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ORIGINAL ARTICLE

How are perceptions of social strain and low support related to Irritable Bowel Syndrome?—A Norwegian twin study

Julia Kutschke[1] | Jennifer R. Harris[2] | May-Bente Bengtson[1]

[1]Vestfold Hospital Trust, Tønsberg, Norway

[2]Division of Health Data and Digitalisation, The Norwegian Institute of Public Health, Oslo, Norway

Correspondence
May-Bente Bengtson, Vestfold Hospital Trust, Lokes vei 10, 3179 Åsgårdstrand, Norway.
Email: maybente.bengtson@gmail.com

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Abstract

Background: Social stress is related to symptom burden of irritable bowel syndrome (IBS). This study explores the associations between IBS and social strain or low support in close relationships, including spouse, friends, and family, in a Norwegian twin cohort.

Methods: The sample included 5442 Norwegian twins aged 40–80, of whom 589 suffer from IBS. We used multivariate structural equation models to estimate genetic and environmental sources of variation and covariation underlying IBS liability, measures of social stress and the relationships between these. The co-twin control design was used to explore the nature of the associations between IBS and social strain or low support using models that test for causality.

Key Results: Genetic effects explained between 30% and 40% of the variation in IBS liability, social strain, and low support. The phenotypic correlations between IBS and social strain (0.20) and between IBS and low support (0.17) were primarily explained by shared genetic pathways. Surprisingly, all the genetic variation underlying the liability to develop IBS was shared with genetic influences underlying social strain and low support. In contrast, most of the nonshared environmental influences accounting for the variation of IBS risk were unique for IBS. The co-twin control analyses suggest that the relationships between IBS and the social measures reflect shared familial rather than causal effects.

Conclusion & Inferences: The genetic variation of IBS risk was fully shared with genetic effects for variation in the social measures, emphasizing the contribution of genes involved in central brain–gut mechanisms to genetic variation in IBS risk.

KEYWORDS
genetics, irritable bowel syndrome, nerve–gut interactions, psychological stress

1 | INTRODUCTION

Irritable bowel syndrome (IBS) is a common chronic disorder affecting ~15% worldwide and is more predominant among women. The diagnosis is based on clinical symptoms including recurrent abdominal pain associated with disturbed bowel function. The pathogenesis of IBS remains unclear, but factors that trigger the stress response in the signaling system between the brain and the gut are risk factors for IBS.[1] These span a broad array of influences, including, for example, bacterial intestinal infections or traumatic events especially in early life.[2,3]

A biopsychosocial model, involving brain–gut interactions and central stress circuits,[4–6] has been used in the last two decades to explain the relationship between psychosocial and physiological factors associated with IBS symptoms and the clinical outcome. Among the psychosocial factors, social stress has been shown to influence various aspects of IBS, including onset of IBS or exacerbation of abdominal symptoms among individuals already suffering from IBS.[7] For instance, Gwee et al. demonstrated that the risk of developing postinfectious IBS was higher among those who experienced chronic interpersonal stressors within 3 months of acute gastroenteritis than among those who did not experience interpersonal strain.[8] Negative interactions and low support in close relationships have been associated with worse IBS symptoms and quality of life impairment, and several studies have suggested that the effects of social interactions on bodily pain are mediated by stress.[9–11] Despite growing evidence linking social stress with IBS, relatively little is known about the factors underlying these associations.

The aims of this study were to explore the nature of the relationships between social strain, low social support, and IBS using data from a sample of Norwegian twins. We exploit features of the twin design to examine three main questions: (a) to what extent do genetic and environmental factors contribute to the relationships between IBS and the social measures, strain, or low support, (b) to what extent are the genetic effects for IBS dependent of genetic effects for the social measures, and (c) are the relationships between the social measures and IBS consistent with a model of causal or shared effects?

Key message

The state of current knowledge

IBS is associated with social stressors

The key question addressed in the paper

To what extent do genetic and environmental factors contribute to the relationships between IBS and social stressors?

Results

IBS and social stressors share genetic pathways

The genetic effects for IBS are fully shared with the genetic effects for social stressors

The importance of the results in the context of the broader field of neurogastroenterology and motility and health and disease

Genes involved in central stress mechanisms in the brain–gut axis are the main source of the genetic variation in IBS risk. IBS treatment should be oriented toward how to deal with or avoid stress

2 | MATERIALS AND METHODS

2.1 | Sample

The data were collected as part of a study on Social Factors and Health.[12] Twins aged 40 to 80 years old (mean age = 61.54 years old) were identified in the Norwegian Twin Registry[13] and invited to complete an extensive questionnaire asking about their physical and mental health and their social relationships. The results reported herein are based on responses from 5442 twins (1986 complete pairs and 1470 single responders). The individual and pairwise response rates were 51% and 37%, respectively. The data are described in more detail elsewhere.[12]

2.2 | Measures

2.2.1 | IBS

The questionnaire included a checklist for 44 illnesses and symptoms, including a question asking: Do you have irritable bowel syndrome (diarrhea and/or constipation related to abdominal pain, at least once a week). There were two response alternatives—"yes" (self-reported) and "yes, diagnosed by a doctor." To increase power, a combined measure of IBS was created which had value of 1 if a twin answered either "yes" (self-reported) or "yes, diagnosed by a doctor," and value of 0 if a twin did not select either of the alternative answers. The decision to collapse these two response categories was based upon analyses testing for differences in the regressions of strain and low support on IBS in the self-reported and the doctor-diagnosed groups, correcting for age and sex (Table S1).

2.2.2 | Strain

The strain measure (Strain) was constructed using four items inquiring about the respondent's perception of strain in each of the following three classes of relationships: spouse/partner, family (excluding co-twin), and friends. The items asked: "how often do they make too many demands on you?", "how often do they criticize you?", "how often do they let you down when you count on them?", "how often do they get on your nerves?". Response categories ranged from 1 to 4 (often, sometimes, rarely and never). Items were reverse-coded, and total Strain across all relationships was calculated as the average value of all the items with high scores indicating high strain which parallel those from the Midlife in the US (MIDUS) study.[14]

2.2.3 | Low support

The measure of Low Support was constructed in a similar way as Strain, as in the MIDUS study,[14] using the average score across three domains (spouse, family, and friends) and four items for each domain ("How often do they really care about you?", "How much do they understand the way you feel about things?", "How much can you rely on them for help if you have a serious problem?", "How much can

you open up to them if you need to talk about your worries?"). The total score for Low Support ranged from 1 to 4 (a lot, some, a little, not at all) with high scores indicating lower levels of support.

2.2.4 | Dichotomous measures of strain and low support

The measures of Strain and Low Support were dichotomized for the co-twin control analyses. The value "1" was assigned to scores within the highest quartile and "0" otherwise; and a twin pair was considered discordant if, in addition to different dichotomous scores, the difference in their continuous scores was greater than or equal to half a standard deviation of the respective measure (0.22 for Strain and 0.20 for Low Support). This was done to ensure that the discordant twins indeed differed in their levels of Strain and Low Support.

2.3 | Analysis

Descriptive analyses were conducted for all measures (Table 1).

