



Associations Between Ayahuasca Use in Naturalistic Settings and Mental Health and Wellbeing Outcomes: Analysis of a Large Global Dataset

Daniel Perkins PhD^{a,b,c}, Jerome Sarris PhD^{b,d,e}, Tessa Cowley-Court PhD^{a,b}, Helena Aicher PhD^f,
Luís Fernando Tófoli PhD^g, Jose Carlos Bouso PhD^{h,i,j}, Emerita Opaleye PhD^k, Andreas Halman PhD^{l,a},
Nicole Galvão-Coelho PhD^k, and Violeta Schubert PhD^l

^aSchool of Population and Global Health, University of Melbourne, Melbourne, Australia; ^bPsychae Institute, Melbourne, Australia; ^cCentre for Mental Health, Swinburne University of Technology, Melbourne, Australia; ^dThe Florey Institute of Neuroscience and Mental Health, Melbourne, Australia; ^eDepartment of Psychiatry, Psychotherapy and Psychosomatics, Psychedelic Research & Therapy Development, University of Zurich, Zurich, Switzerland; ^fInterdisciplinary Cooperation for Ayahuasca Research and Outreach, Faculty of Medical Sciences, State University of Campinas, Campinas, Brazil; ^gInternational Center for Ethnobotanical Education, Research and Service (ICEERS), Barcelona, Spain; ^hMedical Anthropology Research Center, University of Rovira I Virgili, Tarragona, Spain; ⁱDepartment of Neurosciences and Behavior, Ribeirão Preto Medical School, University of São Paulo, São Paulo, Brazil; ^jDepartment of Psychobiology, Universidade Federal de São Paulo, São Paulo, Brazil; ^kDepartment of Physiology and Behavior, Universidade Federal do Rio Grande do Norte, Natal, Brazil; ^lNICM Health Research Institute, Western Sydney University, Sydney, Australia

ABSTRACT

Emerging evidence indicates that ayahuasca consumption may have beneficial mental health effects. This study undertakes the largest analysis to date of associations between naturalistic ayahuasca use and current mental health status via an online cross-sectional survey. The sample included 7,576 participants (average age 41, 47% female) who had consumed ayahuasca in religious, traditional, or non-traditional settings in over 50 countries. Bivariate analysis, multivariate linear regressions and generalized structural equation modeling were used to explore associations between ayahuasca use variables, current mental health (K10, SF-12 MCS), and psychological well-being change (PWG). The number of ayahuasca uses was found to be positively associated with current mental health status (all measures), and this remained highly significant in multivariate models, with little evidence of associations diminishing over time. Variables such as the strength of the mystical experience, self-insights, and community/social variables were also positively associated with current mental health and PWG, while acute extreme fear and integration difficulties were negatively associated. Findings suggest that naturalistic ayahuasca use is associated with better current mental health status and enhanced psychological wellbeing for individuals with and without a history of mental illness, independent of community effects, with certain variables contributing positively or negatively to these effects.

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Introduction

Ayahuasca is a psychoactive plant-based medicinal decoction that has been used by Indigenous communities in the Amazon basin for centuries (Naranjo 1986, Shanon 2002). It is typically made from the *Banisteriopsis caapi* and *Psychotria viridis* plants (Riba et al. 2003), and contains the powerful psychedelic compound N,N-Dimethyltryptamine (DMT) and several beta-carbolines that act synergistically with DMT to support orally bioavailable and enhance the qualitative psychoactive effects (Palhano-Fontes et al. 2014; Ruffell et al. 2020).

Ayahuasca use continues in traditional settings and has spread to non-traditional contexts in South America and internationally (Fotiou 2016; Gearin 2015; Lowell

and Adams 2017; Shanon 2002; Trichter 2010; Tupper 2009). Although still in the early stages, research from nonclinical and clinical settings, including a small number of randomized controlled trials, suggests efficacy for psychiatric conditions via antidepressant (Almeida et al. 2019; Osório et al. 2016; dos Santos et al. 2016; dos Santos et al. 2016; Santos et al. 2018; Sarris et al. 2021), anxiolytic (dos Santos et al. 2016, 2021; Hilber and Chapillon 2005; Santos et al. 2007), and anti-addictive effects (Berlowitz et al. 2019; Bouso and Riba 2014; dos Santos et al. 2016; Nunes et al. 2016; Perkins et al. 2022).

Underpinning neurobiological processes for DMT are suggested to include modulation of serotonergic, dopaminergic and glutamatergic systems via agonism at the 5-HT_{2A}, Sigma 1, and Trace Amine Associated receptors (Berry et al. 2017; Bouso et al. 2021; dos Santos

et al. 2018; Fontanilla et al. 2009; James et al. 2022). Harmala alkaloids are reported to induce neurogenesis, and have monoamine oxidase inhibitor, serotonergic, and selective serotonin reuptake inhibitor effects (dos Santos et al. 2016; Fortunato et al. 2010; Liu et al. 2017; Zhong, Tao, and Yang 2015).

