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Family history of mental illness or alcohol abuse and the irritable bowel syndrome

James R. Knight, M.D.[1], **G. Richard Locke III, M.D.**[2], **Alan R. Zinsmeister, Ph.D.**[3], **Cathy D. Schleck**[3], and **Nicholas J. Talley, M.D., Ph.D.**[2,4]

[1]Division of Hospital Medicine, Department of Internal Medicine and Pediatrics, The Ohio State University Medical Center, Columbus, OH, USA

[2]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

[3]Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA

[4]Faculty of Health and Medicine, University of Newcastle, Callaghan, NSW, Australia

Abstract

Objective—We have observed that many patients with IBS drink very little alcohol, and postulated this may reflect membership in families affected by alcoholism and mental illness. We aimed to evaluate whether a family history of substance or alcohol abuse, or psychiatric illness, is associated with IBS.

Methods—A valid GI questionnaire was mailed to a randomly selected population-based cohort to identify IBS and healthy controls. The electronic medical record was reviewed to record the subjects' self-reported personal and family health histories.

Results—2300 subjects responded (response rate 55%; IBS 13% n=287). 230 subjects with IBS and 318 controls were eligible. Family history of alcohol/substance abuse was reported by 33% of cases and 25% of controls (OR 1.4, 95% CI 1.0–2.1, p=0.06). Family history of psychiatric illness was reported by 37% of cases and 22% of controls (OR 2.0, 95% CI 1.3–2.9, p<0.001). In the absence of a personal history of alcohol use, a family history of alcohol/substance abuse was predictive of IBS status (OR adjusted for age and gender 1.5, 95% CI 1.0–2.3, p=0.05). In the absence of a personal history of alcohol use, reporting both a family history of alcohol/substance abuse and anxiety/depression/mental illness was clearly predictive of IBS status (OR 2.5, 95% CI 1.4–4.5; p<0.005). Substance abuse as a child was associated with an increased risk of IBS (OR 2.3, 95% CI 1.1–4.8; p<0.03).

Conclusion—IBS is independently associated with a family history of psychiatric illness and may be linked to a family history of alcohol/substance abuse.

Correspondence: Nicholas J. Talley, M.D., University of Newcastle, HMRI Building, Level 3, Kookaburra Circuit, New Lambton, NSW 2305, Australia, Phone: 612 4921 6378, Fax: 612 4921 5669, nicholas.talley@newcastle.edu.au.

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Keywords

IBS; alcohol; psychiatric disease

INTRODUCTION

Irritable bowel syndrome (IBS) affects 10% of U.S. adults [1] and is a cause of significant patient suffering and utilization of health-care resources [2, 3]. IBS runs in families [4], and twin studies [5] and prospective population-based studies [6, 7] support familial aggregation. However, the role of nature versus nurture in explaining this association remains uncertain.

Alcohol use does not appear to be increased in IBS compared with controls [8] although not all studies agree [9]. However, alcohol abuse, like IBS, is known to often be a familial disorder. Family, twin, and adoption studies demonstrate that genes are responsible for 50 to 60% of population variance in alcohol abuse [10]. Twin studies also demonstrate that alcohol, marijuana, and other drug use and problem use patterns have a genetic component [11, 12], although there are environmental factors that are also critically important [13]. As with IBS, the exact contribution of these individual components remains to be described.

Vaillant in his classic 60 year Harvard University follow-up study of adolescent men with alcoholism observed that those with a strong family history of alcoholism were more likely to become and remain abstinent, an apparent paradox [14]. Other data suggest similar associations may apply in women too [15]. The epidemiologic and physiologic parallels between IBS and alcoholism prompt the question: Could these two diseases co-aggregate in the same families? We have observed in clinical practice that many patients with IBS drink little or no alcohol, which is consistent with the epidemiological data [6]. However, the literature does not describe the alcohol and substance use and problem use patterns of their family members. We hypothesized *a priori* that IBS is more likely to occur in abstinent members of families with alcohol abuse and mental illness. Our aim was to determine if a family history of alcohol/substance abuse or psychiatric illness is associated with IBS.

METHODS

This study utilized a nested case-control design. Subjects with IBS and controls were selected from a cohort of responders to a population based symptom survey conducted as part of a longitudinal natural history study [16]. The research was approved by the Institutional Review Board of Mayo Clinic.

