

https://dspace.org/

# Association between depressive symptoms and tuberculosis diagnosis stage in older adults a 4year longitudinal cohort study in rural South Africa

**K Eyal; Ryan Wagner; Jennifer Geel**

BMJ PUBLISHING GROUP
https://hdl.handle.net/10539/48330
WOS

Downloaded from a DSpace repository. https://dspace.org/

BMJ Open

# Association between depressive symptoms and tuberculosis diagnosis stage in older adults: a 4-year longitudinal cohort study in rural South Africa

Katherine Eyal ,[1] Ryan Wagner ,[2] Jennifer Ann Geel[3]

**To cite:** Eyal K, Wagner R, Geel JA. Association between depressive symptoms and tuberculosis diagnosis stage in older adults: a 4-year longitudinal cohort study in rural South Africa. *BMJ Open* 2025;**15**:e102839. doi:10.1136/bmjopen-2025-102839

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2025-102839).

Received 27 March 2025
Accepted 12 November 2025

Check for updates

© Author(s) (or their employer(s)) 2025. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ Group.

[1]School of Economics, SALDRU, University of Cape Town, Rondebosch, South Africa
[2]MRC/Wits Agincourt Research Unit, University of the Witwatersrand, Parkton, South Africa
[3]University of the Witwatersrand, Johannesburg-Braamfontein, South Africa

**Correspondence to**
Dr Katherine Eyal;
katherine.eyal@uct.ac.za

## ABSTRACT

**Objectives** While tuberculosis (TB) is associated with increased depressive symptoms, the long-term mental health trajectory post-diagnosis in low-resource settings remains poorly understood. This study investigated the longitudinal progression of depressive symptoms among individuals diagnosed with TB and evaluated whether symptom severity persisted or attenuated over time.

**Design** Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa. Population-based cohort study.

**Setting** Rural Agincourt subdistrict, Mpumalanga province, South Africa, a high-TB-burden, resource-constrained region.

**Participants** Adults aged 40 years and older who were permanent residents of the Agincourt subdistrict (N=5059 at baseline).

**Outcome measures** Depressive symptoms were assessed using the Centre for Epidemiologic Studies Depression Scale (CES-D) 8 (Wave 1) and CES-D 20 (Wave 2), with standardised scores enabling cross-wave comparisons. TB diagnosis status (self-reported) was categorised as recently diagnosed, previously diagnosed or never diagnosed.

**Results** At baseline, HIV prevalence was significantly higher (p<0.001) among those recently diagnosed (37.0%) and previously diagnosed (26.9%) compared with those never diagnosed (10.2%). Individuals recently diagnosed with TB had significantly higher standardised CES-D scores (unadjusted β=0.32, 95% CI 0.15 to 0.50, p<0.001) compared with those never diagnosed, a finding that remained robust after adjusting for socio-demographic and health covariates (β=0.31, 95% CI 0.14 to 0.49, p<0.001). The odds of moderate depressive symptoms (OR=1.70, 95% CI 1.22 to 2.36, p<0.001) and severe depressive symptoms (OR=1.77, 95% CI 1.23 to 2.55, p<0.001) were significantly elevated. By Wave 2 (4-year follow-up), individuals with a recent TB diagnosis remained at a significantly higher risk of severe depression (OR=1.52, 95% CI 1.05 to 2.22, p<0.05).

**Conclusions** A recent TB diagnosis is strongly associated with depressive symptoms at baseline, and with the persistence of severe depressive symptoms 4 years later. These results were robust to a number of sensitivity tests and do not seem to be driven by differences in healthcare utilisation. Integrating mental health support into TB care programmes at all phases of diagnosis and treatment, particularly in low-resource settings, may have significant benefits.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study uses data from the Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community cohort, a well-characterised, population-based dataset spanning multiple years, enabling a detailed examination of the temporal relationship between tuberculosis (TB) diagnosis and mental health outcomes in a high-burden, resource-constrained setting.
⇒ The categorisation of participants into recently diagnosed, previously diagnosed and never diagnosed TB groups provides a methodological framework for examining the trajectory of mental health impacts following tuberculosis diagnosis.
⇒ Depressive symptoms were measured using the Centre for Epidemiologic Studies Depression Scale, a validated psychometric instrument, with standardised scores ensuring comparability between waves.
⇒ The study's multivariable regression models adjusted for a comprehensive range of socio-demographic, socioeconomic and health-related covariates.
⇒ A limitation of the study is its reliance on self-reported TB diagnosis, though the observed patterns align with national TB-HIV coinfection data and sensitivity analyses suggest our main estimates may be conservative.

## INTRODUCTION

Tuberculosis (TB) remains a major global health challenge.[1 2] Despite some success in incidence reduction,[3] South Africa continues to have one of the highest TB burdens globally,[1 3 4] with an estimated incidence of 270 000 cases, and 55 545 deaths attributed to TB in 2023.[3] TB disproportionately affects those of lower socio-economic status,[5–7] exacerbating

health inequalities.[2] Older adults have been identified as an at-risk group for TB,[4 6] as well as TB-HIV coinfection, particularly in rural areas.[4] Approximately 54% of South Africans diagnosed with TB in 2023 were also living with HIV.[3]

Depressive symptoms are common among individuals with TB, with prevalence estimates ranging from 40% to 70%, particularly in low-resource settings.[8–10] Depression is associated with reduced treatment adherence and poorer clinical outcomes,[10–12] with affected individuals having higher odds of treatment default or mortality.[13] This is a particular concern given the emergence of drug-resistant TB strains.[2] Integrating mental health support into TB care may improve outcomes in resource-limited settings.[2 5 9 12 14]

The relationship between TB and depression is influenced by multiple shared risk factors, including poverty,[7] stigma[9] and comorbidities such as HIV, diabetes and malnutrition.[3 12 15–19] HIV co-infection particularly complicates this relationship by increasing TB susceptibility[2] and requiring more complex treatment regimens,[1 3 11] while being associated with higher mortality rates.[1 3 15] Although both mental health treatment[20–22] and socioeconomic interventions[23] show promise in improving TB outcomes, longitudinal evidence examining these interactions remains limited.[9 12]

This study examines the temporal relationship between TB diagnosis and depressive symptoms using a population-based cohort study of older adults, conducted in the Agincourt subdistrict of Mpumalanga province, South Africa.[24] Older adults in South Africa and in this cohort in particular experience a high burden of depression, which is strongly correlated with multimorbidity, poverty and HIV co-infection.[19 24–31] However, the association between mental health and receiving a diagnosis of TB is not well understood in this demographic. This longitudinal study analysed two waves of data (collected in 2014–2015 and 2018–2019) to assess the immediate psychological burden associated with TB diagnosis and whether these associations persist over time, comparing individuals with recent, past and no TB diagnoses in a low-resource setting.

## METHODS

### Study design and setting

Our cohort data is from the Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa (HAALSI),[32] which took place in a rural South African municipality, close to the border with Mozambique. The Agincourt Health and Socio-Demographic Surveillance System (HDSS), a node of the South African Population Research Infrastructure Network, has monitored this rural population continuously since 1992.[24] In 2014–2015, a first wave of interview and biomarker data for the HAALSI study were collected from a sample of men and women aged 40 and older in Agincourt. Two additional waves of data collection took place in 2018–2019 and 2021. The study setting is characterised by a high burden of both communicable diseases, particularly HIV–TB co-infection[33] and non-communicable conditions including depression,[25] with many health challenges exacerbated by socio-economic disadvantage.[30] The HAALSI cohort's longitudinal design, comprehensive health measures and large sample size provide valuable data for investigating the relationship between chronic disease conditions in an ageing rural population,[24] including both physical and mental health outcomes.[34] More details of the HAALSI protocol have been published previously.[24 33 35]

### Data source and participants

Data were drawn from Wave 1 (2014–2015) (n=5059) and Wave 2 (2018–2019) (n=4176) of the HAALSI study, with Wave 3 (2021) (n=3707) used for sensitivity analyses. Participants were adults aged 40 years or older, who were permanent residents of the Agincourt subdistrict.[24] Written informed consent was obtained from participants.[24] For this analysis, individuals were classified by self-reported TB diagnosis at baseline as: never diagnosed (reference category), recently diagnosed (within the past year) or previously diagnosed (more than 1 year before baseline).

### Data collection

Data were collected by trained fieldworkers using computer-assisted personal interviews in the local Xitsonga language.[24] These interviews captured socio-demographic, economic and health information, including self-reported conditions, clinical assessments, physical performance measures, point-of-care biomarkers and dried blood spot collection for HIV testing.[35]

### Patient and public involvement

Patients and the public were not directly involved in this specific analysis regarding study design, outcome measure selection, recruitment or dissemination planning. However, the original HAALSI study from which these data were derived incorporated substantial community engagement through the Agincourt HDSS. This included consultation with local community leaders and residents during the initial study design phase, ongoing feedback sessions throughout data collection and regular community meetings to discuss study findings and their implications for the local population. The research questions and data collection methods of the parent HAALSI study were informed by community priorities identified through these engagement processes.

