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Estimating the effect of anticipated depression treatment-related stigma on depression remission among people with noncommunicable diseases and depressive symptoms in Malawi

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# Abstract

# Purpose

While mental health stigma research is sparse in Malawi, research in other settings suggests that stigma represents a barrier to mental health treatment and recovery. Accordingly, we conducted an analysis to understand the role of treatment-related stigma in depression care in Malawi by estimating the effect of patients' baseline anticipated treatment-related stigma on their 3-month probability of depression remission when newly identified with depression.

# Methods

We conducted depression screening and treatment at 10 noncommunicable disease (NCD) clinics across Malawi from April 2019 through December 2021. Eligible cohort participants were 18–65 years with depressive symptoms indicated by a PHQ-9 score  $\geq$ 5. Question-naires at the baseline and 3-month interviews included a vignette-based quantitative stigma instrument that measured treatment-related stigma, i.e., concerns about external stigma because of receiving depression treatment. Using inverse probability weighting to adjust for confounding and multiple imputation to account for missing data, this analysis relates participants' baseline levels of anticipated treatment stigma to the 3-month probability of achieving depression remission (i.e., PHQ-9 score < 5).

(NDA): https://nda.nih.gov/edit\_collection.html?id= 2822. The SHARP study data available from the NDA should be sufficient to replicate this paper's analyses. Data access requests may be submitted to the NDA in order to receive permission to access these data.

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## Results

Of 743 included participants, 273 (37%) achieved depression remission by their 3-month interview. The probability of achieving depression remission at the 3-month interview among participants with high anticipated treatment stigma (0.31; 95% Confidence Interval [CI]: 0.23, 0.39)) was 10 percentage points lower than among the low/neutral stigma group (risk: 0.41; 95% CI: 0.36, 0.45; RD: -0.10; 95% CI: -0.19, -0.003).

## Conclusion

In Malawi, a reduction in anticipated depression treatment-related stigma among NCD patients initiating depression treatment could improve depression outcomes. Further investigation is necessary to understand the modes by which stigma can be successfully reduced to improve mental health outcomes and quality of life among people living with depression.

# Background

An estimated 13% of the global population live with a mental illness [1, 2], and 4% live with a depressive disorder [1, 2]. Amid effective, cost-efficient depression treatment options [3, 4] treatment gaps persist. Stigma is one barrier to treatment engagement that may exacerbate persistent treatment gaps [5-8]. Stigma is a multidimensional construct that is primarily defined by the "mark" of a discreditable attribute that subsequently reduces or devalues the personhood of people carrying that attribute [9, 10]. This phenomenon of stigma marking can vary based on the visibility of these attributes. Further, the degree to which these attributes are considered discreditable can also vary by social context and over time [11]. Stigmatizing experiences of individuals with mental illness can therefore vary based on the legibility of their symptoms and the discrediting value that such an illness possesses in their society.

Mental illness stigma is of global concern, yet much of the literature describing the manifestations of mental illness stigma to date has centered social norms in Europe and the United States. In sub-Saharan Africa, mental illness stigma research has focused on West Africa, while research in Southern Africa has been sparse. In Malawi, a Southeast African nation, published research on mental illness stigma is gradually expanding. For example, one study has described perceptions of mental illness in the nation's second-largest city, Blantyre; the results demonstrated that stigmatizing beliefs around mental illness vary in prevalence in this area compared to other international studies. For instance, participants attributed the cause of mental illness to God's punishment or other spiritual causes while also attributing mental illness to brain disorders [12]. Our study team has also contributed to the literature around depression stigma in Malawi specifically by validating an instrument to measure treatment-related, disclosurerelated, and negative affect stigma within a population of patients with depression [13]. The scale-up of antidepressant treatment is a high priority for the Malawi Ministry of Health, and quantifiable information about the barriers to such a scale-up, such as stigma, is therefore relevant.

In previous mixed-methods research focused on patients who received depression treatment in Malawi, our study team found that some participants had concerns about treatmentrelated stigma when initiating depression treatment, and they expressed worry that this treatment-related stigma would influence their continued treatment engagement [14]. In Malawi, patients have also cited their support system, their ability to reach the clinic for appointments (either due to material resources, transit access, or work/scheduling), and stressful life events (e.g., a dispute with a partner or family member) as key determinants to attending their care appointments [14–16]. Research in other social contexts has also demonstrated that suboptimal treatment engagement may reduce the effectiveness of depression treatment and increase time to depression remission [7]. Depression remission is a clinically important marker toward full depression recovery [17–19], and prior research indicates that patients with depression who receive clinically appropriate treatment can be expected to achieve remission by 3 months after treatment initiation [20]. Amid the scale-up of depression care in Malawi with sparse literature on stigma, the current study seeks to estimate the effect of patients' baseline anticipated treatment-related stigma on their 3-month probability of achieving depression remission after being newly identified with depression.

