service was compulsory for all men from age 18 years, with exceptions including those with severe medical conditions and entry involved a detailed assessment.[23]

Stress resilience

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Examination of psychological function at the conscription assessment produced a stress resilience score from 1 to 9, categorised as low (1-3), medium (4-6) and high (7-9) to maintain consistency with previous studies.[24 25 26] Following completion of a questionnaire, the interview was carried out by psychologists, whose inter-rater reliability was evaluated on regular basis[27] and estimated to be high (r=0.85) by a study conducted in 1972 and 1973.[28] The interview, which usually took 20-30 minutes, explored experience of potential conflicts or adjustment problems, as well as the ability to take the initiative and assume responsibilities at school, work or home.[28] The measure is based on five- or nine-scale normally distributed ratings of psychological energy, emotional control and social maturity.[26-29] Emotional control evaluated the ability to tolerate psychological stress in general as well as mental stability and emotional maturity.[26-29] Social maturity assessed if individuals were independent, socially extrovert and responsible.[26 27 29] Psychological energy assessed the ability to engage in various activities even when facing adversity. [26 27]

Height and body mass index

Height in centimetres was divided into fifths of the distribution. Heights < 144 cm, weight >178 kg or BMI <15 kg/m^2 were treated as non-valid values and excluded. Body mass index (BMI) was calculated from measures of height and weight and categorised as; underweight (15-18.49 kg/m2), normal weight (18.50-24.99 kg/m^2) and overweight/obese (>25kg/m^2). As there were few obese men at the conscription assessment, the obese and overweight categories (≥ BMI 25 kg/m^2) were combined.

Erythrocyte sedimentation rate

Erythrocyte sedimentation rate (ESR), indicating systemic inflammation, was standardised for erythrocyte volume fraction (EVF) by adjustment[22 23] and grouped into five categories: 1 mm/h, 2-6 mm/h, 7-10 mm/h, 11-14 mm/h and >=15 mm/h. ESR <1 or >98 mm/h and EVF <0.20 or >0.75 were considered as non-valid.

Gastrointestinal diseases at conscription assessment

GI diagnoses up to the time of the conscription assessment were obtained from the Conscription Register and The National Patient Register. The codes used are the Swedish version of the International Classification of Diseases (ICD) revision 8 (ICD-8 codes 530-539, 543, 555-558, 560-577). Appendicitis prior to age 20 years was identified (ICD-8 codes 540-542) in the Conscription Register and surgical procedure codes (4510 and 4511) in the

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National Patient Register. We combined appendectomy and appendicitis prior to age 20 years into a single variable.

Geographical regions

The regions of Sweden used were northern, central and southern.

The National Patient Register

IBD diagnoses in adulthood were identified through ICD 8, 9 or 10 codes in the National Patient Register. Since 1964, the National Board of Health and Welfare has collected information on inpatient diagnoses and the register achieved complete coverage in 1987. The register expanded to include data on outpatient visits in 2001 and approximately 99% of all primary hospital diagnoses are recorded.[30]

IBD diagnoses

Primary and secondary diagnoses in inpatient and outpatient records were identified: CD (563.00 for ICD-8; 555.x for ICD-9; ICD-10 K50.x), and UC (563.10 for ICD-8; 556.x for ICD-9; ICD-10 K51.x). During the follow-up period, 938 and 1,799 men were identified as having diagnoses of CD and UC, respectively. A total of 438 men had records of both CD and UC. The most recent diagnosis was used to define disease phenotype, but the time of the first diagnosis defined disease onset. A total of 286 with UC changed to CD and 152 men with CD changed diagnosis to UC.

Statistical analysis

The association between stress resilience in adolescence and risk of subsequent IBD in adulthood was evaluated by Cox regression. We examined the proportional hazards assumption graphically, with no indication of violation. Separate models were used for CD and UC, with adjustment for parental socioeconomic index (SEI) in childhood, appendicitis prior to age 20 years, region of residence; and markers of potential prodromal disease activity in adolescence (ESR, EVF, height and BMI). We also modelled stress resilience as non-categorical variable to assess linear trend of associations with IBD risk for three-category and nine-category measures of stress resilience. We examined whether stress resilience modifies the association of BMI, height and inflammation in adolescence with IBD risk using stratification and interaction testing. Interaction terms for ESR, height and BMI with stress

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resilience were included in Cox models, with adjustment for the main effects. Age was used as the underlying time scale and all measures were modelled as categorical variables.

Sensitivity analyses

Further analyses assessed if changes in diagnostic accuracy influenced the findings (by the end of the 1970s it was higher) and to assess whether stress resilience in adolescence is associated with a first IBD diagnosis, even after a minimum of 15 years from assessment; as in a previous study.[22] Among those who had IBD diagnoses (638 CD and 1469 UC) during this period (that started 15 years after the conscription assessment), 283 men had both CD and UC diagnosis. As is in the main analysis, the most recent diagnosis was used to define disease phenotype, but the time of the first diagnosis defined disease onset. Men who had IBD diagnosis during the period prior to the start of follow-up were excluded from the analysis (n=1,156). We also conducted a separate analysis excluding men more likely to have undiagnosed disease in adolescence, defined as low EVF (≤39), elevated ESR (≥15) or underweight (BMI 15-18.49 kg/m^2).

SPSS software version 23 and Stata version 13 were used. We considered P-values <0.05 and 95% confidence intervals not including 1.00 as statistically significant.

RESULTS

Participant characteristics

The study comprised 239,591 men followed from four years after the conscription assessment in late adolescence to a maximum of age 57 years (Table 1).