### Measures

Depressive symptoms: The primary outcome in this study was depressive symptoms, which were assessed using the Centre for Epidemiologic Studies Depression Scale (CES-D).[36] The CES-D scale is a validated psychometric instrument that measures depressive symptoms by asking respondents to report how frequently they experienced specific symptoms during the past week. In Wave 1,

participants completed the 8-item version of the CES-D (CES-D 8), with symptom frequency indicated by an answer of 'Yes' or 'No' for whether they experienced each depressive symptom during the past week. Each affirmative response was scored as 1, yielding a sum total score range from 0 to 8.[28] This format was consistent with other Health and Retirement Study surveys at the time.[29 37] In Waves 2 and 3, participants completed the 20-item CES-D (CES-D 20). Each item was scored on a Likert scale based on symptom frequency in the past week as follows: 0 (0 days), 1 (1–2 days), 2 (3–4 days) or 3 (5–7 days), yielding a total summed score range from 0 to 60. The CES-D 20 measures multiple dimensions of depressive symptomatology, including negative affect (feelings of sadness and hopelessness), positive affect (feeling happy or hopeful), somatic problems (sleep disturbances and fatigue) and interpersonal difficulties.[38] Items assessing positive affect were reverse scored to ensure consistent interpretation. Higher CES-D scores indicate a greater burden of depressive symptomatology, and previously published thresholds are used to indicate respondents potentially experiencing clinically relevant depressive symptoms.[36]

To ensure comparability of depressive symptom measures across waves, the Wave 1 CES-D 8 (binary yes/no frequency of symptom responses, with a score range of 0–8) and Wave 2 CES-D 20 (4-point Likert scale frequency of symptom responses, with a score range of 0–60) scores were standardised into z-scores, using wave-specific means and SD. In addition, to support clinically meaningful categorisation, we also used thresholds of CES-D 8≥2 or CES-D 20≥16 to obtain binary indicators of the likely presence of mild-to-moderate depressive symptoms, and CES-D 8≥3 or CES-D 20≥20 for severe depressive symptoms.[39 40] These thresholds are consistent with prior studies in ageing populations,[41 42] and have been used in other studies of the HAALSI cohort.[29 30]

The CES-D has demonstrated strong psychometric properties[36] in diverse populations, including older adults[37–40 43–47] and across different languages.[48 49] The binary CES-D 8 has demonstrated effectiveness in identifying moderate-to-severe depressive symptoms in ageing populations,[41 45] while the CES-D 20 has shown high criterion and predictive validity against other depression scales like the Geriatric Depression Scale.[50] Short forms of the 4-answer item CES-D, such as the CES-D 10, have also demonstrated good construct validity and internal consistency in older adults.[39 44 46 47 49] While the CES-D 20 captures multiple dimensions of depressive symptomatology,[36] the binary CES-D 8 may underestimate symptom severity due to its limited response options and fewer items.[41 45]

Baseline TB diagnosis status: Self-report TB diagnosis was ascertained in Wave 1 using two questions: 'Have you ever been told by a doctor, nurse or other healthcare worker that you have TB?', and if the response was yes, 'Have you been newly diagnosed with TB in the last 12 months?'. Responses were used to classify participants as never diagnosed, recently diagnosed (within 1-year prior to baseline) or previously diagnosed (diagnosis more than 1 year before baseline). While later waves of HAALSI data collection allowed participants to revise their TB diagnosis history, we used Wave 1 reports of new TB diagnosis as these best captured participants' understanding of their diagnostic status at the time of symptom assessment (see online supplemental material S.1).

Covariates: analyses were adjusted for a range of demographic characteristics (age, gender, marital status), socio-economic measures (educational attainment, employment status, a Wealth Index derived via principal component analysis from household asset ownership) and health-related measures (self-reported HIV status, smoking, alcohol consumption and a history of working in mining). These covariates were selected based on their established relationships with both TB and depression in the literature, and the availability of data. To avoid potential over-control bias, these controls are not initially updated in the Wave 2 analysis, as they may be affected by baseline TB diagnosis. Self-rated health and healthcare utilisation data were excluded from the primary models to avoid post-treatment bias, as they may be consequences of TB diagnosis. However, they were included in sensitivity analyses to assess whether their exclusion changed the observed relationships. Similarly, baseline (Wave 1) mental health scores were not included in the main specification, to preserve a direct assessment of baseline associations, but were introduced in sensitivity checks.

## Statistical analysis

All analyses were performed using Stata V.18.0 (StataCorp, College Station, Texas, USA). The analysis sample comprised 4876 participants, including 173 recently diagnosed and 273 previously diagnosed TB cases. To maintain clear temporal sequencing between exposure and outcome, we excluded participants who received TB diagnoses during follow-up. Wave 1 analyses included all participants with available baseline data, while Wave 2 analyses used a balanced panel of participants with data from both waves. The sample provided sufficient cases in each diagnosis category to examine differences in depressive symptoms. We did not conduct post hoc power calculations, as these can be misleading when effect sizes are unknown a priori.[51]

We compared characteristics across three TB diagnostic categories: never diagnosed, recently diagnosed and previously diagnosed. We tested for unadjusted group differences in both baseline characteristics and depressive symptomatology by diagnosis category (using raw and standardised CES-D scores, and binary indicators for moderate and severe symptoms) at both waves. For continuous and ordinal variables, we used the Kruskal-Wallis test, a non-parametric method suitable for comparing multiple independent groups without assuming normal distribution. For categorical variables, we used Fisher's exact test, which is appropriate for small or imbalanced sample sizes.

Our continuous variables were not normally distributed (confirmed by Shapiro-Wilk test and visual inspection). Therefore, we summarised continuous variables using medians and IQRs, and categorical variables using frequencies and percentages. To visualise the distribution of depressive symptoms, we generated kernel density plots of standardised CES-D scores by TB diagnosis status across waves.

In addition, we used multivariable analysis to assess the association between TB diagnosis status and depressive symptoms, adjusting for the relevant baseline characteristics which are expected to be correlated with both mental health and TB diagnosis, some of which are shared risk factors. We analysed standardised CES-D scores using ordinary least squares regression and binary outcomes (moderate and severe depressive symptoms) using logistic regression. All models adjusted for multiple covariates, with TB diagnosis status as the primary independent variable (using 'never diagnosed' as reference). We report coefficients (β) with 95% CIs for linear models and OR with 95% CI for logistic models, using robust SEs. Only complete cases were included in the multivariable regression models. Multicollinearity was assessed in the ordinary least squares estimates using variance inflation factor (VIF) tests, with generalised VIF (GVIF) used for categorical predictors. All models showed VIF/GVIF <5. This study is observational and uses secondary data, and our findings are interpreted as associations rather than causal inferences.

We conducted four categories of sensitivity analyses: (1) specification tests incorporating additional covariates (anthropometric measures which were only available for a portion of the sample, subjective health and healthcare utilisation (in the last 3 months), and alternative specifications of marital status and household size); (2) temporal adjustments including controlling for baseline depressive symptoms, and updating the time-varying controls in Wave 2 analyses; (3) sample composition effects by including those diagnosed with TB in Wave 2, as well as Wave 1 analysis using the balanced panel; and (4) long-term associations using Wave 3 CES-D as the outcome measure. These analyses provided insights into potential mediators of the TB-depressive symptoms relationship while testing the stability of our main findings under different analytical assumptions.

## RESULTS

A total of 5059 adults participated in Wave 1 of the study. Of these, 4939 (97.6%) had complete baseline data including self-reported TB diagnosis status and CES-D scores. The remaining 120 participants (2.4%) were excluded due to missing TB diagnosis status (n=7) or missing CES-D data (n=113). For Wave 1 analyses, we used this full sample of 4939 participants. At Wave 2 follow-up approximately 4 years later, 3900 participants (79.0% of those with complete baseline data) completed the CES-D assessment. Attrition between waves was due to deaths (n=538; 10.9%), refusals (n=253; 5.1%), participants who could not be located (n=28; 0.6%) and incomplete data collection (n=220; 4.5%). The analytical sample for Wave 2 analyses comprised 3738 participants, which excluded 176 participants who reported a new TB diagnosis between waves (figure 1). Attrition patterns varied by baseline TB status: mortality was higher among recently diagnosed participants (20.8%) compared with previously diagnosed (14.7%) and never diagnosed participants (11.7%). The sample sizes reported below in regression analyses vary slightly in comparison to figure 1 due to missing covariate data.