#### **Methods**

#### Parent study

The Sub-Saharan Africa Regional Partnership for Mental Health Capacity Building (SHARP) scale-up study is designed to compare the effect of two clinic-level implementation strategies on the successful integration of depression screening and treatment with other standard care at noncommunicable disease (NCD) clinics in Malawi. To that end, the study team monitored depression screening in 10 NCD clinics in Malawi from May 2019 to November 2021 and recruited eligible consenting participants into the patient cohort. Eligibility criteria required that participants be 18–65 years of age, have elevated depressive symptoms denoted by a score  $\geq$ 5 on the Patient Health Questionnaire (PHQ-9) [21–24], and have a new or current diagnosis of diabetes or hypertension. These two chronic disease diagnoses were selected as part of the SHARP study eligibility criteria because depression often co-exists with hypertension and diabetes, which are rapidly increasing in prevalence in Malawi, and depression is associated with worse clinical outcomes for those comorbid conditions [25-27]. Participants were asked a series of questions, in Chichewa or Chitumbuka, at baseline, 3-month, 6-month, and 12-month follow-up interviews. During the baseline interview, research assistants re-assessed participants for depressive symptoms using the PHQ-9. Participants were excluded from this secondary analysis if they had PHQ-9 scores  $\geq$ 5 at eligibility screening but not at the baseline interview (n = 203). The SHARP study protocol dictated that participants conduct their 3-month interview at exactly 3 months post-consent, but the protocol allowed these 3-month interviews to be scheduled within the bounds of 2 months and 5 months post-consent; 3-month interview data were considered missing if the 3-month interview was conducted outside of the window designated by the study protocol (n = 11). In this analysis, we related patients' baseline levels of anticipated depression treatment stigma to their probability of achieving depression remission by their 3-month follow-up interview.

#### **Exposure definition**

The exposure of interest was high baseline treatment-related stigma (also referred to as treatment carryover), indicated by patients' responses to an instrument that our team has previously validated in this study population [13]. This instrument measures three domains of stigma: *negative affect*, or negative attitudes toward people with depression; *disclosure carryover*, or the stigma that participants expected would result from disclosing depression status; and *treatment carryover*, or participants' concerns that they would be treated as outsiders in their communities as a result of engaging in depression treatment [13, 28, 29]. The stigma instrument measured these domains using a vignette of a woman named Thandi and a series of eight prompts delivered on a 5-point Likert scale (see S1 Appendix for full prompts). Each prompt was written such that agreement indicated endorsement of stigma. Strong agreement was equivalent to 4 points, while strong disagreement was 0 points. Responses were averaged per domain to produce three stigma summary scores per participant. For any domain, a neutral position was indicated by a score of 2 points. There were very few patients who maintained neutral positions on the treatment stigma domain. Thus, high anticipated treatment-related stigma was dichotomized as having a score greater than 2 in the treatment carryover domain. This dichotomy implies that participants in the high stigma group on average agreed with stigmatizing prompts in this domain, and participants not in that group generally disagreed or provided neutral responses to stigmatizing prompts. The two prompts included in the treatment carryover domain asked about whether the patient believed that Thandi (the vignette character) would lose friends if they knew that she was going to the clinic to 1) receive counseling or 2) receive medication for depression.

Our analysis centers anticipated treatment-related stigma for two reasons. First, because the patient population can largely be assumed to be treatment-naïve, the treatment carryover scale at baseline can be expected to capture participants' *anticipated* treatment-related stigma. By contrast, the wording of the other two scales' items is more likely to combine a mixture of participants' experienced stigma and anticipated stigma. Second, based on previous research, we expected that treatment-related concerns would have the most direct impact on treatment initiation and engagement and subsequently depression remission.

#### **Outcome definition**

The primary outcome of interest is depression remission 3 months after study initiation. Depression remission is a binary outcome, defined as having a PHQ-9 score below 5 at the 3-month follow-up interview. Using this cut-off is supported by previous research on depression cut-off scores using the PHQ-9 [21–24]. Participants that answered positively to item 9 of the PHQ-9 (representing suicidal ideation) were still considered as remitted if their total PHQ-9 score was below 5. While suicidal ideation can be a symptom of depression, depression does not represent a necessary cause of suicidal ideation, and we therefore chose to allow flexibility for other etiologies that may also lead to suicidal ideation.

#### Confounders

We used directed acyclic graphs (DAGs) to assist in identifying a sufficient set of confounders to estimate the causal relationship between anticipated treatment-related stigma and subsequent depression remission at the 3-month interview [30–33]. This sufficient set included baseline social support, baseline depressive symptoms, baseline wealth score, baseline adaptive coping behaviors, depression treatment assignment, education level, reported job at baseline, urbanicity, and stressful life events occurring in the three months preceding the baseline interview. While our DAG identified the relevance of patients' diabetes or hypertension morbidity to their depression treatment engagement and remission, it was nonetheless unrelated to patients' anticipated treatment-related stigma and therefore was not defined as a confounder. Social support was measured using the Multidimensional Scale of Perceived Social Support (MSPSS) [34, 35]. Stressful life events were measured using the Life Events Scale, and disjoint indicator variables were created based on the type of stressful life events experienced (see Table 1 for categories) [36, 37]. Adaptive coping behaviors were based on the Brief COPE scale; adaptive coping behaviors were believed to influence the way participants perceived treatment stigma as well as their ability to engage in depression treatment [38]. Treatment assignment is based on the depression treatment that patients were referred to by their clinicians at the NCD clinic at the time of the patients' initial depression screening and SHARP

study referral. Patients reported their education level and current employment during the baseline research interview and this information was encoded in statistical models using disjoint indicator variables. Urbanicity was a categorical variable derived from the NCD clinic that each patient attended: the clinics were classified as urban, peri-urban, or rural; in analyses, it was also encoded as a set of disjoint indicator variables. The wealth score was generated as a weighted factor score based on responses to radio, refrigerator, television, mobile phone, and car ownership, along with responses to whether the household had electricity, how often they worried about money, and how often they went to bed hungry [39, 40]. All scales were coded so that a larger number indicates a greater amount of that construct, e.g., a greater MSPSS score indicates greater social support. As a weighted factor score, the wealth score has a mean of 0 and standard deviation of 1 by design. With the exception of the life events scale, all other scales in this analysis were maintained as continuous variables. Further, to improve model fit, the following functional forms were selected: social support scores were modeled using a quadratic term, depressive symptom scores were modeled using restricted cubic splines with three knots, wealth scores used a quadratic term, and adaptive coping scores used linear splines with two knots.