Table 1 Baseline characteristics of study participants by IBD diagnosis

	No IBD n=236854	CD N=938	UC n=1799
	n (%)	n (%)	n (%)
Stress resilience			
Low	50317 (24.0)	225 (23.5)	423 (21.3)
Moderate	129457 (58.3)	547 (55.1)	990 (54.7)
High	57080 (17.7)	166 (21.4)	386 (24.1)
Mean (SD)	5.1 (1.9)	4.8 (1.8)	4.9 (1.9)
BMI			
Mean (SD) (kg/m2)	21.2 (2.6)	21.0 (2.6)	21.0 (2.5)

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ESR in adolescence			
Mean (SD) (mm/h)	3.4 (3.5)	5.1 (5.9)	3.9 (4.2)
Median (range)	2 (1-89)	3 (1-51)	3 (1-55)
Height			
Mean (SD) (cm)	178.7 (6.4)	178.1 (6.4)	178.1 (6.5)
Parental SEI in 1960			
Manual worker	96493 (40.7)	423 (45.1)	766 (42.6)
Agricultural workers	9046 (3.8)	52 (5.5)	65 (3.6)
Farm owner/managers	23396 (9.9)	65 (6.9)	169 (9.4)
Office workers	65495 (27.7)	230 (24.5)	468 (26)
Business owners/managers	25267 (10.7)	98 (10.5)	182 (10.1)
Others (unknown)	17157 (7.2)	70 (7.5)	149 (8.3)
Appendicitis < 20 years			
No	234935 (99.2)	933 (99.5)	1796 (99.8)
Yes	1919 (0.8)	5 (0.5)	3 (0.2)
Age at diagnosis (years)			
Median (range)		40 (21-57)	47 (22-57)

BMI, body mass index; CD, Crohn's disease; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; n, number; SD, standard deviation; UC, ulcerative colitis; SEI, socioeconomic index.

Men with CD were more likely to have lower stress resilience and raised ESR compared to men with UC and men without IBD. Men with IBD were more likely to have lower parental SEI in childhood compared with men without IBD. Men with UC were less likely to have had an appendectomy or appendicitis prior to age 20 years. The median age of onset was 40 years (range 21-57) for CD and 47 years (range 22-57) for UC.

Stress resilience in adolescence and subsequent Crohn's disease in adulthood

Men with low and moderate stress resilience had an increased risk of subsequent CD compared to men with high stress resilience (table 2). Modelling the three-category variable as a linear measure, the hazard ratios (95% confidence intervals) for the association of stress resilience with CD (the average change in CD risk by one unit change in the three stress resilience categories) are 1.23 (1.11-1.35) and 1.17 (1.06-1.28), before and after adjustment, respectively. Modelling the nine-category measure as linear produces HR of 1.09 (1.05-1.13) and 1.07 (1.03-1.11), respectively. Adjustment for any individual potential confounding factor had little influence on the association of stress resilience with CD, and it was the combined adjustment that had a notable influence (data not shown).

Table 2 Stress resilience in adolescence and subsequent Crohn's disease risk in adulthood at least four years after the conscription assessment

Stress resilience	Events/n	Unadjusted HR	Adjusted* HR

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		(95% CI)	(95% CI)
Main analysis			
Low	225/50965	1.54 (1.26-1.88)	1.39 (1.13-1.71)
Moderate	547/130994	1.43 (1.20-1.70)	1.36 (1.14-1.62)
High	166/57632	Reference	Reference
Sensitivity analysis – excluding those with elevated ESR, low EVF and underweight			
Low	115/41735	1.53 (1.23-1.91)	1.45 (1.16-1.81)
Moderate	301/113417	1.34 (1.11-1.62)	1.32 (1.09-1.59)
High	101/53007	Reference	Reference
Sensitivity analysis – follow-up at least 15 years after the conscription assessment			
Low	147/49278	1.46 (1.15-1.87)	1.37 (1.07-1.75)
Moderate	377/127750	1.42 (1.16-1.76)	1.39 (1.22-1.71)
High	114/55644	Reference	Reference

CI, confidence interval; HR, hazard ratio; n, number.
* Adjusted for BMI, ESR, EVF, height, parental SEI, appendicitis before age 20 and region of residence.

The analysis excluding men more likely to have undiagnosed disease activity in adolescence (table 2) limited the sample to 743 men with CD, and the results are consistent with the main analysis. Also, the association between low stress resilience in adolescence and future risk of CD remained during the follow-up beginning at least 15 years after the conscription assessment in adolescence (table 2). A total of 638 diagnoses of CD were identified and the median age of onset was 47 years (range 33-57). There was no statistically significant interaction between stress resilience and markers of subclinical disease activity in CD (P>0.05 for all, data not shown).

Stress resilience in adolescence and subsequent ulcerative colitis in adulthood

Men with low stress resilience have a statistically significant increased risk of UC during follow-up compared to men with high stress resilience (table 3) while moderate stress resilience was associated with a lower magnitude and non-statistically significant increased risk of UC. Modelling the three-category variable as a linear measure produced hazard ratios for the association of stress resilience with UC of 1.11 (1.04-1.19) and 1.04 (1.21), before and after adjustment, respectively. Modelling the nine-category measure, as linear produced hazard ratios of 1.05 (1.02-1.07) and 1.04 (1.02-1.07), respectively. When potential confounding factors were adjusted for, there was no notable influence on the association of stress resilience with UC for any specific individual factor (data not shown).

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Table 3 Stress resilience in adolescence and subsequent ulcerative colitis risk in adulthood at least four years after the conscription assessment

Stress resilience	Events/n	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
Main analysis			
Low	423/50965	1.24 (1.08-1.42)	1.19 (1.03-1.37)
Moderate	990/130994	1.11 (0.98-1.24)	1.08 (0.96-1.22)
High	386/57632	Reference	Reference
Sensitivity analysis – excluding those with elevated ESR, low EVF and underweight			
Low	339/41735	1.28 (1.10-1.49)	1.26 (1.08-1.47)
Moderate	843/113417	1.15 (1.02-1.31)	1.14 (1.01-1.30)
High	335/53007	Reference	Reference
Sensitivity analysis – follow-up at least 15 years after the conscription assessment			
Low	345/49278	1.26 (1.08-1.46)	1.22 (1.04-1.42)
Moderate	813/127750	1.12 (0.99-1.28)	1.11 (0.97-1.26)
High	311/55644	Reference	Reference

CI, confidence interval; HR, hazard ratio; n, number of subjects.
* Adjusted for BMI, ESR, EVF, height, parental SEI, appendicitis before age 20 years and region of residence.

The analysis excluding men who were more likely to have undiagnosed disease activity in adolescence (table 3) limited the sample to 1,517 men with UC. The results are consistent with main analysis for low stress resilience. Men with moderate stress resilience also had a statistically significant increased risk of UC, compared to men with high stress resilience.
Also, the association between low stress resilience in adolescence and future risk of UC remained during the follow-up beginning at least 15 years after the conscription assessment in adolescence (table 3). A total of 1,469 diagnoses of UC were identified and the median age of onset was 48 years (33-57).

The only evidence of effect modification by stress resilience for the association of prodromal disease activity markers for UC was for BMI (table 4). Underweight was only associated with a raised risk of UC in those with high stress resilience (p for interaction <0.05), suggesting that more aggressive disease in adolescence reduces the apparent protective influence of high stress resilience.