Twin resemblance in monozygotic (MZ) pairs compared to dizygotic pairs (DZ) provides preliminary information about the importance of genetic effects. The within-pair correlation for each trait, IBS, Strain, and Low Support reflects the resemblance between twin 1 and twin 2 for that trait and is called the intraclass correlation. Greater MZ than DZ intraclass correlations suggest that genetic effects contribute to variation in that trait. Likewise, the relationship between traits can be examined by comparing the cross-twin cross-trait correlations in the MZ and DZ pairs. This correlation reflects the relationship of trait 1 in twin 1 with trait 2 in twin 2. If the value of the MZ cross-twin cross-trait correlations exceeds the value of the DZ cross-twin cross-trait correlations, then this would also suggest that genetic factors contribute to the covariation between these traits.

2.3.1 | Model fitting

Biometrical modeling was conducted to investigate our question aimed at quantifying the extent to which genetic and environmental factors contribute to the relationships between the measures under study. These models decompose the phenotypic variances of each of the variables: IBS, Strain, Low Support, into genetic (additive A and/or dominant D) and environmental (shared C and/or unique E) components, and then estimate how these components contribute to the covariance between the variables.[15,16]

We are able to estimate the four genetic and environmental components (A, D, C, and E) because they contribute to resemblance of MZ and DZ pairs in predictable ways. MZ twins are genetically identical while DZ twins share, on average, 50% of their segregating genes (like ordinary siblings). These differences in biological relatedness are used to specify our models. Due to statistical

TABLE 1 Number of cases, concordance rates, prevalence by sex for IBS and dichotomized measures of strain and low support, and correlations with age and sex (by zygosity)

	Cases				Concordant pairs		Discordant pairs		Probandwise concordance (95% CI)		Prevalence, %		Correlation with (95% CI)	
Measure	Total	MZ	DZ	DZO	MZ	DZ	MZ	DZ	MZ	DZ	Males	Females	Age	Sex
Strain	1115	510	571	34	76	57	225	245	0.40 (0.34; 0.47)	0.32 (0.26; 0.38)	18.2	22.3	−0.09 (−0.12; −0.07)	0.04 (0.00; 0.07)
Low Support	1230	557	647	26	83	61	236	279	0.41 (0.35; 0.47)	0.30 (0.25; 0.36)	24.6	21.0	0.05 (0.02; 0.07)	−0.10 (−0.13; −0.07)
IBS	589	270	305	14	29	15	168	175	0.26 (0.18; 0.33)	0.15 (0.08; 0.21)	7.6	13.3	0.02 (−0.02; 0.07)	0.20 (0.14; 0.25)

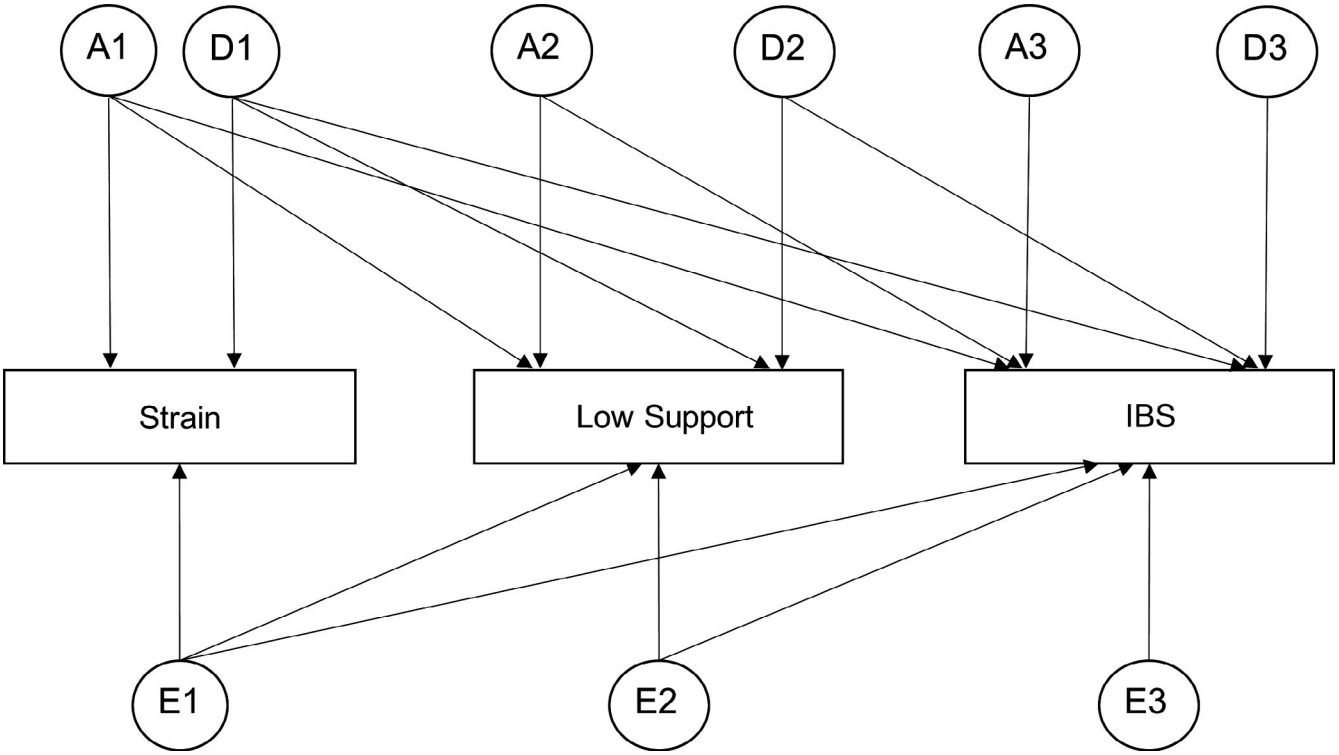

FIGURE 1 Path diagram of the trivariate Cholesky decomposition used for the multivariate analysis. It includes as many latent A, D, and E factors as there are observed variables: A1-A3, D1-D3, and E1-E3. The first latent factor for each type of influence (A, D, and E) loaded on all three measures—Strain, Low Support, and IBS; the second latent factor loaded on Low Support and IBS; and the third factor loaded only on IBS. All components, A, D, and E, were estimated simultaneously

considerations, it is not possible to estimate all four effects (A, D, C, and E) in a single model and, therefore, ACE and ADE models are usually run and their fit statistics are compared. An ADE model is indicated if the observed DZ correlations are less than half the MZ correlations.

First, univariate analysis was performed for each of the three measures to estimate the genetic and environmental variance components. Full models (ACE and ADE) and submodels (AE and DE) were tested. The statistical fit of the submodels was then compared with that of their respective full models using the likelihood ratio chi-square tests (LRT) to determine which effects were significant. Comparisons between non-nested models, ACE and ADE, were also conducted using Akaike's information criterion (AIC) test (lower values indicate a better fit) (Table S2).

Second, we used a Cholesky decomposition model (Figure 1) which allows the covariation between the measures to be decomposed into components that are shared with the other measures in the model. A particular advantage of this model is that it is order dependent, which means that the variance estimates for the last measure will reflect unique effects that are not shared with the other measures in the model. This allows us to estimate the genetic and environmental variance effects for IBS after accounting for the effects shared with Strain and Low Support. From the trivariate Cholesky decomposition model, we obtain the genetic and environmental correlations between each set of variables, and these correlations quantify the extent to which genetic and environmental influences are shared between each sets of variables (IBS-Strain/Low Support and Strain-Low Support).

