Impact of co-morbid common mental disorder symptoms in people with epilepsy in Ethiopia on quality of life and functional disability: cohort study

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Abstract

Background

There is very limited prospective evidence on the impact of co-morbid mental health conditions in people with epilepsy living in low and middle-income countries. The objective of this study was to investigate the impact of common mental disorder (CMD; depression/anxiety) symptoms and risky substance use in people with epilepsy in Ethiopia on quality of life and functioning over six months.

Methods

A prospective cohort study of people with epilepsy was carried out in four districts of south-central Ethiopia. Comorbid CMD symptoms, risky substance uses (exposures) and the primary outcome, quality of life (QoL) was measured at baseline and 6 months follow-up. Secondary outcomes functional disability and seizure frequency were measured at follow-up. Multivariable linear regression was employed to evaluate whether comorbid CMD symptoms predicted a change in QoL and functional disability. Structural equation modelling (SEM) was employed to examine direct and indirect pathways linking co-morbid CMD symptoms with QoL or functional disability.

Results

In the multivariable regression model, neither CMD symptoms (β coef= -0.37, 95%CI -1.30, + 0.55) nor moderate to high risk of alcohol use (β= -0.70, 95% CI -9.20, + 7.81) were significantly associated with a change in QoL, and there was no effect modification by treatment engagement. In SEM, QoL at 6 months was significantly predicted by seizure frequency. The summative effect of CMD on QoL was significant (B= -0.27, 95%CI -0.48, -0.056), although direct and indirect associations were non-significant. Change in functional disability was not significantly associated with baseline CMD symptoms (β coef.= -0.03, 95% CI-0.48,+0.54) or with moderate to high risk of alcohol use (β coef.= -1.31, 95% CI -5.89, 3.26). However, in the SEM model, functional disability at 6 months was predicted by both baseline CMD symptoms (B = 0.24, 95% CI 0.06, 0.41) and seizure frequency (B = 0.67, 95% CI 0.46, 0.87).

Conclusions

In this rural Ethiopian setting, co-morbid CMD symptoms and seizure frequency in PWE independently predicted functional disability in people with epilepsy. The association between CMD symptoms and QoL was less conclusive. Integrated management of mental health and neurological conditions is needed to better address the psychosocial needs and improved functioning of people with epilepsy.

Background

Substantial global evidence indicates that there is a high level of co-morbid common mental disorders (CMD), especially depression and anxiety, among people with epilepsy (PWE) compared to the general population (1–3). The pooled prevalence of anxiety disorders in a meta-analysis of 69 studies in adults with epilepsy was 21.7% (95% confidence interval (CI) 19.2–24.3%), and the prevalence of co-morbid depression (meta-analysis of 95 studies) was 18.9% (95% CI 15.5–22.3%) (3). The pooled prevalence of comorbid alcohol abuse from a meta-analysis of seven studies was 5.6% (0.5–8.7%) and drug abuse was 6.1% (0.6–20.6%) (4). In sub-Saharan Africa, a systematic review of 16 health facility-based studies reported that the prevalence of comorbid depression in people with epilepsy ranged from 6.5–49.3% (5).

Co-morbid CMDs in people with epilepsy have been associated with poorer seizure treatment outcomes and worse patient-reported health outcomes in high-income country settings (1, 6–8). In these settings, there is robust, high-quality evidence that people with epilepsy and comorbid CMD have increased risk of poor seizure control (8), premature mortality (9, 10), anti-seizure medications side effects (7), poor quality of life (QoL) (6, 11–14) and increased functional disability (15, 16). Comorbid CMDs and substance use have been associated with poor treatment adherence (17, 18).

A systematic review and meta-analysis of 19 studies from low- and middle-income countries (LMICs) also found a significant negative association between comorbid depression (pooled effect size (ES) -1.16, 95% CI -1.70, -0.63) or anxiety (pooled ES -0.64, 95% CI -1.14, -0.13) on QoL of people with epilepsy (19). However, all studies were cross-sectional and there was only one study reporting on the association between co-morbidity and functional disability. This evidence gap is important because the predictors of quality of life or functional disability in people with epilepsy living in LMICs may differ due to the role of socio-economic factors and other variations in sociocultural context. The complex inter-relationships between emotional and social factors and QoL and functional disability have not been investigated in a rural, low-income African country. There have also been very few publications on the impact of comorbid substance use disorders on these important outcomes.

