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Intolerance of Uncertainty as a Core Driver of Anxiety and Depression: The Mediating Role of the Gut–brain Axis

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ABSTRACT

Intolerance of uncertainty (IU) is the tendency to react negatively to situations that are unclear, unpredictable, or lacking in information, and it is now regarded as a transdiagnostic risk factor for anxiety and depression. Research on the microbiota–gut–brain axis shows that the gut and brain communicate constantly and that disturbances in this communication accompany anxiety and depressive symptoms, yet the two literatures have developed largely apart. This study integrates them in a conceptual model in which IU (independent variable) influences anxiety and depression (dependent variables) partly through the gut–brain axis (mediator), via stress-system, immune–inflammatory, and behavioural pathways. Six hypotheses are derived and then illustrated in a simulation-based demonstration using a synthetic dataset (N = 400) analysed with parallel mediation, covarying age and gender, and 5,000 bootstrap resamples. In the simulated data, IU predicted gut–brain axis symptom burden (β = .42), which in turn predicted anxiety (β = .21) and depression (β = .31) over and above IU. A significant part of an effect was mediated indirectly by anxiety (ab =.091, 95% CI [.047,.138]; 22% mediated) and depression (ab =.131, 95% CI [.081,.184]; 44% mediated), suggesting partial mediation. In terms of its implications, the paper also concludes by pointing out issues of assessment, psychological treatment, and integrated care while suggesting that the model should be tested in a real, longitudinal sample.

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1. Introduction

Depression and anxiety are the most common mental health illnesses worldwide, they are also known to coexist quite often (Simpson et al., 2021). Because of this overlap, scientists have aimed to find out if there are common or transdiagnostic mechanisms that could explain the possibility of developing both issues in the same indivdual. A very promising theory from psychology is people's inability to tolerate uncertainty as a reason for both conditions to occur (Carleton, 2016a; Gentes & Ruscio, 2011).

A second line of work comes from biology. The gut and the brain are connected through nerves, hormones, immune signals, and chemicals made by gut bacteria. This two-way network is called the microbiota–gut–brain axis (Cryan et al., 2019). Differences in the gut microbiota have been reported in people with anxiety and depression (Simpson et al., 2021).

These two literatures raise a simple question: could a psychological trait such as IU affect mental health partly by changing how the gut and brain communicate? This article argues that this is plausible and testable. It first explains IU and the gut–brain axis, then describes how the two may be connected, proposes a mediation model with hypotheses, and finally illustrates the analysis with a simulated dataset, reporting the full analytic workflow, results, and a discussion of what such results would and would not mean.

2. Intolerance of Uncertainty

2.1 What is intolerance of uncertainty?

Intolerance of Uncertainty (IU) has been consistently related to anxiety. A comprehensive review of many individual studies found that IU is significantly and positively correlated with the symptoms of generalized anxiety disorder, as well as to symptoms of depression and obsessive-compulsive disorder (Gentes & Ruscio, 2011). In a mental health group, IU was linked to symptoms in multiple anxiety disorders and depression, confirming that it plays a cross diagnosis role (McEvoy & Mahoney, 2012). Moreover, neuroscience investigations indicate that expecting an unpredictable future is at the heart of anxiety (Grupe & Nitschke, 2013).

2.2 IU and depression

A relationship between IU and depression has also been found (Gentes & Ruscio, 2011; McEvoy & Mahoney, 2012). A possible reason is that such individuals get anxious about the uncertainties ahead and indulge in repetitive thinking, which they can't help but carry on with as a way through to deal with the situations in a safe way. In the long run, these habitual forms of negative thoughts and avoidances will lead one to less participation in various activities, more hopelessness, and a lower level of feeling of well-being or contentment. Hence, IU may represent an overlapping vulnerability factor for anxiety and depression.

3. The Microbiota–Gut–Brain Axis

3.1 How the gut and brain communicate

The gut–brain axis is a two-way communication system. The main routes are (a) the vagus nerve and the enteric nervous system, (b) the hypothalamic–pituitary–adrenal (HPA) axis, which controls the stress hormone cortisol, (c) the immune system, and (d) substances produced by gut bacteria, such as short-chain fatty acids (Cryan et al., 2019; Dinan & Cryan, 2017). Because the gut also sends signals upward to the brain, bodily sensations from the gut can influence emotion and mood (Mayer, 2011).

3.2 Evidence linking the gut with anxiety and depression

Much of the early evidence comes from animal studies. Germ-free mice show an exaggerated stress response (Sudo et al., 2004), and giving mice a certain *Lactobacillus* strain reduced anxiety- and depression-like behaviour through the vagus nerve (Bravo et al., 2011). Transferring gut microbiota from depressed people into rodents produced depression-like behaviour in the animals (Kelly et al., 2016; Zheng et al., 2016).

Human gut flora is changing during the development of mental illnesses such as depression and anxiety

In humans, a thorough review of 26 studies showed that individuals who experienced anxiety and depression had an increased presence of bacteria that promote inflammatory reactions, while simultaneously there was a reduction in the number of bacteria that are able to produce short-chain fatty acids, one such bacterium being Faecalibacterium (Simpson et al. (, 2021).

One of the biggest studies ever to look at people at-risk, or depressed, reported a significant reduction among depressed persons in the levels of two bacteria Coprococcus and Dialister (Valles-Colomer et al. 2019).

A meta-analysis on the effect of psychiatric disorders found an increasing pro-inflammatory bacterial profile and a decreasing anti-inflammatory bacterial profile (Nikolova et al. (2021). Inflammation is itself a known precipitating factor for depression and other mood disorders (Miller & Raiso, 2016).

On the other hand, the results on changes in overall microbial diversity are very different. Besides the fact that changes in overall species richness are quite inconsistent among studies, the results might be also affected by dietary intake and the use of drugs (Konturek, & Kania-Kulig, 2005: Simpson et al., 2021).