The participant's mental state and quality of acute subjective experiences have been reported to influence therapeutic effects (Haijen et al. 2018; Hartogsohn 2017). Our prior work, for example, highlighted associations between drinkers' perceived safety and support, quality of preparation support provided, and strength of the acute spiritual experience, and changes in anxiety and depression symptoms reduced alcohol and other drug abuse (Perkins et al. 2021b, 2022; Sarris et al. 2021). Community and social connection associated with ayahuasca's group-based format also appears to provide independent mental health benefits (Perkins et al. 2021b).

This paper utilizes a unique international cross-sectional dataset to conduct the largest ever examination of associations between ayahuasca consumption and mental health and wellbeing, including how consumption patterns, acute subjective experiences, and extra-pharmacological variables, may influence these outcomes. The use of such large observational dataset provides unique insights via the collection of ecologically valid health-related data, when compared with clinical trials taking place in controlled settings with stringent inclusion and exclusion criteria. Such evidence is of high value for policy makers considering responses to growing ayahuasca consumption, as well as informing clinical studies with ayahuasca inspired preparations.

Methods

Study design

This study used data from an international online cross-sectional survey of ayahuasca drinkers ($n = 10,836$) from more than 50 countries and a range of contexts of consumption. The survey was translated into five languages other than English (Portuguese, Spanish, Czech, German and Italian) and utilized a nonrandom sampling strategy due to the hidden nature of the ayahuasca population in most countries. All participants provided written informed consent and the study was approved by the University of Melbourne Human Research Ethics Committee (HREC number 1,545,143.3). See Perkins et al. (2021a) for further details of the survey methodology.

Here, we included participants who completed the mental health instruments ($n = 7,576$), which were

contained in a later section of the survey. Demographic and detailed data regarding ayahuasca drinking history were collected as well as lifetime mental health diagnoses. Two primary mental health measures were used: the mental component score (MCS) of the 12-Item Short Form Survey (SF-12) to evaluate current mental health status in accordance with the guidelines for the SF-12 instrument, with scores ranging from 0 to 100 (higher scores signifying better mental health) (Maruish 2012). A commonly used one-factor model was applied for the SF-12 MCS. The Kessler-10 (K10) Psychological Distress Scale measured psychological distress, with scores ranging from 10 to 50 and a higher number indicating greater psychological distress (Kessler et al. 2002). Although multi-factor approaches have been used for the K10 (O'Connor et al. 2012), we applied it as a one-factor model as it was designed and is typically used (Montazeri et al. 2009). Perceived growth in psychological wellbeing (PWG) that individuals perceived after consuming ayahuasca was captured with the Psychological Wellbeing Post-Traumatic Changes Questionnaire. This instrument includes 18 items rated on a 5-point Likert scale and measures changes in five areas: self-acceptance, autonomy, purpose in life, relationships, sense of mastery, and personal growth (Joseph et al. 2012; Perkins et al. 2021b).

The intensity of respondent's subjective spiritual experience was captured via the spirituality item of the Persisting Effects Questionnaire (Griffiths et al. 2011) using a 6-point Likert-scale rating the personal spiritual significance of the experience (responses ranging from "not at all" significant to "the single most spiritually significant experience of my life"). Further, an adapted version of the Short Index of Mystical Orientation (SIMO) was used to assess perceived mystical experiences via nine items rated on 1 to 10 scale (1 was equal to "not at all" and 10 "very much" (Francis and Loudon 2004). An internal consistency reliability analysis was conducted using McDonald's omega. The omega coefficient was found to be 0.864, indicating good internal consistency (McDonald 1999).

We also included several custom questions developed from the ayahuasca literature, including the number and nature of "self-insights" (cf, Perkins et al. 2021a). "Integration difficulties," reflecting adverse mental health or emotional effects in the weeks or months after drinking ayahuasca, was captured via the four items in the Patient Health Questionnaire for Depression and Anxiety (PHQ-4) (Kroenke et al. 2009) plus five additional ayahuasca-specific items (cf. Perkins et al. 2021a). The integration difficulties variable was the total number of difficulties reported (0–9). The

experience of acute extreme fear or panic was measured via a single-item question “Feeling immense fear, panic or that I was going mad or going to die” scored from 0 “Not at all” to 10 “Very much.” Finally, the strength of an individual’s ayahuasca drinking community was assessed by asking if they have a “close community or network of people with whom they drink ayahuasca,” with responses: “not at all,” “slightly,” “moderately,” or “Very much.”

Statistical analyses

Pearson’s χ^2 tests and independent samples t-tests were used to assess differences between categorical and continuous variables, respectively. Pearson or Spearman correlations assessed binary relationships, and multivariate models linear regressions. All were performed using STATA 16. Multicollinearity for multivariate models was assessed and found to be acceptable with VIF values of less than 4 and no Pearson’s or Spearman’s correlations greater than 0.7. Although the dependent variables (K10 SF-12 MCS, PWG) are known to be susceptible to skew, given the very large sample size we elected to use these untransformed to support interpretability and facilitate a clearer understanding of the implications of the findings, as has been done elsewhere in the literature (Dissing et al. 2013; McEvoy and Shand 2008; O’Connor et al. 2012). Further, sensitivity analyses undertaken using square-root transformed versions of these variables (K10, SF-12 MCS, PWG) obtained results with no substantive differences from models using the untransformed variables.