Subjects

With the approval of Mayo Clinic's Institutional Review Board, we used the Rochester project medical record linkage system to draw a series of true random samples, stratified by age and gender, of residents of Olmsted County between 1988 and 1993 [17, 18]. The cohorts were mailed validated gastrointestinal symptom questionnaires. The results of these studies have been reported previously [19, 20]. Initially, the complete (inpatient and outpatient) medical records of these randomly selected subjects were reviewed and subjects were excluded if they had significant illnesses which might cause gastrointestinal symptoms.

In 2003, a new study questionnaire (see below) and an explanatory letter were mailed to a random sample of subjects who had been mailed a prior survey [16]. Reminder letters were mailed at 2, 4 and 7 weeks. Subjects who indicated at any point that they did not wish to complete the survey were not contacted further. Otherwise, non-responders were contacted by telephone at 10 weeks to request their participation and verify their residence within the county. A total of 4196 eligible subjects were mailed a survey. Of these, 2300 (55%) completed the survey, 1025 refused, and 871 did not respond. A detailed investigation has confirmed non-response bias in this population is unlikely [21].

Questionnaire

The Talley Bowel Disease Questionnaire (BDQ) is a self-report instrument that measures symptoms experienced over the prior year [22]. The BDQ has adequate validity [22] and contains a valid measure of non-gastrointestinal somatic complaints, the Somatic Symptom Checklist (SSC) [23].

Nested Case-Control Study

The survey responses were used to identify cases and controls for this study. We identified all respondents who reported symptoms that met the Rome II criteria for IBS [24]. We then selected at random an age and gender frequency-matched control group of subjects without symptoms of IBS, but stratified by age and gender to approximate the age and gender distribution of the cases. To qualify as members of the control group, respondents could not have experienced abdominal pain more than 6 times in the past year and did not report more than one of the following symptoms: mucous in stools, bowel movement frequency less than three per week or more than three per day, feeling of incomplete evacuation after bowel movement, urgency, or bloating.

Chart Review

All Mayo Clinic patients since 1996 have two health history forms on file. One form, the Current Visit Information form (CVI) records information regarding the patient's current health, and the second form, the Patient Family History (PFH), records the individual's past medical history as well as family health history. A copy of the form is provided in Appendix 1. We examined the subjects' personal and family health history forms to assess individual histories of alcohol use, physical or sexual abuse and psychological illness and histories of the same among family members. These forms provide data regarding personal history of anxiety, depression, or mental illness, personal treatment for alcohol or drug abuse, and family history of drug/alcohol abuse or anxiety, depression, or mental illness including father, mother, brothers, sisters, sons, daughters, and grandparents. In addition, the person can rate their level of stress on a 1 to 5 scale with 5 being the highest.

Mayo Medical Center has converted to an electronic medical record (EMR). The reviewer (JRK), blinded to the subjects case-control status, assessed each patient's electronic medical history and excluded those patients that lacked the necessary PFH and CVI forms. Thus, patients seen exclusively at Olmsted Medical Center and never at the Mayo Medical Center were excluded. Other medical exclusion criteria were documented diagnoses of inflammatory bowel disease (IBD), cancer, or colonic surgery in the last year. Of the 666

charts identified for review, 73 (11%) lacked the necessary personal or family history forms, 21 (3.2%) had a history of systemic cancer noted in the EMR within the past year, 13 (2.0%) were missing all data from relevant areas of the form, 7(1.1%) carried a diagnosis of IBD, and 4 (0.6%) had colonic surgery within a year of review. In total, 118 (15.5%) patients were excluded from the study. The reviewer then entered the necessary information into an Excel spreadsheet that was later converted to a SAS® dataset format for data analysis. The first five charts were double-extracted and reliability was 100%, so single extraction was used thereafter.

Definitions

The CVI and PFH contain self-report data. Personal history of alcohol use was defined as any positive response to any alcohol related questions. Personal history of alcohol/drug abuse was defined as any positive response to personal need to cut down on alcohol. Personal history of anxiety/depression/mental illness was defined as any history of anxiety, depression, mental illness, or suicide. Abuse was defined as any positive response to the single abuse question (physical, sexual, or emotional). Stress was defined as any stress level greater than 3 or reporting a stressful situation. Family history of alcohol/substance abuse was defined as a positive response to this question or alcohol or substance abuse endorsed for any individual in the family information portion of the PFH. Similarly, family history of anxiety/depression/mental illness was defined as a positive response to this question or a family history of depression, other mental illness, or suicide attempts among any family members as addressed on the PFH.