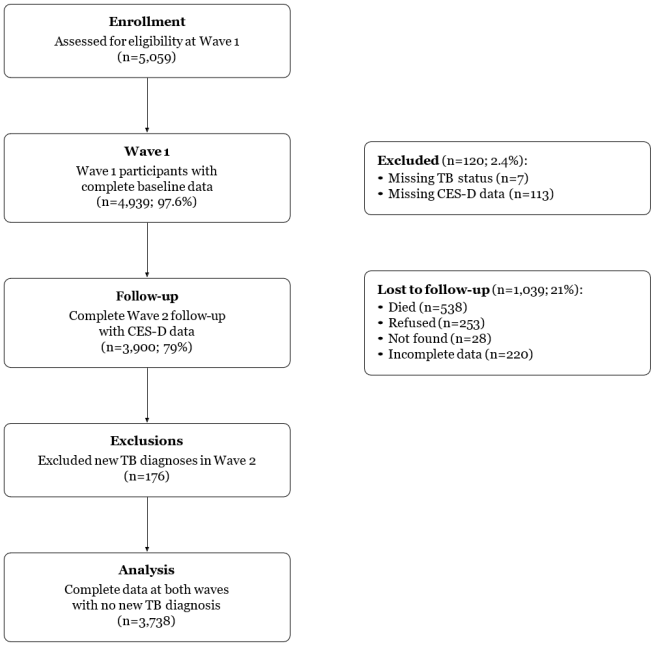



**Figure 1** CONSORT flow diagram of the HAALSI study participants from baseline (Wave 1: November 2014 to November 2015) through Wave 2 (October 2018 to November 2019). The diagram shows participant flow from initial enrolment through Wave 1 and Wave 2 data collection, including exclusions for new TB diagnoses during follow-up. CES-D, Centre for Epidemiologic Studies Depression Scale; CONSORT, Consolidated Standards of Reporting Trials; HAALSI, Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community; TB, tuberculosis.

### Baseline characteristics of participants by tuberculosis diagnosis status

Table 1 presents baseline characteristics of the study population stratified by TB diagnosis status. The sample comprised 4876 individuals, of which 3.5% (173) had been recently diagnosed with TB, 5.6% (273) had a previous diagnosis and 90.9% (4430) reported never having been diagnosed with TB. The median age across the sample was 62.0 years (IQR 52.0–72.0), with no significant differences between the groups (p=0.303). There was a gender difference by TB diagnosis group (p<0.001), with a higher proportion of males among those recently diagnosed (54.3%) and previously diagnosed (60.1%) compared with those never diagnosed (44.9%). Although

**Table 1** Baseline characteristics by TB diagnosis status, HAALSI cohort (2014–2015)

| | Total | No diagnosis | Recently diagnosed | Prior diagnosis | |
|---|---|---|---|---|---|
| | (n=4876) | (n=4430; 90.9%) | (n=173; 3.5%) | (n=273; 5.6%) | P value |
| **Demographic characteristics** | | | | | |
| Age in years | 62.0 (52.0–72.0) | 62.0 (52.0–72.0) | 61.0 (52.0–70.0) | 61.0 (52.0–69.0) | 0.303 |
| Male (%) | 2248 (46.1) | 1990 (44.9) | 94 (54.3) | 164 (60.1) | <0.001 |
| Married (%) | 2487 (51.0) | 2263 (51.1) | 82 (47.4) | 142 (52.0) | 0.597 |
| Born in South Africa (%) | 3404 (69.8) | 3103 (70.1) | 110 (63.6) | 191 (70.0) | 0.192 |
| Household size | 5.0 (3.0–7.0) | 5.0 (3.0–7.0) | 5.0 (3.0–8.0) | 4.0 (3.0–7.0) | 0.259 |
| Ever worked in underground mining (%) | 876 (18.0) | 753 (17.0) | 42 (24.4) | 81 (29.7) | <0.001 |
| **Educational attainment** | | | | | 0.117 |
| No formal education (%) | 2224 (45.8) | 2023 (45.8) | 88 (51.2) | 113 (41.7) | |
| Some primary (1–7 years) (%) | 1655 (34.1) | 1495 (33.9) | 60 (34.9) | 100 (36.9) | |
| 8 or more years of education (%) | 980 (20.2) | 898 (20.3) | 24 (14.0) | 58 (21.4) | |
| **Employment status** | | | | | 0.008 |
| Employed (%) | 776 (16.0) | 716 (16.2) | 18 (10.5) | 42 (15.4) | |
| Not working (not retired) (%) | 2850 (58.6) | 2559 (57.9) | 122 (71.3) | 169 (61.9) | |
| Not working (retired) (%) | 1238 (25.5) | 1145 (25.9) | 31 (18.1) | 62 (22.7) | |
| **Wealth Index quintile** | | | | | 0.009 |
| First (poorest) (%) | 1014 (20.8) | 908 (20.5) | 50 (28.9) | 56 (20.5) | |
| Second (%) | 961 (19.7) | 871 (19.7) | 40 (23.1) | 50 (18.3) | |
| Third (%) | 954 (19.6) | 870 (19.6) | 31 (17.9) | 53 (19.4) | |
| Fourth (%) | 971 (19.9) | 888 (20.0) | 24 (13.9) | 59 (21.6) | |
| Fifth (richest) (%) | 976 (20.0) | 893 (20.2) | 28 (16.2) | 55 (20.1) | |
| **Physical health (measures and behaviours)** | | | | | |
| Ever consumed alcohol (%) | 2170 (44.5) | 1921 (43.4) | 93 (53.8) | 156 (57.4) | <0.001 |
| Ever smoked (%) | 1040 (21.3) | 890 (20.1) | 52 (30.1) | 98 (36.0) | <0.001 |
| Visited a health facility (last 3 months) (%) | 2179 (45.6) | 1920 (44.3) | 102 (59.6) | 157 (57.9) | <0.001 |
| High blood pressure (%) | 2328 (49.5) | 2163 (50.6) | 62 (37.1) | 103 (39.6) | <0.001 |
| Good or very good health (%) | 3319 (68.1) | 3036 (68.6) | 106 (61.3) | 177 (64.8) | 0.063 |
| HIV positive (self-reported) (%) | 588 (12.1) | 451 (10.2) | 64 (37.0) | 73 (26.9) | <0.001 |
| BMI | 26.3 (22.5–31.0) | 26.5 (22.7–31.3) | 24.1 (21.2–29.5) | 24.0 (21.0–27.7) | <0.001 |

Median (IQR: 1st – 3rd). Sample size excludes those diagnosed with TB in Wave 2.
High blood pressure defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg. Continuous and ordinal variables are compared using the Kruskal-Wallis test, and binary and categorical variables using Fisher's exact test. Variables are compared across TB diagnosis status (never diagnosed vs recently vs previously diagnosed). *p<0.1, **p<0.05, ***p<0.01. 95% CIs in parentheses.
BMI, body mass index; HAALSI, Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa; TB, tuberculosis.

marital status did not differ significantly between groups (p=0.597), a slightly lower percentage of individuals recently diagnosed with TB were married (47.4%) compared with 51% in the full sample. Household size showed no statistically significant variation (p=0.259), with a median of five people per dwelling across all groups. Individuals who had recently or previously been diagnosed with TB were more likely to have ever worked in underground mining (24.4% and 29.7%, respectively, p<0.001), compare to those never diagnosed (17%).

Educational attainment was lower among individuals who had received a TB diagnosis. Of those recently diagnosed, 51.2% had no formal education, compared with 41.7% of those previously diagnosed and 45.8% of those never diagnosed; however, this difference was not significant (p=0.117). Employment status varied significantly (p=0.008), with a higher proportion of those recently diagnosed (71.3%) and previously diagnosed (61.9%) not working (excluding retirement) compared with those never diagnosed (57.9%). Wealth distribution also showed significant differences (p=0.028), with those recently diagnosed more likely to fall within the lowest wealth quintile (28.9%) compared with the never diagnosed (20.5%) and previously diagnosed (20.5%) groups.

Several significant health-related measures were associated with TB diagnosis status. Body mass index (BMI)

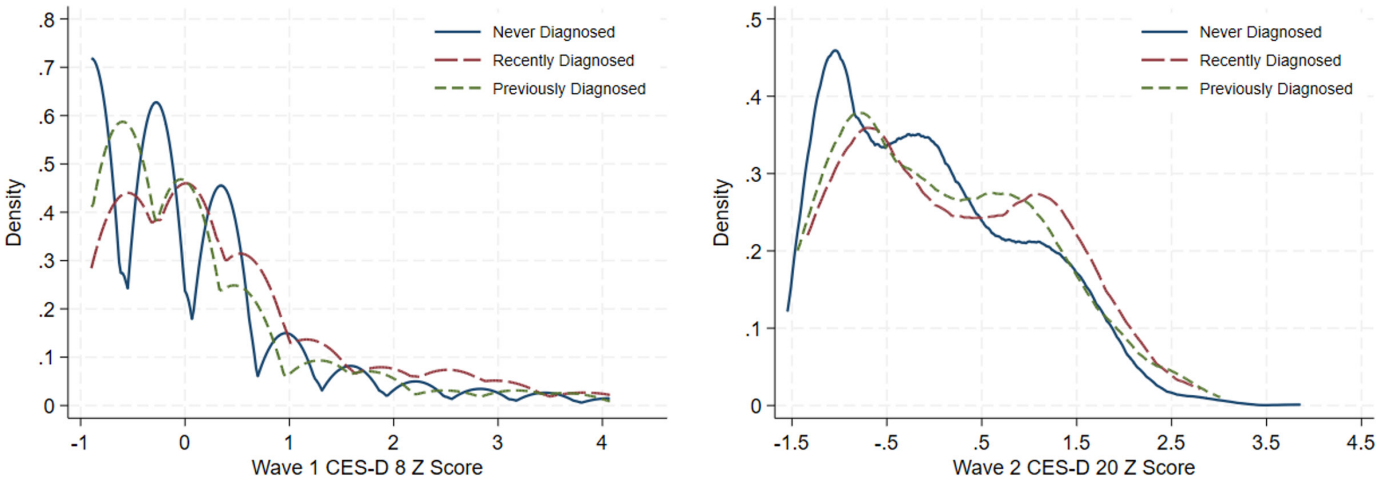



**Figure 2** Kernel density estimates of standardised CES-D scores by TB diagnosis status. CES-D, Centre for Epidemiologic Studies Depression Scale; TB, tuberculosis.