Table 4 BMI in adolescence and subsequent ulcerative colitis risk in adulthood at least four years after the conscription assessment, stratified by stress resilience level

Stress resilience level	Events/n	Unadjusted HR	Adjusted* HR

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		(95% CI)	(95% CI)
Low	423/50965		
Underweight		1.00 (0.77-1.29)	0.99 (0.76-1.28)
Normal weight		Reference	Reference
Obese/overweight		0.79 (0.53-1.16)	0.80 (0.54-1.17)
Moderate	990/130994		
Underweight		0.98 (0.81-1.19)	0.98 (0.81-1.19)
Normal weight		Reference	Reference
Obese/overweight		0.62 (0.46-0.84)	0.61 (0.45-0.82)
High	386/57632		
Underweight		1.71 (1.24-2.36)	1.72 (1.25-2.38)
Normal weight		Reference	Reference
Obese/overweight		1.02 (0.69-1.53)	1.00 (0.67-1.50)

CI, confidence interval; HR, hazard ratio; n, number.
* Adjusted for ESR, EVF, height, parental SEI, appendicitis before age 20 and region of residence.

DISCUSSION

In this national general population-based study of men, we assessed if stress resilience in adolescence is associated with the risk of a diagnosis of IBD in subsequent adulthood, among individuals without any gastrointestinal diagnoses in adolescence. Low stress resilience was associated with an increased risk of both CD and UC, diagnosed at least four years after stress resilience was assessed in adolescence; and the association with CD was of somewhat higher magnitude. The increased risk remained after adjustment for potential risk factors and markers of prodromal disease activity, as well as after exclusion of men with evidence of prodromal disease activity in adolescence and also after extending the follow-up entry to 15 years.

Our findings suggest that stress could contribute to the conversion of subclinical inflammation to symptomatic IBD in individuals at risk of the disease. Rather than stressful exposures, we used stress resilience as a marker of individual susceptibility to stress. Psychosocial stress increases inflammatory cytokines including interleukin (IL)-6, tumour necrosis factor (TNF) alpha and interferons (IFN). Long-term exposure to cytokines may cause impaired negative feedback regulation of HPA axis, resulting in increased cortisol concentrations.[12] Psychosocial stress may also impair intestinal barrier integrity and this may enable commensal bacteria to cross the gastrointestinal mucosa and provoke inflammation and disease.[13] Thus the mechanisms may involve pro-inflammatory influence and mucosal

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immune response or impaired barrier function, but the two potential mechanisms are not mutually exclusive.

We considered a range of potential confounding factors. Socioeconomic and demographic factors in childhood and adolescence, like parental SEI have previously been associated with IBD risk[31] and may be relevant to development of stress resilience. As appendicitis before age 20 years has been associated with a reduced UC risk,[10] we included this measure to increase precision when predicting risk. In this study, as previously observed,[22] we saw evidence of subclinical disease activity in adolescence prior to IBD diagnosis in adulthood: higher inflammation level was associated with raised IBD risk especially in CD, and low BMI was also associated with increased CD risk. Shorter stature in adolescence was associated with increased UC risk while overweight/obesity was associated with reduced risk. Lower BMI is often associated with malabsorption, especially in CD. Reduced growth rate in height can indicate the potential influence of malabsorption on growth in adolescence.[32] We adjusted our analyses for these potential confounding factors (and excluded men with evidence of prodromal disease activity in a sensitivity analysis) as they might influence stress resilience. Adjustment for these factors or exclusion of men has a modest effect on the magnitude of the associations (the association with UC was enhanced in terms of statistical significance), and therefore it is less likely that stress resilience is being driven by early disease activity in adolescence. Further evidence that the direction of the association is from stress resilience to IBD is that the associations persisted after excluding men more likely to have subclinical IBD in adolescence and during the 15 year follow-up, even though this was at ages (20-40 years) when IBD onset is commoner[9] and we had reduced statistical power.

There was no evidence of an interaction between stress resilience and the markers of prodromal disease activity with CD. However, low BMI was a risk for UC only among those with high stress resilience, suggesting that the apparent protective association of high stress resilience with UC is reduced in those with more aggressive subclinical disease in adolescence.

Our results for CD are consistent with The Nurses' Health Study[18] which looked at depressive symptoms and IBD risk and found these to be associated with a two-fold increased CD risk. Unlike that study, we also found a statistically significant association with UC, of lower magnitude than we found for CD. This may be due to statistical power as we had a larger

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number of participants. A case-control study with retrospectively reported stressful exposures[19] and a cohort study of life events[20] found no independent associations with IBD. The differences with our results could be due to a smaller number of events in the other studies, limiting power[19 20] or because they could not address individual variation in susceptibility to stress.

This cohort study had several practical advantages, including; a prospectively collected measure of stress resilience before typical IBD onset age; we took into account potential effects of prodromal disease activity in adolescence; and assessed stress resilience rather than major stressful events as a measure of psychosocial stress, since there are pronounced inter-individual differences in susceptibility to stress.[33] Low stress resilience in adolescence has also been associated with future depression and anxiety, providing evidence that this measure is a stable and persistent characteristic.[26]

Potential limitations include the lack of smoking information, as stress may increase the likelihood of heavier and prolonged smoking.[34] Smoking is associated with increased CD risk and inversely associated with UC.[5] Therefore, smoking might account for some of the association observed in CD (as a mediating mechanism), but cannot explain the observed raised UC risk associated with low stress resilience. Stress resilience was measured once during adolescence. Although we have seen long-term associations into middle age for this measure,[26] it is possible that resilience may change during adulthood thus reducing the precision and possibly the magnitude of our estimates. We were unable to take into account factors like diet, exposure to antibiotics and other personal characteristics that may be related to both stress resilience and IBD risk (including 'triggering events,' stressful or otherwise, that result in frank disease onset), thus residual confounding is possible. We did adjust for parental SEI in childhood as this is relevant to the microbiological landscape during the window of susceptibility in early life.[5] Patients with depression or anxiety (associated with low stress resilience)[26] - may seek medical care frequently.[35] Therefore, it is possible that those with lower stress resilience were more likely to seek medical care, and therefore obtain an IBD diagnosis earlier as IBD diagnostic delay can be common among adults[36] and this could have influenced our results. However, the opposite has been shown to occur: individuals with low stress resilience can be reluctant to seek medical care,[37] resulting in greater diagnostic delay. We know of no evidence to suggest that the genetic susceptibility to IBD influences stress resilience and if there were an association, our adjustment for markers