Statistical Analysis

Logistic regression analyses were used to identify predictors of IBS adjusting for age and gender. In the initial analyses, patient history items were evaluated in univariate models and multiple predictor variable models. The items considered included alcohol/drug abuse (substance abuse), alcohol use, anxiety/depression/mental illness (mental illness), stress, and physical, sexual and/or emotional abuse.

In addition, logistic regression analyses were used to evaluate the association between family history of alcohol/drug abuse and anxiety/depression/mental illness and IBS. The initial evaluation utilized any personal or family history of a disorder as the independent (predictor) variables. The disorders considered included anxiety/depression/mental illness and alcohol/substance abuse. A separate model was evaluated in which histories of a disorder in specific family members were considered as predictor variables (i.e. father, mother, grandparent, sibling, child, and either/or mother and father).

Finally logistic regression models were examined in which the patients' history and family history predictors were evaluated as candidate predictor variables. In one model, four categories of alcohol/substance abuse were created (i.e. neither [the reference group], only personal history, only family history, and both personal and family history). A second model evaluated these same four categories for anxiety/depression/mental illness. Finally, two separate models were examined, one model for negative personal use of alcohol/substance abuse, and a second model for a positive history of alcohol/substance abuse. In each model,

family history of alcohol/substance abuse and anxiety/depression/mental illness were assessed (neither [the reference group], only alcohol/substance abuse, only anxiety/depression/mental illness, and both). Since the hypothesis was that those people who are abstinent from alcohol yet have family members who were alcoholic would be at increased risk of IBS, the analysis specifically evaluated the personal alcohol and family history of alcohol use simultaneously.

RESULTS

Overall, 2300 subjects responded to the questionnaire (response rate 55%). IBS was reported by 13% (n=287). 230 subjects with IBS and 318 controls were eligible after chart review. Cases had a mean age of 62 years and 70% were female, while controls had a mean age of 61 years and 64% were female.

Table 1 summarizes the univariate assessment adjusted for age and gender of the predictor variables, and shows IBS is associated with a personal and family history of mental illness, and a personal history of stress. Thus, a personal history of mental illness and increased personal stress level were predictors of an individual's IBS status (OR adjusted for age and gender 2.4, 95% CI 1.5–3.7, $p<0.001$, and OR 1.9, 95% CI 1.2–2.9, $p<0.01$, respectively). Abuse history, alcohol use, and substance abuse did not demonstrate an independent association with a subject's IBS status. Family history of substance abuse was reported by 33% of cases and 25% of controls (OR adjusted for age and gender 1.4, 95% CI 1.0–2.1, $p=0.06$). Family history of mental illness was reported by 37% of cases and 22% of controls (OR adjusted for age and gender 2.0, 95% CI 1.3–2.9, $p<0.001$). Family history of substance abuse was not independently predictive of IBS given the family history of mental illness.

Table 2 summarizes the associations between substance abuse among specific family members and IBS. In a model that included substance abuse among specific family members (e.g., mother, father, both), only reporting substance abuse as a child was associated with IBS (OR adjusted for age and gender 2.3, 95% CI 1.1–4.8, $p<0.05$).

Table 3 summarizes the associations between psychiatric illness among specific family members and IBS. Reporting a mother, or separately, mental illness as a child was associated with IBS (OR adjusted for age and gender 2.0, 95% CI 1.1–3.6, $p<0.05$, and OR 1.9, 95% CI 1.0–3.6, $p<0.05$; respectively).

We had hypothesized that IBS would be more likely to occur in the abstinent members of families with alcohol abuse and mental illness. In Table 4 we present a model of the associations between personal and family history of alcohol/substance abuse and IBS. The model had a 4-category predictor variable (with "No/No" as the reference), again adjusted for age and gender. It showed that in the absence of a personal history of alcohol use, a family history of alcohol/substance abuse was predictive of IBS status (OR adjusted for age and gender in the model 1.5, 95% CI 1.0–2.3, $p=0.05$). A positive personal history of alcohol abuse and either a positive or negative family history of alcohol/substance abuse were not predictive of IBS status in this model (Table 4). Analysis of family history of

alcohol abuse in the absence of substance abuse was not feasible given the limited number of subjects with such data available.