was significantly lower (p<0.001) among those recently diagnosed (median 23.7, IQR 20.9–27.3) and previously diagnosed (median 23.2, IQR 20.4–26.7) compared with those never diagnosed (median 26.5, IQR 23.1–30.7). HIV prevalence was significantly higher (p<0.001) among those recently diagnosed (37.0%) and previously diagnosed (26.9%) compared with those never diagnosed (10.2%). Smoking rates were higher (p<0.001) among those recently diagnosed (30.1%) and previously diagnosed (36.0%) compared with those never diagnosed (20.1%). Alcohol consumption was more prevalent (p<0.001) among those recently diagnosed (53.8%) and previously diagnosed (57.4%) compared with those never diagnosed (43.4%). Healthcare utilisation was more frequent (p<0.001) among those recently diagnosed (59.6%) and previously diagnosed (57.9%) compared with those never diagnosed (44.3%). Good or very good self-reported health was less common among those recently diagnosed (61.3%) compared with those previously diagnosed (64.8%) and never diagnosed (68.6%) (p=0.063).

In figure 2 we show kernel density estimates of standardised CES-D scores, stratified by TB diagnosis status, at both Wave 1 and Wave 2. A smoother distribution can be seen in Wave 2, as the range of raw CES-D scores in Wave 1 and Wave 2 is 0–8 and 0–60, respectively. Those with a recent TB diagnosis at Wave 1 have a higher density of depressive symptoms compared with those never diagnosed or previously diagnosed. By Wave 2, while the distribution of CES-D scores for the recently diagnosed group showed some attenuation, it remained elevated relative to the other groups.

In table 2 we compare and test for significant differences in depressive symptoms, both in raw scores and binary cut-offs indicating moderate or severe depressive symptoms, stratified by TB diagnosis status.

**Table 2** Depressive symptoms by TB diagnosis status, HAALSI cohort (2014–2015)

| Wave | Mental health measure | Total | No diagnosis | Recently diagnosed | Prior diagnosis | P value |
|---|---|---|---|---|---|---|
| **Wave 1** | | **n=4767** | **n=4335** | **n=168** | **n=264** | |
| | CES-D 8 score (0–8) | 1.0 (0.0 to 2.0) | 1.0 (0.0 to 2.0) | 2.0 (1.0 to 3.0) | 1.0 (0.0 to 2.0) | 0.001 |
| | Wave 1 CES-D z-score | −0.3 (−0.9 to 0.3) | −0.3 (−0.9 to 0.3) | 0.3 (−0.3 to 1.0) | −0.3 (−0.9 to 0.3) | 0.001 |
| | Moderate depressive symptoms (%) | 1806 (38.0) | 1628 (37.7) | 84 (50.3) | 94 (35.6) | 0.003 |
| | Severe depressive symptoms (%) | 803 (16.9) | 716 (16.6) | 44 (26.3) | 43 (16.3) | 0.006 |
| **Wave 2** | | **n=3738** | **n=3415** | **n=121** | **n=202** | |
| | CES-D 20 score (0–60) | 13.0 (6.0 to 22.0) | 13.0 (6.0 to 21.0) | 14.0 (7.0 to 24.0) | 14.0 (7.0 to 23.0) | 0.072 |
| | Wave 2 CES-D z-score | −0.2 (−0.9 to 0.8) | −0.2 (−0.9 to 0.7) | −0.1 (−0.8 to 1.0) | −0.1 (−0.8 to 0.9) | 0.072 |
| | Moderate depressive symptoms (%) | 1541 (41.2) | 1389 (40.7) | 57 (47.1) | 95 (47.0) | 0.084 |
| | Severe depressive symptoms (%) | 1111 (29.7) | 989 (29.0) | 50 (41.3) | 72 (35.6) | 0.003 |

Moderate depressive symptoms were defined as CES-D 8 score ≥2 for Wave 1 and CES-D 20 score ≥16 for Wave 2, while severe depressive symptoms were defined as CES-D 8 score ≥3 for Wave 1 and CES-D 20 score ≥20 for Wave 2. Variables are tested for significant differences across TB diagnosis status (never diagnosed vs recently vs previously diagnosed). *p<0.1, **p<0.05, ***p<0.01. Median and IQR values are reported for continuous variables, with counts and percentages for binary indicators. Per wave, sample sizes exclude those missing CES-D scores and TB diagnostic data, and those diagnosed with TB in Wave 2.
CES-D, Centre for Epidemiologic Studies Depression Scale; HAALSI, Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa ; TB, tuberculosis.

At baseline (Wave 1), depressive symptoms showed significant variation across TB diagnosis groups. The median CES-D 8 score was highest among participants recently diagnosed with TB (2.0, IQR 1.0–3.0), compared with those previously diagnosed (1.0, IQR 0.0–2.0) and those never diagnosed (1.0, IQR 0.0–2.0) (p=0.001). The proportion of participants with moderate depressive symptoms (CES-D 8 score ≥2) was higher among recently diagnosed participants (50.3%) compared with previously diagnosed (35.6%) and never diagnosed participants (37.7%) (p=0.003). Similarly, severe depressive symptoms (CES-D 8 score ≥3) were more common in the recently diagnosed group (26.3%) compared with previously diagnosed (16.3%) and never diagnosed groups (16.6%) (p=0.006).

At follow-up (Wave 2 of table 2), using the CES-D 20 scale, differences in depressive symptoms persisted. Median CES-D 20 scores were higher in both recently diagnosed (14.0, IQR 7.0–24.0) and previously diagnosed groups (14.0, IQR 7.0–23.0) compared with the never diagnosed group (13.0, IQR 6.0–21.0), though this difference did not reach statistical significance (p=0.072). Moderate depressive symptoms (CES-D 20 score ≥16) were present in similar proportions among recently diagnosed (47.1%) and previously diagnosed participants (47.0%), both higher than in never diagnosed participants (40.7%) (p=0.084). The proportion with severe depressive symptoms (CES-D 20 score ≥20) remained significantly higher in recently diagnosed participants (41.3%) compared with previously diagnosed (35.6%) and never diagnosed participants (29.0%) (p=0.003).

## Multivariable regression analysis

Table 3 presents results from regression analyses assessing the association between TB diagnosis status and depressive symptoms across Waves 1 and 2. Four models were reported for each wave: unadjusted linear regression examining standardised CES-D scores (Model 1), adjusted linear regression controlling for demographic, socio-economic and health covariates (Model 2), adjusted logistic regression estimating the odds of moderate depressive symptoms (Model 3) and adjusted logistic regression estimating the odds of severe depressive symptoms (Model 4).

At Wave 1, individuals recently diagnosed with TB exhibited significantly higher standardised CES-D 8 scores than those never diagnosed in the unadjusted model (β=0.52, 95% CI 0.24 to 0.81, p<0.001). This association remained statistically significant in the adjusted model (β=0.45, 95% CI 0.18 to 0.73, p<0.001). Previously diagnosed individuals also showed elevated CES-D 8 scores (unadjusted: β=0.23, 95% CI 0.04 to 0.41, p<0.05; adjusted: β=0.24, 95% CI 0.05 to 0.42, p<0.05).

In adjusted logistic regression models, recently diagnosed individuals had significantly higher odds of both moderate (OR=1.69, 95% CI 1.17 to 2.44, p<0.001) and severe depressive symptoms (OR=1.64, 95% CI 1.18 to 2.28, p<0.05). Previously diagnosed individuals had significantly higher odds of moderate depressive symptoms (OR=1.50, 95% CI 1.16 to 1.95, p<0.001).