The objective of this study was to investigate the impact of having comorbid CMD symptoms and/or risky substance use on QoL and functioning over a six-month follow-up period. The study had the following hypothesis: CMD symptoms would, directly and indirectly, predict change in QoL and functional disability through the effect on seizure frequency.

Methods

Design

A primary healthcare-based prospective cohort study of people with epilepsy.

2.2 Setting

The study was conducted in the Gurage zone in the Southern Nations, Nationalities, and Peoples' Region (SNNPR) of south-central Ethiopia. The Gurage zone is predominantly rural, characterised by fertile semi-

mountainous terrain. Welkite town is its administrative center. The study was conducted in four districts (Sodo, Eja, Wolikete, and Kebena), with a total estimated population of 450,000-500,000 people. The Ethiopian health care system is divided into three tiers of service delivery. The first level consists of primary healthcare units (health posts and primary health care (PHC) centres) and primary hospitals. PHC centres are generally staffed by nurses and health officers, serving a population of 25,000–40,000 people. Health posts are staffed by one or two community health extension workers, serving a population of 3000–5000 people. Secondary-level services are provided by general hospitals and serve as referral centres from the primary hospitals; and tertiary-level services include specialized hospitals.

This study was nested in the scale-up phase of the **PR**ogramme for **I**mproving **M**ental Health Car**E** (PRIME) project which was a UK Department for International Development (DfID-funded) research programme consortium across five LMIC(Ethiopia, South Africa, Uganda, India, and Nepal) (20). PRIME aimed to provide comprehensive evidence on how to integrate and scale up care for people with psychosis, depression, epilepsy, and/or alcohol use disorders. The focus was on integration in primary health care (PHC) settings using the World Health Organization's mental health Gap Action Programme (mhGAP) intervention guide (21–23). The programme of care was first implemented in the Sodo district (8 PHC centres) and, from 2016 onwards, scaled up to the other 14 districts in the Gurage zone (one PHC centre per district). The four study districts for the current study were selected purposively because of their high commitment to integrating mental health care and logistical considerations.

Source population

The source population for this study was all people with a provisional diagnosis of convulsive epilepsy living in the four study districts of the Gurage zone.

Screening and recruitment of study participants

Case detection was carried out by community key informants and health extension workers (HEWs) who had been trained for two days to recognize people who may have active convulsive epilepsy, augmented by house-to-house screening by HEWs (21). Screen-positive individuals were referred to the nearby PHC centre and the diagnosis of epilepsy was confirmed by PHC workers who had been trained through PRIME and applied diagnostic algorithms outlined in the mhGAP intervention guide. This two stage screening method has been used previously (24) and was implemented in the PRIME study (21). The project psychiatric nurse then screened for eligibility, assessed for capacity to consent to participate in the study, and obtained informed consent before a person was recruited into this cohort study.

Inclusion criteria: (a) PHC worker diagnosis of active convulsive epilepsy: two or more unprovoked convulsions separated by greater than 24 hours, with one convulsion taking place within the preceding 12 months (25, 26); (b) Aged 18 years or above; (c) No plans to out-migrate in the next 12 months.

Exclusion criteria: (a) Communication difficulties due to cognitive or intellectual disability; (b) Unable to converse in Amharic, the official language of Ethiopia; (c) Lacking the capacity to consent after a psychiatric nurse assessment using the standardised approach used previously in this setting (27).

Sample size determination

Based on a large, prospective study, the mean quality of life score for people with epilepsy and depression was estimated to be 31.7 (SD = 13.06) compared to 19.3 (SD = 13.87) in those without depression (13). A total sample of 50 participants (25 with and 25 without co-morbid mental disorder) would be sufficient to detect this difference, with alpha 0.05 and power 0.8. To allow for the detection of a smaller difference in means (mean difference of 5.0), the required sample size was 88 in each group. To take account of clustering by district (n = 4), we assumed an intra-cluster correlation of 0.01 (28), resulting in a design effect of 1.21. Allowing for a 20% loss to follow-up, a total sample of 256 was required (128 per group).

Measurement:

Eligible people who gave informed consent to participate were interviewed at baseline (T_0), and again after six months (T_1) of follow-up. The hypothesised conceptual model is shown in Fig. 1.