#### Missing data

A complete case analysis would exclude 69 (9%) participants due to missing data. Thus, to avoid loss in precision and possibly validity (assuming data missingness is not completely at random) [41–46], missing data were addressed using multiple imputation with chained equations. Data were assumed to be missing at random conditional on the exposure, outcome, and confounders described previously. In addition to these variables, the following partially observed variables were included in the imputation model: baseline health-related quality of life score (SF-8) [47, 48], baseline anxiety score (GAD-7) [49], baseline PTSD checklist (PCL-C) [50, 51], and stressful life events between baseline and 3-month follow-up. Fully observed variables included patient's PHQ-9 score from original eligibility screening, whether they were prescribed antidepressant medication after their initial screening, whether they were referred for supportive counseling after their initial screening, patient sex, patient education level, clinic, and patient age. Chained equations were conducted sequentially in order of least

	Baseline			3 Months		
Variable	Mean	SD	Missing	Mean	SD	Missing
Age (Years)	50.8	9.9	0			
Time Between Baseline and 3-Month Interview (Days)				100.1	17.7	48
Depressive Symptoms (PHQ-9; scale range: 0-27)	9.3	3.9	4	5.9	3.9	51
Anxiety Symptoms (GAD-7; scale range: 0-21)	7.1	4.2	2	4.6	3.8	49
Stressful Life Events (LES; scale range: 0-14)	3	2.3	0	2.4	2.2	47
PTSD Symptoms (PCL-C; scale range: 17–85)	42.9	14.6	1	35.2	13.6	49
Social Support (MSPSS; 0–24)	17.2	4.2	5	17.4	4	52
Stigma Sub-Scale: Treatment Stigma (scale range; 0–4)	1.4	1.1	1	1.2	1	52
Stigma Sub-Scale: Negative Affect (scale range; 0–4)	2.2	1	4	1.9	1	49
Stigma Sub-Scale: Disclosure Carryover (scale range; 0–4)	2.4	1.2	6	2.4	1.1	55
Standardized SF8 Score <sup>1</sup>	0.2	0.9	16	0.1	1	56
Standardized Wealth Score <sup>1</sup>	0	1	1			
Adaptive Coping Behaviors (Brief COPE; scale range: 0–15)	7.5	3	1	7.4	3.3	56

Table 1. Summary of the analysis cohort (N = 743).

(Continued)

Table 1. (Continued)

	1	Baseline		3 Months			
Variable	Mean	SD	Missing	Mean	SD	Missing	
	N	%		N	%		
Sex							
Male	158	21%					
Female	585	79%					
Education level							
No Formal School	119	16%					
Standard 1–5	238	32%					
Standard 6–8	221	30%					
Secondary School	128	17%					
Postsecondary School	37	5%					
Employment							
Farmer	328	44%					
Business Owner	131	18%					
Homemaker	142	19%					
Other Employment	92	12%					
Not Currently Employed	46	6%					
Missing	4	1%					
Urbanicity							
Rural	139	19%					
Peri-urban	472	64%					
Urban	132	18%					
Baseline treatment referrals							
Only Antidepressant Medication	116	16%					
Only Counseling	580	78%					
Both Medication and Counseling	38	5%					
Neither	9	1%					
High anticipated treatment-related stigma							
No	563	76%		570	77%		
Yes	179	24%		121	16%		
Missing	1	0%		52	7%		
Stressful Life Events—Baseline							
Employment Related	128	17%		124	17%		
Safety Related	40	5%		21	3%		
Personal Health Related	181	24%		152	20%		
Romantic Relationship Related	22	3%		12	2%		
Family Relationship Related	214	29%		168	23%		
Death Or Illness of Loved One	11	1%		7	1%		
Missing	2	0%		52	7%		
Depression remission (PHQ9<5) at 3-month interview							
No				418	56%		
Yes				273	37%		
Missing				52	7%		

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missing (n = 1) to most missing variable (n = 52). In total, 50 imputed data sets were generated with 500 iterations per imputation.

#### Analytical approach

We estimated the marginal 3-month risk difference (RD) for depression remission contrasting high vs. low/neutral anticipated treatment-related stigma using inverse probability weighting. We estimated inverse probability of treatment (IPT) weights via a logistic regression model that predicted the probability of observing a positive exposure given a sufficient set of correctly specified confounding variables [52, 53]. Weights were assigned by predicting the probability of having high anticipated treatment stigma conditional on confounding variables (i.e., propensity score) and then separately predicting the crude probability of the high anticipated treatment stigma in each imputed data set, per participant. Stabilized weights for participants who were observed as having high anticipated stigma were applied by dividing the crude probability of having high anticipated stigma by the conditional probability. Likewise, stabilized weights for participants who were observed as having low/neutral anticipated stigma were applied by dividing the conditional probability of having low/neutral anticipated stigma by the crude probability of having low/neutral anticipated stigma. While the estimand of interest in this analysis was the average treatment effect using inverse probability of treatment weights, we used the same propensity scores to generate weights that would additionally estimate the average treatment effect in the treated (ATT) and untreated (ATU); we present all estimates in the main text (Table 2). Graphical and summary diagnostics were used to investigate misspecification of weights, and the diagnostics for these weights are also presented in the supplementary material (S2-S4 Tables, S1-S4 Figs).

After assessing the balance of covariates in the weighted population, we fit a weighted linear regression model that regressed depression remission at 3-month follow-up onto anticipated treatment-related stigma at baseline. Due to the computational complexity of combining multiple imputation with bootstrap methods, the confidence intervals were generated from multiple imputation alone and likely represent a conservative variance estimate [54–56]. All statistical analyses were conducted using Stata 16.1 [57].

