**Supplementary note: Heritability on the liability scale for inflammatory bowel disease in twin studies**

We estimated the heritability for Crohn’s disease (CD) and ulcerative colitis (UC) using all published twin studies to date(2). So far, there have been four published twin studies for IBD, originating from Sweden(3–5), Denmark(6, 7), UK(8, 9) and Germany(10). The raw data from these four cohorts are summarized in Table S9. For CD, 41 out of 122 monozygotic twin pairs were concordant for disease status, and 11 out of 216 dizygotic twin pairs were concordant for disease status. For UC, 22 of 151 monozygotic twin pairs were concordant for disease status, and 9 out of 223 dizygotic twin pairs were concordant. CD shows a higher twin concordance than UC.

As the prevalence varies in the reported countries(11), we adopted prevalences of 0.005 and of 0.0025 for CD and UC, respectively. Following Tysk’s procedure(3), given the number of index cases (proband), which are both affected twin cases diagnosed independently, and the number of secondary cases, which are discovered by interview, the heritability of CD and UC can be estimated as , in which and are intra-class correlations for monozygotic twins and dizygotic twins, respectively, on the scale of liability. The intra-class correlation is estimated using Reich’s method(12), which is an extension of Falconer’s method(13).

**Heritability on the liability scale for CD and UC**

As the type of the proband concordance in the UK cohort was not reported, we calculated the heritability by setting all concordant UK IBD twins as either index cases (Table S10) or secondary cases (Table S12).

For CD, the estimated heritability was 0.786 0.143 when the UK concordant twins were set to index cases, and 0.912 0.135 when set to secondary cases. The mean of these estimates was used (0.804 0.139).

For UC, the estimated heritability was 0.718 0.133 when the UK concordant twins were set to index cases, and 0.622 0.133 when set to secondary cases. As for CD, the mean of these estimates was used (0.667 0.133).

Our estimation assumed no non-additive genetic variation on the scale of liability, and assumed that twin concordance due to shared environmental factors is the same for MZ and DZ twin pairs.

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Table S9 Summary of published twin data for inflammatory bowel disease

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Disease | Cohort | Total | Concordant pairs | Index case pairs () | Secondary to the interview () |
| CD | Swedish MZ | 33 | 9 | 6 | 3 |
|  | Danish MZ | 10 | 5 | 2 | 3 |
|  | UK MZ | 48 | 16 |  |  |
|  | German MZ | 31 | 11 | 11 | 0 |
|  |  |  |  |  |  |
|  | Swedish DZ | 50 | 1 | 0 | 1 |
|  | Danish DZ | 27 | 0 | 0 | 0 |
|  | UK DZ | 81 | 8 |  |  |
|  | German DZ | 58 | 2 | 2 | 0 |
|  |  |  |  |  |  |
| UC | Swedish MZ | 41 | 6 | 0 | 6 |
|  | Danish MZ | 21 | 3 | 1 | 2 |
|  | UK MZ | 52 | 7 |  |  |
|  | German MZ | 37 | 6 | 6 | 0 |
|  |  |  |  |  |  |
|  | Swedish DZ | 49 | 3 | 1 | 2 |
|  | Danish DZ | 43 | 2 | 0 | 2 |
|  | UK DZ | 68 | 3 |  |  |
|  | German DZ | 63 | 1 | 1 | 0 |

Notes:

1 Initially, the Swedish twin data, with 80 twins, was published in 1989. In 2003 they were revisited, and in 2011 another 39 and 54 twins were included for CD and UC, respectively. The Danish cohort was published in 2000 and revisited in 2005. The UK sample was published in 1996 and updated in 1998. The German twins data was published in 2005.

2 In the UK cohort, the numbers for the index cases and secondary cases discovered by interview was not reported.

Table S10 The combined cohort assuming all UK concordant twins are index cases.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Disease | Cohort | Total () | Concordant pairs | Index case pairs () | Secondary to the interview () | Proband concordance rate |
| CD | MZ | 122 | 41 | 35 | 6 | 0.48 |
|  | DZ | 216 | 11 | 10 | 1 | 0.093 |
|  |  |  |  |  |  |  |
| UC | MZ | 151 | 22 | 14 | 8 | 0.218 |
|  | DZ | 223 | 9 | 5 | 4 | 0.039 |

Notes

Proband concordance rate , according to Tysk, C, et al.

Table S11 Summary statistics for calculating heritability for CD and UC

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Disease |  | Prevalence |  |  |  |  |  |
| CD | Population | 0.005 | 2.576 | 0.0145 | 2.900 |  |  |
|  | MZ | 0.48 | 0.050 | 0.398 | 0.829 | 0.879 (0.047) |  |
|  | DZ | 0.093 | 1.323 | 0.166 | 1.785 | 0.486 (0.055) |  |
|  |  |  |  |  |  |  | 0.786 (0.143) |
|  |  |  |  |  |  |  |  |
| UC | Population | 0.0025 | 2.807 | 0.00776 | 3.104 |  |  |
|  | MZ | 0.218 | 0.779 | 0.295 | 1.353 | 0.724 (0.045) |  |
|  | DZ | 0.039 | 1.762 | 0.084 | 2.15 | 0.375 (0.049) |  |
|  |  |  |  |  |  |  | 0.718 (0.133) |

Notes

is the threshold given the prevalence in the standard normal distribution.

is the density of the threshold in the standard normal distribution.

is the intensity of selection.

is the intraclass correlation, in which is the threshold given the population prevalence and is the threshold given the relationship—MZ or DZ.

The sampling variance, , which is calculated is in parentheses. is the number affected.

, and .

Table S12 Combined cohort assuming all UK cases secondary cases

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Disease | Cohort | Total | Concordant pairs | Indexls case pairs () | Secondary to the interview () | Proband concordance rate |
| CD | MZ | 122 | 41 | 19 | 22 | 0.426 |
|  | DZ | 216 | 11 | 2 | 9 | 0.060 |
|  |  |  |  |  |  |  |
| UC | MZ | 151 | 22 | 7 | 15 | 0.184 |
|  | DZ | 223 | 9 | 2 | 7 | 0.049 |

Table S13 Summary statistics for calculating heritability for CD and UC

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Disease |  | Prevalence |  |  |  |  |  |
| CD | Population | 0.005 | 2.576 | 0.0145 | 2.900 |  |  |
|  | MZ | 0.426 | 0.187 | 0.392 | 0.920 | 0.852 (0.044) |  |
|  | DZ | 0.060 | 1.55 | 0.119 | 1.983 | 0.394 (0.051) |  |
|  |  |  |  |  |  |  | 0.912 (0.135) |
|  |  |  |  |  |  |  |  |
| UC | Population | 0.0025 | 2.807 | 0.00776 | 3.104 |  |  |
|  | MZ | 0.184 | 0.900 | 0.266 | 1.446 | 0.597 (0.043) |  |
|  | DZ | 0.049 | 1.654 | 0.101 | 2.061 | 0.296 (0.051) |  |
|  |  |  |  |  |  |  | 0.602 (0.133) |