Primary outcome (T_0 and T_1)

Quality of life was measured using the 10-item Quality of Life in Epilepsy questionnaire (QOLIE-10-p) (29). This questionnaire was derived from the original 89-item version QOLIE-89 with an additional eleventh item to give a weighted total score (30). The 10-item questionnaire has seven components: one item for each of five domains (seizure worry, overall quality of life, emotional well-being, energy, and cognitive functioning), two items on medication effects (physical effects, mental effects); and three items on social function (work, driving, social function). The total mean score ranges from 0-100 with a higher score indicating better quality of life. For this study, the instrument was adapted and construct validity was established (31). The English version of the QOLIE-10–p was initially designed to be self-administered. For this study the instrument was translated into Amharic, which is the local language, by the principal investigator and it was then back translated to English language by a non-mental health professional. The final Amharic version of the instrument was prepared after discussion of a group of psychiatrists with expertise in the area(31).

Secondary outcomes (T_0 and T_1)

Functional disability: was measured using the World Health Organization Disability Assessment Schedule version 2.0 (12 item WHODAS-2) (32). The WHODAS-2 is a generic instrument that measures health-related functional disability in six domains of life during the previous 30 days. Each item is scored on a Likert scale starting from “no difficulty” 1 to “mild” 2, “moderate” 3, “severe” 4, or “extreme” difficulty 5. The recommended polytomous scoring method was used for analysis. A higher total score indicates a higher functional disability. WHODAS-2 has been validated in people with chronic diseases, including epilepsy (33), and in Ethiopia (34). The 12 item even has shown superiority in understand ability and contextual relevance in a study done in people with severe mental disorders in the Ethiopian setting (34).

Primary exposure (T_0 only)

Common mental disorder (depression, anxiety, and somatic) symptoms: The Self Report Questionnaire (SRQ-20) was developed by World Health Organization (WHO) to screen for CMD symptoms in the past 30 days (35). The SRQ-20 items ask about depressive, anxiety, somatic symptoms, and suicidal ideation. The total score is calculated by summing up all positive symptoms, ranging from 0–20. The SRQ-20 was previously translated into Amharic and validated in perinatal women (36) and at primary healthcare level (36–38). A score of eight was the optimum cut-off point for detection of depression at PHC level (37). For people with epilepsy in the same setting the optimum cut-off score of SRQ-20 indicating common mental disorder was greater or equal to 9 (39).

Substance use: risky use of alcohol, khat, and tobacco was measured using the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)(40). The ASSIST has eight questions, with questions one to seven asking about use and problems related to substance use, and the eighth question inquiring about the use of injectable drugs. The total score for specific substance involvement is calculated by summation of the assigned numerical numbers from questions number 2–7 for each substance class. Low risk is indicated by a score of 0–10 for alcohol and 0–3 for other substances, moderate risk is 11–26 for alcohol and 4–26 for other substances, and high risk is indicated by a score of 27 and above. The ASSIST has been contextually adapted in multiple countries including in Africa and Ethiopia (40–42). For this study, the ASSIST was modified to assess commonly used substances in the southern part of Ethiopia: alcohol and khat (43, 44).

Potential confounding variables (T_0 only)

Socio-demographic characteristics: age, sex, education, marital status, income.

Epilepsy-related factors: duration of epilepsy and seizure frequency. At baseline, seizure frequency in the past one month was measured. At the follow-up time-point, the numbers of seizures in the last 6 months were recorded as follows: number per week (if < 1/day), number per month (if < 1/week), and number in the last 6 months (if < 1/month). The severity of seizures was grouped into three categories based on their frequency in the past 6 months: seizure:-None, low to moderate (1–2 seizures), and high seizure severity (greater and equal to 3 seizures). This categorization of seizure severity has been used in an African setting in a previous study (45).

Social support: This was measured using the Oslo-3 item Social Support scale (OSSS-3)(46). The OSSS-3 is a brief measurement of social functioning and has three items: The total score ranges from 3–14 with a higher score indicating better social support. OSSS-3 has been validated in an African setting (47) and has been used in several studies in Ethiopia (48).