4. How IU May Affect the Gut–Brain Axis

No study has examined directly if IU causes an alteration of gut microbiota. Yet, current studies suggest three possible pathways for it.

4.1 Pathway 1: The stress-system People who have high levels of IU tend to see uncertainty as a potential threat, and, thus, their stress response systems might be active continuously. This chronic stress situation may involve HPA axis and the sympathetic nervous system (Chrousos, 2009). Also, stress has effects on gut motility, gut permeability, and the composition of microbiota (Foster et al., 2017; Karl et al., 2018).

Symptoms of IBS commonly overlap with GAD and PD, as per the available literature (Gros et al., 2009). In a study of a few participants with IBS and GAD, a cognitive-behavioural programme targeting IU decreased both GI symptoms and the level of cortisol (Ezzati et al., 2021). Of course, being a small, quasi-experimental study, the findings here do not offer any strong evidence yet.

4.2 Pathway 2: The immune and inflammatory

A persistent stress can weaken the intestinal barrier leading to bacterial products leak that, in turn, triggers a low-grade systemic inflammation (Foster et al., 2017).

Cytokines from this inflammation then find their way to the brain affecting mood which, in turn, increases anxiety (Miller & Raison, 2016).

This mechanism relates the distress caused by uncertainty to the microbial-related inflammatory changes observed in people with anxiety/depression (Simpason et al., 2021).

4.3 Pathway 3: Daily life activity

Also, IU is a way of shaping daily life and behaviour. The person who is in a worried state most of the time may have trouble falling asleep at night, or their eating habit is out of control, they prefer food which can make their feeling comforted, they skip their exercise routine, or social meals altogether. These are all unhealthy patterns of life which may have effects on health of the gut.

This explanation though makes sense, has only been tested through experiments, and future studies should include measuring and controlling these variables since dietary factors have been found to be one of the major confounding variables (Simpson et al., 2021).

4.4 A two-way cycle

The relationship is probably not one-directional. Unpredictable gut sensations, such as sudden pain or urgency, are themselves a form of uncertainty. A person high in IU may read these signals as dangerous, which raises anxiety and further disturbs the gut (Mayer, 2011). This creates a possible vicious cycle between IU, gut symptoms, and emotional distress.

5. Proposed Conceptual Model and Hypotheses

Based on the above, this article proposes that IU is the independent variable, anxiety and depression are the dependent variables, and the gut–brain axis

is the mediator. The expected relationships are shown in Figure 1. Partial mediation is expected because IU is also likely to affect anxiety and depression directly through worry, rumination, and avoidance.

Figure 1: *Proposed parallel mediation model. Path a links intolerance of uncertainty (X) to gut–brain axis dysfunction (M); paths b_1 and b_2 link M to anxiety and depression, controlling for X; paths c'_1 and c'_2 are the direct effects of X. Indirect effects are the products $a \times b_1$ and $a \times b_2$.*

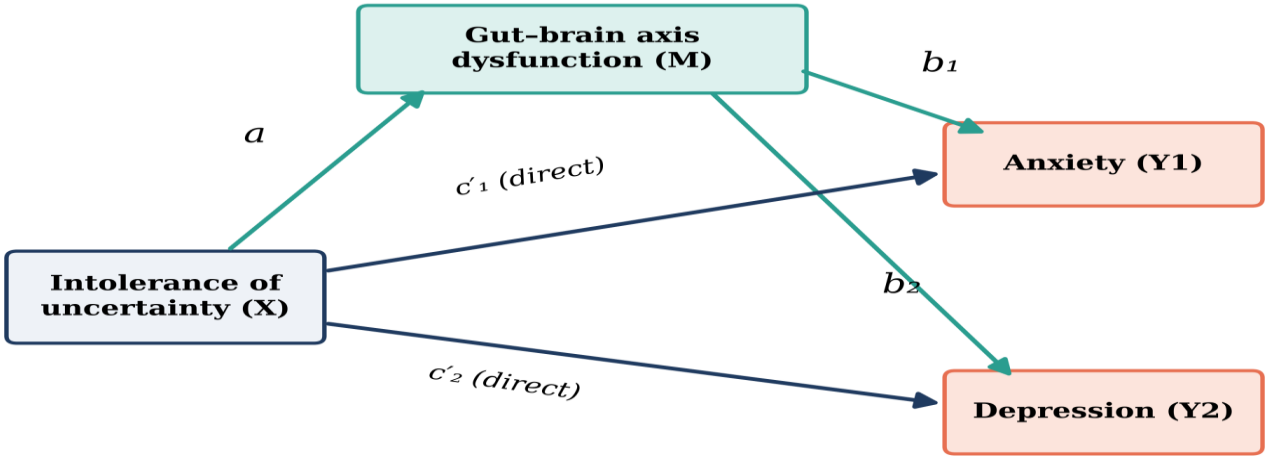


Table 1: *Proposed Hypotheses*

No.	Hypothesis
H1	Intolerance of uncertainty will positively predict anxiety.
H2	Intolerance of uncertainty will positively predict depression.
H3	Intolerance of uncertainty will positively predict gut–brain axis dysfunction (path a).
H4	Gut–brain axis dysfunction will positively predict anxiety (path b_1) and depression (path b_2), after controlling for intolerance of uncertainty.
H5	Gut–brain axis dysfunction will partly mediate the relationship between intolerance of uncertainty and anxiety ($a \times b_1$).
H6	Gut–brain axis dysfunction will partly mediate the relationship between intolerance of uncertainty and depression ($a \times b_2$).