IBS is measured as a dichotomy; this approach, a liability threshold model, assumes a latent continuous underlying liability to develop IBS which is normally distributed.[16,17] Sex and age effects were estimated on the means for all three measures.

A bootstrapping technique[18] (5000 replicates) was used to derive the 95% confidence intervals (CIs) for all the estimates from the biometrical analyses.

Co-twin control design

Next, a co-twin control design was employed to test whether the relationships between IBS and social measures are most consistent with a model of causality or shared genetic and/or environmental effects.[19] To test whether IBS is causal to Strain/Low Support, we analyzed pairs who were IBS discordant, meaning that only one of the twins in the pair has IBS. In this way, we can use the co-twin without IBS as a control. Further, to test whether Strain/Low Support is causal to IBS, we analyzed pairs discordant for Strain/Low Support. For example, in the latter case, the odds ratio (OR) for IBS when exposed to Strain/Low Support was estimated in MZ and DZ pairs and unrelated individuals and compared (Figure 2).

If Strain/Low Support is a causal factor for IBS, then the expected risk of developing IBS would be greater (OR > 1) among those with higher values of Strain/Low Support compared to those with lower values. A causal model would therefore predict a similar increase in

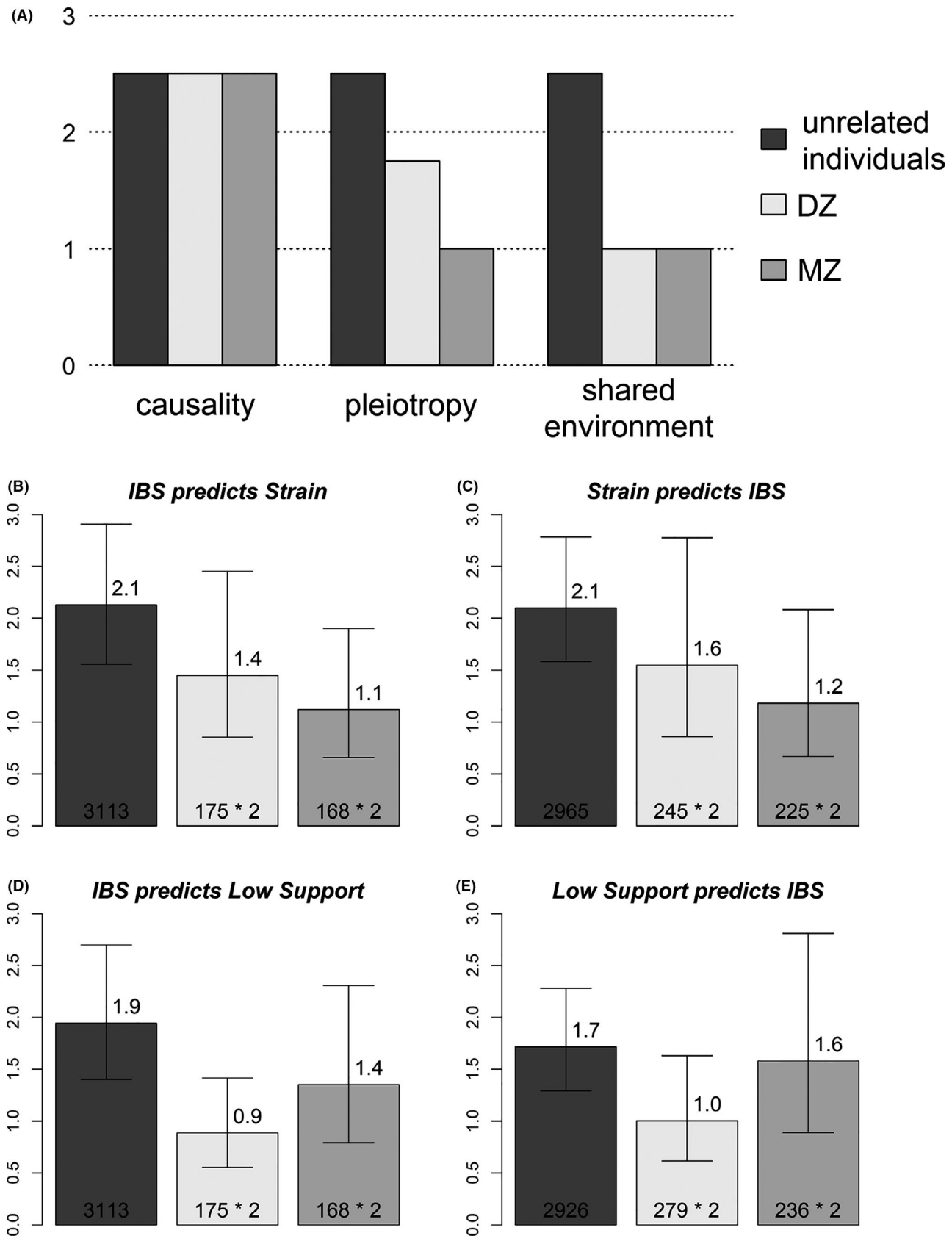

FIGURE 2 Co-twin control analysis. Panel A—illustration of the expected odds ratios under different types of relationships: causality, pleiotropy, and shared environment. Panels B, C, D, and E—OR's and their corresponding 95% CIs from the analysis. The numbers inside each bar is the sample size. Figures A and C—twins are discordant for IBS; Figure B—twins are discordant for Strain; Figure D—twins are discordant for Low Support

the OR for an individual with high Strain/Low Support regardless of whether they were from discordant MZ or DZ pairs or unrelated individuals. In contrast, if shared genetic effects (pleiotropy) explain the relationship between the exposure and IBS, then the OR would still be >1 in the unrelated individuals, equal to 1 in the MZ twins because they are genetically identical and have inherited the same risk genes, and intermediate between these two values in the DZ twins. If shared environmental factors underlie this relationship, the OR would be equal to 1 for both MZ and DZ twins and greater than 1 in the unrelated individuals.

Combinations of these three mechanisms (causality, pleiotropy, and shared environmental effects) are also possible and would result in mixed patterns.

To explore the most plausible model underlying the relationships between IBS and Strain or Low Support, we conducted three sets of logistic regression analyses, correcting for twin dependency, to estimate the odds ratios among the unrelated individuals, discordant MZ, and discordant DZ twins: (a) causal model with $\beta_{unrel} = \beta_{DZ} = \beta_{MZ}$, that is, OR are the same across these three groups; (b) shared environment model with $\beta_{unrel} > \beta_{DZ} = \beta_{MZ} = 0$, that is, OR are similar for MZ and DZ twins and larger than 1 for the unrelated individuals; (c) pleiotropy model with $\beta_{unrel} = 2\beta_{DZ}$ and $\beta_{MZ} = 0$, that is, OR for MZ twins is equal to one. Here, β_{unrel}, β_{DZ}, and β_{MZ} are regression coefficients. The best model was chosen based on the AIC value (Table S3).

The sample of unrelated individuals for each of the four scenarios was comprised from the single responders and one twin from each concordant pair.[19] All analyses were conducted with the OpenMx package[20] in R.[21]

3 | RESULTS

In total, 356 twins (6.5%) reported IBS symptoms (self-reported), 21 twins (0.4%) answered "yes, diagnosed by a doctor"; 211 twins (3.4%) chose both options, self-reported and "diagnosed by a doctor." Merging self-reported and doctor-diagnosed groups (described in Methods) resulted in 589 IBS cases (7.5%).