Factor hypothesised to be on the causal pathway

Perceived stigma was measured using the stigma section of the Family Interview Schedule (FIS) questionnaire (49). This instrument has been translated into Amharic and has been used previously in

rural Ethiopia to measure stigma in people with epilepsy and their caregivers and those with mental disorders (50, 51). Each item is rated in a four-point scale 0 “not at all”, 1 “sometimes”, 2 ”often”, and 3 “a lot” regarding the perceived stigma. A total score of one and above is considered as having the experience of perceived stigma.

Hypothesised effect modifier: epilepsy treatment engagement

Treatment engagement was operationalized as the number of times the person attended the PHC centre in the preceding 6 months. Self-reported attendance was recorded and augmented by a medical record review. Good treatment engagement was defined as attending ≥ 4 times during the follow-up period.

Data collection and management

All measures were carried out by experienced lay data collectors who have completed secondary school education. The lay data collectors were trained on the administration of the questionnaire for five days and practiced through role play before administering them to study participants. Immediately after the completion of data collection, the field supervisor checked the questionnaires for completeness. Data were double-entered using Epi-data version 3.1(52).

Data analysis

Data were analysed using STATA version 17 (53). For continuous variables, indicators of central tendency were calculated depending on the distribution (mean with standard deviation (sd) or median with Interquartile range (IQR)). Percentages and frequencies were used to summarize categorical variables. Simple descriptive analyses were used to summarise the socio-demographic and clinical characteristics at T_0 and T_1. Wilcoxon ranked sum test or Fisher’s exact test was used to examine the statistical significance of differences in baseline characteristics of those who were lost to follow-up and those who remained in the cohort. The dependent variables of change in quality of life and change in functional disability were calculated by subtracting the total scores at T_1 from T_0.

Univariate and multivariable linear regression models were fitted to evaluate whether the primary exposure (comorbid CMD symptoms) predicted a change in the outcome variables (QOL and functional disability) adjusting for baseline outcome data. The pre-defined potential confounding variables (measured at the baseline) were also entered into the multivariable model. The risk of alcohol use was entered into the model separately from the total SRQ-20 score (CMD symptoms). Effect modification by number of PHC centre visits (treatment engagement) was tested using interaction terms with a total SRQ-20 score. A likelihood ratio test was used to examine statistical significance.

Structural equation modelling (SEM) was then conducted using R version 4.3 (54) to examine direct and indirect pathways through seizure frequency linking co-morbid CMD symptoms with QoL or functional disability. The direct and indirect pathways linking to the outcome were drawn based on the pre-

hypothesised conceptual model (Additional file 1). Separate SEM was fitted for QoL and functional disability as two separate outcomes.

Before fitting the full SEM, CFA was carried out for each of the latent constructs of CMD symptoms, stigma, quality of life, and functional disability to examine the fit of the measurement models. The goodness of fit of the models was checked for each latent construct using the Root Mean Square Error Approximation (RMSEA), Tucker-Lewis Index (TLI), and Comparative Fit Index (CFI). The significance of factor loadings of each item and the plausibility of the loadings were also examined. Weighted least square estimation was used for the complete data. The SEM was fitted again after multiple imputations of missing data using a chained Eq. (55).

Results

Socio-demographic and clinical characteristics

The study was conducted from March 2017 to June 2018. At T_0, 237 participants were recruited. Of these, 92.4% (n = 219) were assessed after 6 months. There were two deaths and 16 participants could not be traced. Participants who were lost to follow-up were more likely to be single or previously married, had worse QoL, higher functional disability, had increased seizure frequency, and more stressful life events compared to those who remained in the cohort. See Additional file 2.

Those participants who remained in the cohort had a median age of 32 years (IQR 22, 42), two-thirds were males (60.3%) and 56.6% had no formal education. Most of them (88.1%) resided in a rural area and nearly half (46.1%) were married (Table 1). All participants were diagnosed with generalised seizures, with a median of one seizure per month.

Changes over the follow-up period

Over the 6 month follow-up period, participants attended the PHC centre a median of 5 times (IQR 5–6) for epilepsy and/or mental health care. The median score for CMD symptoms and the risk of alcohol use decreased from baseline to the 6 months follow-up assessment (Table 1). There was a positive change in QoL (mean QOLIE-10p score = 18.92 (SD = 38.19)) and improvement in functional disability (mean = -6.77; SD = -19.11).