6. Method

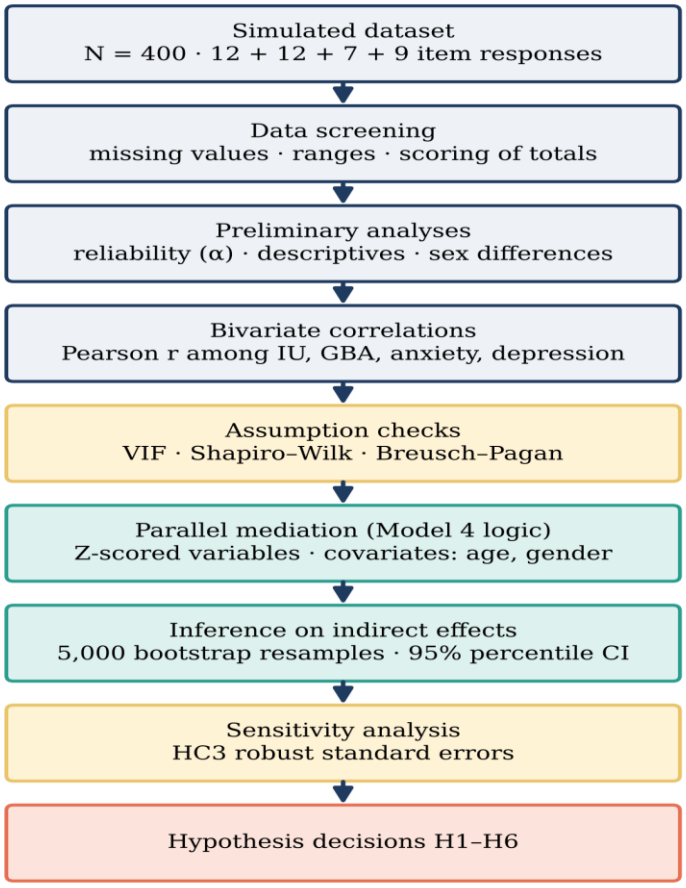
6.1 Design and data source

The hypotheses were examined in a simulation-based demonstration. A synthetic cross-sectional dataset of $N = 400$ cases with item-level responses was generated in Python (random seed 2026) with a built-in data-generating model in which IU influences gut–brain axis symptoms and both influence anxiety and depression. Using simulated data allows the full analytic pipeline, from scoring and reliability analysis to bootstrapped mediation. It also means that effect sizes reflect the parameters chosen by the simulation and carry no

information about real people. For a genuine test of mediation, a longitudinal design with at least two or three measurement occasions is strongly preferable, because the cause must precede the effect (Maxwell & Cole, 2007).

The simulated sample contained 202 women (50.5%) and 198 men (49.5%), aged 18 to 51 years (M = 28.20, SD = 7.15). There were no missing values. Figure 2 summarises the analytic workflow.

Figure 2: *Flowchart of the analytic workflow, from the simulated dataset to hypothesis decisions. IU = intolerance of uncertainty; GBA = gut–brain axis; VIF = variance inflation factor; HC3 = heteroscedasticity-consistent standard errors.*



6.2 Measures

- *Intolerance of uncertainty:* the 12-item Intolerance of Uncertainty Scale (Carleton et al., 2007), rated 1–5; total scores range from 12 to 60, with higher scores indicating greater IU.
- *Anxiety:* the 7-item Generalized Anxiety Disorder scale (GAD-7; Spitzer et al., 2006), rated 0–3; total scores range from 0 to 21.
- *Depression:* the 9-item Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001), rated 0–3; total scores range from 0 to 27.
- The Gut-Brain axis symptom load is measured by 12-item stomach symptom items that reflect a person's stress and mood, each item is answered to the level from 1 to 5 (the overall result is 12 60; higher scores show higher workload). This item serves as a good example which substitutes for standardized tests such as the Gastrointestinal Symptom Rating Scale by Svedlund and colleagues (1988). We did not model biological markers proposed before (stool microbiology analysis, short-chain fatty acids, C-reactive protein, cortisol).

- Age (in years) and gender (female = 1, male = 0) are confounding variables.
- Nutritional value, rest, drugs and BMI which are significant confounding variables in real research were not included.

6.3 Data analysis

Scale scores were calculated as the sum of individual items, and internal consistency as Cronbach's alpha estimation. For each group of symptoms descriptive statistics, measures of skewness, kurtosis were computed, and Welch's t-test with Cohen's d for measuring gender differences. Relations were investigated through Pearson correlations.

Moderation analyses have been designed in line with the framework ofPROCESS Model 4 (Hayes, 2018). First, the mediator is anxiety, then depression, with the mediator and covariates being the same variable in each instance, equivalent to a model in parallel of two outcomes. Except for the variable gender all other variables have been mean standardized by the researcher so that coefficients can serve as standard estimate.

Paths like the one from IU to Gut-Brain axis (Path a) and from Gut-Brain axis to outcome after controlling for IU (Path b), total effect c, the component of the direct effect which is unconfounded by the mediator c' was estimated with the least squares method and each model was adjusted for age and gender.

The indirect effect (*ab*) was tested with 5,000 percentile bootstrap resamples and a 95% confidence interval; an indirect effect was considered significant when the interval excluded zero (Preacher & Hayes, 2008; Shrout & Bolger, 2002). The Sobel (1982) test is reported for reference only. The proportion mediated was computed as *ab*/*c*. Differences between the two indirect effects were examined with the bootstrap distribution of their difference.

Multicollinearity (variance inflation factors), residual normality (Shapiro–Wilk), and homoscedasticity (Breusch–Pagan) were checked. Because symptom scales are typically skewed, models were re-estimated with HC3 heteroscedasticity-consistent standard errors (Long & Ervin, 2000) as a sensitivity analysis. Significance was set at $\alpha = .05$ (two-tailed). Analyses were run in Python using pandas, SciPy, and statsmodels.

