# No Evidence of Sex Differences in Heritability of Irritable Bowel Syndrome in Swedish Twins

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Studies have shown that familial aggregation is of importance for abdominal symptoms including irritable bowel syndrome and there are a few reports of a moderate heritability for irritable bowel syndrome. Sex differences in prevalence and incidence of irritable bowel syndrome have been demonstrated however less is known about sex differences in heritability. The objective was to investigate whether there were sex differences in heritability of irritable bowel syndrome while accounting for different prevalences among women and men in different age groups. A sample of 45,750 Swedish twins, whereof 16,961 were complete twin pairs, participated in a telephone interview. The sample was divided into three age groups (40–54, 55–64 and 65 years and older) and the diagnosis of irritable bowel syndrome was operationally defined with a number of disorder specific symptoms. Standard biometrical model fitting analyses were conducted using raw ordinal data from same-sex and opposite-sex twins. The prevalence of irritable bowel syndrome was greater among women than men and more prevalent at younger ages (e.g., women 10.3%, men 6.3% at ages 40–54 years vs. women 6.1%, men 4% at ages over 65 years). The heritability of the disorder was approximately 25% in all age groups. We found no evidence for sex differences in heritability in any of the age groups, however, models allowing prevalences of irritable bowel syndrome to differ between sexes and age groups fitted best.

Irritable bowel syndrome (IBS) is relatively common and symptoms are reported in 5 to 20% of European and United States populations. IBS is more prevalent among women than men (Drossman et al., 2002; Talley, 2005; Thompson, 1997). The syndrome is characterized by recurrent abdominal problems such as pain, diarrhea or constipation, and feelings of abdominal distension. IBS is commonly described as a multifactorial disorder that may have a genetic component but many pieces to the etiology of the disorder still remain to be explored. In the last decade several studies have examined the role of familial factors in the etiology of IBS. These studies have shown that familial aggregation is of importance for abdominal symptoms including IBS (Kalantar et al., 2003a, 2003b; Locke 3rd et al., 2000; Talley & Spiller, 2002). However, familial aggregation does not distinguish between effects due to genetic influences or to shared exposure to environmental factors, including learned responses to abdominal problems.

Previous twin studies of functional bowel symptoms and IBS have shown somewhat inconsistent results concerning the genetic contribution to the etiology of the disorder. In these studies the heritability of IBS ranges from 0 to 57% (Bengtson et al., 2006; Lembo et al., 2007; Levy et al., 2001; Mohammed et al., 2005; Morris-Yates et al., 1998). Moreover, in one of these studies a parental history of IBS was a stronger predictor of IBS than having a twin with IBS. The authors suggested that social learning was equally or more important than genetic factors in the etiology of the disorder (Levy et al., 2001). This was also supported in one twin study that found shared environments to be of greater importance than genetic influences for the disorder (Mohammed et al., 2005). Nonetheless, the majority of the previous twin studies have found genetic susceptibility to be of importance for development of IBS but knowledge is scarce regarding sex differences in the etiology of IBS given the findings of higher prevalence and incidence among women than men.

The aim of this population-based twin study was to investigate the relative contribution of genetic and