The mean values for Strain (range from 1 to 4) were 1.74 (SD = 0.43) and 1.76 (SD = 0.45) for males and females, respectively. The corresponding values for Low Support were 1.51 (SD = 0.40) for males and 1.45 (SD = 0.39) for females. Descriptive information, including frequencies, the number of pairs concordant and discordant for IBS, the dichotomized measures of Strain and Low Support, and the probandwise concordance rates (calculated as the ratio of twice the number of concordant pairs divided by twice the number of concordant pairs plus the number of discordant pairs),[22] is presented in Table 1 by zygosity.

3.1 | Sex and age effects on IBS

Age was not associated with IBS, whereas sex correlated positively with IBS reflecting a greater prevalence among females than males (13.3% versus 7.6%) (Table 1).

3.2 | Twin correlations

IBS correlations with Strain and Low support are equal to 0.20 (0.14; 0.26) and 0.17 (0.12; 0.23), respectively, while correlation between Strain and Low Support is higher, 0.40 (0.37; 0.43). Higher intraclass correlations for MZ twins compared to DZ twins for IBS, Strain, and Low Support (Table 2) are consistent with genetic effect for these measures. Moreover, the magnitude of DZ correlations is less than half of the magnitude of the MZ correlations for all three measures, indicating that dominant genetic effects may account for some of the variation and suggests an ADE model.

The cross-twin cross-trait correlations (Table 2) among the MZ pairs exceed the DZ values for the associations between Strain and Low Support and between IBS and Strain implying that common genetic factors explain these relationships. In contrast, the correlations between IBS and Low Support do not vary between the MZ and DZ pairs, indicating that this association may be explained by shared environmental effects. However, the overlap in confidence intervals between MZ and DZ estimates hampers clear differentiation between the importance of genetic and shared familial effects.

3.3 | Univariate twin analyses

The results comparing the fit of the univariate models that were analyzed to decompose the variance of each measure (Strain, Low

TABLE 2 Intraclass correlations (on the main diagonal, in bold—for MZ twins) and cross-twin cross-trait correlations

	Strain	Low support	IBS
Strain	**0.38 (0.32; 0.43)** & 0.17 (0.11; 0.23)	0.12 (0.07; 0.16)	0.10 (0.03; 0.17)
Low Support	**0.19 (0.14; 0.22)**	**0.39 (0.34; 0.44)** & 0.13 (0.07; 0.20)	0.13 (0.05; 0.20)
IBS	**0.16 (0.09; 0.23)**	**0.12 (0.05; 0.18)**	**0.31 (0.16; 0.45)** & 0.08 (−0.10; 0.25)

Note: Strain and Low Support were regarded as continuous measures here. Below diagonal and in bold for MZ twins, above the diagonal for DZ twins.

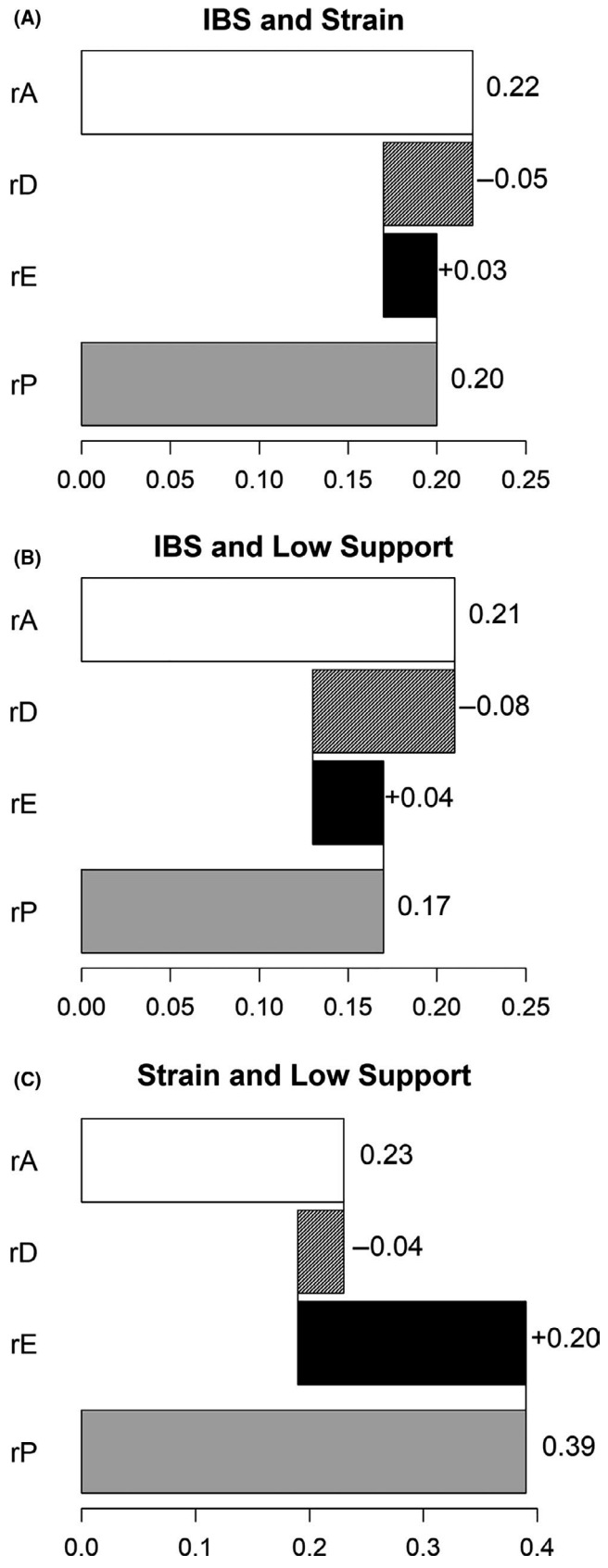

FIGURE 3 Waterfall plots depicting absolute contribution of the additive genetic (rA), dominant genetic (rD) and nonshared environmental (rE) correlation into the phenotypic correlation (rP)

TABLE 3 Correlations between Strain, Low Support and IBS—phenotypic and by variance component

	rP			rA			rD			rE		
	Strain	Low support	IBS	Strain	Low support	IBS	Strain	Low support	IBS	Strain	Low support	IBS
Strain	1			1			1			1		
Low Support	0.39 (0.36; 0.43)	1		0.96 (0.52; 1.00)	1		−0.33 (−1.00; 0.90)	1		0.32 (0.27; 0.38)	1	
IBS	0.20 (0.14; 0.25)	0.17 (0.12; 0.22)	1	0.87 (0.27; 1.00)	0.98 (0.46; 1.00)	1	−0.57 (−1.00; 1.00)	−0.58 (−1.00; 0.47)	1	0.05 (−0.05; 0.16)	0.06 (−0.04; 0.17)	1

Note: rP—pairwise phenotypic correlation, rA—pairwise additive genetic correlation, r D—pairwise dominant genetic correlation, rE—pairwise environmental correlation.