7. Results

7.1 Preliminary analyses

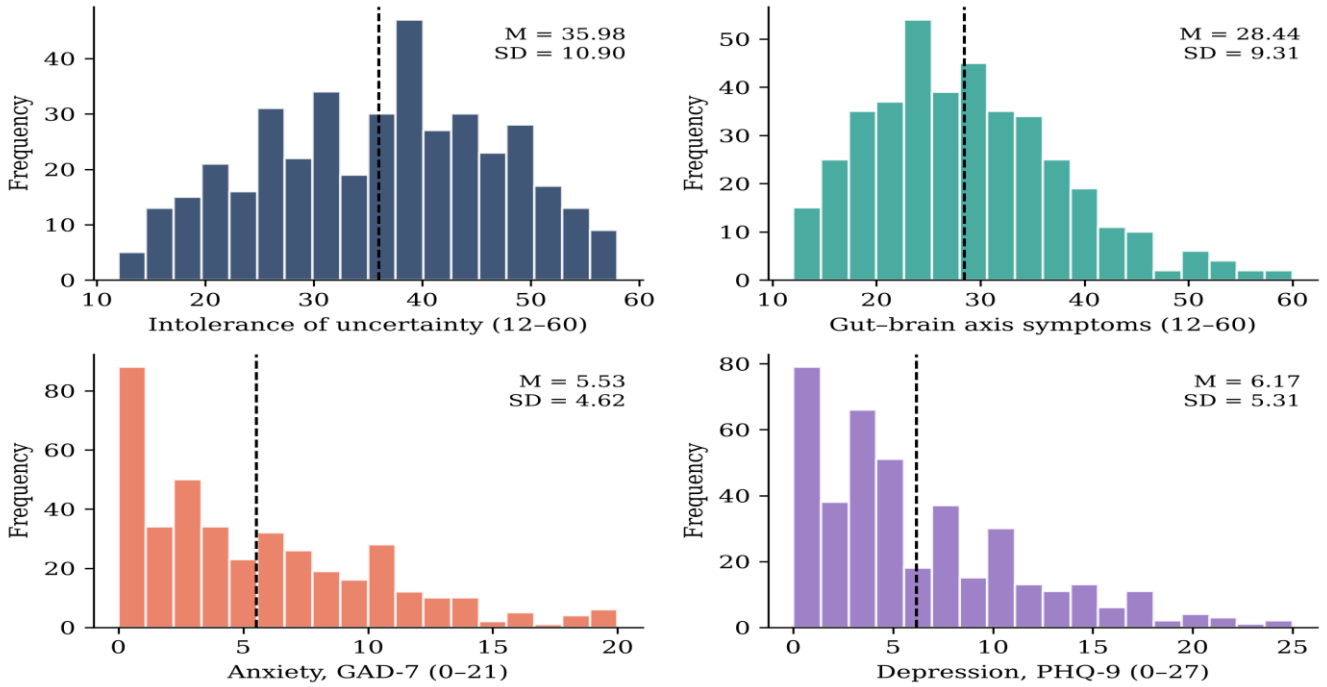
All four scales showed good internal consistency (Cronbach's $\alpha = .91$ for IU, .88 for gut–brain axis symptoms, .85 for anxiety, and .85 for depression; Table 2). Mean IU was 35.98 (*SD* = 10.90) and was approximately symmetric, whereas the gut–brain axis, anxiety, and depression scores were positively skewed (skewness = 0.64, 0.97, and 1.06, respectively), as is typical of symptom measures in non-clinical samples (Figure 3). Using conventional screening cut-offs, 19.5% of the sample scored 10 or above on the GAD-7 and 24.0% scored 10 or above on the PHQ-9.

Table 2: *Descriptive Statistics and Internal Consistency (N = 400)*

Scale	Items	Observed range	*M*	*SD*	Skewness	Kurtosis	α
Intolerance of uncertainty	12	12–58	35.98	10.90	-0.08	-0.89	.91
Gut–brain axis symptoms	12	12–60	28.44	9.31	0.64	0.25	.88
Anxiety (GAD-7)	7	0–20	5.53	4.62	0.97	0.42	.85
Depression (PHQ-9)	9	0–25	6.17	5.31	1.06	0.66	.85

Note. *IU = intolerance of uncertainty; GBA = gut–brain axis. Kurtosis is excess kurtosis. Data are simulated.*

Figure 3: *Distributions of the four scale scores. Dashed lines mark the sample means.*



Gender differences were small (Table 3). Women reported higher gut–brain axis symptom burden than men (M = 29.49 vs. 27.37; t = 2.29, p = .022, d = 0.23), whereas differences in IU (t = 1.23, p = .219, d = 0.12), anxiety (t = 1.58, p = .114, d = 0.16), and depression (t = 1.45, p = .149, d = 0.14) were not significant. Gender was therefore retained as a covariate in all models.

Table 3: *Gender Differences on Study Variables*

Variable	Women *M* (*SD*)	Men *M* (*SD*)	*t*	*p*	*d*
Intolerance of uncertainty	36.64 (10.92)	35.30 (10.86)	1.23	.219	0.12
Gut–brain axis symptoms	29.49 (9.25)	27.37 (9.27)	2.29	.022	0.23
Anxiety	5.89 (4.86)	5.16 (4.34)	1.58	.114	0.16
Depression	6.54 (5.37)	5.78 (5.22)	1.45	.149	0.14

Note. *Welch's t tests (df ≈ 398). d = Cohen's d (positive = higher in women).*

7.2 Bivariate associations

All variables were positively and significantly correlated (all *p*s < .001; Table 4, Figure 4). IU was moderately associated with gut–brain axis symptoms (r = .43), anxiety (r = .42), and depression (r = .31). Gut–brain axis symptoms were in turn associated with anxiety (r = .36) and depression (r = .39). Anxiety and depression were correlated at r = .24. These associations are shown graphically in Figure 5. By Cohen's (1988) conventions, all correlations fall in the small-to-medium range, and no correlation among the predictors approached a level that would suggest redundancy.

