

# Inflammatory bowel disease and laterality: is left handedness a risk?

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## Abstract

**Background**—Left handedness has been associated with inflammatory bowel disease (IBD) and autoimmune diseases.

**Aims**—To determine whether left handedness is associated with IBD in two prospective national birth cohorts.

**Methods**—Subjects with Crohn's disease (CD) and ulcerative colitis (UC) were identified from two national longitudinal birth cohorts at age 26 years (1970 British Cohort Study (BCS70), born in 1970) and age 33 years (National Child Development Study (NCDS), born in 1958). Laterality was determined at age 10 (BCS70) or seven (NCDS) years, based on hand preference for writing and foot preference for kicking a ball (BCS70 only). Multiple logistic regression was used to assess the relationship of handedness with CD, UC, and IBD in the cohorts combined and adjusted for sex.

**Results**—Both cohorts combined showed increased adjusted relative odds of 2.13 (95% confidence interval (CI) 0.97–4.65;  $p=0.059$ ), 2.13 (95% CI 0.92–4.91;  $p=0.077$ ), and 2.13 (95% CI 1.20–3.78;  $p=0.010$ ) for CD, UC, and IBD, respectively in left handers.

**Conclusions**—The study suggests a link between IBD and left handedness which may be genetic and/or environmental in origin.

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Keywords: inflammatory bowel disease; handedness

Left handedness has been associated with various diseases, many of which are thought to have an autoimmune origin. These include asthma and other atopic conditions, migraine, thyroid disease, type I diabetes mellitus, autism, developmental learning disorders, and acquired immunodeficiency syndrome.<sup>1–5</sup>

The inflammatory bowel diseases (IBDs) Crohn's disease (CD) and ulcerative colitis (UC) have also been linked with left handedness in some but not all studies. Geschwind and Behan originally described an association in 1982 based on self reporting of immune disorders in customers using a specialised shop for left handers.<sup>4</sup> A case control study later found a significant increased odds ratio (OR) for left handedness in those with CD (OR 2.5, 95% confidence interval (CI) 1.5–4.2), UC (OR 2.9, 95% CI 1.4–5.9), and IBDs overall (OR 2.7, 95% CI 1.7–4.4) after adjusting for sex.<sup>6</sup> However, a hospital based case control study of 83 subjects with CD or UC failed to find such an association.<sup>7</sup>

A meta-analysis of these studies supported a significant association between left handedness and IBD overall (OR 2.01, 95% CI 1.35–2.98).<sup>8</sup> Other studies have included both CD and UC with other diseases of “immune disorders” but have had insufficient numbers of patients to analyse them separately.<sup>9 10</sup>

We have used prospectively collected data from two national population based birth cohorts to examine the risk of IBD in relation to hand preference. When combined, these form the largest and only nationally representative study in which the association between handedness and IBD has been examined. The study design therefore had the advantage of reducing many of the potential biases associated with previous case control studies.

## Subjects and measures

### SUBJECTS

This study used data from two nationally representative birth cohort studies: the 1970 British Cohort Study (BCS70) and the National Child Development Study (NCDS). These prospective ongoing studies follow all those born during one week (5–11 April 1970 for the BCS70 and 3–9 March 1958 for the NCDS) who live in Great Britain.<sup>11</sup>

For the BCS70, a postal self completion survey was conducted in 1995–6 when cohort members were aged 25–26 years. This asked if they had “ever had or been told by a doctor that you had a diagnosis of Crohn's disease, ulcerative colitis”. Data collected from an earlier BCS70 survey at 16 years, in addition, identified two cohort members with IBD. All self reported cases of IBD were contacted again by post to confirm their responses and to seek permission to contact their physician to confirm the diagnosis.<sup>12</sup>

The response rate of those subjects traced at age 26 years in the BCS70 cohort was 77%.<sup>12</sup> Of 8150 subjects from the BCS70 used in these analyses, 21 had CD and 19 had UC.

For the NCDS, the diagnosis of IBD was established using the international coding of disease codes reported at face to face interviews when subjects were 23 or 33 years old. The response rate of those traced at 33 years was 85%.<sup>13</sup> Physicians were not asked to confirm these diagnoses. Of 9771 subjects from the NCDS used in these analyses, 17 had CD and 16 had UC.

### Abbreviations used in this paper: IBD,

inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; OR, odds ratio; BCS, British Cohort Study; NCDS, National Child Development Study.