#### **Ethics statement**

This study was approved by the University of North Carolina Biomedical Institutional Review Board (UNC IRB) and the Malawi National Health Science Research Committee (NHSRC). Additional information regarding the ethical, cultural, and scientific considerations specific to inclusivity in global research is included in the Supporting Information (S1 Checklist).

#### Results

In total, 946 participants enrolled in the SHARP cohort and completed their baseline interview; 743 (79%) participants had a PHQ-9 score  $\geq$  5 at the time of baseline re-assessment and

Table 2. Estimates of standardized 3-month risk of depression remission, Risk Difference (RD), and 95% Confidence Intervals (CI) using inverse probability	
weighting $(N = 743)$ .	

Estimand	Risk Group	Risk	95% CI	RD	95% CI
Average Treatment Effect	High Anticipated Treatment-Related Stigma	0.31	(0.23, 0.39)	-0.10	(-0.19, -0.003)
	Low/Neutral Anticipated Treatment-Related Stigma	0.41	(0.36, 0.45)	0.	
Average Treatment Effect in the Treated	High Anticipated Treatment-Related Stigma	0.32	(0.25, 0.39)	-0.07	(-0.16, 0.04)
	Low/Neutral Anticipated Treatment-Related Stigma	0.39	(0.31, 0.46)	0.	
Average Treatment Effect in the Untreated	High Anticipated Treatment-Related Stigma	0.30	(0.21, 0.40)	-0.11	(-0.21, -0.01)
	Low/Neutral Anticipated Treatment-Related Stigma	0.41	(0.37, 0.45)	0.	

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therefore met study inclusion criteria; 695 (95%) of these participants completed their 3-month follow-up interview within the appropriate window. Based on the imputation methods described previously, we were able to conduct analyses on the full sample of 743 participants. Table 1 represents the distribution of relevant variables prior to imputation; See S1 Table for the distribution of variables in the post-imputation data. The median number of days between the baseline interview and 3-month interview was 93 days (IQR:14 days). In general, this sample of participants had high levels of baseline social support (mean: 17.2, SD: 4.2) and post-traumatic stress symptoms (mean: 42.9; SD: 14.6; Table 1). The sample was also majority female (n = 585; 79%; Table 1), and the mean age was 51 years (SD: 9.9; Table 1). Most patients in this cohort (n = 618; 83%) were referred to counseling during their initial screening, and 154 (21%) were prescribed antidepressant medication during their initial screening. Only 9 (1%) patients were not referred to any treatment at initial screening. All 9 of these patients had PHQ-9 scores that would indicate treatment. Ultimately, 273 (37%) patients achieved depression remission by their 3-month interview (Table 1).

Patients' baseline treatment-related stigma scores indicated that most participants carried low or neutral levels of anticipated treatment-related stigma (n = 563; 76%; Table 1). On average, baseline treatment-related stigma scores tended to be lower than the scores for other stigma domains. For example, the average treatment-related stigma score was 1.4 (SD: 1.1), while the average disclosure carryover score was 2.4 (SD: 1.2; Table 1). Within the two treatment-related stigma prompts, 30% of patients (n = 223) agreed or strongly agreed that Thandi would lose friends if they found out that she was receiving counselling, and 27% (n = 200) agreed or strongly agreed that Thandi would lose friends if people found out that she took depression medication. Very few ( $\leq$ 20 patients) remained neutral when responding to each of these two prompts.

Finally, the IPT weighted estimate demonstrated that the risk of depression remission at the 3-month interview among participants with high anticipated treatment-related stigma was 0.31 (95% Confidence Interval [CI]: 0.23, 0.39; Table 2). Compared to the low/neutral treatment-related stigma group (risk: 0.41; 95% CI: 0.36, 0.45), the high treatment-related stigma group was 10 percentage points less likely to achieve depression remission by the 3-month interview (RD: -0.10; 95% CI: -0.19, -0.003; Table 2).

### Discussion

In this prospective analysis of anticipated treatment-related stigma and depression remission among people with hypertension or diabetes in Malawi, we saw that many participants (37%) achieved depression remission by their 3-month interview. Our analysis further demonstrated that achieving depression remission by the 3-month interview varied by anticipated depression treatment-related stigma, which was measured at the baseline interview. We estimated that the standardized risk (or probability) of remission at the 3-month interview was 41% among participants with low or neutral levels of anticipated treatment-related stigma, compared to 31% among the high anticipated treatment stigma group. The results suggest that, if we were to organize an intervention on treatment-related stigma that moved all participants from the high anticipated stigma group to the low/neutral group, we would expect to see a 10 percentage point increase in depression remission at the 3-month follow-up period in this population.

This study's findings align with other research globally that has demonstrated the detrimental effects of treatment stigma on continued treatment engagement and recovery from mental illness [5–8, 58–60]. Still, while several studies—the current analysis included—have identified stigma as an important barrier to public health efforts to improve access and engagement in clinically appropriate mental healthcare, there remains uncertainty on the most effective means to meaningfully reduce stigma and improve mental health outcomes. Moreover, some research has shown that stigma reduction efforts tailored to the general public have failed at reducing key stigma targets, such as social distance toward individuals living with mental illness [61–64]. We believe that the current study contributes to this discussion by identifying anticipated treatment stigma among people with depression as a key domain that could be targeted for intervention to improve the probability of depression remission within the target 3-month window. While more research is warranted, it is possible that intervening on treatment-related stigma among people with depression and their immediate support network could increase their probability of depression by increasing support and reducing stigma around depression care-seeking. Indeed, in prior qualitative work our study team conducted among patients with perinatal depression, participants expressly identified the need for social support in coping with their depressive symptoms [15].