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of prodromal disease activity in adolescence would help to tackle confounding. The results apply to men up to age 57 years and may not be applicable to old ages or to women. During the study period, there could have been some variation in diagnostic accuracy but the majority of IBD diagnoses would have involved colonoscopy with histological and radiological criteria.[38 39] Colonoscopy has been used in Sweden since the late 1970s[40] and is currently used as a diagnostic procedure in the majority of IBD patients.[41 42] Sensitivity analyses beginning at least 15 years after the conscription assessment, a period when endoscopy was the main diagnostic method for IBD,[41 42] did not have a major impact on our results, still some inaccuracy cannot be ruled out. Some men changed diagnosis, usually beginning with UC then revised to CD (we used the later diagnosis but the first date to define events), as is often reported, as the distinction between CD and UC is not always possible,[38] particularly as some features of CD may be undetected at the early stages of the disease and histopathological details have to be available.[39] The average age of IBD diagnosis indicates a slightly later onset than commonly reported, but the ages at diagnosis are consistent with other studies in Sweden conducted during the same time period.[38 39] In particular, CD patients who had colorectal or small bowel disease were older at diagnosis.[39]

In summary, lower stress resilience in adolescence, is associated with an increased risk of IBD diagnosis in adulthood, possibly through pro-inflammatory influences or reduction of intestinal barrier integrity.

Contributors

SM and CM developed the hypothesis and design of the study. CM identified codes. CM prepared data and conducted analysis with the support from AH. SM, CM, KF and JH interpreted the study results. CM developed first manuscript, and all authors edited critically and approved the final manuscript.

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Data sharing statement: Our ethical approval does not permit us to share personal information.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on page, No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Abstract, page1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract, page1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
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	4-6
Bias	9	Describe any efforts to address potential sources of bias	Sensitivity analyses, see page 7
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-6

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Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	Sensitivity analyses, see page 7
		(*c*) Explain how missing data were addressed	Excluded, see page 4
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	See page 7
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	7-10
		(b) Give reasons for non-participation at each stage	No
		(c) Consider use of a flow diagram	No
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7 and table 1
		(b) Indicate number of participants with missing data for each variable of interest	No
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 1
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
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	8-11 and tables 2-3
		(*b*) Report category boundaries when continuous variables were categorized	4-6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of	13-14

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		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	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-14
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	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

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BMJ Open

Stress resilience and the risk of inflammatory bowel disease: cohort study of men living in Sweden

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Epidemiology
Keywords:	Inflammatory bowel disease < GASTROENTEROLOGY, EPIDEMIOLOGY, GASTROENTEROLOGY

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Title page

Manuscript title: Stress resilience and the risk of inflammatory bowel disease: cohort study of men living in Sweden

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ABSTRACT

Objective: To determine if low psychosocial stress resilience in adolescence (increasing chronic stress arousal throughout life) is associated with an increased inflammatory bowel disease (IBD) risk in adulthood. Subclinical Crohn's disease (CD) and ulcerative colitis (UC) can exist over many years and we hypothesise that psychosocial stress may result in conversion to symptomatic disease through its pro-inflammatory or barrier function effects.

Design: National register-based cohort study of men followed from late adolescence to middle age.

Setting: A general population cohort of men in Sweden.

Participants: Swedish population-based registers provided information on all men born between 1952 and 1956 who underwent mandatory Swedish military conscription assessment (n=239,591). Men with any gastrointestinal diagnoses (except appendicitis) prior to follow-up were excluded.

Primary outcome measures: An inpatient or outpatient diagnosis of Crohn's disease or ulcerative colitis recorded in the Swedish Patient Register (1970-2009).

Results: A total of 938 men received a diagnosis of CD and 1,799 UC. Lower stress resilience in adolescence was associated with increased IBD risk, with unadjusted hazard ratios (95% confidence intervals) of 1.54 (1.26-1.88) and 1.24 (1.08-1.42), for CD and UC, respectively. After adjustment for potential confounding factors, including markers of subclinical disease activity in adolescence they are 1.39 (1.13-1.71) and 1.19 (1.03-1.37).

Conclusions: Lower stress resilience may increase the risk of a diagnosis of IBD in adulthood, possibly through an influence on inflammation or barrier function.

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Strengths and limitations of this study

- This study used a prospectively collected measure of stress resilience (susceptibility to stress) in adolescence to examine its association with the risk of subsequent Crohn's disease and ulcerative colitis in adulthood.
- Stress resilience was measured before typical IBD onset age, and potential effects of prodromal disease activity in adolescence were taken into account in the analysis.
- Although some data suggest that stress resilience is stable over time, a potential disadvantage is that this study only measured it at one point in time.
- As we examined only stress resilience and did not have a direct measure of coping to capture the extent to which situations were perceived as stressful, we may have underestimated the magnitude of associations between stress resilience and IBD.
- The study did not have a measure of smoking and while this could be a pathway relevant to CD, it cannot explain the increased risk of UC.
- The results are based on men up to middle age and may not be applicable to older ages or to women.

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INTRODUCTION

The aetiology of inflammatory bowel disease (IBD) - Crohn's disease (CD) and ulcerative colitis (UC) - is believed to involve an interaction between genetic and environmental factors that results in an atypical immune response to gut microbiota.[1-3] Genetic factors are clearly important in the aetiology,[1 4] but the importance of environmental factors is signalled by temporal trends in incidence.[5] It appears that exposures in early life are potentially relevant to bowel colonisation and homeostasis,[6] such as infections and antibiotic therapy,[7] are particularly important in determining lifetime IBD risk suggesting a long and silent natural history[8] as frank disease onset occurs in adulthood.[9] Acute appendicitis before age 20 years has been linked consistently with a reduced risk of UC,[10 11] and it has been suggested recently that this may be due to genetic factors influencing risk of both appendicitis and UC risk.[11] Some exposures in adulthood may be risks,[5] but the best documented risk is cigarette smoking, which is associated with an increased risk of CD, but a reduced risk of UC.[5]

Psychosocial stress may increase inflammation, including through sympathetic nervous system influences,[12] and as subclinical low-grade inflammation related to IBD can exist over many years,[8] it is possible that stress may result in conversion to symptomatic IBD. Inflammation can increase permeability and compromise the integrity of the gastrointestinal mucosal barrier thus stress may promote passage over the epithelial barrier of bacterial pathogens and activate mucosal immune responses.[13]

Studies of psychosocial stress and IBD exacerbations have generated inconsistent results.[14-17] Low levels of stress and better coping strategies are associated with reduced risk of both CD and UC relapses in prospective studies[14 15] but not life events.[16 17] Psychosocial stress was associated with an increased risk of CD but not UC in a prospective cohort study[18] but not in other studies.[19 20] To our knowledge, no previous study has considered individual variation in stress susceptibility – a potentially important determinant of chronic stress arousal.[21] Here we use Swedish register data to examine the association of stress resilience in adolescence with CD and UC risk in subsequent adulthood.