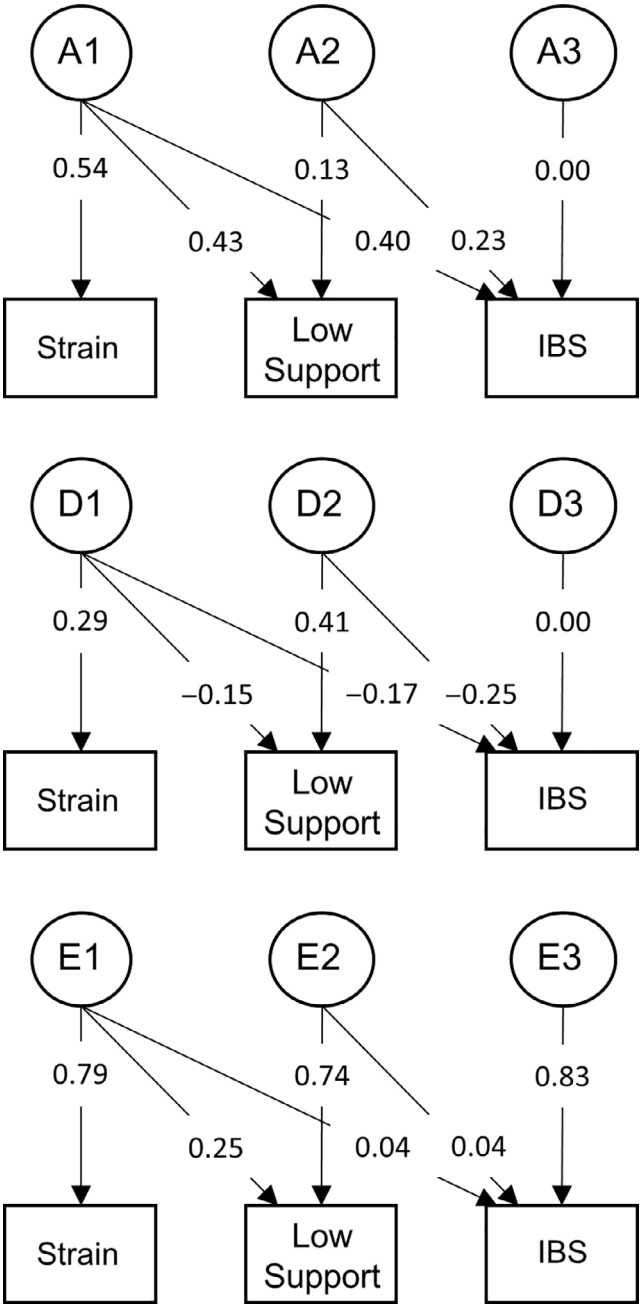

FIGURE 4 Standardized path estimates from the trivariate Cholesky decomposition. To estimate the residual genetic and environmental effects for IBS after accounting for effects that covary with both Strain and Low Support, we ordered the measures with Strain first, then Low Support, and then IBS. The first latent factor for each type of influence (A, D, and E) loaded on all three measures—Strain, Low Support and IBS; the second latent factor loaded on Low Support and IBS; and the third factor loaded only on IBS

Support and IBS) into genetic (A, D) and environmental (E) factors are reported in Table S2. The lowest AIC values, indicating best model fit, were observed for an AE model for Strain and a DE model for both Low Support and IBS. However, the 95% CIs for D estimates (data not shown) overlapped substantially with the confidence intervals for the A estimates, making it difficult to differentiate between A and D effects. Thus, we maintained the full ADE model for each of the three measures in the trivariate analysis rather than selecting a simplified AE model.

3.4 | Multivariate twin analyses

Standardized variances and covariances (with 95% CI) from the full trivariate Cholesky decomposition model are reported in Table S4. The standardized components of variance for each trait with 95% CI (main diagonal in Table S4) represent the percentage of the total trait variance which is attributable to genetic or environmental influences.

Genetic effects [additive (A) and nonadditive (D)] account for 30%–40% of the variance, whereas nonshared environmental influences (E) account for 61%–69% of the total variance of each measure. For IBS, we see from the diagonal values in Table S4 that 21% of the variance in risk to develop IBS is explained by A, 9% by D and 69% by E. The total genetic variance (30%) represents the sum of A and D effects. Similarly, for Strain, 29% of the variance is explained by A, 9% by D, and 62% by E. The corresponding figures for Low Support are as follows: 21%, 19%, and 61%.

Genetic and environmental correlations between the measures were calculated based on the results from the Cholesky decomposition (Table 3). Genetic correlations (rA) were close to 1 for all relationships, whereas the nonshared environmental correlation (rE) between IBS and social measures was weak and close to zero. The nonadditive genetic correlations (rD) between the measures were all negative, and the respective 95% CI's all contained zero. Due to negative rD, we computed the absolute, and not the relative (percentage), contribution of rA, rD, and rE to the phenotypic correlations (Appendix S1). Figure 3 shows that the phenotypic correlations between IBS and social measures are largely explained by the genetic correlation between these measures. In contrast, the correlation between Strain and Low support is equally explained by shared genetic and shared environmental factors

3.4.1 | Covariance structure

Standardized path estimates from the multivariate analysis are presented in Figure 4 (calculations of variances based on the path estimates are explained in Appendix S2).

The Cholesky decomposition model (Figure 4) provides additional information about the standardized covariance structure and the proportion of genetic and environmental variance that is shared between the included variables (for calculation, see Appendix S2). IBS is ordered last in our Cholesky model so that we can estimate the residual genetic (A3, D3) and environmental effect (E3) for IBS after accounting for the effects shared with Strain and Low Support. As seen in Figure 4, the paths A3 and D3 are estimated to be zero, which suggests that genetic factors that contribute to the variance in risk of IBS are almost entirely shared with those that affect variance in Strain (A1 and D1) and Low Support (A2 and D2). In other