To minimize the potential bias associated with participants not completing certain questions/sections within the survey, we utilized multiple imputation for the imputation of missing data for independent variables in multivariate models. We used the *mi impute chained* command in STATA with imputations undertaken using the *regress* with 20 datasets ($m = 20$) imputed for the analysis.

The generalized structural equation modeling (GSEM) function in STATA was used to identify a final model reflecting a network of associations between demographic variables, ayahuasca variables and mental health and wellbeing outcomes. GSEM offers high predictive power due to its ability to combine generalized linear models and structural equation modeling, simultaneously considering direct and indirect effects of interacting factors. An initial hypothesized model was iterated by adding or removing paths and assessing fit, and selection of the final model was based on linear model results, theoretical justification, significance of coefficients and minimum information criteria.

Statistical significance was considered as a p value of <0.05 .

Results

Sample characteristics

Respondent characteristics, split by ayahuasca church/non-ayahuasca church due to notable differences in patterns of use (Perkins et al. 2021b), are reported in Table 1. For both groups, the average age was 41 years, with high levels of university education, and a greater proportion of males (~53%). Significant differences were observed between the ayahuasca church and other contexts groups, with the latter group more likely to have a lifetime mental health diagnosis (Table 1).

Times consumed and current mental health

Greater lifetime ayahuasca use was associated with better current mental health, shown via lower mean K10 scores (indicating lower psychological distress) for those with (decrease of 0.53 points per additional category of use, 95%CI: 0.44, 0.61) and without (decrease of 0.33 points per category, 95%CI: 0.30, 0.37) a lifetime mental health diagnosis, and higher SF-12 MCS scores (better mental health) for both of these groups (with a lifetime diagnosis, increase of 1.10 points per use category, 95% CI: 0.97,1.24; without a lifetime diagnosis, increase of 0.69 points per category, 95%CI: 0.61,0.77) (see Figure 1). A similar pattern was observed for perceived change in psychological wellbeing, with the lifetime mental health diagnosis group showing a mean increase of 1.24 points (95%CI: 1.11,1.36) on the PWG scale for each higher category of ayahuasca consumption, and the no lifetime diagnosis group a mean increase of 1.35 points (95%CI: 1.26,1.44) (see Figure 1).

Mystical experience, self-insights and mental health

Pearson and Spearman correlation coefficients identified significant associations ($p < .0001$) between current mental health (K10 and SF-12 MCS) and perceived growth in psychological wellbeing (PWG) with five variables associated with ayahuasca drinking (SIMO score, PEQ-S, self-insights, extreme fear, and integration difficulties) and two community/social variables (ayahuasca church and ayahuasca community). These associations were observed in respondents both with and without a lifetime mental health diagnosis, although some associations were weak (see Table 2).

Of the ayahuasca variables, integration difficulties (adverse mental health effects in the weeks/months after

Table 1. Sample characteristics^{a,b}.

	Non-ayahuasca church ^c	Ayahuasca church	Statistical test
	% (n)	% (n)	
Sex	(3,893)	(3,456)	$\chi^2 = 0.2, p < .649$
Female	47.3	46.8	
Male	52.7	53.2	
Age ^d	(3,889)	(3,438)	$T(7,325) = -0.5, p = .633$
Mean age (SD)	41.0 (11.5)	40.8 (12.9)	
University education	(3,900)	(3,460)	$\chi^2 = 1.6, p = .213$
Yes	63.4	64.5.1	
Region of residence	(3,622)	(3,454)	$\chi^2 = 3.4e + 03, p < .001^{***}$
Brazil	14.72	83.4	
Other Latin America	9.39	0.5	
Europe	42.90	7.5	
North America	23.92	7.7	
Australia & NZ	7.81	0.8	
Asia and Middle East	1.26	0.1	
Times drunk ayahuasca (lifetime)	(3,874)	(3,196)	$\chi^2 = 3.6e + 03, p < .001^{***}$
1	11.9	1.8	
2-3	19.9	2.4	
4-5	14.8	1.5	
6-10	16.4	2.9	
11-20	12.9	3.6	
21-50	12.2	9.5	
51-100	5.9	10.6	
101-200	2.9	12.2	
201-500	1.8	27.6	
500-5000	1.4	27.8	
Lifetime mental health diagnosis	(4,248)	(3,822)	
Any	42.6	31.3	$\chi^2 = 100.5, p < .001^{***}$
Number (SD) ^d	0.9 (1.3)	0.5 (0.9)	$T(7,388) = 13.5; p < .001^{***}$
Kessler 10 (current) ^d	(3,288)	(3,302)	
Mean score (SD)	15.04 (5.5)	12.85 (3.6)	$T(7,139) = -20.50; p < .001^{***}$
Kessler 10 by group	(3,907)	(3,476)	$\chi^2 = 229.8, p < .001^{***}$
Likely to be well	84.16	94.99	
Likely to have mild mental disorder	8.88	3.31	
Likely to have moderate mental disorder	3.86	1.06	
Likely to have a severe mental disorder	3.10	0.63	
SF-12 (current) ^d	(3,751)	(3,390)	
Mean score (SD)	48.1 (9.9)	52.4 (7.7)	$T(7,139) = -20.50; p = .000$