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MATERIALS AND METHODS

Study population

The study population, and measures have been described in detail elsewhere.[22 23] Briefly, the participants were males born during 1952-1956. Most men were 18-19 years of age when they attended compulsory Swedish military conscription assessments during 1969-1976. The follow-up period for CD and UC was from four years after the conscription assessment (to reduce the possibility of reverse causation, such that symptomatic disease reduced stress resilience), until diagnosis, migration, death, or end of the study, 31st December 2009 (to a maximum age of 57 years).

The entire cohort comprised 284,198 males. Exclusions were for female sex, uncertain vital status or personal number, emigration or death before follow-up (n=5,504). Men who emigrated or died before the follow-up period were excluded because they could not contribute to the results. We also excluded men who were assessed before 17 years of age, did not undertake part of the conscription assessments or had missing data (n=35,101). Additionally, cohort members were excluded if they had any gastrointestinal diagnoses (except appendicitis), including IBD, at the conscription assessment including when recorded in the Patient Register prior to follow-up (n=4,002). In total 44,607 (15.7 %) men were excluded. The majority of the exclusions (11.7% of the cohort) were due to missing data for variables used in the analysis.

Data sources and measures

Socioeconomic and demographic data

Parental socioeconomic index (SEI) during childhood was obtained using the Population and Housing Census in 1960. We classified parental occupation into business owners/managers, farm owner/managers, manual workers, agricultural workers, office workers, and other. Data on date of birth, sex, region of residence, vital status (dead or alive) and migration were obtained from the Total Population Register.

The Swedish Military Service Conscription Register

Military service was compulsory for all men from age 18 years, with exceptions including those with severe medical conditions and entry involved a detailed assessment.[23]

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Stress resilience

Examination of psychological function at the conscription assessment produced a stress resilience score from 1 to 9, categorised as low (1-3), medium (4-6) and high (7-9) to maintain consistency with previous studies.[24 25 26] Following completion of a questionnaire, the interview was carried out by psychologists, whose inter-rater reliability was evaluated on regular basis[27] and estimated to be high (r=0.85) by a study conducted in 1972 and 1973.[28] The interview, which usually took 20-30 minutes, explored experience of potential conflicts or adjustment problems, as well as the ability to take the initiative and assume responsibilities at school, work or home.[28] The measure is based on five- or nine-scale normally distributed ratings of psychological energy, emotional control and social maturity.[26-29] Emotional control evaluated the ability to tolerate psychological stress in general as well as mental stability and emotional maturity.[26-29] Social maturity assessed if individuals were independent, socially extrovert and responsible.[26 27 29] Psychological energy assessed the ability to engage in various activities even when facing adversity. [26 27]

Height and body mass index

Height in centimetres was divided into fifths of the distribution. Heights < 144 cm, weight >178 kg or BMI <15 kg/m^2 were treated as non-valid values and excluded. Body mass index (BMI) was calculated from measures of height and weight and categorised as; underweight (15-18.49 kg/m2), normal weight (18.50-24.99 kg/m^2) and overweight/obese (>25kg/m^2). As there were few obese men at the conscription assessment, the obese and overweight categories (≥ BMI 25 kg/m^2) were combined.

Erythrocyte sedimentation rate

Erythrocyte sedimentation rate (ESR), indicating systemic inflammation, was standardised for erythrocyte volume fraction (EVF) by adjustment[22 23] and grouped into five categories: 1 mm/h, 2-6 mm/h, 7-10 mm/h, 11-14 mm/h and >=15 mm/h. ESR <1 or >98 mm/h and EVF <0.20 or >0.75 were considered as non-valid.

Gastrointestinal diseases at conscription assessment

GI diagnoses up to the time of the conscription assessment were obtained from the Conscription Register and The National Patient Register. The codes used are the Swedish version of the International Classification of Diseases (ICD) revision 8 (ICD-8 codes 530-539,

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543, 555-558, 560-577). Appendicitis prior to age 20 years was identified (ICD-8 codes 540-542) in the Conscription Register and surgical procedure codes (4510 and 4511) in the National Patient Register. We combined appendectomy and appendicitis prior to age 20 years into a single variable.

Geographical regions

Sweden was divided into northern, central and southern regions.

The National Patient Register

IBD diagnoses in adulthood were identified through ICD 8, 9 or 10 codes in the National Patient Register. Since 1964, the National Board of Health and Welfare has collected information on inpatient diagnoses and the register achieved complete coverage in 1987. The register expanded to include data on outpatient visits in 2001 and approximately 99% of all primary hospital diagnoses are recorded.[30]

IBD diagnoses

Primary and secondary diagnoses in inpatient and outpatient records were identified: CD (563.00 for ICD-8; 555.x for ICD-9; ICD-10 K50.x), and UC (563.10 for ICD-8; 556.x for ICD-9; ICD-10 K51.x). During the follow-up period, 938 and 1,799 men were identified as having diagnoses of CD and UC, respectively. A total of 438 men had records of both CD and UC. The most recent diagnosis was used to define disease phenotype, but the time of the first diagnosis defined disease onset. A total of 286 with UC changed to CD and 152 men with CD changed diagnosis to UC.

Statistical analysis

The association between stress resilience in adolescence and risk of subsequent IBD in adulthood was evaluated by Cox regression. We examined the proportional hazards assumption graphically, with no indication of violation. Separate models were used for CD and UC, with adjustment for parental socioeconomic index (SEI) in childhood, appendicitis prior to age 20 years, region of residence; and markers of potential prodromal disease activity in adolescence (ESR, EVF, height and BMI). We also modelled stress resilience as an ordinal or continuous variable to assess linear trend of associations with IBD risk for three-category and nine-category measures of stress resilience. We examined whether stress resilience modifies the association of BMI, height and inflammation in adolescence with IBD risk using

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stratification and interaction testing. Interaction terms for ESR, height and BMI with stress resilience were included in Cox models, with adjustment for the main effects. Age was used as the underlying time scale and unless otherwise specified, all measures were modelled as categorical variables.