At Wave 2, the association between recent TB diagnosis and depressive symptoms persisted but attenuated in adjusted models. Recently diagnosed individuals had higher standardised CES-D 20 scores in unadjusted analyses (β=0.19, 95% CI 0.00 to 0.38, p<0.05), but this association was no longer statistically significant after adjustment (β=0.14, 95% CI −0.05 to 0.33). The odds of moderate depressive symptoms remained significantly elevated for recently diagnosed individuals (OR=1.52, 95% CI 1.04 to 2.22, p<0.05), while the odds of severe depressive symptoms were not statistically significant. Previously diagnosed individuals showed a trend towards higher odds of moderate depressive symptoms (OR=1.31, 95% CI 0.97 to 1.79, p<0.1).

## Sensitivity analyses

In table 4, we tested the robustness of the associations between TB diagnosis and depressive symptoms through several approaches:

**Table 3** Multivariable regression analysis: baseline TB status and mental health outcomes

| Dependent variable | | CES-D score | CES-D score | Moderate depression | Severe depression |
|---|---|---|---|---|---|
| **Wave** | **Diagnosis category** | **Model 1 Coeff (95% CI)** | **Model 2 Coeff (95% CI)** | **Model 3 OR (95% CI)** | **Model 4 OR (95% CI)** |
| Wave 1 (N=4706) | Recently diagnosed | 0.32 (0.15 to 0.50)*** | 0.31 (0.14 to 0.49)*** | 1.70 (1.22 to 2.36)*** | 1.77 (1.23 to 2.55)*** |
| | Previously diagnosed | 0.01 (–0.12 to 0.13) | 0.03 (–0.10 to 0.16) | 0.96 (0.73 to 1.26) | 1.03 (0.73 to 1.45) |
| Wave 2 (N=3702) | Recently diagnosed | 0.19 (0.00 to 0.38)** | 0.14 (–0.05 to 0.33) | 1.17 (0.81 to 1.70) | 1.52 (1.05 to 2.22)** |
| | Previously diagnosed | 0.11 (–0.04 to 0.25) | 0.09 (–0.05 to 0.24) | 1.27 (0.95 to 1.70) | 1.32 (0.97 to 1.79)* |

Models 1–2 show coefficients using standardised CES-D scores as the dependent variable (CES-D 8 in Wave 1, CES-D 20 in Wave 2). Models 3–4 present ORs using binary indicators for moderate and severe depression with established cut-offs. Models 2–4 adjust for demographic, socio-economic and physical health characteristics. Adjusted model sample sizes are reported (Model 2). *p<0.1, **p<0.05, ***p<0.01. 95% CIs in parentheses.
CES-D, Centre for Epidemiologic Studies Depression Scale; HAALSI, Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa; TB, tuberculosis.

Table 4 Sensitivity analysis: multivariable regression analysis for baseline TB status and mental health outcomes

| Wave | Diagnosis category | Model 1 Coeff (95% CI) | Model 2 Coeff (95% CI) | Model 3 OR (95% CI) | Model 4 OR (95% CI) |
|---|---|---|---|---|---|
| **Original** | | | | | |
| Wave 1 (N=4706) | Recently diagnosed | 0.32 (0.15 to 0.50)*** | 0.31 (0.14 to 0.49)*** | 1.70 (1.22 to 2.36)*** | 1.77 (1.23 to 2.55)*** |
| | Previously Diagnosed | 0.01 (–0.12 to 0.13) | 0.03 (–0.10 to 0.16) | 0.96 (0.73 to 1.26) | 1.03 (0.73 to 1.45) |
| Wave 2 (N=3702) | Recently diagnosed | 0.19 (0.00 to 0.38)** | 0.14 (–0.05 to 0.33) | 1.17 (0.81 to 1.70) | 1.52 (1.05 to 2.22)** |
| | Previously diagnosed | 0.11 (–0.04 to 0.25) | 0.09 (–0.05 to 0.24) | 1.27 (0.95 to 1.70) | 1.32 (0.97 to 1.79)* |
| **1. Specification robustness tests** | | | | | |
| 1A. Including subjective health in covariates | | | | | |
| Wave 1 (N=4704) recently diagnosed | | 0.32 (0.15 to 0.50)*** | 0.28 (0.11 to 0.45)*** | 1.64 (1.18 to 2.28)*** | 1.69 (1.17 to 2.44)*** |
| Previously diagnosed | | 0.01 (–0.12 to 0.13) | 0.02 (–0.11 to 0.14) | 0.94 (0.71 to 1.23) | 0.99 (0.69 to 1.40) |
| Wave 2 (N=3700) recently diagnosed | | 0.19 (0.00 to 0.38)** | 0.14 (–0.05 to 0.33) | 1.17 (0.81 to 1.70) | 1.52 (1.04 to 2.22)** |
| Previously diagnosed | | 0.11 (–0.04 to 0.25) | 0.10 (–0.05 to 0.24) | 1.27 (0.95 to 1.70) | 1.31 (0.97 to 1.79)* |
| 1B. Including healthcare utilisation in covariates | | | | | |
| Wave 1 (N=4611) recently diagnosed | | 0.32 (0.15 to 0.50)*** | 0.28 (0.11 to 0.46)*** | 1.61 (1.16 to 2.23)*** | 1.62 (1.12 to 2.34)** |
| Previously diagnosed | | 0.01 (–0.12 to 0.13) | 0.02 (–0.11 to 0.15) | 0.95 (0.72 to 1.25) | 1.00 (0.70 to 1.42) |
| Wave 2 (N=3625) recently diagnosed | | 0.19 (0.00 to 0.38)** | 0.14 (–0.05 to 0.34) | 1.20 (0.82 to 1.75) | 1.54 (1.05 to 2.25)** |
| Previously diagnosed | | 0.11 (–0.04 to 0.25) | 0.09 (–0.06 to 0.23) | 1.25 (0.93 to 1.68) | 1.29 (0.95 to 1.75) |
| **2. Temporal relationships and controls** | | | | | |
| 2A. Including Wave 1 mental health as a covariate | | | | | |
| Wave 2 (N=3680) recently diagnosed | | 0.19 (0.00 to 0.38)** | 0.13 (–0.06 to 0.32) | 1.16 (0.80 to 1.70) | 1.53 (1.04 to 2.23)** |
| Previously diagnosed | | 0.11 (–0.04 to 0.25) | 0.10 (–0.05 to 0.24) | 1.27 (0.95 to 1.70) | 1.32 (0.97 to 1.79)* |
| 2B. Updated time-varying covariates | | | | | |
| Wave 2 (N=3643) recently diagnosed | | 0.19 (0.00 to 0.38)** | 0.19 (0.00 to 0.38)** | 1.31 (0.90 to 1.91) | 1.74 (1.19 to 2.55)*** |
| Previously diagnosed | | 0.11 (–0.04 to 0.25) | 0.13 (–0.02 to 0.27)* | 1.33 (0.99 to 1.79)* | 1.40 (1.03 to 1.90)** |
| **3. Sample selection and composition** | | | | | |
| 3A. Including those diagnosed with TB in Wave 2 | | | | | |
| Wave 1 (N=4874) recently diagnosed | | 0.32 (0.15 to 0.50)*** | 0.32 (0.14 to 0.49)*** | 1.70 (1.23 to 2.36)*** | 1.77 (1.23 to 2.55)*** |
| Previously diagnosed | | 0.01 (–0.12 to 0.13) | 0.03 (–0.09 to 0.16) | 0.96 (0.73 to 1.26) | 1.02 (0.72 to 1.45) |
| Wave 2 (N=3861) recently diagnosed | | 0.18 (–0.01 to 0.37)* | 0.12 (–0.07 to 0.31) | 1.13 (0.78 to 1.64) | 1.47 (1.01 to 2.13)** |
| Previously diagnosed | | 0.09 (–0.05 to 0.24) | 0.08 (–0.07 to 0.23) | 1.23 (0.92 to 1.64) | 1.27 (0.94 to 1.73) |
| 3B. Balanced panel analysis | | | | | |
| Wave 1 (N=3680) recently diagnosed | | 0.33 (0.12 to 0.53)*** | 0.32 (0.11 to 0.52)*** | 2.00 (1.37 to 2.94)*** | 2.06 (1.34 to 3.16)*** |
| Previously diagnosed | | 0.01 (–0.14 to 0.15) | 0.04 (–0.11 to 0.18) | 0.94 (0.69 to 1.29) | 1.13 (0.76 to 1.67) |
| **4. Long-term effects** | | | | | |
| 4A. Wave 3 CES-D outcomes | | | | | |
| Wave 3 (N=3160) recently diagnosed | | –0.10 (–0.29 to 0.09) | –0.10 (–0.30 to 0.10) | 0.84 (0.55 to 1.27) | 0.91 (0.58 to 1.42) |
| Previously diagnosed | | –0.03 (–0.18 to 0.13) | –0.02 (–0.18 to 0.13) | 0.94 (0.68 to 1.29) | 1.12 (0.80 to 1.55) |

Sensitivity analyses replicating table 3. Models 1–2 show coefficients using standardised CES-D scores as the dependent variable. Models 3–4 present ORs for moderate and severe depressive symptoms indicators. All models use TB diagnosis status as the key independent variable. Models 2–4 adjust for demographic, socio-economic and physical health characteristics. *p<0.1, **p<0.05, ***p<0.01. 95% CIs in parentheses.
CES-D, Centre for Epidemiologic Studies Depression Scale; TB, tuberculosis.