^aPercentages may not sum to 100.0% due to rounding; ^b"(n)" indicates valid (non-missing) sample for each item; ^c'non-ayahuasca church' includes traditional, non-traditional, mixed and other contexts ^dIndependent samples T-test. *** $p < .001$.

use) were most strongly and consistently associated with poorer current mental health per the K10 and SF-12 MCS ($r > .32$). Experiencing extreme fear displayed a similar but weaker association ($r > .20$). For individuals with a lifetime mental health diagnosis, the number of self-insights gained was weakly associated with better mental health on both scales ($r \sim .20$), with a relatively weaker strength of association between spiritual experience intensity (SIMO and PEQ-S), and SF-12 MCS for those with a lifetime mental health diagnosis. A somewhat opposite pattern was seen for PWG, with moderate-to-strong positive associations present for the SIMO and number of self-insights for individuals both with and without a lifetime mental health diagnosis ($r = 0.38$ to 0.49), while experiencing extreme fear and integration difficulties showed weak (negative) associations. The community/social variables were also associated with better current mental health, with these associations generally stronger for the lifetime mental health diagnosis group ($r_s = 0.22$ to 0.31). Community/social variables showed stronger correlations with better

current mental health than variables directly associated with the ayahuasca experience (i.e., subjective spiritual experience and self-insights obtained). Conversely, correlations with PWG were weaker than those for the ayahuasca experience variables, being low for ayahuasca church ($r_s = 0.22$ to 0.28) and moderate for the ayahuasca community ($r_s = 0.35$ to 0.36).

Multivariate models

Multiple linear regressions were performed to investigate the influence of all ayahuasca drinking variables and selected covariates (Table 3). These provide added rigor to the analysis by adjusting for co-variables that may influence outcomes. The regressions were conducted separately for those with and without a prior mental health condition for each of the three dependent variables, Kessler 10, SF-12 MCS, and PWG.

The number of times ayahuasca had been consumed remained significantly associated with better mental

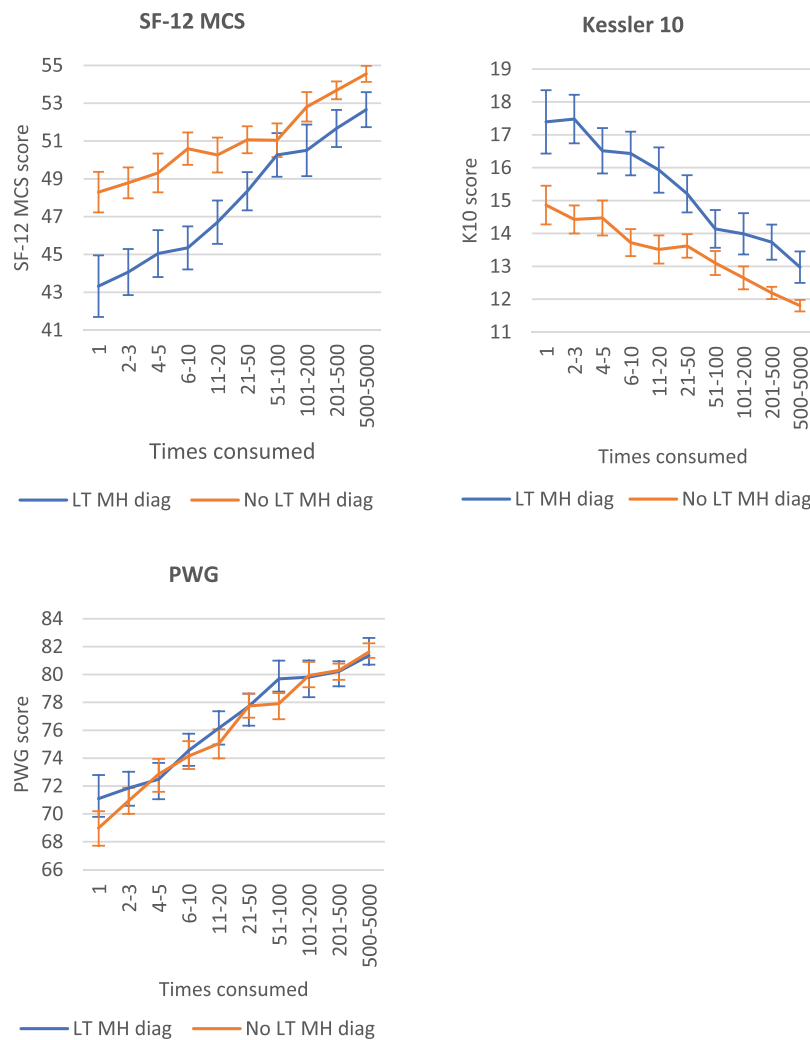


Figure 1. Current mental health and perceived change in psychological wellbeing by number of times ayahuasca consumed and lifetime mental health diagnosis (error bars = 95% CI). LT = Lifetime; MH = Mental Health; K-10 = Kessler 10; SF-12 MCS = SF-12 Mental Component Score; PWG = Psychological Wellbeing Growth.