Sensitivity analyses

Further analyses assessed if changes in diagnostic accuracy influenced the findings (by the end of the 1970s it was higher) and to assess whether stress resilience in adolescence is associated with a first IBD diagnosis, even after a minimum of 15 years from assessment; as in a previous study.[22] Among those who had IBD diagnoses (638 CD and 1469 UC) during this period (that started 15 years after the conscription assessment), 283 men had both CD and UC diagnosis. As is in the main analysis, the most recent diagnosis was used to define disease phenotype, but the time of the first diagnosis defined disease onset. Men who had IBD diagnosis during the period prior to the start of follow-up were excluded from the analysis (n=1,156). We also conducted a separate analysis excluding men more likely to have undiagnosed disease in adolescence, defined as low EVF (≤39), elevated ESR (≥15) or underweight (BMI 15-18.49 kg/m^2).

SPSS software version 23 and Stata version 13 were used. We considered P-values <0.05 and 95% confidence intervals not including 1.00 as statistically significant.

RESULTS

Participant characteristics

The study comprised 239,591 men followed from four years after the conscription assessment in late adolescence to a maximum of age 57 years (Table 1).

Table 1 Baseline characteristics of study participants by IBD diagnosis

	No IBD n=236854	CD N=938	UC n=1799
	n (%)	n (%)	n (%)
Stress resilience			
Low	50317 (24.0)	225 (23.5)	423 (21.3)
Moderate	129457 (58.3)	547 (55.1)	990 (54.7)
High	57080 (17.7)	166 (21.4)	386 (24.1)

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Mean (SD)	5.1 (1.9)	4.8 (1.8)	4.9 (1.9)
BMI			
Mean (SD) (kg/m2)	21.2 (2.6)	21.0 (2.6)	21.0 (2.5)
ESR in adolescence			
Mean (SD) (mm/h)	3.4 (3.5)	5.1 (5.9)	3.9 (4.2)
Median (range)	2 (1-89)	3 (1-51)	3 (1-55)
Height			
Mean (SD) (cm)	178.7 (6.4)	178.1 (6.4)	178.1 (6.5)
Parental SEI in 1960			
Manual worker	96493 (40.7)	423 (45.1)	766 (42.6)
Agricultural workers	9046 (3.8)	52 (5.5)	65 (3.6)
Farm owner/managers	23396 (9.9)	65 (6.9)	169 (9.4)
Office workers	65495 (27.7)	230 (24.5)	468 (26)
Business owners/managers	25267 (10.7)	98 (10.5)	182 (10.1)
Others (unknown)	17157 (7.2)	70 (7.5)	149 (8.3)
Appendicitis < 20 years			
No	234935 (99.2)	933 (99.5)	1796 (99.8)
Yes	1919 (0.8)	5 (0.5)	3 (0.2)
Age at diagnosis (years)			
Median (range)		40 (21-57)	47 (22-57)

BMI, body mass index; CD, Crohn's disease; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; n, number; SD, standard deviation; UC, ulcerative colitis; SEI, socioeconomic index.

Men with CD were more likely to have lower stress resilience and raised ESR compared to men with UC and men without IBD. Men with IBD were more likely to have lower parental SEI in childhood compared with men without IBD. Men with UC were less likely to have had an appendectomy or appendicitis prior to age 20 years. The median age of onset was 40 years (range 21-57) for CD and 47 years (range 22-57) for UC.

Stress resilience in adolescence and subsequent Crohn's disease in adulthood

Men with low and moderate stress resilience had an increased risk of subsequent CD compared to men with high stress resilience (table 2). Modelling the three-category variable as a linear measure, the hazard ratios (95% confidence intervals) for the association of stress resilience with CD (the average change in CD risk by one unit change in the three stress resilience categories) are 1.23 (1.11-1.35) and 1.17 (1.06-1.28), before and after adjustment, respectively. Modelling the nine-category measure as linear produces HRs of 1.09 (1.05-1.13) and 1.07 (1.03-1.11), respectively. Adjustment for any individual potential confounding factor had little influence on the association of stress resilience with CD, and it was the combined adjustment that had a notable influence (data not shown).

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Table 2 Stress resilience in adolescence and subsequent Crohn's disease risk in adulthood at least four years after the conscription assessment

Stress resilience	Events/n	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
Main analysis			
Low	225/50965	1.54 (1.26-1.88)	1.39 (1.13-1.71)
Moderate	547/130994	1.43 (1.20-1.70)	1.36 (1.14-1.62)
High	166/57632	Reference	Reference
Sensitivity analysis – excluding those with elevated ESR, low EVF and underweight			
Low	115/41735	1.53 (1.23-1.91)	1.45 (1.16-1.81)
Moderate	301/113417	1.34 (1.11-1.62)	1.32 (1.09-1.59)
High	101/53007	Reference	Reference
Sensitivity analysis – follow-up at least 15 years after the conscription assessment			
Low	147/49278	1.46 (1.15-1.87)	1.37 (1.07-1.75)
Moderate	377/127750	1.42 (1.16-1.76)	1.39 (1.22-1.71)
High	114/55644	Reference	Reference

CI, confidence interval; HR, hazard ratio; n, number.
* Adjusted for BMI, ESR, EVF, height, parental SEI, appendicitis before age 20 and region of residence.

The analysis excluding men more likely to have undiagnosed disease activity in adolescence (table 2) limited the sample to 743 men with CD, and the results are consistent with the main analysis. Also, the association between low stress resilience in adolescence and future risk of CD remained during the follow-up beginning at least 15 years after the conscription assessment in adolescence (table 2). A total of 638 diagnoses of CD were identified and the median age of onset was 47 years (range 33-57). There was no statistically significant interaction between stress resilience and markers of subclinical disease activity in CD (P>0.05 for all, data not shown).