This study is not without its limitations. First, the treatment-related stigma scale focused on lost friendships, and a longer instrument may have been able to capture other features of treatment-related stigma concerns more fully. Second, as with all studies using latent variables to measure constructs, this study is vulnerable to measurement error. However, the latent variables used in this analysis were measured using validated instruments, providing further confidence that the variables represent their respective constructs [13, 14, 36–38, 51, 65, 66]. We anticipate that most measurement error occurred non-differentially, and we therefore expect that measurement error would more likely bias the current results toward a null treatment effect rather than a more extreme effect estimate [67]. Nevertheless, it is possible that participants modified their responses due to social desirability bias, and in such cases there may have been non-differential measurement bias in certain constructs used in this analysis; it would be difficult to predict the direction of such a bias [68], but we do not expect such a bias to have affected a large proportion of the participant sample. Finally, it is possible that a small number of participants (n  $\leq$  7) who were identified with depression and enrolled in the cohort had a history of depression treatment-in such a case, it could represent unmeasured confounding for this analysis. However, SHARP study data suggest that it is very rare (< 1%) for any participant to have a history of receiving depression care, and we therefore assumed that all patients in the sample were treatment naïve.

The study also has a number of strengths. First, we used a multidimensional stigma instrument, which allowed us to deconstruct the relationship between specific dimensions of stigma and other latent constructs. Second, the study had high participant retention, and the potential impact of missing data was addressed through multiple imputation assuming missingness to be at random conditional on measured variables. Third, the study used inverse probability weighting to estimate the total effect of anticipated treatment-related stigma on the 3-month probability of depression remission. Using a weighting approach in this analysis was important because it allowed us to estimate more policy-relevant effect estimates by reporting a risk difference rather than an odds ratio—while odds ratios are useful in many studies, our outcome of interest (depression remission) was far too prevalent for the odds ratio to approximate more easily interpretable measures such as the risk ratio [69].

Mental health stigma is ubiquitous and varies in degree by illness and social context, among other factors. In Malawi, a reduction in anticipated depression treatment-related stigma could improve depression remission outcomes. In this study, we found that patients with high anticipated treatment-related stigma had a 10-point reduction in their 3-month probability of depression remission. This suggests that patients who anticipate experiencing greater social isolation as a result of receiving depression treatment may not engage with treatment equally to those who do not have such heightened concerns. In order to improve depression outcomes for all patients with depression, it is necessary to address treatment-related stigma among these patients and their immediate support networks. Further investigation is warranted to fully understand the modes by which such interventions on treatment-related stigma can be successfully reduced to improve mental health outcomes and quality of life among people living with depression.

## Supporting information

**S1 Checklist. Inclusivity in global research.** (PDF)

**S1 Appendix. Stigma questionnaire.** (PDF)

**S1 Table.** Post-imputation distribution of analysis variables that required imputation (N = 743). Data distributions reported in this table were drawn from the 1st imputed data set. Only imputed analytic variables (analytic variables that previously had missing observations) are displayed here. (PDF)

S2 Table. Pre- and post-weight distributions of variables used to design inverse probability of treatment weights (N = 743). Data distributions reported in this table were drawn from the 1st imputed data set. Only variables used in the design of the inverse probability weights are displayed here.



S3 Table. Post-weight distributions after applying inverse probability weights to estimate the average treatment effect in the treated<sup>2</sup> (N = 743). Data distributions reported in this table were drawn from the 1st imputed data set. Only variables used in the design of the inverse probability weights are displayed here. (PDF)

S4 Table. Post-weight distributions after applying inverse probability weights to estimate the average treatment effect in the untreated<sup>2</sup> (N = 743). Data distributions reported in this table were drawn from the 1st imputed data set. Only variables used in the design of the inverse probability weights are displayed here. (PDF)

S1 Fig. Pre- and post-weight distributions of baseline adaptive coping behaviors by treatment group (N = 743). Data distributions reported in this table were drawn from the 1st imputed data set.

(TIF)

**S2 Fig. Pre- and post-weight distributions of baseline wealth score by treatment group** (N = 743). Data distributions reported in this table were drawn from the 1st imputed data set. (TIF)

**S3 Fig. Pre- and post-weight distributions of baseline depressive symptoms by treatment group (N = 743).** Data distributions reported in this table were drawn from the 1st imputed data set. (TIF)

**S4 Fig. Pre- and post-weight distributions of baseline social support by treatment group** (N = 743). Data distributions reported in this table were drawn from the 1st imputed data set. (TIF)

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#### References

- 1. Population, total—World | Data. In: The World Bank [Internet]. [cited 21 Sep 2020]. Available: https:// data.worldbank.org/indicator/SP.POP.TOTL?locations=1W
- James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018; 392: 1789–1858. https://doi.org/10.1016/S0140-6736(18)32279-7 PMID: 30496104
- Abas M, Bowers T, Manda E, Cooper S, Machando D, Verhey R, et al. 'Opening up the mind: problemsolving therapy delivered by female lay health workers to improve access to evidence-based care for depression and other common mental disorders through the Friendship Bench Project in Zimbabwe. International Journal of Mental Health Systems; London. 2016; 10. http://dx.doi.org.libproxy.lib.unc. edu/10.1186/s13033-016-0071-9 PMID: 27175215
- 4. Chibanda D, Mesu P, Kajawu L, Cowan F, Araya R, Abas MA. Problem-solving therapy for depression and common mental disorders in Zimbabwe: piloting a task-shifting primary mental health care intervention in a population with a high prevalence of people living with HIV. BMC Public Health. 2011; 11: 1–10. https://doi.org/10.1186/1471-2458-11-828 PMID: 22029430
- Clement S, Schauman O, Graham T, Maggioni F, Evans-Lacko S, Bezborodovs N, et al. What is the impact of mental health-related stigma on help-seeking? A systematic review of quantitative and qualitative studies: 17.
- Fox AB, Smith BN, Vogt D. How and when does mental illness stigma impact treatment seeking? Longitudinal examination of relationships between anticipated and internalized stigma, symptom severity, and mental health service use. Psychiatry Research. 2018; 268: 15–20. <u>https://doi.org/10.1016/j.psychres.2018.06.036 PMID: 29986172</u>
- Sirey JA, Bruce ML, Alexopoulos GS, Perlick DA, Friedman SJ, Meyers BS. Stigma as a Barrier to Recovery: Perceived Stigma and Patient-Rated Severity of Illness as Predictors of Antidepressant Drug Adherence. PS. 2001; 52: 1615–1620. https://doi.org/10.1176/appi.ps.52.12.1615 PMID: 11726752
- Stangl AL, Earnshaw VA, Logie CH, van Brakel W, C. Simbayi L, Barré I, et al. The Health Stigma and Discrimination Framework: a global, crosscutting framework to inform research, intervention development, and policy on health-related stigmas. BMC Medicine. 2019; 17: 31. <u>https://doi.org/10.1186/ s12916-019-1271-3 PMID: 30764826</u>
- 9. Goffman E. Stigma: Notes on the Management of Spoiled Identity. Simon and Schuster; 2009.