Table 2. Correlation coefficients between ayahuasca drinking and community variables, and current mental health status and perceived change in psychological wellbeing.

	Kessler 10 ^a		SF-12 MCS ^b		PWG ^c	
	No MH disorder (n = 4,375)	Any MH disorder (n = 2,841)	No MH disorder (n = 4,735)	Any MH disorder (n = 2,841)	No MH disorder (n = 4,735)	Any MH disorder (n = 2,841)
	r=	r=	r=	r=	r=	r=
Ayahuasca drinking						
SIMO total ^d	−0.085***	−0.127***	0.113***	0.192***	0.382***	0.425***
PEQ-S ^e	−0.071***	−0.081***	0.088***	0.138***	0.260***	0.270***
Self-insights ^d	−0.087***	−0.198***	0.092***	0.226***	0.428***	0.487***
Extreme fear ^d	0.214***	0.245***	−0.218***	−0.202***	−0.115***	−0.113***
Integration ^d difficulties	0.360***	0.380***	−0.335***	−0.320***	−0.082***	−0.159***
Community/ social	r _s	r _s	r _s	r _s	r _s	r _s
Aya. church ^e	−0.196***	−0.226***	0.201***	0.239***	0.282***	0.220***
Aya. community ^e	−0.164***	−0.258***	0.201***	0.309***	0.348***	0.362***

***p < .0001.

^aKessler 10 psychological distress scale (higher score = higher distress); ^bSF-12 Mental Health Component Score (higher score = better mental health);

^cPsychological Wellbeing Growth (higher score = greater psychological wellbeing growth); ^dPearson correlation coefficients; ^eSpearman correlation coefficients.

Table 3. Associations between demographic and ayahuasca drinking variables, and current mental health status and perceived change in psychological wellbeing.

Dependent variable	Kessler 10 ^a				SF-12 MCS ^b				PWG ^c			
	No MH disorder (n = 4,735)		Any MH disorder (n = 2,841)		No MH disorder (n = 4,735)		Any MH disorder (n = 2,841)		No MH disorder (n = 4,735)		Any MH disorder (n = 2,841)	
Group	B (SE)	P=	B (SE)	P=	B (SE)	P=	B (SE)	P=	B (SE)	P=	B (SE)	P=
Covariates												
Age (decades)	−0.33 (0.04)		−0.37 (0.09)		0.97 (0.09)		0.7 (0.16)		−0.18 (0.1)	0.074	0.03 (0.14)	0.861
Female	0.47 (0.1)		0.17 (0.19)	0.359	−0.87 (0.22)		−0.64 (0.34)	0.058	0.66 (0.24)	0.006	1.56 (0.31)	
University education	0.31 (0.11)	0.004	0.44 (0.19)	0.025	−0.97 (0.23)		−1.41 (0.35)		−1.68 (0.25)		−0.61 (0.32)	0.058
No. MH diagnoses			0.69 (0.08)				−0.65 (0.15)				−0.01 (0.14)	0.958
Ayahuasca drinking												
Number of times drunk ^e	−0.13 (0.03)		−0.11 (0.05)	0.026	0.19 (0.06)	0.001	0.34 (0.09)		0.63 (0.07)		0.29 (0.09)	0.001
Ayahuasca church ^f	−0.28 (0.15)	0.070	−0.16 (0.26)	0.535	0.87 (0.32)	0.006	0.31 (0.47)	0.504	0.58 (0.35)	0.097	0.06 (0.44)	0.900
Ayahuasca community ^g	−0.27 (0.06)		−0.57 (0.11)		0.68 (0.12)		1.32 (0.19)		0.79 (0.14)		1.24 (0.18)	
SIMO total	−0.02 (0)		−0.03 (0.01)		0.05 (0.01)		0.07 (0.01)		0.13 (0.01)		0.14 (0.01)	
PEQ-S	−0.35 (0.05)		−0.27 (0.1)	0.006	0.63 (0.11)		0.67 (0.18)		1.43 (0.12)		1.30 (0.17)	
Self-insights	−0.01 (0.03)	0.587	−0.30 (0.05)		0.03 (0.06)	0.643	0.40 (0.1)		1.04 (0.06)		1.39 (0.09)	
Extreme fear	0.11 (0.02)		0.17 (0.03)		−0.28 (0.04)		−0.24 (0.06)		−0.28 (0.04)		−0.29 (0.05)	
Integration difficulties	0.67 (0.03)		0.75 (0.04)		−1.22 (0.06)		−1.13 (0.08)		−0.38 (0.07)		−0.57 (0.07)	
Years since drunk ^h	0.03 (0.01)	0.048	0.03 (0.03)	0.268	−0.07 (0.03)	0.013	−0.04 (0.05)	0.455	−0.01 (0.03)	0.664	−0.04 (0.05)	0.477