Stress resilience in adolescence and subsequent ulcerative colitis in adulthood

Men with low stress resilience have a statistically significant increased risk of UC during follow-up compared to men with high stress resilience (table 3) while moderate stress resilience was associated with a lower magnitude and non-statistically significant increased risk of UC. Modelling the three-category variable as a linear measure produced hazard ratios for the association of stress resilience with UC of 1.11 (1.04-1.19) and 1.04 (1.21), before and after adjustment, respectively. Modelling the nine-category measure, as linear produced hazard ratios of 1.05 (1.02-1.07) and 1.04 (1.02-1.07), respectively. When potential

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confounding factors were adjusted for, there was no notable influence on the association of stress resilience with UC for any specific individual factor (data not shown).

Table 3 Stress resilience in adolescence and subsequent ulcerative colitis risk in adulthood at least four years after the conscription assessment

Stress resilience	Events/n	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
Main analysis			
Low	423/50965	1.24 (1.08-1.42)	1.19 (1.03-1.37)
Moderate	990/130994	1.11 (0.98-1.24)	1.08 (0.96-1.22)
High	386/57632	Reference	Reference
Sensitivity analysis – excluding those with elevated ESR, low EVF and underweight			
Low	339/41735	1.28 (1.10-1.49)	1.26 (1.08-1.47)
Moderate	843/113417	1.15 (1.02-1.31)	1.14 (1.01-1.30)
High	335/53007	Reference	Reference
Sensitivity analysis – follow-up at least 15 years after the conscription assessment			
Low	345/49278	1.26 (1.08-1.46)	1.22 (1.04-1.42)
Moderate	813/127750	1.12 (0.99-1.28)	1.11 (0.97-1.26)
High	311/55644	Reference	Reference

CI, confidence interval; HR, hazard ratio; n, number of subjects.
* Adjusted for BMI, ESR, EVF, height, parental SEI, appendicitis before age 20 years and region of residence.

The analysis excluding men who were more likely to have undiagnosed disease activity in adolescence (table 3) limited the sample to 1,517 men with UC. The results are consistent with main analysis for low stress resilience. Men with moderate stress resilience also had a statistically significant increased risk of UC, compared to men with high stress resilience. Also, the association between low stress resilience in adolescence and future risk of UC remained during the follow-up beginning at least 15 years after the conscription assessment in adolescence (table 3). A total of 1,469 diagnoses of UC were identified and the median age of onset was 48 years (33-57).

The only evidence of effect modification by stress resilience for the association of prodromal disease activity markers for UC was for BMI (table 4). Underweight was only associated with a raised risk of UC in those with high stress resilience (p for interaction <0.05), suggesting that more aggressive disease in adolescence reduces the apparent protective influence of high stress resilience.

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Table 4 BMI in adolescence and subsequent ulcerative colitis risk in adulthood at least four years after the conscription assessment, stratified by stress resilience level

Stress resilience level	Events/n	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
Low	423/50965		
Underweight		1.00 (0.77-1.29)	0.99 (0.76-1.28)
Normal weight		Reference	Reference
Obese/overweight		0.79 (0.53-1.16)	0.80 (0.54-1.17)
Moderate	990/130994		
Underweight		0.98 (0.81-1.19)	0.98 (0.81-1.19)
Normal weight		Reference	Reference
Obese/overweight		0.62 (0.46-0.84)	0.61 (0.45-0.82)
High	386/57632		
Underweight		1.71 (1.24-2.36)	1.72 (1.25-2.38)
Normal weight		Reference	Reference
Obese/overweight		1.02 (0.69-1.53)	1.00 (0.67-1.50)

CI, confidence interval; HR, hazard ratio; n, number.
* Adjusted for ESR, EVF, height, parental SEI, appendicitis before age 20 and region of residence.

DISCUSSION

In this national general population-based study of men, we assessed if stress resilience in adolescence is associated with the risk of a diagnosis of IBD in subsequent adulthood, among individuals without any gastrointestinal diagnoses in adolescence. Low stress resilience was associated with an increased risk of both CD and UC, diagnosed at least four years after stress resilience was assessed in adolescence; and the association with CD was of somewhat higher magnitude. The increased risk remained after adjustment for potential risk factors and markers of prodromal disease activity, as well as after exclusion of men with evidence of prodromal disease activity in adolescence and after extending the follow-up entry to 15 years after the assessment of stress resilience.

Rather than stressful exposures, we used stress resilience as a marker of individual susceptibility to stress. Psychosocial stress increases inflammatory cytokines including interleukin (IL)-6, tumour necrosis factor (TNF) alpha and interferons (IFN). Long-term exposure to cytokines may cause impaired negative feedback regulation of HPA axis, resulting in increased cortisol concentrations.[12] Psychosocial stress may also impair intestinal

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barrier integrity and this may enable commensal bacteria to cross the gastrointestinal mucosa and provoke inflammation and disease.[13] Thus the mechanisms may involve pro-inflammatory influence and mucosal immune response or impaired barrier function, but the two potential mechanisms are not mutually exclusive. A pro-inflammation tendency associated with low stress resilience could be of a systemic nature or specific to some organ systems, such as the gut. Previously, we found no association of stress resilience with multiple sclerosis,[25] where inflammation is confined to the central nervous system compartment and is thus potentially protected from some forms of systemic inflammation. In contrast, we found low stress resilience is associated with a raised risk of ischaemic stroke[24] and coronary heart disease.[31] Inflammation is implicated in the aetiology of these diseases, suggesting that there may be a somewhat general pro-inflammatory tendency among those with low resilience. The hazard ratios for the association of stress resilience with IBD are of relatively small magnitude and this is consistent with our interpretation that stress does not initiate pathogenesis but may influence conversion from subclinical to frank symptomatic disease. While this suggests that stress may be implicated in disease progression, this study provides insufficient evidence to suggest stress is of major clinical importance in determining IBD risk.

We considered a range of potential confounding factors. Socioeconomic and demographic factors in childhood and adolescence, like parental SEI have previously been associated with IBD risk[32] and may be relevant to development of stress resilience. As appendicitis before age 20 years has been associated with a reduced UC risk,[10] we included this measure to increase precision when predicting risk. In this study, as previously observed,[22] we saw evidence of subclinical disease activity in adolescence prior to IBD diagnosis in adulthood: higher inflammation level was associated with raised IBD risk especially in CD, and low BMI was also associated with increased CD risk. Shorter stature in adolescence was associated with increased UC risk while overweight/obesity was associated with reduced risk. Lower BMI is often associated with malabsorption, especially in CD. Reduced growth rate in height can indicate the potential influence of malabsorption on growth in adolescence.[33] We adjusted our analyses for these potential confounding factors (and excluded men with evidence of prodromal disease activity in a sensitivity analysis) as they might influence stress resilience. Adjustment for these factors or exclusion of men has a modest effect on the magnitude of the associations (the association with UC was enhanced in terms of statistical significance), and therefore it is less likely that stress resilience is being driven by early disease activity in adolescence. Further evidence that the direction of the association is from stress resilience to

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IBD is that the associations persisted after excluding men more likely to have subclinical IBD in adolescence and during the 15-year follow-up, even though this was at ages (20-40 years) when IBD onset is commoner[9] and we had reduced statistical power.