- Pescosolido BA, Martin JK, Long JS, Medina TR, Phelan JC, Link BG. "A Disease Like Any Other"? A Decade of Change in Public Reactions to Schizophrenia, Depression, and Alcohol Dependence. Am J Psychiatry. 2010; 167: 1321–1330. https://doi.org/10.1176/appi.ajp.2010.09121743 PMID: 20843872
- Pescosolido ACK Bernice A. Countries and Cultural Differences in the Stigma of Mental Illness: The East–West Divide—Anne C. Krendl, Bernice A. Pescosolido, 2020. Journal of Cross-Cultural Psychology. 2020 [cited 16 Nov 2020]. Available: http://journals.sagepub.com/doi/10.1177/0022022119901297
- Crabb J, Stewart RC, Kokota D, Masson N, Chabunya S, Krishnadas R. Attitudes towards mental illness in Malawi: a cross-sectional survey. BMC Public Health. 2012; 12: 541. <u>https://doi.org/10.1186/</u> 1471-2458-12-541 PMID: 22823941
- Dussault JM, Zimba C, Malava J, Akello H, Stockton MA, Udedi M, et al. "Thandi should feel embarrassed": describing the validity and reliability of a tool to measure depression-related stigma among patients with depressive symptoms in Malawi. Soc Psychiatry Psychiatr Epidemiol. 2021 [cited 20 Nov 2021]. https://doi.org/10.1007/s00127-021-02202-w PMID: 34800138
- Dussault J, Akiba CF, Zimba C, Malaya J, Akello H, Stockton M, et al. Measuring depression-related stigma in depression care: a mixed-methods approach. Brief Presentation presented at: CUGH 2022; 2022 Apr 28; Virtual.
- LeMasters K, Dussault J, Barrington C, Bengtson A, Gaynes B, Go V, et al. "Pain in my heart": Understanding perinatal depression among women living with HIV in Malawi. Montazeri A, editor. PLoS ONE. 2020; 15: e0227935. https://doi.org/10.1371/journal.pone.0227935 PMID: 32502150
- Kulisewa K, Dussault JM, Gaynes BN, Hosseinipour MC, Go VF, Kutengule A, et al. The feasibility and acceptability of a task-shifted intervention for perinatal depression among women living with HIV in Malawi: a qualitative analysis. BMC Psychiatry. 2022; 22: 833. https://doi.org/10.1186/s12888-022-04476-z PMID: 36581849
- 17. Mendlewicz J. Towards achieving remission in the treatment of depression. Dialogues Clin Neurosci. 2008; 10: 371–375. https://doi.org/10.31887/DCNS.2008.10.4/jmendlewicz PMID: 19170394
- Thase ME. Achieving Remission and Managing Relapse in Depression. J Clin Psychiatry. 2003; 64: 335. PMID: 14700448
- Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, et al. Conceptualization and Rationale for Consensus Definitions of Terms in Major Depressive Disorder: Remission, Recovery, Relapse, and Recurrence. Archives of General Psychiatry. 1991; 48: 851–855. <u>https://doi.org/10.1001/archpsyc.</u> 1991.01810330075011 PMID: 1929776
- Pence BW, Gaynes BN, Atashili J, O'Donnell JK, Kats D, et al. Feasibility, safety, acceptability, and preliminary efficacy of measurement-based care depression treatment for HIV patients in Bamenda, Cameroon. Aids and Behavior. 2014; 18: 1142–1151. <u>https://doi.org/10.1007/s10461-014-0727-x</u> PMID: 24558099
- Udedi M, Muula AS, Stewart RC, Pence BW. The validity of the patient health Questionnaire-9 to screen for depression in patients with type-2 diabetes mellitus in non-communicable diseases clinics in Malawi. BMC Psychiatry. 2019; 19. https://doi.org/10.1186/s12888-019-2062-2 PMID: 30813922
- Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001; 16: 606–613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x PMID: 11556941
- Levis B, Benedetti A, Thombs BD. Accuracy of Patient Health Questionnaire-9 (PHQ-9) for screening to detect major depression: individual participant data meta-analysis. BMJ. 2019;365. https://doi.org/10. 1136/bmj.l1476 PMID: 30967483
- 24. Gilbody S, Richards D, Brealey S, Hewitt C. Screening for Depression in Medical Settings with the Patient Health Questionnaire (PHQ): A Diagnostic Meta-Analysis. J GEN INTERN MED. 2007; 22: 1596–1602. https://doi.org/10.1007/s11606-007-0333-y PMID: 17874169
- Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet. 2007; 370: 851–858. https://doi.org/ 10.1016/S0140-6736(07)61415-9 PMID: 17826170
- Folb N, Timmerman V, Levitt NS, Steyn K, Bachmann MO, Lund C, et al. Multimorbidity, control and treatment of non-communicable diseases among primary healthcare attenders in the Western Cape, South Africa. S Afr Med J. 2015; 105: 642–647. https://doi.org/10.7196/samjnew.8794 PMID: 26449692
- Msyamboza KP, Kathyola D, Dzowela T. Anthropometric measurements and prevalence of underweight, overweight and obesity in adult Malawians: nationwide population based NCD STEPS survey. Pan Afr Med J. 2013; 15: 108. https://doi.org/10.11604/pamj.2013.15.108.2622 PMID: 24244794
- Pescosolido BA, Martin JK. The Stigma Complex. Annu Rev Sociol. 2015; 41: 87–116. https://doi.org/ 10.1146/annurev-soc-071312-145702 PMID: 26855471