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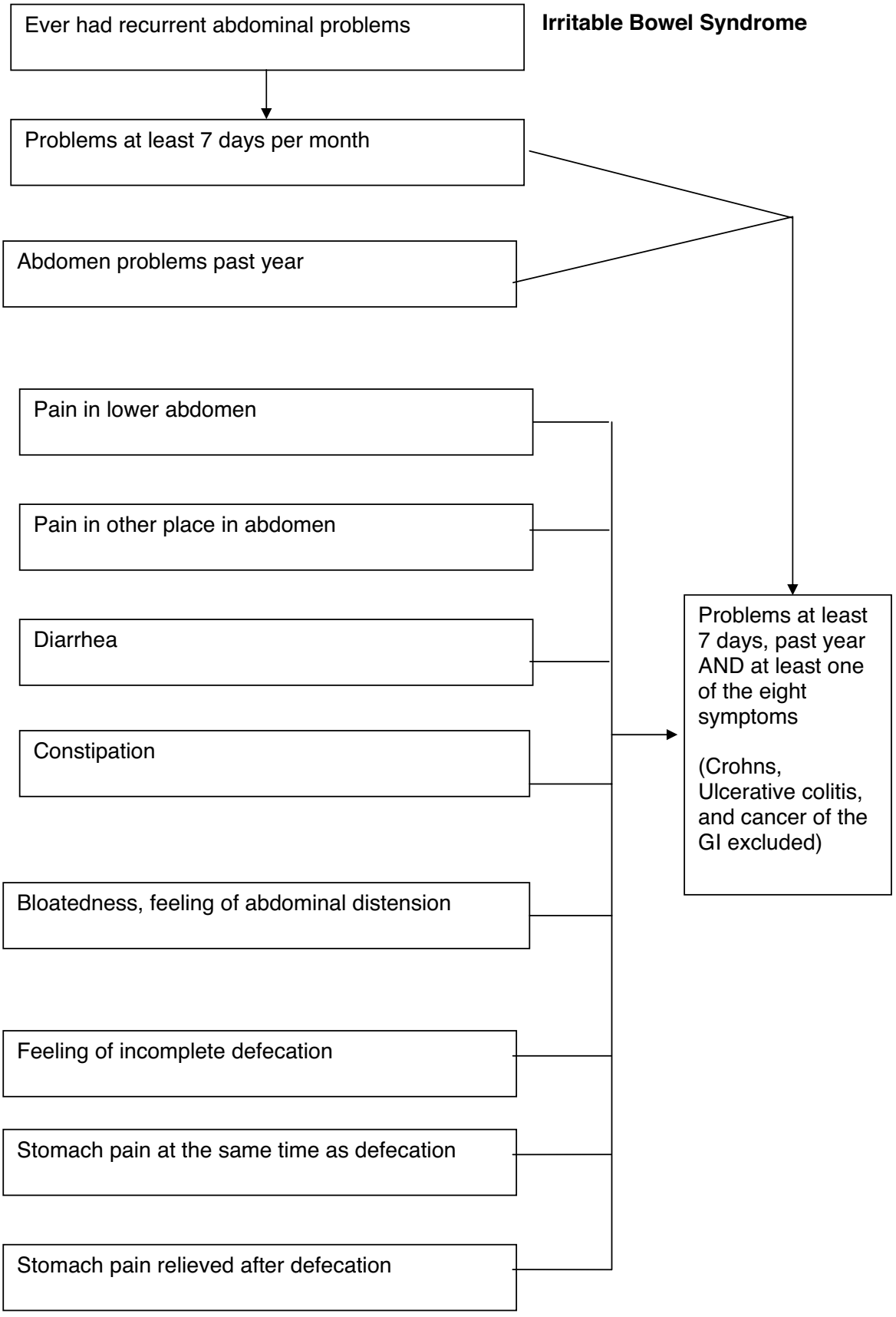


**Figure 1**

Definition of irritable bowel syndrome (IBS) in Swedish twins.