Table 4: *Pearson Correlations Among Study Variables*

Variable	1	2	3	4
1. Intolerance of uncertainty	—			
2. Gut–brain axis symptoms	.43***	—		
3. Anxiety	.42***	.36***	—	
4. Depression	.31***	.39***	.24***	—

Note. *N = 400. *** p < .001.*

Figure 4: *Correlation matrix of the four study variables (*** p < .001).*

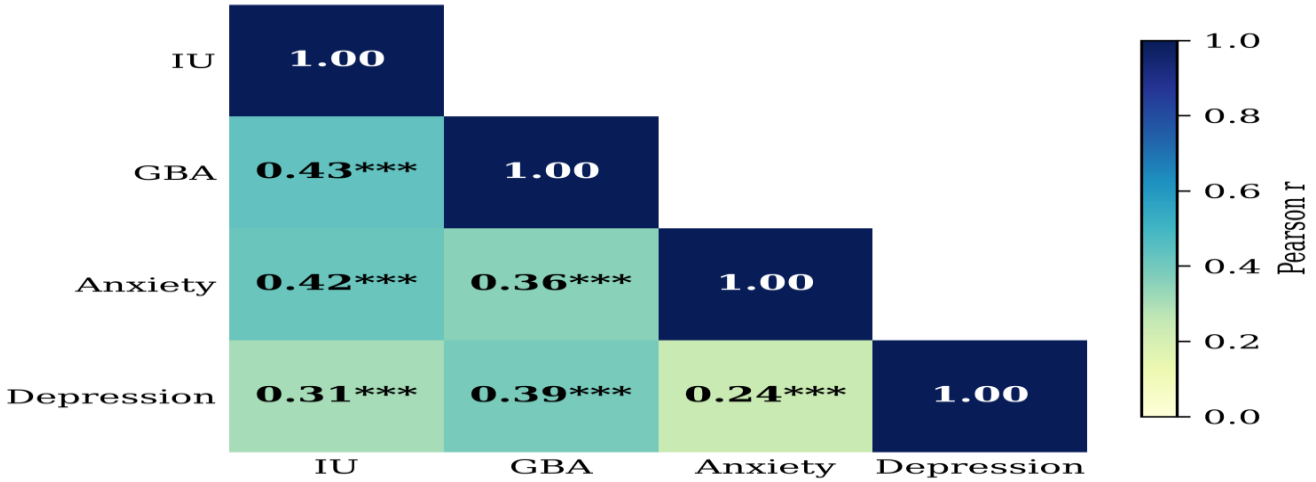
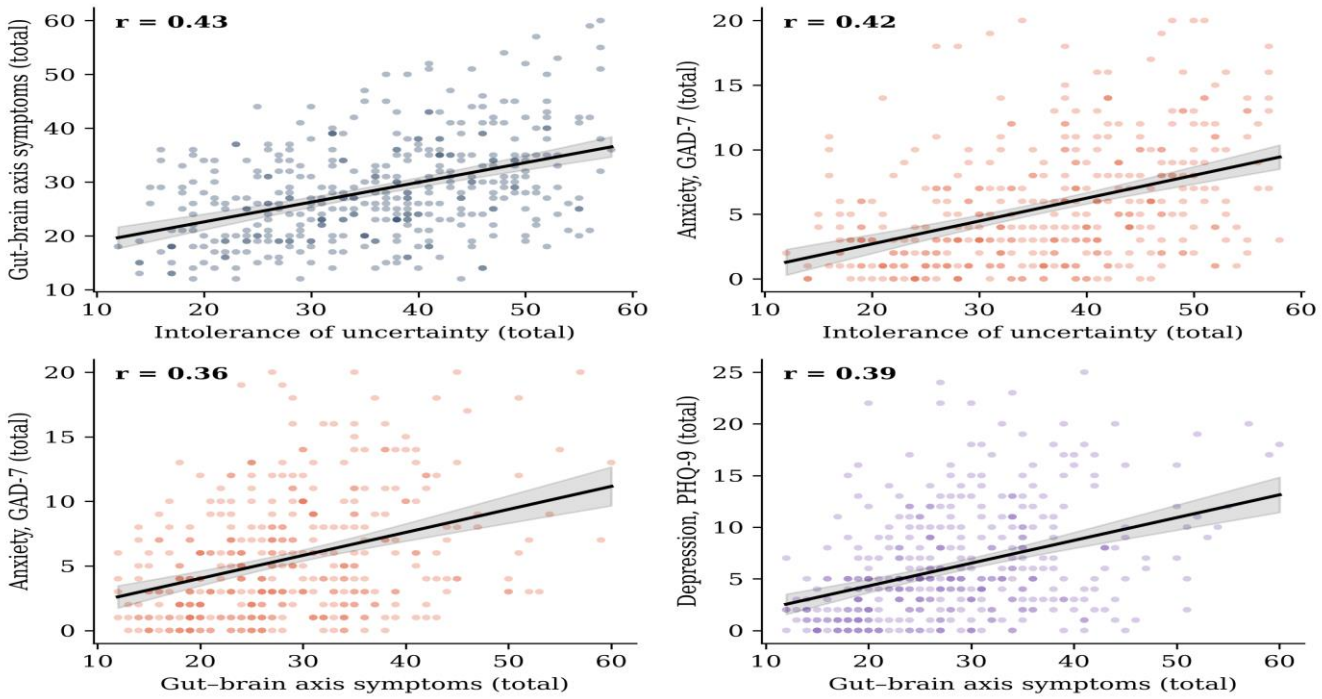


Figure 5: *Scatterplots with least-squares regression lines and 95% confidence bands for the key bivariate relationships in the mediation model.*



7.3 Assumption checks and sensitivity analysis

Multicollinearity was not a concern (maximum VIF = 1.24). Residuals from both outcome models departed from normality (Shapiro–Wilk *p*s < .001), and the Breusch–Pagan test indicated heteroscedasticity for anxiety (p = .003) and depression (p < .001). These violations are expected for skewed symptom scores and are the reason percentile bootstrap intervals, which do not assume normality of the indirect effect, were used for inference rather than the Sobel test. As a sensitivity check, the outcome models were re-estimated with HC3 standard errors. The conclusions did not change: for anxiety, IU (β = .31, p < .001) and gut–brain axis symptoms (β = .21, p < .001) remained significant predictors, and for depression, IU (β = .17, p < .001) and gut–brain axis symptoms (β = .31, p < .001) did so as well.