^aKessler 10 psychological distress scale (higher score = higher distress); ^bSF-12 Mental Health Component Score (higher score = better mental health); ^cPsychological Wellbeing Growth (higher score = greater psychological wellbeing growth); ^dNumber of lifetime mental health diagnoses; ^elifetime uses of ayahuasca (categories as per Table 1); ^flast drank with an ayahuasca church; ^gdrink ayahuasca with a close community; ^hnumber of years since last drank ayahuasca; **p* < 0.05, ***p* < 0.01 ****p* < 0.001.

health (lower K10 and higher SF-12 MC) and higher perceived PWG for those with and without a lifetime mental health diagnosis. A similar pattern was evident for the spirituality variables (SIMO and PEQ-S), which were significantly associated with the three dependent variables (in a beneficial direction) in all models. The number of self-insights obtained was significantly related to better current mental health (lower K10 and higher SF-12 MC) for the lifetime mental health diagnosis group, with each additional self-insight reported resulting in a 0.30-point reduction in K10 score and 0.40-point increase in SF-12 MCS. However, no significant association was found for the group without a lifetime mental health diagnosis. Self-insights were associated with significantly higher reported PWG for both groups.

Experiencing integration difficulties in the weeks or months following consumption, as well as extreme fear during an ayahuasca session were both associated with significantly poorer current mental health (higher K10 and lower SF-12 MCS) and lower reported PWG, for both the lifetime and no lifetime mental health diagnosis groups. This association is stronger for integration difficulties. Among the two communities/social variables, drinking with an ayahuasca church and drinking with a strong community of people, only the latter remained significantly associated with improved mental health and PWG in all multivariate models, with relatively strong effects in those with a lifetime mental health diagnosis compared to those without. The only significant association for drinking with an ayahuasca church was a higher

SF-12 MCS for the no lifetime mental health diagnosis group. The number of years since ayahuasca was last drunk showed a very slight negative association with current mental health status for those without a lifetime mental health diagnosis (a 0.03-point increase in K10 and 0.07-point decrease in SF-12 MCS per year), but no significant effect was found for those with a mental health diagnosis, or for either group in relation to PWG.

Being female was associated with greater perceived improvement in PWG for both groups, while having a university education negatively associated with PWG for those without a lifetime mental health diagnosis.

GSEM analysis

Our previous work with a subset of the same dataset exploring context of use effects (Perkins et al. 2021a) utilized Generalised Structural Equation Modelling (GSEM) to explore both direct and indirect effects of various variables. Results indicated that mental health effects associated with ayahuasca were largely predicted indirectly through changes in psychological wellbeing. To investigate these relationships, we conducted a GSEM analysis on the full dataset, which provided sample sizes over 60% larger. As shown in Table 4, the results indicate that four out of six ayahuasca variables (number of times drunk, SIMO score, number of self-insights, experiencing extreme fear) indirectly predicted mental health outcomes (measured by K10 and SF-12 scales) primarily through changes in psychological wellbeing (PWG). Conversely, the other two ayahuasca variables (drinking

Table 4. Generalised structural equation Model (GSEM) of demographic variables, ayahuasca drinking variables, intermediate and final mental health and well-being outcomes of drinkers ($n = 7,318$).

	Coef.	Std. Err.	z	P	95% Conf. Interval	
SF12 MCS (n = 6,784)						
PWG	0.324	0.010	33.320	<0.001	0.305	0.343
Female	-1.104	0.185	-5.960	<0.001	-1.467	-0.741
Integration difficulties	-1.083	0.044	-24.350	<0.001	-1.171	-0.996
Age (decades)	0.927	0.077	11.990	<0.001	0.775	1.078
No. MH diagnoses	-1.159	0.081	-14.380	<0.001	-1.317	-1.001
Ayahuasca community	0.875	0.087	10.050	<0.001	0.704	1.045
_cons	21.720	0.803	27.060	<0.001	20.147	23.293
PWG (n = 7,318)						
Female	0.939	0.193	4.870	<0.001	0.562	1.317
Self-insights	1.285	0.050	25.660	<0.001	1.187	1.383
SIMO total	0.173	0.006	28.410	<0.001	0.161	0.185
Integration difficulties	-0.511	0.048	-10.620	<0.001	-0.606	-0.417
Ayahuasca church	0.545	0.042	12.880	<0.001	0.462	0.628
Age (decades)	-0.208	0.082	-2.530	0.011	-0.370	-0.047
No. MH diagnoses	0.083	0.085	0.980	0.326	-0.083	0.250
Ayahuasca community	1.041	0.107	9.740	<0.001	0.831	1.250
Extreme fear	-0.296	0.032	-9.110	<0.001	-0.359	-0.232
_cons	54.539	0.593	92.020	<0.001	53.378	55.701
Kessler 10 (n = 6,942)						
PWG	-0.154	0.005	-30.350	<0.001	-0.164	-0.144
Female	0.534	0.097	5.520	<0.001	0.344	0.723
Integration difficulties	0.681	0.023	29.330	<0.001	0.635	0.726
Age (decades)	-0.391	0.040	-9.720	<0.001	-0.470	-0.313
No. MH diagnoses	0.800	0.042	19.040	<0.001	0.718	0.883
Ayahuasca community	-0.353	0.045	-7.760	<0.001	-0.442	-0.264
_cons	26.654	0.418	63.760	<0.001	25.835	27.473
var(e.SF-12 MCS)	57.85324	0.9930267			55.93932	59.83265
var(e.PWG)	66.52464	1.099769			64.40368	68.71545
var(e.Kessler 10)	15.9602	0.2709329			15.43792	16.50015
cov(e.SF-12 MCS, e.Kessler 10)	18.93376	0.4326174	-43.77	<0.001	-19.78167	-18.0858