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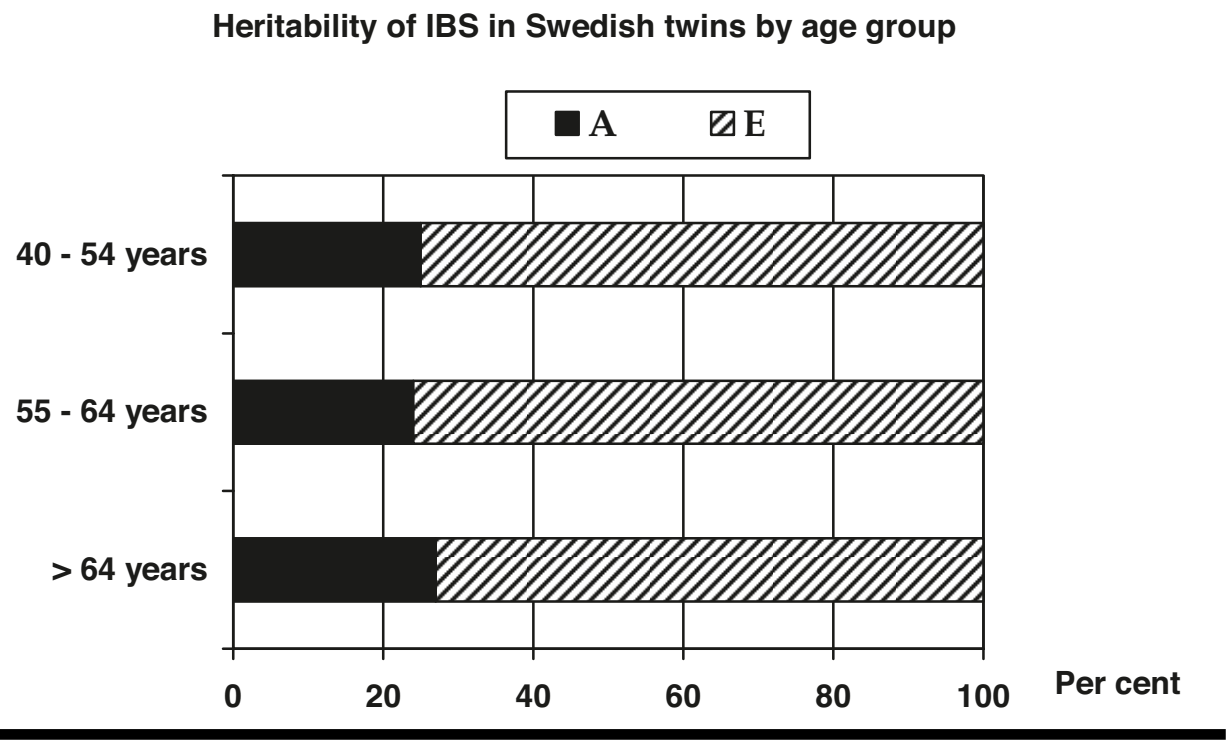


**Figure 2**

Heritability of irritable bowel syndrome (IBS) in Swedish twins by age group.

environmental factors to IBS, including both monozygotic (MZ) and same and opposite-sex dizygotic (DZ) twin pairs in order to test for sex-specific genetic influences on IBS. Based on previous findings in the literature, we expect IBS to be more prevalent among women than men and this sex difference is more pronounced at younger ages. Against the background of mixed reports of the relative importance of genetic influences we expect a moderate heritability and that there are sex differences in genetic influences on IBS.

## Materials and Methods

### Sample

Data were collected between 1996 and 2002 when the Screening Across the Lifespan Twin study (SALT) was conducted. All adult twins born 1958 or earlier from the Swedish Twin Registry (Lichtenstein et al., 2002) were contacted for a computer-assisted telephone interview. Of 63,041 individuals, 45,750 (72.5%) participated, including both members of 16,961 pairs (pairwise response rate 54%). The sample of responders included 11,142 MZ twins, 17,337 same-sex DZ twins, 16,419 opposite-sex DZ (OS) twins, and 852 twins of unknown zygosity. Age at interview ranged from 40 to 103 years of age (mean = 59.28 years, *SD* = 11.11). The male portion of the sample was 46.4%.