- Griffiths KM, Christensen H, Jorm AF. Predictors of depression stigma. BMC Psychiatry. 2008; 8: 25. https://doi.org/10.1186/1471-244X-8-25 PMID: 18423003
- PEARL J. Causal diagrams for empirical research. Biometrika. 1995; 82: 669–688. <u>https://doi.org/10.1093/biomet/82.4.669</u>
- Hernán MA, Hernández-Díaz S, Werler MM, Mitchell AA. Causal Knowledge as a Prerequisite for Confounding Evaluation: An Application to Birth Defects Epidemiology. American Journal of Epidemiology. 2002; 155: 176–184. https://doi.org/10.1093/aje/155.2.176 PMID: 11790682
- Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999; 10: 37–48. PMID: 9888278
- VanderWeele TJ, Robins JM. Directed Acyclic Graphs, Sufficient Causes, and the Properties of Conditioning on a Common Effect. American Journal of Epidemiology. 2007; 166: 1096–1104. <u>https://doi.org/ 10.1093/aje/kwm179 PMID: 17702973</u>
- Stewart RC, Umar E, Tomenson B, Creed F. Validation of the multi-dimensional scale of perceived social support (MSPSS) and the relationship between social support, intimate partner violence and antenatal depression in Malawi. BMC Psychiatry. 2014; 14: 180. <u>https://doi.org/10.1186/1471-244X-14-180 PMID</u>: 24938124
- Zimet GD, Dahlem NW, Zimet SG, Farley GK. The Multidimensional Scale of Perceived Social Support. Journal of Personality Assessment. 1988; 52: 30–41. https://doi.org/10.1207/s15327752jpa5201\_2
- Leserman J, Ironson G, O'Cleirigh C, Fordiani JM, Balbin E. Stressful Life Events and Adherence in HIV. AIDS Patient Care STDS. 2008; 22: 403–411. <u>https://doi.org/10.1089/apc.2007.0175</u> PMID: 18373416
- Sarason IG, Johnson JH, Siegel JM. Assessing the impact of life changes: Development of the Life Experiences Survey. Journal of Consulting and Clinical Psychology. <u>https://doi.org/10.1037//0022-006x.46.5.932</u> PMID: 701572; 46: 932.
- Carver CS. You want to measure coping but your protocol' too long: Consider the brief cope. Int J Behav Med. 1997; 4: 92. https://doi.org/10.1207/s15327558ijbm0401\_6 PMID: 16250744
- **39.** DiStefano C, Zhu M, Mindrila D. Understanding and Using Factor Scores: Considerations for the Applied Researcher. Practical Assessment, Research & Evaluation. 2009; 14.
- Smits J, Steendijk R. The International Wealth Index (IWI). Soc Indic Res. 2015; 122: 65–85. <u>https://doi.org/10.1007/s11205-014-0683-x</u>
- 41. Stuart EA, Azur M, Frangakis C, Leaf P. Multiple Imputation With Large Data Sets: A Case Study of the Children's Mental Health Initiative. American Journal of Epidemiology. 2009; 169: 1133–1139. <u>https://doi.org/10.1093/aje/kwp026 PMID: 19318618</u>
- Madley-Dowd P, Hughes R, Tilling K, Heron J. The proportion of missing data should not be used to guide decisions on multiple imputation. Journal of Clinical Epidemiology. 2019; 110: 63–73. https://doi. org/10.1016/i.jclinepi.2019.02.016 PMID: 30878639
- Dong Y, Peng C-YJ. Principled missing data methods for researchers. Springerplus. 2013; 2: 222. https://doi.org/10.1186/2193-1801-2-222 PMID: 23853744
- 44. Little RJA, Rubin DB. Statistical Analysis with Missing Data. John Wiley & Sons; 2019.
- Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009; 338: b2393. <u>https:// doi.org/10.1136/bmj.b2393</u> PMID: 19564179
- **46.** Greenland S, Finkle WD. A Critical Look at Methods for Handling Missing Covariates in Epidemiologic Regression Analyses. American Journal of Epidemiology. 1995; 142: 1255–1264. https://doi.org/10. 1093/oxfordjournals.aje.a117592 PMID: 7503045
- 47. Bost JE, Williams BA, Bottegal MT, Dang Q, Rubio DM. The 8-Item Short-Form Health Survey and the Physical Comfort Composite Score of the Quality of Recovery 40-Item Scale Provide the Most Responsive Assessments of Pain, Physical Function, and Mental Function During the First 4 Days After Ambulatory Knee Surgery with Regional Anesthesia. Anesthesia & Analgesia. 2007; 105: 1693–1700. <a href="https://doi.org/10.1213/01.ane.0000287659.14893.65">https://doi.org/10.1213/01.ane.0000287659.14893.65</a> PMID: 18042869
- Onagbiye SO, Moss SJ, Cameron M. Validity and reliability of the Setswana translation of the Short Form-8 health-related quality of life health survey in adults. Health SA Gesondheid (Online). 2018; 23: 1–6. https://doi.org/10.4102/hsag.v23i0.1092 PMID: 31934383
- Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7. Archives of Internal Medicine. 2006; 166: 1092–1097. <u>https://doi.org/10.1001/</u> archinte.166.10.1092 PMID: 16717171
- Weathers FW, Litz BT, Herman DS, Huska JA, Keane TM, et al. The PTSD Checklist (PCL): Reliability, validity, and diagnostic utility. annual convention of the international society for traumatic stress studies, San Antonio, TX. San Antonio, TX; 1993.