SF-12 MCS = SF-12 Mental Component Score (higher score = better mental health); PWG = Psychological Wellbeing Growth (higher score = greater psychological wellbeing growth); Female = female gender; Integration difficulties = number of adverse mental health effects in the weeks/months following the ayahuasca experience; Ayahuasca church = drinking ayahuasca within a church context; No. MH diagnoses = number of lifetime mental health diagnoses; Ayahuasca community = drinking ayahuasca with a close community; Self-insights = number of self-insights obtained; SIMO total = Short Index of Mystical Orientation (higher score = stronger acute mystical experience); Extreme fear = extreme fear during the acute experience; Kessler 10 = Kessler 10 psychological distress scale (higher score = higher distress)

with a close community and integration difficulties) had a direct and significant impact on both psychological wellbeing changes and current mental health status.

Additionally, demographic variables age and gender significantly predicted both psychological wellbeing change and current mental health status. The number of lifetime mental health diagnoses solely predicted of current mental health status without significantly influencing PWG but was retained to improve overall model fit.

Discussion

With growing research and community interest in the potential therapeutic use of ayahuasca, our global dataset of 7,576 drinkers provides unique insights into possible mental health effects associated with naturalistic use. We identified significant positive associations between the number of ayahuasca uses and current mental health status (measured via the K10 and SF-12) and reported psychological wellbeing improvement (PWG), for individuals both with and without

a lifetime mental health diagnosis. These associations were evident in bivariate analysis and remained highly significant in multivariate models, with little evidence of these diminishing over time.

Additionally, we found various ayahuasca experience variables to be associated with current mental health and PWG. Consistent with studies of other psychedelics where subjective mystical experiences have predicted therapeutic outcomes (Russ et al. 2019), we found highly significant associations (in bivariate, multivariate and GSEM models) between our two spiritual experience variables and both current mental health and PWG. Interestingly, a small ayahuasca clinical trial reported subjective mystical experience, measured via the MEQ-30 (Mystical Experience Questionnaire) ($n = 15$) and the HRS (Hallucinogen Rating Scale) ($n = 27$), to have little association with therapeutic outcomes (Palhano-Fontes et al. 2019). Similarly, an observational study ($N = 63$) found no association between the MEQ and mental health improvements at 6 months (Ruffell et al. 2021). These contrasting results may reflect differing

instruments or sample sizes. We have previously reported that self-insights gained during the ayahuasca experience are associated with reduced current alcohol and drug use (Perkins et al. 2022), and here similarly identified self-insights to be associated with better current mental health and greater PWG. In a recent online sample with 441 responses, better outcomes in tobacco smoking cessation were associated with the MEQ-30 mystical experiences subscale applied to a single ayahuasca experience (Daldegan-Bueno et al. 2022). This aspect of the ayahuasca experience has also been suggested in qualitative studies to be associated with beneficial mental health effects (Freckska, Bokor, and Winkelman 2016; Lafrance et al. 2017; Liester and Prickett 2012; Perkins et al. 2022).

Community and social connection variables, such as drinking with an ayahuasca church and strength of the ayahuasca drinking community, were consistently associated with better current mental health and greater PWG in bivariate analysis. However, after adjusting for covariates in the multivariate models, drinking with an ayahuasca church was only significantly associated with better current mental health for those without a lifetime mental health diagnosis and was not associated with PWG. Similarly, drinking with an ayahuasca church did not add sufficient predictive power to the GSEM model to be retained. In contrast, the strength of the ayahuasca community remained highly significantly associated across all multivariate and GSEM models, suggesting that community/social connection benefits can be attained in both non-church and church contexts, and that membership of a formal ayahuasca church provides little additional benefit for those with a mental health diagnosis. We hypothesize that the nature of the ayahuasca experience may accelerate emotional bonding and connection, as it involves profound emotional processing, introspection, and vulnerability, typically in a residential setting with a group of people.