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Table 1 Relative odds for the association between left handedness and sex in two national birth cohorts

Sex	Left handed subjects (%)	Relative odds (95% CI)	Pearson's two tailed p value
Male	1045/8379 (12.5%)	1.28 (1.17–1.41)	0.000
Female	882/8818 (10.0%)	1.00	

Despite loss to follow up in both cohorts since their inception, cohort members for whom data were available were broadly representative of the original cohorts, with approximately two thirds of both cohorts used in the analyses having a father with a manual social class.<sup>14 15</sup>

#### MEASURES

Midwives recorded the sex of each subject at birth in 1958 (NCDS) or 1970 (BCS70).

For the BCS70, handedness and foot preference were ascribed following a medical examination and interview at age 10 years. The child was asked: "which hand is used for writing?" and "which foot is used for kicking a ball?" Responses of right, left, either, or unknown were recorded.

For the NCDS, the response of parents at interview with a health visitor was recorded in 1965 when the children were seven years old. The question "does the mother think the child is: right handed, left handed, mixed right and left, or don't know" was used.

Responses of "either" in the BCS70 or "mixed right and left" in the NCDS were excluded from the analysis.

#### STATISTICAL ANALYSIS

The two cohorts were combined to increase statistical power. Cross tabulation was used to investigate the relationship between sex and IBD and sex and handedness, as sex was considered to be a potential confounding factor. Adjustment was similarly made for cohort.

Cross tabulation and Pearson's  $\chi^2$  test were used to assess the relationships between handedness and UC, CD, and IBD. These were performed after combining both cohorts. Due to the small numbers, the Fisher's exact test was used to assess foot preference to kick a ball in the BCS70. Relative odds were calculated with 95% CI. All p values reported were two tailed. Logistic regression analysis was used to adjust for sex and birth cohort.

#### Results

Complete data on handedness and sex were available for 8134/9757 (83%) subjects from the BCS70 who responded at age 26 years and from 9062/11184 (81%) subjects from the NCDS who responded at age 33 years. Overall,

71 patients with complete data available for analysis were identified with IBD (38 with CD and 33 with UC).

For foot preference, data from 7691/9757 (78%) and 8134/9757 (83%) subjects from the BCS70, respectively, were available for analysis (20 with CD, 18 with UC).

#### HANDEDNESS AND SEX

Sex was considered to be a potential confounding factor even though there was no statistically significant association between CD, UC, or IBD combined and sex in this study. Left handedness showed a statistically significant association with male sex in both cohorts combined ( $\chi^2=26.3$ ,  $p=0.000$ ) (table 1).

#### COHORT AND IBD

There were 31 patients with IBD in the NCDS and 40 in the BCS70 who had complete data available for analysis. A diagnosis of IBD was more likely in the BCS70 cohort than in the NCDS (unadjusted OR 1.44, 95% CI 0.9–2.37;  $p=0.109$ ).

#### HANDEDNESS AND IBD

Both cohorts showed increased relative odds for IBD in left handers. These were statistically significant for the BCS70 (adjusted for sex, OR 2.28, 95% CI 1.08–4.79; Fisher's  $p=0.031$ ) but not for the NCDS (adjusted for sex, OR 1.94, 95% CI 0.79–4.75; Fisher's  $p=0.147$ ).

Left handers had increased relative odds for both CD and UC when analysed as separate diseases in the combined cohorts although this was not statistically significant. Adjusting for sex and cohort did not alter the significance of the association (table 2)

IBD (CD or UC) was significantly associated with left handedness when the two cohorts were combined. Again, adjusting for sex and cohort did not alter these findings significantly (table 2).

#### FOOT PREFERENCE AND IBD

Data on foot preference were only available for the BCS70 cohort. There was no statistically significant association between foot preference and CD. For those with UC, 27.8% showed left foot preference compared with 12.7% of those without the disease (unadjusted relative odds 2.64, 95% CI 0.94–7.42; Fisher's two tailed  $p=0.069$ ). After adjusting for sex, the relative odds for disease in those reporting left foot preference were 0.79 (95% CI 0.18–3.39;  $p=0.747$ ) 2.59 (95% CI 0.92–7.30;  $p=0.073$ ), and 1.56 (95% CI 0.69–3.56;  $p=0.291$ ) for CD, UC, and IBD, respectively.