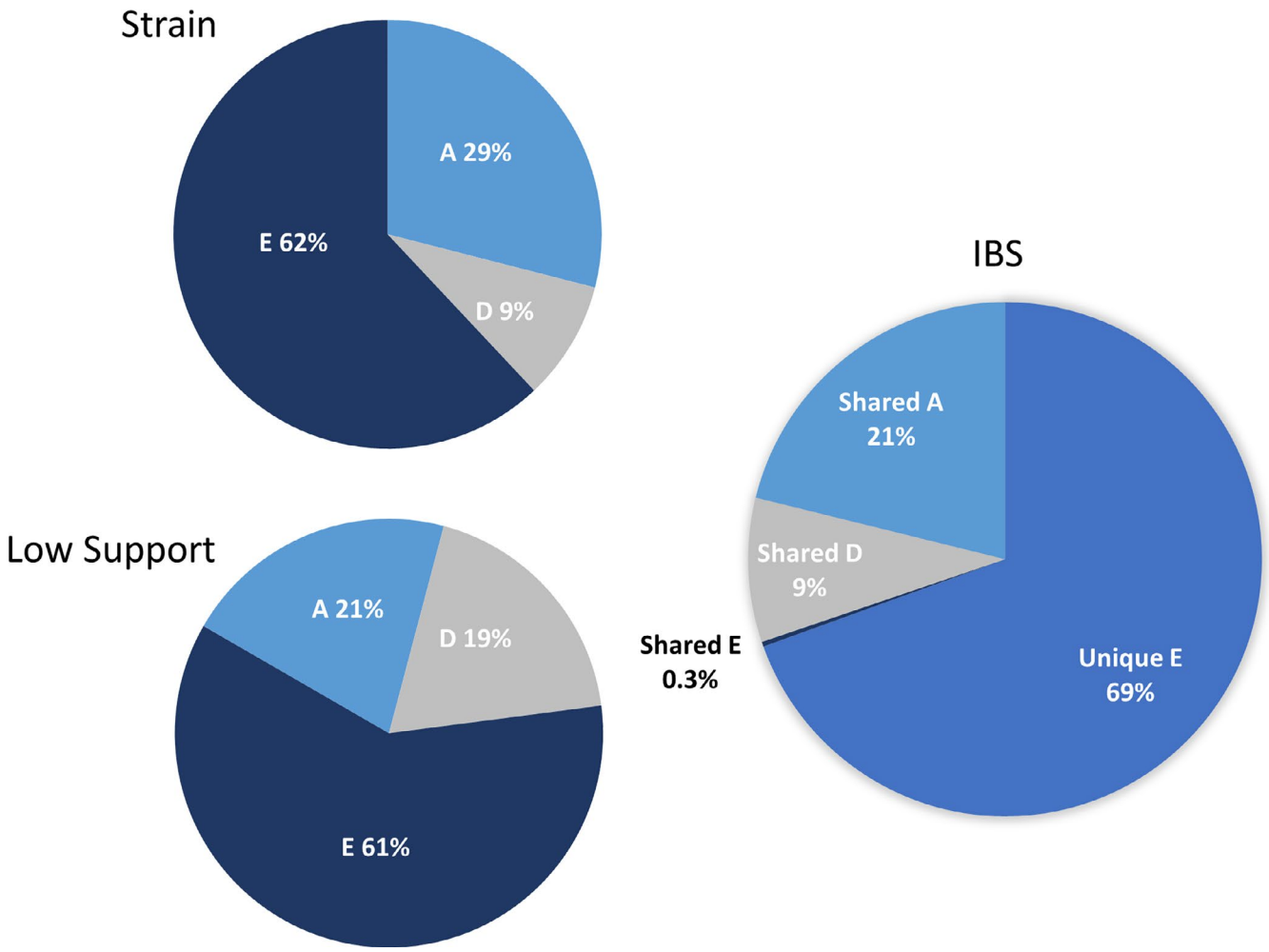

FIGURE 5 Variance decomposition of Strain, Low Support, and IBS risk into genetic and environmental components. For IBS risk, the pie chart is further specified to indicate the percent of variance which is shared with the social measures and which is unique to IBS risk. For Strain and Low Support, additive genetic (A), nonadditive (D), and nonshared environmental (E) variance are shown

words, after sequentially regressing out genetic effects for Strain and Low support, there were no residual (unique) genetic effects on IBS liability (A3 and D3). In contrast, most of the nonshared environmental variance for the liability to develop IBS was not shared with the other measures. The results of the variance decomposition into genetic and environmental components for all three measures are depicted in a pie diagram (Figure 5). For IBS risk, the pie chart is further specified to indicate the percent of variance which is shared with the social measures and which is unique to IBS risk.

3.5 | Co-twin control analyses

Figure 2 presents the resulting ORs from the co-twin control analyses and respective sample sizes. The ORs for experiencing high strain/low support given a history of IBS; and for IBS given a high level of strain/low level of support were significantly greater than 1 only in unrelated individuals, but not in the discordant MZ and DZ pairs. The pattern of ORs observed between IBS and Strain and between IBS and Low Support does not favor a causal explanation. Rather, the pattern suggests that shared influences explain the relationships between IBS and social measures, either environmental or genetic effects, or a combination of these. Further comparisons using statistical criteria (AIC values) to determine which model fit the data best indicated that shared (familial) effects best explain the relationships between IBS and Strain/Low Support (Table S3). However, it was difficult to differentiate between shared environmental effects and shared genetic effects, due to low power. The power of the analyses including the MZ and DZ twin pairs ranged between 17.5% and 27.3%.

4 | DISCUSSION

The present study explored the nature of the relationships between IBS, social strain, and low support using the classical twin approach and the co-twin control design in a Norwegian twin cohort. Our main findings reveal that genetic effects contribute modestly to variation in all three measures, and there is considerable overlap between these genetic effects in explaining the

covariation between measures. Furthermore, there was no evidence of independent genetic effects on the liability to develop IBS after accounting for genetic variation shared with Strain and Low Support. Finally, the relationships between IBS and Strain or Low Support most likely reflect the effects of shared familial factors rather than causal mechanisms. Our study was underpowered to differentiate whether these shared familial effects were explained by shared environmental effects or shared genes. However, the multivariate analyses provided evidence for a high genetic correlation between IBS and the social strain and support measures (Table 3) which suggests that that these shared familial effects are mainly genetic. To our knowledge, this is the first study to explore genetic and environmental determinants underlying the associations between IBS and social measures.

4.1 | IBS prevalence

The IBS group included both the self-reported-IBS and doctor-diagnosed IBS because the groups did not differ with regards to their scores on social measures (Table S1).

The question for IBS was: "Do you have irritable bowel syndrome (diarrhea and/or constipation related to abdominal pain, at least once a week)" with two responses: "yes" and/or "yes, diagnosed by doctor." In agreement with several investigations, our data reveal that approximately one-third of the self-reported IBS twins were doctor-diagnosed[23,24] The IBS prevalence of 7.5% in this twin cohort was very similar to the prevalence found in the background population (8.4%).[25] The prevalence of IBS was twice as high among females (13.3%) than among males (7.6%) in our twin cohort and is consistent with reports from most studies.[26,27]

4.2 | Genetic and environmental sources of variation for IBS

The classical twin design provides estimates of genetic sources of variation without performing analyses of specific gene variants. This is possible because MZ twins have identical genotypes; thus, they share all genetic effects (rare and common variants) which may act in an additive or a nonadditive fashion. In contrast, the DZ pairs share, on average, 50% of their segregating genes; thus, they are correlated only 0.5 for additive and 0.25 for dominance effects. These differences enable us to estimate all the genetic variation in the population under study without knowing which specific genes are involved or whether those genes act in an additive or nonadditive manner.

The results from the variance component analyses revealed a heritability of 30% for the liability to develop IBS, with 21% due to additive genetic effects and 9% due to nonadditive genetic effects (Table S4). We based our analyses on the full ADE model, because we lack statistical power to differentiate between the additive and dominant genetic effects. IBS is a complex polygenic disorder; the additive effects of common genetic variants constitute the bulk of the genetic variance of IBS.[28–30] Even so, some polymorphisms known to influence the risk of developing IBS in a subset of patients are rare gene variants with high penetrance.[31,32] Further, a family study by Fiskerstand et al. demonstrated a pattern of dominant inheritance for symptoms of IBS.[33]

The relative importance of nonadditive (dominant) genetic variation in complex traits is not well known. Most often genome-wide association studies are aimed at identifying single nucleotide polymorphisms (SNP) that are associated with complex traits. These typically rely on additive models, so the SNP data provide narrow sense heritability that does not include effects due to dominance. However, Zhu et al. estimated dominant genetic variation in human complex traits by applying a method which enabled independent estimates of A and D, using genome-wide SNP data of 79 quantitative traits in 6715 unrelated European Americans.[34] They found that the average estimate of dominant variance across all the traits was approximately one-fifth of that for the additive variance.