In Table 5 we next evaluated the associations between personal and family history of anxiety/depression/mental illness and IBS. This model showed that any personal history of depression/mental illness was predictive of IBS status in either the presence or absence of a family history of mental illness (OR adjusted for age and gender 3.0, 95% CI 1.6–5.5, $p<0.005$ and OR 2.0, 95% CI 1.0–3.9, $p<0.05$, respectively). In the absence of a personal history of anxiety/depression/mental illness, a positive family history was also predictive of IBS status (OR adjusted for age and gender 1.9, 95% CI 1.2–3.1, $p<0.01$).

As summarized in Table 6, we lastly tested the associations between family history of anxiety/depression/mental Illness and alcohol/substance abuse in combination with the presence or absence of a personal history of alcohol use and IBS. We found that in the absence of a personal history of alcohol use, a positive family history of anxiety/depression/mental illness alone was predictive of IBS status (OR adjusted for age and gender 2.2, 95% CI 1.3–3.7, $p<0.005$). In the absence of a personal history of alcohol use, reporting a family history of both alcohol/substance abuse and anxiety/depression/mental illness was also predictive of IBS status (OR adjusted for age and gender 2.5, 95% CI 1.4–4.5, $p<0.005$). However, in the absence of a personal history of alcohol use, a family history of alcohol/substance abuse alone (without mental illness) was not predictive. In the presence of a positive personal history of alcohol use, neither a positive family history of alcohol/substance abuse, anxiety/depression/mental illness, nor a combination of both was predictive of IBS status (Table 6).

DISCUSSION

Based on our clinical experience, we hypothesized that alcohol abstinence or avoidance is more frequent in IBS because subjects have been exposed to alcohol abuse and mental illness in their families. In this population-based study, IBS was not associated with a personal history of alcohol use and was independently associated with a family history of mental illness. When individual family members' alcohol/substance abuse and mental illness histories were analyzed separately, there was a significant association between IBS status and reporting children with mental illness or alcohol/substance abuse problems. Reporting a mother with mental illness was also associated with IBS. The reported substance abuse and mental illness status of other relatives was not significantly associated with an individual's IBS status. IBS was also associated with a personal history of stress and mental illness.

Consistent with most epidemiological data [6], we did not find that IBS was associated with alcohol use in this study. This is in contrast to one study that reported individuals who abused alcohol were significantly more likely to suffer from IBS than control patients [9]; selection bias may account for these findings. Notably, we observed here that in the absence of a personal history of alcohol use, the combination of a positive family history of both alcohol/substance abuse and anxiety/depression/mental illness was an independent predictor of IBS status, and the associated odds ratio was larger than that observed for family history of anxiety/depression/mental illness alone. However, reporting family history of alcohol

abuse without a family history of mental illness was not a significant predictor. In the presence of a personal history of alcohol use, neither family history of alcohol/drug abuse, anxiety/depression/mental illness, nor a combination of both, was a predictor of IBS status.

Alcoholism and IBS may both be related to disturbances of serotonin (5HT) physiology. Defects in serotonin signaling in the colon have been observed in IBS with diarrhea or constipation [25]. Blocking 5HT3 receptors is efficacious in diarrhea-predominant IBS, and 5HT4 receptor agonists have shown benefit for constipation-predominant IBS [26]. Alcohol has been shown to potentiate central 5HT as a part of the pathway leading to the rewarding release of dopamine, a possible mechanism for alcoholism [13]. Furthermore, 5HT3 receptor antagonists have shown significant benefits in the treatment of biologically predisposed alcoholic patients through a postulated central effect [27]. Based on the observation that there is less alcoholism in IBS, we speculate there may be a connection between lack of alcohol abuse and IBS through serotonin pathways that require exploration in future research. Further, we cannot exclude our findings being more related to individuals struggling with the parenting style of any type of mental illness rather than a specific effect of alcohol use in the family or a shared genetic background altering serotonin pathways. Alternative explanations also need to be considered although data are lacking. For example, some patients with IBS may restrict their diet in attempt to control symptoms (such as follow a gluten-free diet or low fructan diet, or limit caffeine), and might limit alcohol use as a reflection of their attempt to cope with their symptoms.