Table 2 Relative odds for the association between left handedness and inflammatory bowel diseases (IBD) in two national birth cohorts combined

	No left handed with disease (%)	No left handed without disease (%)	Unadjusted relative odds (95% CI)	Adjusted relative odds* (95% CI)
CD	8/38 (21.1%)	1919/17158 (11.2%)	2.12 (0.97–4.63) $p=0.067$	2.12 (0.97–4.64) $p=0.059$
UC	7/33 (21.2%)	1920/17163 (11.2%)	2.14 (0.93–4.93) $p=0.089$	2.12 (0.92–4.90) $p=0.078$
IBD combined	15/71 (21%)	1912/17125 (11%)	2.13 (1.20–3.78) $p=0.008$	2.13 (1.19–3.77) $p=0.010$

CD, Crohn's disease; UC, ulcerative colitis.

\*Adjusted for sex and cohort.

## Discussion

This study supports the original findings of Geschwind and Behan<sup>4</sup> and Searleman and Fugagli<sup>6</sup> by demonstrating a statistically significant twofold increased risk of IBD in left handed subjects. The increased relative odds for foot preference observed for UC also endorses these data.

The study has the advantage of using data from two population based national cohort studies thus avoiding many of the potential biases found in case control studies. Case ascertainment in these studies was likely to be complete as they both reported a very high prevalence of IBD.<sup>12,13</sup> In both cohorts, those responding to the disease surveys at 26 (BCS70) and 33 (NCDS) years were largely representative of the original birth cohorts with some additional loss to follow up of those whose fathers were Registrar General's social class V at the time of their birth.<sup>14,15</sup> However, social class was not associated with handedness or IBD in either cohort and therefore is unlikely to be a confounding factor.<sup>12,13</sup>

Male subjects were significantly more likely to be left handed than females, a finding that has been previously reported.<sup>16</sup> However, sex was not associated with the risk of CD, UC, or IBD combined in either cohort in this study, and was therefore unlikely to be a confounding factor as it has been in other studies. Adjusting for sex or cohort did not significantly alter the relationships found between left handedness and IBD (table 2). Cohort members from the BCS70 (born 1970) were more likely to have IBD than those in the NCDS (born 1958) and this follows recent temporal trends in IBD prevalence.<sup>12</sup>

Eleven percent of subjects without IBD reported using their left hand preferentially for writing. This was similar in both cohorts, and is similar to that reported in the control groups of earlier case control studies.<sup>6,7</sup> We did not assess the degree of handedness but as we excluded those who responded "either" or "mixed right and left" to handedness questions, subjects included in the study will be those with the most extreme lateralisation of hand preference. Some misclassification of hand and foot preference will have occurred but this is not likely to have resulted in systematic bias as lateralisation was determined at least two years (and usually more than 10 years) before the onset of symptoms of IBD was made in any of the subjects.

Left foot preference was increased in those with UC (OR 2.59) although this was not statistically significant and was based on a small number of cases from one cohort only. However, foot preference is thought to have a less consistent association with cerebral lateralisation than left handedness.<sup>17</sup>

The association between left handedness and IBD is important as it suggests that the two may share common aetiological influences or may indicate a marker of susceptibility. These could reflect shared genetic traits, environmental factors acting in early life, or a combination of these.

One controversial hypothesis suggests that the influences of testosterone (excess production or increased sensitivity to it) in utero may alter growth of the left cerebral hemisphere and the thymus simultaneously, resulting in an association between left handedness and certain T cell dependent immune disorders.<sup>18</sup> Some small immunological studies have supported this theory by finding different T cell subsets,<sup>19</sup> cytokines,<sup>20</sup> and autoantibodies<sup>21</sup> between left and right handers. However, the aetiological processes involved in IBD and other immune mediated diseases reported in association with left handedness are poorly understood and the model has received much criticism.<sup>8</sup>

Seasonal differences in the birth of left handed girls (but not boys) have been reported,<sup>22</sup> suggesting that environmental factors (possibly infectious agents) may be important. Seasonal differences in birth of subjects with IBD are also described.<sup>23,24</sup> Excess female subjects with IBD, especially CD, have also been reported in some studies.<sup>25</sup>

Genetic explanations of the association between left handedness and autoimmune diseases have been suggested. Different HLA haplotypes have been described between left and right handers that may also be found in some diseases, including UC,<sup>26</sup> although these are inconsistent.<sup>27</sup>

In summary, this study has found an increased risk of IBD, in particular UC, in left handed subjects from two national birth cohorts. Such an association may help elucidate the aetiological processes leading to IBD although at present the mechanisms remain uncertain.

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