On the other hand, both extreme fear during the ayahuasca experience and the number of adverse mental health effects (i.e., integration difficulties) experienced in the weeks or months following the ayahuasca ceremony were associated with poorer current mental health and reduced PWG in bivariate analysis, with these associations remaining highly significant in multivariate and GSEM models. Research with psilocybin and other psychedelics has reported challenging experiences to have no association, or even a positive association, with therapeutic outcomes (Barrett et al. 2016; Russ et al. 2019); however, we note that a single item on our survey (feeling immense fear, panic or that “I was going mad or going to die”) identified specific elements of

challenging experiences. Research with psilocybin has suggested that factors such as the intensity, duration of struggle, and degree to which the challenging experience achieved a resolution or emotional breakthrough may influence long-term mental health effects, and these would be valuable to explore in future research with ayahuasca (Barrett et al. 2016; Carbonaro et al. 2016).

Our findings are broadly consistent with a range of other studies that have reported mental health and well-being benefits associated with ayahuasca consumption in naturalistic settings (Barbosa et al. 2009; Bouso et al. 2012, 2015; González et al. 2020; Grob et al. 1996; Halpern et al. 2008; Jiménez-Garrido et al. 2020). However, unlike these previous studies, in which it has been unclear the extent to which outcomes have been associated with broader group membership and social connection benefits versus ayahuasca consumption per se, our study is able to investigate these effects separately. We show that while these factors make an important contribution to mental health and wellbeing benefits reported by drinkers, ayahuasca drinking variables remain robustly associated with such outcomes after adjusting for these factors.

Our GSEM analysis provides confirmation of the pathways by which ayahuasca consumption may affect mental health and wellbeing outcomes. Of particular note is data confirming the key mediating role of perceived change in psychological wellbeing, which suggests that beneficial mental health change may be driven by positive gains in broader psychological wellbeing, rather than simply a reduction of anxiety and depression symptoms. This feature could be of particular value in the treatment of clinical symptoms such as anhedonia.

A major strength of our study is the large and cross-cultural sample, which enables the detection of associations with mental health outcomes that are difficult to identify in smaller interventional or observational studies. However, the study design also has several limitations. The nonrandom, self-selected sample poses a risk of bias toward respondents for whom the ayahuasca experience felt significant, potentially more often in a positive way, and who were therefore motivated to spend time completing the lengthy survey. This may result in an inflation of positive versus less positive participant responses. Data collected were self-reported, and some items involved retrospective assessments of things that may have occurred a considerable time ago, although this did not apply to the mental health measures (K10 and SF-12). The cross-sectional study design also means we lack data on prior mental health status, and we cannot rule out

the possibility that better mental health at the time of the survey simply reflected better initial mental health. To account for this, we used the number of lifetime mental health diagnoses as a proxy for lifetime mental health status, though this may not be a completely accurate substitute. Similarly, we cannot exclude that healthier participants may tend to engage more in ayahuasca ceremonies. More broadly, we note that although the cross-sectional study design enables the identification of associations, it is not able to establish causality.

The prior or concurrent use of other psychedelics or other psychoactive botanicals was not included in this study and may be a potential confounding factor. The survey was translated into five languages, and some (including the K10 and SF-12 MCS), but not all of the measures used, had been previously developed and validated for use with these languages. A detailed analysis of language group invariance is beyond the scope of this study, but may influence results. Finally, around 30.1% of respondents did not complete the mental health sections of the survey and were excluded from the analysis. This excluded group were found to not differ significantly from the study sample in the proportion of males and females ($\chi^2 = 1.10$, $p < .295$), number of times they had consumed ayahuasca ($\chi^2 = 15.58$, $p < .076$), and proportion reporting drinking with an ayahuasca church ($\chi^2 = 0.07$, $p < .781$), but were on average slightly younger, 38.90 vs 40.88 $T(10,687) = -7.69$, $p < .001$, and less likely to have a university education, 56.1% vs 64.4% ($\chi^2 = 66.2$, $p < .001$). Although, these differences were relatively minor, they do present another potential source of selection bias.

Conclusions

Our study highlights apparent enduring beneficial mental health and wellbeing effects of naturalistic ayahuasca consumption for individuals with and without a lifetime mental health diagnosis, including a robust positive association between the number of times ayahuasca has been consumed and better current mental health status. Further, the data points to the importance of the subjective phenomenology of the experience itself and psychotherapy-relevant processes (particularly subjective spiritual experience and number of self-insights). Findings of positive changes in psychological wellbeing are also noteworthy and enable a broadening of focus from mere symptom reduction as a treatment outcome toward improving wellbeing and quality of life.

In relation to the potential clinical use of ayahuasca, our data suggests that treatment protocols will be more

effective where they facilitate strong subjective mystical experiences, reduce the risk of experiencing extreme fear, provide effective post-acute support for processing and resolving psychological and emotional difficulties with integration, and consider the use of group-based therapeutic elements.

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ORCID

Daniel Perkins PhD  <http://orcid.org/0000-0002-2055-1649>
 Luís Fernando Tófoli PhD  <http://orcid.org/0000-0003-2262-8272>
 Andreas Halman PhD  <http://orcid.org/0000-0001-5248-4121>

Data availability statement

The datasets presented in this article are not readily available because Ethics approval and consent signed by participants was for data access by research team members only. Declaration of interest

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