7.4 Path a: IU predicting gut–brain axis symptoms (H3)

After controlling for age and gender, IU significantly predicted gut–brain axis symptom burden (β = .42, *SE* = .05, 95% CI [.33, .51], t = 9.33, p < .001; Table 5). The model explained 19.3% of the variance in gut–brain axis symptoms, $F(3, 396) = 31.48$, p < .001. Neither age (β = -.01, p = .777) nor gender (p = .057) was a significant predictor. H3 was supported.

7.5 Total effects and the gut–brain axis as a mediator of anxiety (H1, H4, H5)

IU had a significant total effect on anxiety (c = .40, p < .001), supporting H1. When the gut–brain axis was added to the model, it significantly predicted anxiety (b = .21, *SE* = .05, p < .001), and the direct effect of IU remained significant but was reduced (c' = .31, p < .001; Table 5, Figure 6A). The model explained 23.4% of the variance in anxiety, $F(4, 395) = 30.11$, p < .001. Age was negatively related to anxiety (β = -.14, p = .002), while gender was not (p = .613).

The indirect effect of IU on anxiety through the gut–brain axis was significant (ab = .091, bootstrap *SE* = .023, 95% CI [.047, .138]; Table 6, Figure 7A), and the Sobel test agreed (z = 3.96, p < .001). Approximately 22% of the total effect of IU on anxiety was transmitted through the gut–brain axis (Figure 8). Because both the indirect and the direct effects were significant, the pattern is consistent with partial mediation. H4 (for anxiety) and H5 were supported.

7.6 The gut–brain axis as a mediator of depression (H2, H4, H6)

IU also had a significant total effect on depression (c = .30, p < .001), supporting H2. The gut–brain axis predicted depression over and above IU (b = .31, *SE* = .05, p < .001), and the direct effect of IU was reduced but remained significant (c' = .17, p < .001; Figure 6B). The model explained 18.0% of the variance in depression, $F(4, 395) = 21.62$, p < .001. The indirect effect was significant (ab = .131, bootstrap *SE* = .026, 95% CI [.081, .184]; Sobel z = 5.09, p < .001), accounting for about 44% of the total effect (Figure 8), again indicating partial mediation. H4 (for depression) and H6 were supported.

The indirect effect was numerically larger for depression than for anxiety, whereas the direct effect of IU was larger for anxiety. However, the bootstrap confidence interval for the difference between the two indirect effects included zero (difference = .040, 95% CI [-.020, .103]), so there is no evidence that the gut–brain axis mediates the two outcomes to different degrees.

Table 5: *Standardised Regression Coefficients for the Mediation Models*

Predictor	Model 1: Gut–brain axis	Model 2: Anxiety	Model 3: Depression
Intolerance of uncertainty	.42*** (.05)	.31*** (.05)	.17*** (.05)
Gut–brain axis	—	.21*** (.05)	.31*** (.05)
Age	-.01 (.05)	-.14** (.04)	-.07 (.05)
Gender (female = 1)	.17 (.09)	.05 (.09)	.04 (.09)
R^2	.19	.23	.18
F	31.48***	30.11***	21.62***

Note. *Cells show standardised coefficients with standard errors in parentheses. Age and the outcomes were z-standardised; gender was entered as a 0/1 dummy, so its coefficient is in outcome standard-deviation units. ** p < .01. *** p < .001.*

Table 6: *Direct, Indirect, and Total Effects of Intolerance of Uncertainty*

Effect	Anxiety	Depression
a: IU → gut–brain axis	.42 [.33, .51]	.42 [.33, .51]
b: gut–brain axis → outcome	.21 [.12, .31]	.31 [.21, .41]
c: total effect	.40 [.31, .49]	.30 [.21, .39]
c′: direct effect	.31 [.22, .41]	.17 [.07, .27]
ab: indirect effect (bootstrap)	.091 [.047, .138]	.131 [.081, .184]
Proportion mediated (*ab*/*c*)	22.5%	43.6%

Note. *Standardised coefficients with 95% confidence intervals in brackets. Intervals for a, b, c, and c′ are from OLS; intervals for ab are percentile bootstrap intervals (5,000 resamples). All paths are adjusted for age and gender.*

Figure 6: *Standardised path models for (A) anxiety and (B) depression. Coefficients are adjusted for age and gender. *** p < .001; ab = indirect effect with 95% bootstrap confidence interval.*