Only a few studies have examined the association between family history of mental illness and IBS. One small (70 subject) interview study did demonstrate a significant relationship between reporting relatives with depression and IBS. There was no relationship observed between family history of alcohol dependency, anxiety, schizophrenia, or suicide [28]. Masand, et al. observed an increased family history of bowel disease in patients with depression and IBS compared to those with depression but without IBS [29].

A collection of medical and psychiatric conditions have been labeled the Affective Spectrum Disorder (ASD) which includes IBS as well as panic disorder, social phobias, bulimia, depression, obsessive compulsive disorder, and post-traumatic stress disorder. Hudson showed familial co-aggregation of the disorder’s collective conditions [30]. However, the study was unable to show familial co-aggregation of any of the individual ASD forms, including IBS, with major depressive disorder. Also of note, while they discovered an individual aggregation of alcohol abuse with IBS, they were also unable to demonstrate familial co-aggregation of IBS with alcohol abuse.

The current study data are consistent with early life adversity and poor parenting being risk factors for IBS. Those reporting both a family history of alcohol and substance abuse and mental illness were over two times more likely to have IBS, suggesting parents who are alcoholic or mentally disturbed may have a particular adverse impact on their children leading to adult IBS. A systematic review of 25 articles identified early childhood trauma including abuse and affluent childhood socioeconomic status were predictors of adult IBS [31] consistent with recent population-based data from Australia [32]. Animal model research has identified that early life stress can alter the brain-gut axis and gut visceral

sensation via microbial, immune and stress cortisol pathways [33]. We further observed those having a child with substance abuse or mental illness were also at a two fold higher risk of IBS which may reflect a shared genetic contribution [34] or possibly evidence of intergenerational familial dysfunction and abnormal learned behavior [35].

Several limitations of this study need to be considered. The CVI and PFH forms, while used across the Mayo Clinic's practice, have excellent face validity but have not otherwise been validated as a research tool. The family data is based on the subject's responses and not directly from family members, and thus misclassification may have occurred. These two forms are specific to the Mayo Clinic and thus patients seen only at Olmsted Medical Center were not included (n=45). The survey was mailed to responders to past surveys and had a 54% response rate, thus response bias could be an issue but other work from our group suggests this is unlikely [36]. One of the strengths of the study is that because a population-based survey approach was utilized, there was no health care seeking bias. The population affected by IBS that actively seeks health care for their symptoms is different than the affected population at large [37]. Cases and controls were selected the same way. While underreporting of alcoholism or mental illness in the family is possible in those with IBS, this bias should have favored finding no associations and may indicate the results here are conservative. Both groups had to return surveys, and the age and gender distributions were kept similar; this design minimizes many sources of bias. We did apply Rome II rather than Rome III criteria as the survey was performed prior to the release of Rome III but these criteria are similar and discriminate IBS from disease with comparable sensitivity and specificity [38]. We were not able to ask the IBS patients why they do not drink alcohol, and longitudinal data are needed to further tease out the relationships.

In conclusion, this study has shown that while alcohol use does not seem to be a risk factor for IBS, a family history of mental illness appears to be. Furthermore, in those with IBS who do not drink alcohol, a family history of mental illness and alcohol or substance abuse appears to be relevant. Future research needs to assess the reasons why IBS patients may drink little or no alcohol and the timing of when family mental illness or parental alcoholism occurred in the life of IBS cases. We postulate that there is a common gene or set of genes that gives a propensity for IBS and alcohol abuse or mental illness. However, we speculate that gene environment interactions likely modify the risk such that, for example, alcohol abuse might be actually protective for the phenotypic expression of IBS. Certainly these results are also consistent with an environmental explanation that having family members with mental illness especially mothers and children may lead to IBS. Further work is necessary to tease out this nature versus nurture relationship and this may help elucidate the pathogenesis of IBS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- The exact causes of IBS are largely unknown but IBS runs in families
- We found IBS is not associated with a personal history of alcohol use
- IBS is associated with a family history of mental illness
- IBS is associated with a personal history of stress and mental illness
- A positive family history of alcohol/substance abuse & mental illness predicts IBS