1. Model specification: Adding potential mediators as controls—baseline subjective health (Panel 1A, table 4) and healthcare utilisation in the past 3 months (Panel 1B, table 4)—led to slightly smaller sample sizes and modest decreases in coefficients and ORs while maintaining significance levels. In additional tests not reported here, results remained robust when including BMI (available for a subset) and alternative specifications of demographic variables (marital status, household size). Additionally, mixed-effects models accounting for the repeated-measures structure of the data yielded consistent results, with minimal within-person correlation across waves (intraclass correlation <0.05) confirming the robustness of our wave-specific analytical approach (supplementary material S.2, online supplemental table S1).

2. Potential temporal confounding: Including Wave 1 CES-D scores as baseline controls in Wave 2 estimates (Panel 2A, table 4) yielded results quantitatively similar to our primary analyses. To account for possible correlations between baseline TB status and Wave 2 characteristics, we controlled for Wave 2 measurements of socio-demographic and health variables (Panel 2B, table 4: age, marital status, household size, mining employment, wealth, employment status, HIV status, alcohol use and smoking). These estimates showed stronger associations: the relationship between recent TB diagnosis and standardised CES-D scores increased and became statistically significant, while both recent and previous diagnosis groups showed significantly higher odds of severe depressive symptoms.
3. Sample composition: Relaxing our exclusion of Wave 2 TB diagnoses (Panel 3A, table 4) increased sample sizes (Wave 1: 4706–4874; Wave 2: 3702–3861) without substantive changes to results. Analysis of a balanced panel (participants with CES-D data in both waves, Panel 3B, table 4) reduced the Wave 1 sample to 3680. In this balanced sample, associations between baseline TB diagnosis and Wave 1 standardised CES-D scores remained positive and significant, with notably larger ORs for severe depressive symptoms (OR=2.06, 95% CI 1.34 to 3.16).
4. Long-term associations: We examined associations with Wave 3 depressive symptoms (standardised CES-D 20 scores and binary indicators) collected during the COVID-19 pandemic in 2021 (Panel 4A, table 4). No significant relationships were found between baseline TB diagnosis status and Wave 3 depressive symptoms.

## DISCUSSION

This study provides novel evidence on the relationship between TB and mental health in older adults using the HAALSI cohort. The estimated TB prevalence in this rural South African population was 10%, based on self-reported diagnoses, suggesting a higher disease burden than reported in national estimates.[4] Participants with TB diagnoses exhibited well-documented risk factors:[3] they were more likely to be male, have a history of underground mining, report lower socioeconomic status, engage in alcohol and tobacco use and have lower BMI. Our key finding was a strong temporal association between TB diagnosis and depressive symptoms: individuals with recent diagnoses had significantly higher standardised depression scores at baseline and increased odds of both moderate and severe depressive symptoms, compared with those with past diagnoses or no TB history. The risk of severe depressive symptoms persisted 4 years later, potentially indicating a psychological burden from diagnosis that may extend beyond the immediate treatment period. These associations remained robust after adjusting for potential mediators of the relationship which may have been affected by prior TB diagnosis, and known risk factors of both conditions. While TB-diagnosed individuals showed higher healthcare utilisation, suggesting potential treatment-seeking behaviour differences, the relationship between diagnosis status and mental health persisted after accounting for these differences. The findings also remained stable under alternative model specifications and differences in sample composition and covariates.

A key strength of this study is its use of a large, longitudinal dataset, with rich demographic, health and socioeconomic data.[24] The HAALSI study provided a valuable opportunity to investigate the depression-TB association in a cohort study which reported high rates of follow-up, with survey interviews taking place in the home. The repeated nature of the data allowed us to add evidence to the less developed research base on individuals diagnosed with TB in the longer term,[52] as well as, importantly, adding the needed benefit of a larger sample size and greater statistical power in analysis.[52–54] While the HAALSI cohort has been extensively studied to document the burden of depressive symptoms among older adults and their association with adverse health outcomes,[28–31 55–57] TB-specific mental health research within this cohort remains limited. Using validated screening tools,[36 48] our analysis leverages detailed diagnosis timing data, as well as two survey waves to examine the immediate psychological burden associated with TB diagnosis, and to assess whether these associations persist over time. Our three-group approach, combined with longitudinal follow-up, provides a more nuanced understanding of the temporal relationship between TB diagnosis and mental health than traditional binary (TB/no TB) comparisons. We also test for the presence of any significant association between baseline TB diagnosis and depressive symptoms in Wave 3 (data collected in 2021, during the COVID-19 pandemic more than 5 years post baseline). The lack of any significant association provides reassurance that the associations observed at baseline and 4-year follow-up reflect a genuine TB-specific psychological burden rather than unobserved confounding factors, as any such factors would likely persist across waves. Another potential confounder, that of psychiatric side effects from TB medications contributing to depressive symptoms in recently diagnosed patients, this mechanism cannot explain the persistent elevation in severe depressive symptoms we observed 4 years after diagnosis, when patients are less likely to still be receiving treatment.[2]

A number of limitations were present in this analysis. While the cohort size is substantial, the relatively low prevalence of TB (approximately 10%) limits statistical power for detailed subgroup analyses or investigation of interaction effects, particularly when stratifying by diagnosis timing. The unique composition of the HAALSI cohort, with approximately 30% of participants born outside South Africa, may limit generalisability to the broader South African population, although we found no significant differences in diagnosis status between South African-born and foreign-born participants. Differences in CES-D scale versions across waves may introduce measurement

error,[41] particularly given the range differences in raw CES-D scores in each wave.[28] To this end, CES-D scores were standardised, and we refrain from cross-wave analysis which differentiates the two scores, even when standardised. We observed attrition across waves, and thus the potential for sample selection bias in our results. However, this bias was more likely to be an underestimate rather than an overestimate of the associations: mortality was substantially higher among recently diagnosed patients with TB, suggesting that the Wave 2 results likely underestimated the true relationship between TB and depressive symptoms, as those who died may have had more severe disease and potentially worse mental health outcomes. In addition, the associations observed when using a balanced panel analysis also suggested the main estimates may be conservative in Wave 1. This differential attrition strengthens rather than undermines our finding of persistent elevated risk at follow-up, as it suggests this relationship remains detectable even after the likely loss of the most severely affected individuals. Our reliance on self-reported diagnosis status is a limitation, though one shared by many large-scale epidemiological studies[7 15 58] that have successfully used self-reported TB as an informative measure.[5 10 11] In regions with a high HIV-TB burden like South Africa, validation studies have shown that self-reported TB prevalence estimates tend to underestimate rather than overestimate true TB prevalence.[15 59] The high prevalence of HIV co-infection in our TB-diagnosed participants aligns with expectations from national estimates,[1 4] suggesting our self-reported data captures known epidemiological patterns. Given that our study found significant associations between TB diagnosis and depressive symptoms despite likely under-reporting, our estimates may be conservative—the true relationship could be stronger if all TB cases were captured. While clinical verification would be ideal, the likely direction of any measurement bias (toward underestimation) strengthens rather than undermines our key findings.

Despite being neglected in TB research,[60] mental health disorders are observed as the most common disability among individuals with TB,[60] with rates of prevalence similar to those with other chronic diseases such as HIV, diabetes mellitus and cancer.[60] Depression is often under-diagnosed, especially in a context of low treatment availability in low-income areas, or its symptoms are conflated with those of TB.[54] Those with depressive symptoms during TB treatment follow heterogeneous trajectories, with symptom severity associated with higher rates of mortality and loss to follow-up.[52 54] Those diagnosed with depression are themselves at higher risk for TB (and other chronic conditions), with depressive symptom severity associated with higher risk.[53] Our findings align with and extend prior research showing high prevalence of depressive symptoms among patients diagnosed with TB in resource-limited settings.[9 10] These results align with emerging evidence that the relationship between TB and depression is both persistent and bidirectional,[54] with the topic of bidirectionality particularly under-researched.[53]

Previous research within the HAALSI cohort has demonstrated that depressive symptoms are highly prevalent and persistent among individuals with chronic diseases and socio-economic stressors,[29] with specific patterns of vulnerability by gender.[28] These patterns are reflected in our study, where the socio-economic impact of TB—including income loss[61] and reduced work capacity resulting from persistent physical disability[60]—may create conditions for chronic psychological distress long after bacteriological cure, particularly in resource-constrained settings like rural South Africa.[5–7] The persistent relationship between TB diagnosis and depressive symptoms we observed is particularly concerning, as depression has been linked to treatment default and reduced medication adherence in patients with TB.[13 14] The persistence of depressive symptoms 4 years post-diagnosis observed in our cohort may reflect multiple underlying mechanisms. Beyond the psychosocial impact of TB diagnosis and treatment, the relationship is influenced by multiple shared risk factors including poverty,[7] stigma[9] and comorbidities such as HIV, diabetes and malnutrition.[3 12 15–19 54 60] The existence of these common risk factors supports conceptualising TB-depression as a syndemic, where poverty, stigma and biological factors interact synergistically to worsen both conditions.[54 60]