- Verhey R, Chibanda D, Gibson L, Brakarsh J, Seedat S. Validation of the posttraumatic stress disorder checklist– 5 (PCL-5) in a primary care population with high HIV prevalence in Zimbabwe. BMC Psychiatry. 2018; 18: 1–8. https://doi.org/10.1186/s12888-018-1688-9 PMID: 29685117
- Snowden JM, Rose S, Mortimer KM. Implementation of G-Computation on a Simulated Data Set: Demonstration of a Causal Inference Technique. American Journal of Epidemiology. 2011; 173: 731–738. https://doi.org/10.1093/aje/kwg472 PMID: 21415029
- Cole SR, Hernán MA. Constructing Inverse Probability Weights for Marginal Structural Models. Am J Epidemiol. 2008; 168: 656–664. https://doi.org/10.1093/aje/kwn164 PMID: 18682488
- Efron B, Tibshirani R. Bootstrap Methods for Standard Errors, Confidence Intervals, and Other Measures of Statistical Accuracy. Statistical Science. 1986; 1: 54–75. https://doi.org/10.1214/ss/ 1177013815
- 55. Rubin DB. Multiple imputation for nonresponse in surveys. New York: Wiley; 1987.
- Schomaker M, Heumann C. Bootstrap Inference When Using Multiple Imputation. Stat Med. 2018; 37: 2252–2266. https://doi.org/10.1002/sim.7654 PMID: 29682776
- 57. StataCorp. Stata Statistical Software: Release 16. College Station, TX: StataCorp, LLC; 2019.
- Ahmedani BK. Mental Health Stigma: Society, Individuals, and the Profession. J Soc Work Values Ethics. 2011; 8: 4-1–4–16.
- Gearing RE, MacKenzie MJ, Ibrahim RW, Brewer KB, Batayneh JS, Schwalbe CSJ. Stigma and Mental Health Treatment of Adolescents with Depression in Jordan. Community Mental Health Journal. 2015; 51: 111–117. https://doi.org/10.1007/s10597-014-9756-1 PMID: 25027014
- **60.** Stigma Thornicroft G. and discrimination limit access to mental health care. Epidemiol Psichiatr Soc. 2008; 17: 14–19.
- Kvaale EP, Gottdiener WH, Haslam N. Biogenetic explanations and stigma: a meta-analytic review of associations among laypeople. Soc Sci Med. 2013; 96: 95–103. https://doi.org/10.1016/j.socscimed. 2013.07.017 PMID: 24034956
- Kvaale EP, Haslam N, Gottdiener WH. The "side effects" of medicalization: a meta-analytic review of how biogenetic explanations affect stigma. Clin Psychol Rev. 2013; 33: 782–794. <u>https://doi.org/10.1016/j.cpr.2013.06.002</u> PMID: 23831861
- 63. Norms C on the S of CBHS, Board on Behavioral C, Education D of B and SS and, National Academies of Sciences E. Approaches to Reducing Stigma. Ending Discrimination Against People with Mental and Substance Use Disorders: The Evidence for Stigma Change. National Academies Press (US); 2016. Available: http://www.ncbi.nlm.nih.gov/books/NBK384914/
- Schlier B, Schmick S, Lincoln TM. No matter of etiology: biogenetic, psychosocial and vulnerabilitystress causal explanations fail to improve attitudes towards schizophrenia. Psychiatry Res. 2014; 215: 753–759. https://doi.org/10.1016/j.psychres.2013.12.056 PMID: 24485063
- 65. Mughal AY, Devadas J, Ardman E, Levis B, Go VF, Gaynes BN. A systematic review of validated screening tools for anxiety disorders and PTSD in low to middle income countries. BMC Psychiatry. 2020; 20: 338. https://doi.org/10.1186/s12888-020-02753-3 PMID: 32605551
- 66. Roberts B, Browne J, Ocaka KF, Oyok T, Sondorp E. The reliability and validity of the SF-8 with a conflict-affected population in northern Uganda. Health Qual Life Outcomes. 2008; 6: 108. <u>https://doi.org/10.1186/1477-7525-6-108 PMID: 19055716</u>
- Wacholder S, Hartge P, Lubin JH, Dosemeci M. Non-differential misclassification and bias towards the null: a clarification. Occup Environ Med. 1995; 52: 557–558. https://doi.org/10.1136/oem.52.8.557
  PMID: 7663646
- Yland JJ, Wesselink AK, Lash TL, Fox MP. Misconceptions About the Direction of Bias From Nondifferential Misclassification. American Journal of Epidemiology. 2022; 191: 1485–1495. <u>https://doi.org/10.1093/aje/kwac035 PMID: 35231925</u>
- Davies HTO, Crombie IK, Tavakoli M. When can odds ratios mislead? BMJ. 1998; 316: 989–991. https://doi.org/10.1136/bmj.316.7136.989 PMID: 9550961