Most of the variation in liability to develop IBS was explained by nonshared environmental factors (69%), which is congruent with findings from earlier twin studies.[29,30,35] Although we are unable to model these effects directly in our data, examples of nonshared environmental factors that might have an impact on either brain- or gut-related mechanisms are restricted fetal growth, early traumatic events and chronic stressors,[28,36,37] and diet, use of antibiotics and bacterial gastroenteritis, respectively.[38]

4.3 | The relationships between IBS, social strain, and support

Our study is based on a population-based sample of twins. We find that the prevalence of IBS among the twins in our study reflects that in the background singleton population,[25] and there is no reason to believe that extent to which genetic and environmental influences that explain the covariation between the traits we have studied would differ between a twin and nontwin population.

The phenotypic correlations reveal that IBS is associated with social strain (0.20) and low support (0.17). These findings are congruent with those earlier studies reporting an association between IBS and supportive or negative interactions in close relationships. Lackner et al[11,39] demonstrated that social interactions influenced global severity of IBS symptoms through the level of stress.

Social relationships have been widely recognized as a protective factor for physical and mental health.[40] Two mechanisms are believed to underly the beneficial effect of social support from close relationships, the direct positive effect and the buffering effect by dampening the activity in the hypothalamus–pituitary–adrenal (HPA) axis, and the release of the stress hormone cortisol.[41]

The present suggests that the associations between IBS and social measures were explained almost exclusively by common additive genetic effects (Figure 4).

Our findings are also consistent with those from candidate gene studies showing associations between stress-related gene variants and IBS in patients who have experienced stressful life events. Examples of such genes, that might partly explain the correlation between IBS and social stressors, include inflammation-related genes and those involved in regulation of the HPA axis and the serotonergic and adrenergic signaling system.[2,42–44]

4.4 | Genetic variation for the liability to develop IBS is shared with social measures

A novel and interesting finding of the present study was that genetic influences explaining variation in liability of IBS risk were fully shared with genetic effects for variation in social measures (Figure 4). The order of the measures in the Cholesky decomposition model (Figure 4) permits us to differentiate between genetic effects shared between IBS and the social measures and genetic effects unique for IBS. Since we did not find unique genetic effects for the liability to develop IBS (A3, D3) after accounting for the shared genetic effect with social measures, we conclude that genes involved in the central stress mechanisms are the main source of the genetic variance of IBS risk.

The bidirectional communication along the brain–gut axis underlies the hypothesis that IBS symptoms can arise from two pathways: (a) the central pathway mediated through the brain involving pain, emotions, cognitions, and psychosocial mechanisms and (b) the peripheral pathway mediated through the gut, involving interactions between the microbiota and the mucosal immune system. This was nicely illustrated by Jeffrey et al. in subsets of patients with IBS based on gut microbial signatures.[45] Although genetic and environmental factors underlying the development of IBS presumably vary between these two pathways, the resulting clinical presentation of IBS may be quite similar. Our results emphasize the contribution of the underlying genetic influences of brain-related mechanisms to the genetic variance of IBS risk.

In contrast to the variance of IBS risk explained by genetic influences, the variance explained by nonshared environmental effects was almost exclusively unique for IBS. We do not have specific measures of nonshared environment, but to the extent that these are not shared within pairs, differences in diet, acute gastroenteritis, and antibiotic use could be examples of nonshared environmental factors that might alter the microbiome and, in interaction with the mucosal immune system, trigger the HPA axis by peripheral mechanisms of IBS.

4.5 | Limitations

One limitation of this study is that the support and strain measures are non-normally distributed. Skewed distributions in the analyses using the nontransformed, continuous measures could affect both the model fit statistics and could lead to an underestimation of A with overestimates of D and E in our ADE model.[46] Another limitation is low statistical power due to sample size. Although this is among the largest twin studies of IBS, we still lack power for robust tests to differentiate the importance of specific effects. For example, we could not reliably resolve A from D effects in the univariate analyses or conclude the role of D in contributing to the covariation between IBS and Strain or Low Support. Therefore, we advise caution in interpreting estimates of the relative importance of A versus D estimated in our models and the role of D in the covariance analyses. Further, it was difficult to differentiate between shared environmental effects and genetic effects in the co-twin control analyses.

5 | CONCLUSION

Our results suggest that variation in IBS risk, Strain, and Low Support is partly explained by the same genes, but not by the same nonshared environmental factors. A large proportion of the genetic effects for Strain and Low Support were shared with IBS. A novel finding is that the genetic influences explaining variation in the liability to develop IBS were fully shared with genetic effects for variation in the social measures. In contrast, nonshared environmental influences affecting the liability to develop IBS were, largely, unique to IBS. These findings suggest that genes involved in central stress mechanisms in the brain–gut axis are the main source of the genetic variation in IBS risk. Peripheral stress mechanisms of IBS, including interactions between mucosal immunity and inflammatory responses and the HPA axis, might be influenced mainly by environmental factors influencing the microbiota, such as diet, antibiotics, and especially acute gastroenteritis.

Based on the observed risk pattern in the co-twin control analyses, we conclude that shared familial effects, rather than causal mechanisms, best explain the relationship between IBS and social strain or low support. By disentangling genetic and environmental influences shared by IBS and social measures using twin modeling, this study contributes to the understanding of the genetic architecture of IBS.

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CONFLICT OF INTEREST

The authors listed below do not have any financial or other relationship (s) to disclose: Julia Kutschke, Jennifer Ruth Harris, and May-Bente Bengtson

AUTHOR CONTRIBUTIONS

JK, JRH and MBB conceptualized and designed the work. JK and JRH analyzed and interpreted the data. JK and MBB wrote the paper. All authors contributed to drafting and editing the manuscript. All authors have read and approved the manuscript for

publication., Project administration, MBB, Supervision and mentorship, JRH.

ETHICAL APPROVAL

Ethics approval for this study was granted by was the Regional Committees for Medical and Health Research Ethics (REK sørøst, Norway, #2014/360). All procedures performed in studies involving human participants were in accordance with the ethical standards of this national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

DATA AVAILABILITY STATEMENT

The consent given by the participants does not open for storage of data on an individual level in repositories or journals. Researchers who want access to data sets for replication should submit an application to datatilgang@fhi.no. Access to data sets requires approval from the Regional committees for medical and health research ethics in Norway and a formal contract with The Norwegian Twin Registry.