Table 1

Univariate associations of the predictor variables with IBS

	Case (n) %	Control (n) %	OR*	95%CI	p-value
Personal History					
Alcohol Use	(139) 60%	(200) 63%	0.8	0.6–1.2	0.33
Alcohol/Drug Abuse	(18) 8%	(21) 7%	1.3	0.7–2.5	0.48
Anxiety/Depression/Mental Illness	(57) 25%	(38) 12%	2.4	1.5–3.7	0.0002
Abuse†	(12) 5%	(8) 3%	2.1	0.8–5.1	0.12
Stress	(55) 24%	(47) 15%	1.9	1.2–2.9	0.006
Family History					
Alcohol/Drug Abuse	(77) 34%	(81) 25.5%	1.44	1.0–2.1	0.06
Anxiety/Depression/Mental Illness	(84) 37%	(71) 22.3%	1.97	1.3–2.9	0.0005

*Adjusted for age and gender

†Abuse was defined as any positive response to the single abuse questions (physical, sexual, or emotional)

Table 2

Associations between substance abuse among specific family members and IBS

Family History: Alcohol/Drug Abuse	Case (n) %	Control (n) %	OR*	95%CI	p-value
Mother	(12) 5%	(8) 3%	1.9	0.7–4.8	0.19
Father	(33) 14%	(42) 13%	0.9	0.5–1.5	0.64
Mother or Father†	(43) 19%	(45) 14%	1.4	0.8–2.1	0.20
Sibling	(33) 14%	(30) 9%	1.5	0.9–2.6	0.15
Grandparent	(14) 6%	(15) 5%	1.2	0.5–2.6	0.68
Child	(21) 9%	(12) 4%	2.3	1.1–4.8	0.03

*Adjusted for age and gender

†Both are counted as just 1.

Table 3

Associations between psychiatric illness among specific family members and IBS

Family history: Anxiety/Depression/Mental Illness	Case (n) %	Control (n) %	OR*	95%CI	p-value
Mother	(29) 12.6%	(21) 6.6%	2.0	1.1–3.6	0.03
Father	(13) 5.7%	(15) 4.7%	1.0	0.4–2.3	0.97
Mother or Father†	(37) 16.1%	(31) 9.8%	1.7	1.0–2.9	0.03
Sibling	(32) 13.9%	(27) 8.5%	1.6	0.9–2.7	0.13
Grandparent	(6) 2.6%	(10) 3.1%	0.6	0.2–2.0	0.45
Child	(25) 10.9%	(19) 6.0%	1.9	1.0–3.6	0.04

*Adjusted for age and gender

†Both are counted as just 1.

Table 4

Associations between personal and family history of alcohol/substance abuse and IBS[#]

Personal History	Family History	Cases (n) %	Controls (n) %	OR[*]	95% CI	p-value
Yes	**No**	(6) 3%	(12) 4%	0.8	0.3–2.2	0.68
No	**Yes**	(67) 30%	(73) 24%	1.5	1.0–2.3	0.05
Yes	**Yes**	(10) 4%	(8) 3%	1.9	0.7–5.5	0.22
No	**No**	(143) 63%	(214) 70%	1.0	ref[†]	

[*] Adjusted for age and gender

[†] ref = reference group

[#] Presents the results for a model in which the 4 combinations were included as predictor variables.

Table 5

Associations between personal and family history of anxiety/depression/mental illness and IBS

Personal History	Family History	Cases (n) %	Controls (n) %	OR*	95% CI	p-value
Yes	**No**	(22) 10%	(18) 6%	2.0	1.0–3.9	0.047
No	**Yes**	(50) 22%	(51) 17%	1.9	1.2–3.1	0.007
Yes	**Yes**	(34) 15%	(20) 7%	3.0	1.6–5.5	0.0004
No	**No**	(120) 53%	(217) 71%	1.0	ref†	

*Adjusted for age and gender

†ref = reference group

Table 6

Associations between family history of anxiety/depression/mental Illness and alcohol/substance abuse in combination with the presence or absence of a personal history of alcohol use and IBS

Family History	Negative Personal History of Alcohol Use			Positive Personal History of Alcohol Use		
	OR*	95% CI	p-value	OR*	95% CI	p-value
Alcohol/Drug Abuse	1.5	0.9–2.5	0.17	3.1	0.7–14	0.14
Depression/Mental Illness	2.2	1.3–3.7	0.003	2.4	0.2–40	0.54
Both	2.5	1.4–4.5	0.002	1.8	0.4–7.6	0.41
Neither	1.0	ref†		0.9	0.3–2.6	0.81

*Adjusted for age and gender

†ref = reference group