In order to establish the zygosity of the same-sex twin pairs, the question 'During childhood, were you and your twin partner as like as two peas in a pod?' was asked at the time of registry compilation. If both individuals of a pair responded *alike* they were classified as MZ, if both responded *not alike* they were classified as DZ. If twins in a pair did not agree on this item, the question was repeated in the SALT interview. If the twins were still in disagreement, the answer to the question, 'How often did strangers have difficulty distinguishing between you and your twin partner when you were children?' was used. If both individuals of a pair responded *almost always or always* or *often* they were classified as MZ. If both individuals of a pair responded *seldom* or *almost never or never*, they were classified as DZ. The zygosity diagnosis was confirmed using DNA markers in a subset (*N* = 199 pairs) in the sample, and proved correct in 99% of the pairs. A more detailed description of the SALT study has been published elsewhere (Lichtenstein et al., 2002; Pedersen et al., 2002).

The study was reviewed and approved by the Ethical Committee of the Karolinska Institutet, the Swedish Data Inspection Board, and the IRB of the University of Southern California.

### Measures

The diagnosis of IBS was operationally defined using the following specific symptoms: pain in lower abdomen, pain in other place in abdomen, diarrhea, constipation, feeling of abdominal distension, feeling of incomplete defecation, and abdominal pain with onset at defecation or relieved pain after defecation. Following a positive response to two introductory questions reading 'Have you ever had recurrent



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abdominal problems during the past year' and 'Did the problems occur during at least 7 days per month', the individuals were asked about the specific symptoms. Persons with at least one of the above eight symptoms were defined as IBS patients (see flowchart Figure 1). Individuals with a history of the following organic gastrointestinal diseases were excluded: inflammatory bowel disease (morbus Crohn, ulcerative colitis), peptic ulcer disease and gastrointestinal (GI) cancer. The sample was divided into three age groups, 40–54 years, 55–64 years and 65 years and older.

#### Analytical Procedure

In order to investigate the heritability of IBS we used standard biometrical genetic model-fitting methods (Neale & Maes, 2002). We fitted genetic models to the raw ordinal data by Maximum Likelihood (ML) using Mx (Neale et al., 2002). Our analyses focused on fitting models allowing for additive (A) genetic effects plus shared (C) and nonshared (E) environmental effects. The goodness-of-fit of the full ACE model was then compared to that of the submodels by likelihood ratio chi-square tests. Akaike's Information Criterion (AIC), which is an index of both goodness-of-fit and parsimony, is calculated for each model and the model with the lowest AIC index is chosen as the best fitting model. Inclusion of opposite-sex twins provides an opportunity to test whether different genes and different environments are operating in men than in women (Neale & Cardon, 1992). In order to obtain parameter estimates for $a^2$, $c^2$, $e^2$ and a parameter, $R_g$, which indicates whether genetic effects are the same or different for the two sexes, we used all six groups simultaneously (MZ male, DZ male, MZ female, DZ female, DZ opposite-sex male–female, DZ opposite-sex female-male) and a series of models were then tested in three age groups (40–54, 55–64 and 65 years and older). We started out by fitting a model with free parameter and different prevalence estimates for women and men in the three age groups, thereafter the following models were tested: in Model 2 free ACE parameters, but same prevalence for men and women, and free $R_g$ were estimated. Model 3 included free ACE parameters, but same prevalence for men and women, and $R_g$ fixed at .5. Model 4 constrained ACE parameters and prevalence to be equal across sex, and $R_g$ fixed at .5. Models 5–7 were submodels AE, CE and E respectively. Model 8 assumed different prevalences for men and women, $R_g$ fixed at .5, and ACE parameters were free. In Model 9 parameter estimates were fixed to be equal for men and women. Models 10–12 were submodels AE, CE and E, respectively.

## Results

Among the total number of responders, 3241 subjects were identified as IBS cases. The most frequently reported symptoms were feelings of abdominal distension (bloatedness; 72.6%), feeling of incomplete defecation (57%), pain in lower abdomen (42.8%), stomach pain relieved after defecation (38%), and constipation (37%); 16.8% of the cases reported only one symptom and 54.8% had three or more symptoms.