When contextualising our findings within other chronic infectious diseases in South Africa, the relationship between TB and depression is persistent, with implications for both conditions. The high TB-HIV co-infection rate observed in our sample (37% among recently diagnosed patients with TB) is lower than national estimates which have reported rates ranging from approximately 59% to 73% in South Africa.[3 4] This comorbidity complicates both mental health and TB treatment approaches. While HIV is associated with increased TB susceptibility[2] and more complex treatment regimens,[1 3] our findings suggest that TB diagnosis itself carries significant psychological burden regardless of HIV status. This distinct pattern has implications for when and how mental health interventions should be deployed within TB care programmes. The bidirectional relationship between TB and depression[54]—where each condition may worsen outcomes for the other—highlights the potential public health impact of integrated screening and treatment approaches,[13] particularly in the context of South Africa's high disease burden and resource constraints.[1–4]

Our finding that severe depressive symptoms are present and persist 4 years post-diagnosis has important clinical and public health implications for older adults. That recently diagnosed patients with TB have significantly higher odds of severe depressive symptoms at, or close to, the time of TB diagnosis suggests that mental health integration into TB care should be prioritised during early treatment phases, and such intervention is likely to reduce loss to follow-up, particularly among those experiencing growing trajectories in depressive symptoms.[52] Both mental health treatment[20–22] and socio-economic interventions[23] show promise in improving

TB outcomes, with particularly strong evidence for the effectiveness of integrated approaches. The WHO and South African TB treatment guidelines already emphasise patient-centred care; expanding this framework to include routine mental health screening and basic psychological support could be achieved with minimal additional resources.[1 3] This is particularly important in the South African context, where TB disproportionately affects those of lower socio-economic status[5–7] and older adults.[4 6] Ensuring access to psychological support during early TB treatment could improve adherence, quality of life and overall health outcomes,[54 61] particularly among subgroups such as those who report smoking and alcohol use behaviours,[52 54] and those with drug-resistant TB.[60] Additionally, integrating TB care with other support programmes that address both mental health and TB risk factors is crucial, including nutritional support[3 19] and financial assistance to help offset the economic burden of treatment.[61] Such comprehensive support systems could help break the cycle between poverty, poor mental health and TB that affects many communities.[9 54]

Future research priorities should focus on several key areas: first, investigating the mechanisms linking TB and depression, particularly in the context of HIV co-infection, which was highly prevalent in our sample; second, examining how social determinants, stigma and biological factors interact to influence both conditions; third, conducting intervention studies to assess the effectiveness of integrated mental health services in TB care[54] and finally, examining the differential health trajectories of people diagnosed with TB as a function of their initial mental health scores.[52 54] Particular attention should be paid to identifying high-risk patients early and determining the optimal timing, duration and intensity of psychological support throughout the TB treatment journey. Understanding these aspects could significantly improve both treatment adherence[2] and long-term mental health outcomes in this vulnerable population. This research, along with other studies using HAALSI data, demonstrates the value of comprehensive datasets that capture detailed health, socio-economic and demographic information. Expanding this research to nationally representative populations could inform the development of integrated care models that effectively address both the mental health burden and socio-economic challenges of TB, particularly for vulnerable older adults in resource-limited settings.

**Acknowledgements** The authors are grateful to the HAALSI study participants and the Agincourt community for their long-term commitment to the research programme. We also acknowledge the contributions of the HAALSI study teams who made this work possible. The authors thank Murray Leibbrandt for thoughtful discussion and development of the statistical framework, and seminar participants at the UCT School of Economics for valuable feedback.

**Contributors** KE conceived the study, designed the methodology, curated and analysed the data, interpreted the results and wrote the original draft. RW provided expertise on the HAALSI cohort and Agincourt HDSS context, contributed to study design and interpretation, guided longitudinal analysis and critically reviewed the manuscript. JAG contributed to the conceptual framework, provided medical research expertise, critically reviewed the manuscript and contributed to interpretation of results. All authors read and approved the final manuscript. KE is responsible for the overall content as guarantor. Artificial intelligence tools were used for proofreading and cross-checking of reporting results during manuscript preparation. Claude 4.5 Sonnet and ChatGPT 5 were used.

**Funding** This study was supported by funding from the National Institute on Aging (NIA) of the National Institutes of Health (NIH) for the Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa (HAALSI) Waves 4 and 5 (grant numbers 1P01AG041710-01A1 and 5P01AG041710-05). The HAALSI and HAALSI-HARPs surveys were funded by the NIA of the NIH (grant numbers P01 AG041710 and R01 AG051144).

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** Ethical approval was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical) (approval number: M141159), the Harvard T.H. Chan School of Public Health (approval number: C13-1608-02) and the Mpumalanga Provincial Research and Ethics Committee. Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available in a public, open access repository. All study data from the Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa (HAALSI) are publicly available through the following repositories: the Harvard Center for Population and Development Studies (https://haalsi.org/data), the Inter-university Consortium for Political and Social Research (ICPSR) at the University of Michigan (https://www.icpsr.umich.edu) and the INDEPTH Data Repository (https://indepth-ishare.org/index.php/catalog/113). These datasets are accessible immediately and indefinitely following publication, with no additional permissions required; users must cite the original data source.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: https://creativecommons.org/licenses/by-nc/4.0/.

**ORCID iDs**
Katherine Eyal https://orcid.org/0000-0003-1974-5195
Ryan Wagner https://orcid.org/0000-0003-2741-3676

## REFERENCES

1 World Health Organization. Global tuberculosis report. Geneva World Health Organization; 2022.
2 Agyeman AA, Ofori-Asenso R. Tuberculosis—an overview. *J Public Health Emerg* 2017;1:7.
3 World Health Organization. Global tuberculosis report 2024. World Health Organization; 2024.
4 Akokuwebe ME, Osuafor GN, Idemudia ES. Prevalence and association of HIV and tuberculosis status in older adults in South Africa: an urgent need to escalate the scientific and political attention to aging and health. *Front Public Health* 2024;12:1245553.
5 Alene KA, Clements ACA, McBryde ES, *et al*. Mental health disorders, social stressors, and health-related quality of life in patients with multidrug-resistant tuberculosis: A systematic review and meta-analysis. *J Infect* 2018;77:357–67.
6 South African Medical Research Council and Human Sciences Research Council. The first national TB prevalence survey, South Africa 2018: short report. Technical report. Pretoria South African Medical Research Council; 2018.