There was no evidence of an interaction between stress resilience and the markers of prodromal disease activity with CD. However, low BMI was a risk for UC only among those with high stress resilience, suggesting that the apparent protective association of high stress resilience with UC is reduced in those with more aggressive subclinical disease in adolescence.

Our results for CD are consistent with The Nurses' Health Study[18] which looked at depressive symptoms and IBD risk and found these to be associated with a two-fold increased CD risk. Unlike that study, we also found a statistically significant association with UC, of lower magnitude than we found for CD. This may be due to statistical power as we had a larger number of participants. A case-control study with retrospectively reported stressful exposures[19] and a cohort study of life events[20] found no independent associations with IBD. The differences with our results could be due to a smaller number of events in the other studies, limiting power[19 20] or because they could not address individual variation in susceptibility to stress.

This cohort study had several practical advantages, including; a prospectively collected measure of stress resilience before typical IBD onset age; we took into account potential effects of prodromal disease activity in adolescence; and assessed stress resilience rather than major stressful events as a measure of psychosocial stress, since there are pronounced inter-individual differences in susceptibility to stress.[34] Some men were excluded due to missing conscription assessment data: as this tended to be for men unsuitable for military service (not all tests were required) then the population, while broadly representative, would have excluded those in somewhat worse health.

Potential limitations include the lack of smoking information, as stress may increase the likelihood of heavier and prolonged smoking.[35] Smoking is associated with increased CD risk and inversely associated with UC.[5] Therefore, smoking might account for some of the association observed in CD (as a mediating mechanism), but cannot explain the observed raised UC risk associated with low stress resilience. Stress resilience was measured once

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during adolescence. Although we have seen long-term associations into middle age for this measure with future depression and anxiety, providing evidence that this measure is a stable and persistent characteristic,[26] it is possible that resilience may change during adulthood thus reducing the precision and possibly the magnitude of our estimates. Further potential limitations are that we do not have direct information on how stress is perceived, as captured by instruments such as the Perceived Stress Scale (PSS),[36] nor do we have direct information on coping strategies which are an important component of stressful experiences.[36 37] Could some men with higher stress resilience have attempted to falsify their results towards lower resilience, and therefore avoid some aspects of military service? We have no evidence of this but if this were the case, it would produce more conservative estimates. We have observed higher magnitude and consistent associations with other diseases, including depression and anxiety[26] in subsequent adulthood indicating this is unlikely to be a major problem.

We were unable to take into account factors like diet, exposure to antibiotics and other personal characteristics that may be related to both stress resilience and IBD risk (including 'triggering events,' stressful or otherwise, that result in frank disease onset), thus residual confounding is possible. We did adjust for parental SEI in childhood as this is relevant to the microbiological landscape during the window of susceptibility in early life.[5] Patients with depression or anxiety (associated with low stress resilience)[26] - may seek medical care frequently.[38] Therefore, it is possible that those with lower stress resilience were more likely to seek medical care, and therefore obtain an IBD diagnosis earlier as IBD diagnostic delay can be common among adults[39] and this could have influenced our results. However, the opposite has been shown to occur: individuals with low stress resilience can be reluctant to seek medical care,[40] resulting in greater diagnostic delay. We know of no evidence to suggest that the genetic susceptibility to IBD influences stress resilience and if there were an association, our adjustment for markers of prodromal disease activity in adolescence would help to tackle confounding. The results apply to men up to age 57 years and may not be applicable to old ages or to women.

The positive predictive value (PPV), indicating the proportion of registered diagnosis that are correct in the NPR is estimated 85-95% for common diagnoses.[30] A recent validation of IBD diagnoses in the NPR, using more detailed and accurate information, reported a PPV of 90% for UC and 81% for CD for patients who did not subsequently change diagnosis between UC and CD.[41] Where such changes in diagnosis occurred, only 8% of UC and 6% CD diagnoses

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were classified as non-IBD[41] (change in IBD diagnosis only occurred in a minority of our study population). While we cannot rule out the possibility of some influence of error, this suggests diagnostic inaccuracy is unlikely to account for our results, particularly as we performed sensitivity analyses to exclude the first 15 years of follow-up when diagnostic accuracy may have been less reliable due to less frequent use of endoscopy: this did not alter our results notably. The average age of IBD diagnosis indicates a slightly later onset than commonly reported, but the ages at diagnosis are consistent with other studies in Sweden conducted during the same time period.[42 43] In particular, CD patients who had colorectal or small bowel disease were older at diagnosis.[43]

In summary, lower stress resilience in adolescence, is associated with an increased risk of IBD diagnosis in adulthood, possibly through pro-inflammatory influences or reduction of intestinal barrier integrity.

Contributors

SM and CM developed the hypothesis and design of the study. CM identified codes. CM prepared data and conducted analysis with the support from AH. SM, CM, KF and JH interpreted the study results. CM developed first manuscript, and all authors edited critically and approved the final manuscript.

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Ethical permission: The Uppsala Regional Ethics Committee provided approval for the project (Dnr 2014/324). Ethical permission was given for access to data from national registers in a form where the identities of individuals could not be revealed to the researchers. Consent from the individual cohort members was not required.

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Data sharing statement: Our ethical approval does not permit us to share personal information.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on page, No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Abstract, page1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract, page1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
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	4-6
Bias	9	Describe any efforts to address potential sources of bias	Sensitivity analyses, see page 7
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-6

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Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	Sensitivity analyses, see page 7
		(*c*) Explain how missing data were addressed	Excluded, see page 4
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	See page 7
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	7-10
		(b) Give reasons for non-participation at each stage	No
		(c) Consider use of a flow diagram	No
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8 and table 1
		(b) Indicate number of participants with missing data for each variable of interest	No
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 1
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
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	8-11 and tables 2-3
		(*b*) Report category boundaries when continuous variables were categorized	4-6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of	13-15

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		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	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-15
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	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

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