**Table 1**

Number of Cases and Prevalence's of IBS by Sex and Age Groups in the Swedish Screening Across the Lifespan Twin Study

| Age at interview | IBS sample | | Prevalence | | |
|---|---|---|---|---|---|
| | Cases | Healthy | Total | Men | Women |
| 40–54 years | 1392 | 15,213 | 8.38% | 6.28% | 10.31% |
| 55–64 years | 1141 | 13,833 | 7.62% | 5.49% | 9.54% |
| > 65 years | 708 | 12,926 | 5.19% | 4.02% | 6.12% |
| Total | 3241 | 41,972 | 7.17% | 5.37% | 8.74% |

**Table 2**

Tetrachoric Correlations and Number of Twin Pairs (in Parentheses) in 5 Zygosity Groups by Age Group and Sex

| Age at interview | Zygosity | Men | Women | Opposite sex |
|---|---|---|---|---|
| 40–54 years | MZ | .22 (763) | .27 (979) | |
| | DZ | .20 (1097) | .11 (1252) | .07 (2466) |
| 55–64 years | MZ | .16 (680) | .26 (835) | |
| | DZ | −.07 (960) | .23 (1157) | .04 (2059) |
| > 65 years | MZ | .30 (416) | .33 (626) | |
| | DZ | .24 (674) | .13 (983) | −.07 (1450) |

IBS is more prevalent among women than men, and the difference more pronounced at younger ages (see Table 1).

Tetrachoric correlations for each zygosity group are presented in Table 2 by age group and sex. The correlations in the MZ twin pairs were higher than the correlations for DZ twin pairs in both sexes, suggesting a significant contribution of genetic factors in IBS. The correlations for MZ female twin pairs are somewhat higher than the MZ male correlations suggesting sex differences in heritability. Further, the correlations in DZ opposite-sex twin pairs were lower than the correlation for DZ same-sex twin pairs, suggesting sex differences in genetic effects for IBS.

When diarrhea predominant symptoms or constipation predominant symptoms were examined, the correlations were nearly identical to those for the IBS definition, suggesting that there is no differential heritability for subtypes.

Before conducting the genetic analyses, we started with a saturated model, and were able to constrain the thresholds for IBS to be equal in Twin 1 and Twin 2 in a pair, in MZ and DZ same-sex pairs and in same-sex and opposite-sex pairs.

We then began the formal model fitting with a full model (Model 1 in Table 3). In Model 1, additive genetic effects (A), shared environmental effects (C) and nonshared environmental effects (E) were allowed to vary across sexes, different prevalences were allowed for males and females (two thresholds), and the genetic correlation for opposite-sex twins ($r_g$) was



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**Table 3**

Estimates of Genetic and Environmental Effects from Univariate Model-Fitting for IBS in 3 Age Groups