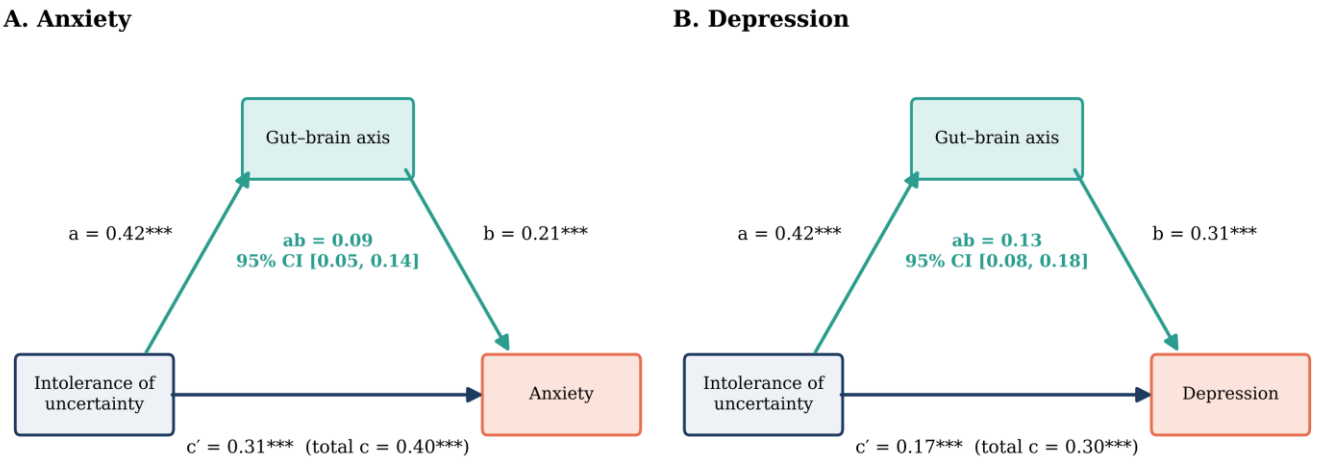


Figure 7: *Bootstrap distributions (5,000 resamples) of the standardised indirect effect for (A) anxiety and (B) depression. Dashed lines mark the 95% confidence limits; the red line marks zero.*

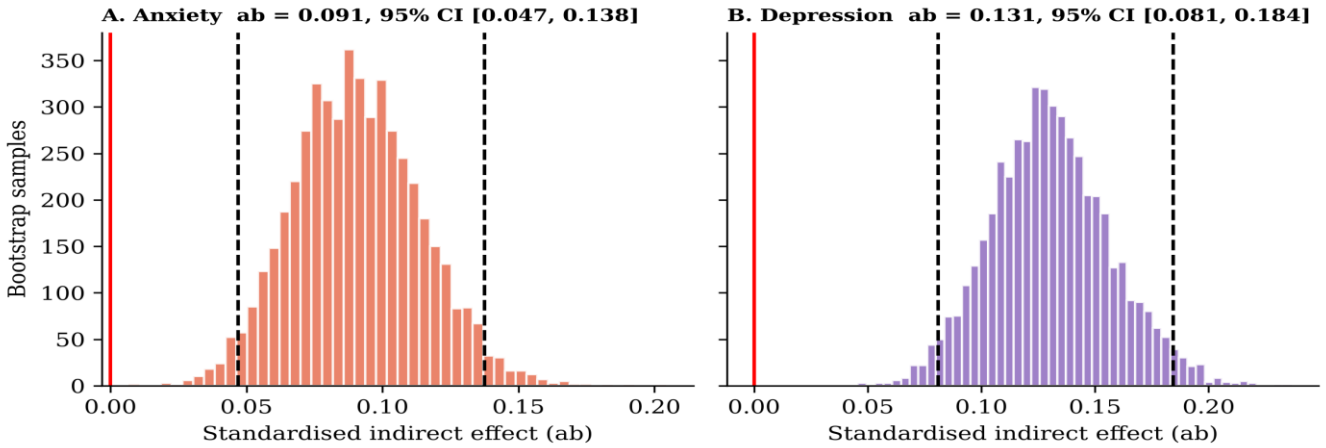
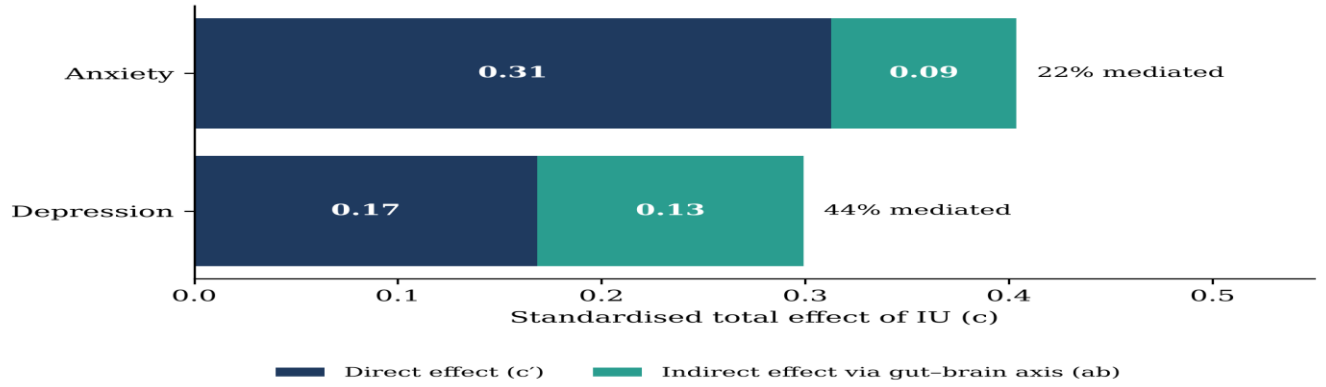


Figure 8: *Decomposition of the total effect of IU into direct (c′) and indirect (ab) components for anxiety and depression.*



7.7 Summary of hypothesis tests

Table 7 summarises the decision for each hypothesis. All six hypotheses were supported in the simulated data, with the pattern of significant indirect and direct effects indicating partial rather than full mediation.