7 Cuadros DF, Tomita A, Vandormael A, *et al*. Spatial structure of depression in South Africa: A longitudinal panel survey of a nationally representative sample of households. *Sci Rep* 2019;9:979.
8 Amreen NR. Psychiatric Co-Morbidity and its Associated Risk Factors among Tuberculosis Patients. *PJMHS* 2022;16:67–9.
9 Khan MM, Jafari MA, Rahman N, *et al*. Depression amongst Patients with Pulmonary Tuberculosis: A Cross-Sectional Study. *Pakistan J Chest Med* 2021;27:170–6.
10 Duko B, Bedaso A, Ayano G. The prevalence of depression among patients with tuberculosis: a systematic review and meta-analysis. *Ann Gen Psychiatry* 2020;19:30.
11 Galea JT, Chu AL, Sweetland AC, *et al*. Latent TB and depressive symptoms in household contacts of persons with active TB. *Int J Tuberc Lung Dis* 2023;27:682–7.
12 Wagnew F, Gray D, Tsheten T, *et al*. Effectiveness of nutritional support to improve treatment adherence in patients with tuberculosis: a systematic review. *Nutr Rev* 2024;82:1216–25.
13 Ugarte-Gil C, Ruiz P, Zamudio C, *et al*. Association of Major Depressive Episode with Negative Outcomes of Tuberculosis Treatment. *PLoS ONE* 2013;8:e69514.
14 Pasha A, Siddiqui H, Ali S, *et al*. Impact of integrating mental health services within existing tuberculosis treatment facilities. *Med Access Point Care* 2021;5:23992026211011314.
15 Tomita A, Smith CM, Lessells RJ, *et al*. Space-time clustering of recently-diagnosed tuberculosis and impact of ART scale-up: Evidence from an HIV hyper-endemic rural South African population. *Sci Rep* 2019;9:10724.
16 Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS Med* 2008;5:e152.
17 Baker MA, Harries AD, Jeon CY, *et al*. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. *BMC Med* 2011;9:81.
18 Shaji B, Arun Thomas ET, Sasidharan PK. Tuberculosis control in India: Refocus on nutrition. *Indian J Tuberc* 2019;66:26–9.
19 Naidoo I, Charlton KE, Esterhuizen TM, *et al*. High risk of malnutrition associated with depressive symptoms in older South Africans living in KwaZulu-Natal, South Africa: a cross-sectional survey. *J Health Popul Nutr* 2015;33:19.
20 Farooq S, Tunmore J, Comber R. Pharmacological or non-pharmacological interventions for treatment of common mental disorders associated with Tuberculosis: A systematic review. *Chron Respir Dis* 2021;18:14799731211003937.
21 van Hoorn R, Jaramillo E, Collins D, *et al*. The Effects of Psycho-Emotional and Socio-Economic Support for Tuberculosis Patients on Treatment Adherence and Treatment Outcomes - A Systematic Review and Meta-Analysis. *PLoS One* 2016;11:e0154095.
22 Agbeko CK, Mallah MA, He B, *et al*. Mental Health Status and Its Impact on TB Treatment and Its Outcomes: A Scoping Literature Review. *Front Public Health* 2022;10:855515.
23 Klein K, Bernachea MP, Irribarren S, *et al*. Evaluation of a social protection policy on tuberculosis treatment outcomes: A prospective cohort study. *PLoS Med* 2019;16:e1002788.
24 Gómez-Olivé FX, Montana L, Wagner RG, *et al*. Cohort Profile: Health and Ageing in Africa: A Longitudinal Study of an INDEPTH Community in South Africa (HAALSI). *Int J Epidemiol* 2018;47:689–690j.
25 Peltzer K, Phaswana-Mafuya N. Depression and associated factors in older adults in South Africa. *Glob Health Action* 2013;6:1–9.
26 Tomita A, Burns JK. Depression, disability and functional status among community-dwelling older adults in South Africa: evidence from the first South African National Income Dynamics Study. *Int J Geriatr Psychiatry* 2013;28:1270–9.
27 Geldsetzer P, Vaikath M, Wagner R, *et al*. Depressive Symptoms and Their Relation to Age and Chronic Diseases Among Middle-Aged and Older Adults in Rural South Africa. *The Journals of Gerontology* 2019;74:957–63.
28 Adams LB, Farrell M, Mall S, *et al*. Dimensionality and differential item endorsement of depressive symptoms among aging Black populations in South Africa: Findings from the HAALSI study. *J Affect Disord* 2020;277:850–6.
29 Jennings EA, Chinogurei C, Adams L. Marital experiences and depressive symptoms among older adults in rural South Africa. *SSM Ment Health* 2022;2:100083.
30 Pengpid S, Peltzer K. Chronic conditions and incident and persistent depressive symptoms among ageing adults in rural South Africa. *Psychol Health Med* 2024;29:712–20.
31 Payne CF, Mall S, Kobayashi L, *et al*. Life-Course Trauma and Later Life Mental, Physical, and Cognitive Health in a Postapartheid South African Population: Findings From the HAALSI study. *J Aging Health* 2020;32:1244–57.
32 Berkman LF. Health and aging in Africa: a longitudinal study of an INDEPTHcommunity in South Africa [HAALSI]: agincourt, South Africa, 2015-2022. Inter-university Consortium for Political and Social Research; 2023. Available: https://doi.org/10.3886/ICPSR36633.v4
33 Kabudula CW, Houle B, Ohene-Kwofie D, *et al*. Mortality transition over a quarter century in rural South Africa: findings from population surveillance in Agincourt 1993-2018. *Glob Health Action* 2021;14:1990507.
34 Peltzer K. Longitudinal analysis of HIV risk behaviour patterns and their predictors among public primary care patients with tuberculosis in South Africa. *SAHARA-J: J Soc Aspects HIV/AIDS* 2018;15:1–6.
35 Wade AN, Payne CF, Berkman L, *et al*. Multimorbidity and mortality in an older, rural black South African population cohort with high prevalence of HIV findings from the HAALSI Study. *BMJ Open* 2021;11:e047777.
36 Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. *Appl Psychol Meas* 1977;1:385–401.
37 Glymour MM, Maselko J, Gilman SE, *et al*. Depressive symptoms predict incident stroke independently of memory impairments. *Neurology (ECronicon)* 2010;75:2063–70.
38 Cosco TD, Lachance CC, Blodgett JM, *et al*. Latent structure of the Centre for Epidemiologic Studies Depression Scale (CES-D) in older adult populations: a systematic review. *Aging Mental Health* 2020;24:700–4.
39 Andresen EM, Malmgren JA, Carter WB, *et al*. Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). *Am J Prev Med* 1994;10:77–84.
40 Beekman AT, Deeg DJ, Van Limbeek J, *et al*. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. *Psychol Med* 1997;27:231–5.
41 Sharp ES, Suthers KM, Crimmins E, *et al*. Does “no” mean “sometimes”? How older adults respond to the same depression symptoms with different response formats. *Clin Gerontol* 2009;32:371–8.
42 Vilagut G, Forero CG, Barbaglia G, *et al*. Screening for Depression in the General Population with the Center for Epidemiologic Studies Depression (CES-D): A Systematic Review with Meta-Analysis. *PLoS ONE* 2016;11:e0155431.
43 Lewinsohn PM, Seeley JR, Roberts RE, *et al*. Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychol Aging* 1997;12:277–87.
44 Briggs R, Carey D, O’Halloran AM, *et al*. Validation of the 8-item Centre for Epidemiological Studies Depression Scale in a cohort of community-dwelling older people: data from The Irish Longitudinal Study on Ageing (TILDA). *Eur Geriatr Med* 2018;9:121–6.
45 Karim J, Weisz R, Bibi Z, *et al*. Validation of the Eight-Item Center for Epidemiologic Studies Depression Scale (CES-D) Among Older Adults. *Curr Psychol* 2015;34:681–92.
46 Mohebbi M, Nguyen V, McNeil JJ, *et al*. Psychometric properties of a short form of the Center for Epidemiologic Studies Depression (CES-D-10) scale for screening depressive symptoms in healthy community dwelling older adults. *Gen Hosp Psychiatry* 2018;51:118–25.
47 O’Halloran AM, Kenny RA, King-Kallimanis BL. The latent factors of depression from the short forms of the CES-D are consistent, reliable and valid in community-living older adults. *Eur Geriatr Med* 2014;5:97–102.
48 Baron EC, Davies T, Lund C. Validation of the 10-item Centre for Epidemiological Studies Depression Scale (CES-D-10) in Zulu, Xhosa and Afrikaans populations in South Africa. *BMC Psychiatry* 2017;17:6.
49 Malakouti SK, Pachana NA, Naji B, *et al*. Reliability, validity and factor structure of the CES-D in Iranian elderly. *Asian J Psychiatr* 2015;18:86–90.
50 Park SH, Lee H. Is the center for epidemiologic studies depression scale as useful as the geriatric depression scale in screening for late-life depression? A systematic review. *J Affect Disord* 2021;292:454–63.
51 Zhang Y, Hedo R, Rivera A, *et al*. Post hoc power analysis: is it an informative and meaningful analysis? *Gen Psychiatr* 2019;32:e100069.
52 Ruiz-Grosso P, Loret de Mola C, Otero L, *et al*. Are trajectories of depressive symptoms during the first half of drug-sensitive pulmonary tuberculosis treatment associated with loss to follow-up? A secondary analysis of longitudinal data. *BMJ Open* 2023;13:e068235.

53 Oh KH, Choi H, Kim EJ, *et al*. Depression and risk of tuberculosis: a nationwide population-based cohort study. *Int J Tuberc Lung Dis* 2017;21:804–9.
54 Sweetland AC, Kritski A, Oquendo MA, *et al*. Addressing the tuberculosis-depression syndemic to end the tuberculosis epidemic. *Int J Tuberc Lung Dis* 2017;21:852–61.
55 Peltzer K. Mental health, lifestyle factors and subsequent falls among ageing adults in South Africa. *J Psychol Afr* 2023;33:412–6.
56 Peltzer K, Pengpid S. Impact of Somatic Conditions and Lifestyle Behaviours on Depressive Symptoms and Low Life Satisfaction among Middle-Aged and Older Adult Men in South Africa. *J Mens Health* 2023;18:194.
57 Pengpid S, Peltzer K. Mental morbidity and its associations with socio-behavioural factors and chronic conditions in rural middle- and older-aged adults in South Africa. *J Psychol Afr* 2020;30:257–63.
58 Naidoo P, Simbayi L, Labadarios D, *et al*. Predictors of knowledge about tuberculosis: results from SANHANES I, a national, cross-sectional household survey in South Africa. *BMC Public Health* 2016;16:276.
59 Nicholson TJ, Hoddinott G, Seddon JA, *et al*. A systematic review of risk factors for mortality among tuberculosis patients in South Africa. *Syst Rev* 2023;12:23.
60 Alene KA, Wangdi K, Colquhoun S, *et al*. Tuberculosis related disability: a systematic review and meta-analysis. *BMC Med* 2021;19:203.
61 Foster N, Vassall A, Cleary S, *et al*. The economic burden of TB diagnosis and treatment in South Africa. *Soc Sci Med* 2015;130:42–50.