ORCID

May-Bente Bengtson https://orcid.org/0000-0002-5615-7141

REFERENCES

1. Fukudo S, Kanazawa M. Gene, environment, and brain-gut interactions in irritable bowel syndrome. *J Gastroenterol Hepatol*. 2011;26(Suppl 3):110–115.
2. Gupta A, Labus J, Kilpatrick LA, et al. Interactions of early adversity with stress-related gene polymorphisms impact regional brain structure in females. *Brain Struct Function*. 2016;221(3):1667–1679.
3. Klem F, Wadhwa A, Prokop LJ, et al. Prevalence, risk factors, and outcomes of irritable bowel syndrome after infectious enteritis: a systematic review and meta-analysis. *Gastroenterology*. 2017;152(5):1042–1054.e1041.
4. Mayer EA, Tillisch K. The brain-gut axis in abdominal pain syndromes. *Annu Rev Med*. 2011;62:381–396.
5. Drossman DA. Presidential address: gastrointestinal illness and the biopsychosocial model. *Psychosom Med*. 1998;60(3):258–267.
6. Tanaka Y, Kanazawa M, Fukudo S, Drossman DA. Biopsychosocial model of irritable bowel syndrome. *J Neurogastroenterol Motil*. 2011;17(2):131–139.
7. Chang L. The role of stress on physiologic responses and clinical symptoms in irritable bowel syndrome. *Gastroenterology*. 2011;140(3):761–765.
8. Gwee K-A, Leong Y-L, Graham C, et al. The role of psychological and biological factors in postinfective gut dysfunction. *Gut*. 1999;44(3):400–406.
9. Gerson MJ, Gerson CD. The importance of relationships in patients with irritable bowel syndrome: a review. *Gastroenterol Res Pract*. 2012;2012:157340.
10. Gerson M-J, Gerson CD, Awad RA, et al. An international study of irritable bowel syndrome: family relationships and mind-body attributions. *Soc Sci Med (1982)*. 2006;62(11):2838–2847.
11. Lackner JM, Brasel AM, Quigley BM, et al. The ties that bind: perceived social support, stress, and IBS in severely affected patients. *Neurogastroenterol Motil*. 2010;22(8):893–900.
12. Kutschke J, Falch A, Brandt I, et al. Social factors and health. *Nor J Epidemiol*. 2016;26(1–2):93–102.
13. Nilsen TS, Brandt I, Magnus P, Harris JR. The Norwegian Twin registry. *Twin Res Hum Genet*. 2012;15(6):775–780.
14. Sutphen SK. *How healthy are we?: A national study of well-being at midlife*. 1. 3. University of Chicago Press: [press release]. Orvill G Brim; 2004.
15. MC N. Biometrical models in behavior genetics. In: Kim Y-K, ed. *Handbook of behavior genetics*. New York, NY: Springer; 2009.
16. Posthuma D, Beem AL, de Geus EJ, et al. Theory and practice in quantitative genetics. *Twin Res*. 2003;6(5):361–376.
17. Hill WG, Mackay TFDS. Falconer and Introduction to quantitative genetics. *Genetics*. 2004;167(4):1529–1536.
18. Bradley E, Tibshirani RJ. *An introduction to Bootstrap*. 1993:321–389.
19. Ligthart L, Boomsma DI. Causes of comorbidity: pleiotropy or causality? Shared genetic and environmental influences on migraine and neuroticism. *Twin Res Human Genet*. 2012;15(2):158–165.
20. Neale MC, Hunter MD, Pritikin JN, et al. OpenMx 2.0: extended structural equation and statistical modeling. *Psychometrika*. 2016;81(2):535–549.
21. The Development Core team, *R. a language and environment for statistical computing*. version 2.6.2. Vienna: R Foundation for statistical Computing; 2015.
22. McGue M. When assessing twin concordance, use the probandwise not the pairwise rate. *Schizophr Bull*. 1992;18(2):171–176.
23. Hungin AP, Whorwell PJ, Tack J, Mearin F. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. *Aliment Pharmacol Ther*. 2003;17(5):643–650.
24. Wilson S, Roberts L, Roalfe A, Bridge P, Singh S. Prevalence of irritable bowel syndrome: a community survey. *Br J Gen Pract*. 2004;54(504):495–502.
25. Vandvik PO, Lydersen S, Farup PG. Prevalence, comorbidity and impact of irritable bowel syndrome in Norway. *Scand J Gastroenterol*. 2006;41(6):650–656.
26. Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. *Clin Epidemiol*. 2014;6:71–80.
27. Chial HJ, Camilleri M. Gender differences in irritable bowel syndrome. *J Gend-Specif Med*. 2002;5(3):37–45.
28. Bengtson MB, Ronning T, Vatn MH, Harris JR. Irritable bowel syndrome in twins: genes and environment. *Gut*. 2006;55(12):1754–1759.
29. Lembo A, Zaman M, Jones M, Talley NJ. Influence of genetics on irritable bowel syndrome, gastro-oesophageal reflux and dyspepsia: a twin study. *Aliment Pharmacol Ther*. 2007;25(11):1343–1350.
30. Morris-Yates A, Talley NJ, Boyce PM, Nandurkar S, Andrews G. Evidence of a genetic contribution to functional bowel disorder. *Am J Gastroenterol*. 1998;93(8):1311–1317.
31. Beyder A, Mazzone A, Strege PR, et al. Loss-of-function of the voltage-gated sodium channel NaV1.5 (channelopathies) in patients with irritable bowel syndrome. *Gastroenterology*. 2014;146(7):1659–1668.
32. Henström M, Diekmann L, Bonfiglio F, et al. Functional variants in the sucrase-isomaltase gene associate with increased risk of irritable bowel syndrome. *Gut*. 2018;67(2):263–270.
33. Fiskerstrand T, Arshad N, Haukanes BI, et al. Familial diarrhea syndrome caused by an activating GUCY2C mutation. *N Engl J Med*. 2012;366(17):1586–1595.
34. Zhu Z, Bakshi A, Vinkhuyzen A, et al. Dominance genetic variation contributes little to the missing heritability for human complex traits. *Am J Hum Genet*. 2015;96(3):377–385.
35. Mohammed I, Cherkas LF, Riley SA, Spector TD, Trudgill NJ. Genetic influences in irritable bowel syndrome: a twin study. *Am J Gastroenterol*. 2005;100(6):1340–1344.

36. Mayer EA. Gut feelings: the emerging biology of gut-brain communication. *Nat Rev Neurosci*. 2011;12(8):453–466.
37. Heitkemper MM, Cain KC, Burr RL, Jun SE, Jarrett ME. Is childhood abuse or neglect associated with symptom reports and physiological measures in women with irritable bowel syndrome? *Biological Res Nursing*. 2011;13(4):399–408.
38. Harper A, Naghibi MM, Garcha D. The role of bacteria, probiotics and diet in irritable bowel syndrome. *Foods (Basel, Switzerland)*. 2018;7(2):13.
39. Lackner JM, Gudleski GD, Firth R, et al. Negative aspects of close relationships are more strongly associated than supportive personal relationships with illness burden of irritable bowel syndrome. *J Psychosom Res*. 2013;74(6):493–500.
40. Taylor SE, Klein LC, Lewis BP, Gruenewald TL, Gurung RA, Updegraff JA. Biobehavioral responses to stress in females: tend-and-befriend, not fight-or-flight. *Psychol Rev*. 2000;107(3):411–429.
41. Cohen S, Wills TA. Stress, social support, and the buffering hypothesis. *Psychol Bull*. 1985;98(2):310–357.
42. Kilpatrick LA, Labus JS, Coveleskie K, et al. The HTR3A polymorphism c. -42C>T is associated with amygdala responsiveness in patients with irritable bowel syndrome. *Gastroenterology*. 2011;140(7):1943–1951.
43. Labus JS, Dinov ID, Jiang Z, et al. Irritable bowel syndrome in female patients is associated with alterations in structural brain networks. *Pain*. 2014;155(1):137–149.
44. Orand A, Gupta A, Shih W, et al. Catecholaminergic gene polymorphisms are associated with GI symptoms and morphological brain changes in irritable bowel syndrome. *PLoS One*. 2015;10(8):e0135910.
45. Jeffery IB, O'Toole PW, Öhman L, et al. An irritable bowel syndrome subtype defined by species-specific alterations in faecal microbiota. *Gut*. 2012;61(7):997–1006.
46. Derks EM, Dolan CV, Boomsma DI. Effects of censoring on parameter estimates and power in genetic modeling. *Twin Res*. 2004;7(6):659–669.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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