Table 7: *Summary of Hypothesis Tests*

No.	Test	Key result	Decision
H1	IU → anxiety (total effect)	β = .40, *p* < .001	Supported
H2	IU → depression (total effect)	β = .30, *p* < .001	Supported
H3	IU → gut–brain axis (path *a*)	β = .42, *p* < .001	Supported
H4	Gut–brain axis → anxiety / depression, controlling for IU	β = .21 / .31, *p*s < .001	Supported
H5	Indirect effect on anxiety	*ab* = .091, CI [.047, .138]	Supported (partial)

No.	Test	Key result	Decision
H6	Indirect effect on depression	*ab* = .131, CI [.081, .184]	Supported (partial)

8. Discussion

This article suggested that the gut, brain axis could partly explain the influence of intolerance of uncertainty (IU) on anxiety and depression, and they showed through an illustration how their idea can be verified with a parallel mediation model.

The parallel mediation model in the simulated dataset behaved as a result of being in line with the theory: higher IU meant higher gut, brai-axis symptoms' burden; higher gut-brain symptom burden resulted in more anxiety and depression over time, even when IU was taken into account; and in both steps, the indirect effects did significantly differ from zero. The direct effect of IU still explained a portion of anxiety and depression, so, overall the pattern of partial mediation is the one corresponding with the hypothesis grounded on theoretical bases (since IU should also be via worry, rumination & avoidance (Carleton, 2016a; McEvoy & Mahoney, 2012)).

This paper pointed out two noteworthy aspects of the findings. One is the size of indirect effect. The mediation by the gut, brain axis accounted for a bit more than the total change for depression (about 44%) than it did for anxiety (about 22%), which could imply a more physical path to depression. Nonetheless, the bootstrap contrast revealed that two indirect effects cannot be reliably distinguished statistically, and since the proportion-mediated measures tend to be very sensitive, this difference is not meaningful. The second thing is that intolerance of uncertainty is more directly related to anxiety than depression, in fact, it's almost as though it is a natural pairing and it fits the established view that IU is extremely connected to worry and anticipatory anxiety (Grupe & Nitschke, 2013).

The discussion presents several realistic aspects for future research. As the symptom scales displayed skewedness, and the model's residuals indicated issues with normality and heterogeneity, Sobel test would definitely lose credibility to bootstrap intervals and robust standard errors, whereas results based on HC3 errors were no different. The insignificant gender difference of gut, brain axis symptoms aligns well with the fact that female gender seems to be more prone to functional gastrointestinal disorders at large, reported by various clinical studies, and in turn it supports the idea of gender being included as a covariate in the actual study. Likewise, the inverse correlation between age and anxiety indicates that age should be taken into account.

We need to make sure it is very clear what these findings do not imply. The simulated data results are reflections of our selected parameters and they have nothing in common with the real world properties, in principle. With real-life data too, the mediating model that is cross-sectional in nature cannot demonstrate that IU results in gut changes which ultimately lead to emotional symptoms; in a paper called "On a method for cross-validation with mediation models", Maxwell and Cole (2007) argue that estimates of indirect effects from cross-sectional surveys might be biased when compared to those drawn from longitudinal ones, and finally the opposite sequencing, gut symptoms being a catalyst for uncertainty-related distress, is equally reasonable when we keep in mind the mutual relationship given in Section 4.4 (Mayer, 2011).

9. Implications

- Assessment: Doctors who are dealing with anxiety or depression patients must ask about gastrointestinal symptoms and assess IU, since they could both be of relevance. Psychological therapy: CBT that targets IU may assist not only worry and bad mood, but also stress-related somatic symptoms (Ezzati et al., 2021). However, this requires further larger-scale studies.

- Multidisciplinary care: Nutritional support as well as microbiota-specific strategies sometimes referred to as psychobiotics are, perhaps, useful additions, albeit the evidence base is still evolving (Sarkar et al., 2016).
- Study: The model presents a possibility for linking psychology, gastroenterology and neuroscience with its use in south Asian communities being desirable. It is a bonus for those researchers that the script presented with the analysis in the current paper was tested on itemized real-life data and still works.

10. Limitations and Future Directions

Thi article has a number of limitations. Firstly, the quantitative analysis is based exclusively on a computer-generated dataset and therefore cannot provide evidence for empirical claims. Secondly, the dataset used is only of one period of time and it is not possible for mediation to demonstrate causation until there is a design that is longitudinal in nature or an experiment.

Moreover, the gut-brain axis was operationalised in terms of a self-report symptom index, which can be viewed just as a vague reflection of a vast biological system and that is without even mentioning the microbiome, inflammatory markers, or cortisol information.

In fourth place, the simulated situation was devoid of crucial confounding variables namely diet quality, sleep, physical activity, medication, and body mass index.

Fifthly, the majority of the biological evidence supporting this article is based on animal experiments which are not always indicative of results in human beings whereas human microbiome research is very inconsistent and strongly influenced by factors such as diet, medication, and lifestyle (Simpson et al., 2021).

Possible steps for further research include:

- gathering actual data with the help of validated gut symptom instruments such as the GSRS and, if circumstances permit, also using stool microbiota, short-chain fatty acids, C-reactive protein, and cortisol; utilising a longitudinal structure encompassing at least three times and employing cross-lagged or latent-growth mediation methods; conducting studies comparing models to identify relationships where the gut symptoms are the starting point of IU; and planning the sample size by means of power analysis for mediation.
- Furthermore, investigations may be carried out on clinical groups and among the South Asian population.

11. Conclusion

Not being able to handle the unknown is a significant indicator of mental health problems such as anxiety and depression whereas it is biologically plausible for these effects to be partially mediated through interactions between the gut and brain. Based on a combination of findings in both areas of research, this article provides you with a straightforward illustration of a concept, as well as with four testable hypotheses and an entirely outlined analytic plan. It was run on simulated data and showed the expected partial mediation for both outcomes. It is only by carrying out research and recording changes in both psychological and biological variables that we can confirm once and for all if the gut-brain pathway is truly a part of the mechanism through which IU (Intolerance of Uncertainty) influences emotional wellbeing.

Declarations of Conflicting Interest

The author declared no potential conflicts of interest with respect to research.

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