| Model | Parameter estimate | | | | | | | Fit of model | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Men | | | Women | | | | | | | |
| | $a^2$ | $c^2$ | $e^2$ | $a^2$ | $c^2$ | $e^2$ | $R_g$ | –2LL | AIC | *df* | *p* |
| Age group 40–54 year | | | | | | | | | | | |
| 1 | .0477 | .1781 | .7742 | .2555 | .0041 | .7404 | .5 | 7437.214 | | 13,214 | |
| 2 | .0194 | .2404 | .7402 | .2525 | .0039 | .7436 | .5 | 7495.289 | 56.076 | 13,215 | .00 |
| 3 | .0477 | .1781 | .7742 | .2555 | .0041 | .7404 | .5 | 7437.214 | –2.00 | 13,215 | > .99 |
| 4 | .2449 | < .0001 | .7550 | .2449 | < .0001 | .7550 | .5 | 7438.274 | -6.94 | 13,218 | .90 |
| 5[a] | .2450 | — | .7550 | .2450 | — | .7550 | .5 | 7438.274 | –8.94 | 13,219 | .958 |
| 6 | — | .1581 | .8419 | — | .1581 | .8419 | .5 | 7441.089 | –6.124 | 13,219 | .567 |
| 7 | — | — | 1.00 | — | — | 1.00 | .5 | 7458.314 | 9.101 | 13,220 | .002 |
| Age group 55–64 year | | | | | | | | | | | |
| 1 | .097 | .0008 | .902 | .064 | .196 | .739 | .5 | 6197.275 | | 11,526 | |
| 2 | .204 | < .0001 | .795 | .043 | .212 | .743 | .457 | 6272.556 | 73.28 | 11,527 | .00 |
| 3 | .097 | .0008 | .902 | .065 | .196 | .739 | .5 | 6197.275 | –2.00 | 1,1527 | > .99 |
| 4 | .235 | < .0001 | .764 | .235 | < .0001 | .764 | .5 | 6201.258 | –4.018 | 11,530 | .408 |
| 5[a] | .235 | — | .765 | .235 | — | .765 | .5 | 6201.258 | –6.018 | 11,531 | .552 |
| 6 | — | .149 | .850 | — | .149 | .850 | .5 | 6206.977 | –4.298 | 11,531 | .336 |
| 7 | — | — | 1.0 | — | — | 1.0 | .5 | 6215.452 | 6.177 | 11,532 | .006 |
| Age group ≥ 65 year | | | | | | | | | | | |
| 1 | .159 | .152 | .685 | .3308 | < .0001 | .6691 | –.2629 | 3502.537 | | 8410 | |
| 2 | .199 | .171 | .624 | .313 | < .0001 | .6863 | –.2834 | 3502.990 | 17.453 | 8411 | .00 |
| 3 | .1085 | .1908 | .7006 | .3248 | .004 | .6712 | .5 | 3502.537 | –1.975 | 8411 | .876 |
| 4 | .2687 | < .0001 | .7313 | .2687 | < .0001 | .7313 | .5 | 3506.011 | –4.526 | 8414 | .482 |
| 5[a] | .2687 | — | .7313 | .2687 | — | .7313 | .5 | 3506.011 | –6.526 | 8415 | .627 |
| 6 | — | .1453 | .8547 | — | .1453 | .8547 | .5 | 3508.582 | –3.955 | 8415 | .302 |
| 7 | — | — | 1.0 | — | — | 1.0 | .5 | 3514.157 | –0.380 | 8416 | .071 |

Note: [a] Best fitting model according to AIC is the AE model (same estimate for men and women), $R_g$ fixed to .5, different prevalence's for males and females, that is, no sex differences in genetic effects or variance components, only sex differences in prevalence — no shared environmental effects

estimated. Secondly, we tested for the same prevalence in males and females (Model 2) which resulted in deterioration of fit. In Models 3 to 7 we assumed different prevalence's for males and females as supported by prevalence estimates presented in Table 1.

We fixed the genetic correlation for the opposite-sex twins to be equal to that for same-sex DZ pairs (Model 3, $r_g$ = .5) and an improvement of fit was achieved. In addition, Model 4 constrained ACE to be equal for males and females. Working from Model 4, we compared the equal ACE model to an AE model (Model 5). The latter model was preferred to the ACE model by the AIC criterion because of greater parsimony. The CE model (Model 6) was then fitted resulting in a poorer fit than the AE model according to AIC. Model 7, the E model, which assumes no resemblance for IBS fitted poorly and was also rejected. Model fitting results are presented in Table 3.

For all age groups, the best fitting model according to AIC was the AE model (Model 5) with no shared environment (C), with the same estimates for men and women and $r_g$ fixed to .5. The heritability estimates with 95% confidence intervals (CI) were 24.5% (14–35%), 23.5% (11–35%) and 26.8% (8.5–44%) in each of the age groups 40–54, 55–64 and 65 years and older. We found no sex differences in genetic effects or variance components, however, prevalences differed between sexes.

We then tested if the same model fit the data in all three age groups and we found no significant differences between groups ($\Delta$ –2LL = 2.82, $\Delta$ *df* = 2, $p$ = .24). Models with different thresholds for men and women in the different age groups fit best.

## Discussion

This study investigated whether there are sex differences in heritability of IBS in a Swedish twin sample of adults above 40 years of age. We found no evidence for such effects in any of the age groups (40–54, 55–64 and 65 years and older) but prevalence of IBS differed between sexes and age groups. IBS was more prevalent among women than men in all age groups. Younger adults (40–54 years) had a higher prevalence of IBS than older adults (65 years and older) in line with our expectations and previous research in the area. The heritability of IBS was approximately 25% in all three age groups in our study.

To the best of our knowledge, five twin studies investigating the contribution of genetic and environmental factors to the etiology to IBS have been presented so far (Bengtson et al., 2006; Lembo et al., 2007; Levy et al., 2001; Mohammed et al., 2005; Morris-Yates et al., 1998). Two of these include opposite-sex twins (Bengtson et al., 2006; Levy et al., 2001), though without an aim or the



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possibility to look at sex-specific genetic effects. Results from the Norwegian study by Bengtson and colleagues (2006) suggest sex-specific effects as indicated by lower DZ opposite-sex correlations as compared to DZ same-sex correlations, similar to what we found in the present study. However, they were unable to calculate heritability estimates for men or to test for sex-specific effects due to lack of concordant MZ male twin pairs although their sample was large ($n$ = 12,700; Bengtson et al., 2006). The heritability in the present study was 25%, of equal importance for women and men, and was half that among females in the Norwegian sample (48%). One explanation of the differences between Norway and Sweden could be that the Norwegian twins were younger (less than 40 years) than the Swedish twins (40 years and older). It is also possible that not only the prevalence of a disorder varies with age and sex, but also the influence of genetic and environmental factors. Alternatively the Norwegian twin population is more homogeneous in some respect, such as dietary habits, than the Swedish twin population; hence environmental variance decreases which results in a greater heritability. Why do the results from the five twin studies differ? One reason could be that different criteria were used to define IBS. One study used the symptom-based Rome II criteria (Mohammed et al., 2005), another defined IBS by use of self-reported symptoms (Lembo et al., 2007), and two used self-reported IBS (Bengtson et al., 2006; Levy et al., 2001), yet another study used a medical diagnosis of functional abdominal symptoms (Morris-Yates et al., 1998).

#### Strengths and Limitations

This was a large population-based study including both same-sex and opposite-sex twin pairs. Ascertainment bias that sometimes is a problem in twin studies was unlikely to occur since the telephone interview was extensive and included questions about most common complex diseases and symptoms with no special emphasis given to gastrointestinal problems. Our symptom-based definition of IBS was perhaps slightly stricter than the Rome II criteria and could explain the lower prevalence of IBS in the present study. Our definition differs by including those who have abdominal problems at least 7 days per month, while Rome II asks for problems of at least 12 weeks in the preceding 12 months. Comparison of these definitions was done to determine concordance between the IBS definitions and reliability of the IBS definition. Results of the comparison in IBS definition yielded a good to excellent reliability ($\kappa$ = .92), and 99% concordance in IBS case status, and we therefore believe that our definition of IBS is close to the Rome II criteria. More plausible though is that differences in results emerge from the fact that different age groups were investigated. As already mentioned, prevalence of IBS differs with age and sex.

#### Conclusion

This study is complementary to previous twin studies suggesting that there is a genetic component involved in the etiology of IBS in midlife and later. The present study also includes opposite-sex twins and was large enough to evaluate sex-specific genetic effects that have not been reported earlier. In this study we demonstrate that there is no sex difference in heritability of IBS, even though the prevalence of the disorder differs with age and sex. Having in mind that the few studies conducted in this area report mixed results, further research is needed that explore the biological markers and pathways for the disorder. Better understanding of the environmental factors could also contribute to developing tools for preventing and treating IBS.

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