Status at 6 months

At six months, almost half of the participants (45.2%) were seizure-free. Almost all (n = 189, 90%) were taking one anti-seizure medication (phenobarbitone) and 10% (n = 21) were taking two (phenobarbitone plus either carbamazepine or valproate). Only 8.2% (n = 17) were on any psychotropic medication.

Table 1
Characteristics of participants at T_0 (n = 237) and T_1 (n = 219) (6 months)

Characteristics		Baseline (T_0) n (%)	End-line (T_1) n (%)
Age	In years	Median 30 (IQR 22, 42)	Median 32 (IQR 22, 42)
Sex	Male	140 (59.1)	132 (60.3)
	Female	97 (40.1)	87 (39.7)
Residence	Rural	208 (87.8)	193 (88.1)
	Urban	29 (12.2)	26 (11.9)
Education	No formal education	135 (57.0)	124 (56.6)
	Formal education	102 (43.0)	95 (43.4)
Marital status	Single, divorced, or widowed	114 (48.1)	101 (53.9)
	Married	123 (51.9)	118 (46.1)
Relative wealth	Low or very low	169 (71.3)	155 (70.8)
	Average or above	68 (28.7)	64 (29.2)
Prescribed psychotropic medication (n = 207)	No	-	190 (91.8)
	Yes	-	17 (8.2)
Common mental disorder (CMD) symptoms	Total SRQ-20 score	Median = 7 (IQR 3, 12)	Median = 3 (IQR 1, 7)
Risk of alcohol use (ASSIST score)	Low (ASSIST < 10)	126 (67.4)	147 (82.6)
	Moderate (ASSIST 11–26)	34 (18.2)	28 (15.7)
	High (ASSIST > 27)	27 (14.4)	3 (1.7)
Quality of life	Weighted QOLIE-10 score	Median 42.2 (IQR 28.7, 66.6)	Median 71.6 (IQR 45.8, 93.5)
Seizure frequency in the past 6 months	0		99 (45.2)
	1		87 (39.7)
	≥ 2		33 (15.1)

Characteristics		Baseline (T_0)	End-line (T_1)
		n (%)	n (%)
Social support	OSSS-3 total score	Mean 11.0 (SD 1.8)	Mean 11.2 (SD 1.39)

*ASSIST- Alcohol, Smoking and Substance Involvement Screening Test, OSSS- Oslo Social Support scale, QOLIE- Quality of Life in Epilepsy questionnaire, SRQ-20- Self Reported Questionaire, WHODAS-, World Health Organization Disability Assessment Schedule

Regression analysis: Quality of life

CMD symptoms were not significantly associated with a change in the QoL in the crude or adjusted regression analysis (adjusted β coef= -0.37, 95%CI -1.30, 0.55) (Table 2). Seizure frequency was significantly associated with a decreased change in the QoL in the multivariable model (β coef = -1.73, 95% CI -2.73, -0.74). When the risk of alcohol use was entered into the multivariable model instead of the SRQ-20 score, there was no significant association between moderate to high-risk alcohol use and change in the QoL (β coef. = -0.70, 95% CI -9.20, + 7.81) compared to low-risk alcohol use.

Those participants who had good treatment engagement had a better change in QoL than those with poor treatment engagement (β coef.=14.6, 95% CI 3.70, 25.51) in the univariable analysis. Treatment engagement did not significantly modify the association between CMD symptoms (SRQ-20 score) and QoL (interaction coefficient = 1.03, 95% CI -0.93, 3.0; Likelihood ratio test χ^2 =3.48, p = 0.18).

Table 2
Univariable and multivariable regression analysis of factors associated with a change in quality of life score/ change in functional disability between T_1 and T_0 (6 months)

		Change in quality of life		Change in functional disability	
Characteristics		**Crude β coef. (95% CI)**	**Adj. β coef. (95% CI)**	**Crude β coef. (95% CI)**	**Adj. β coef. (95% CI)**
CMD symptoms (total SRQ-20 score at baseline)		-0.79 (-1.67, + 0.09)	-0.37 (-1.30, + 0.55)	0.23 (-0.26, + 0.72)	0.03 (-0.48, + 0.54)
Sex	Female	-5.60 (-12.99, + 1.79)	-4.36 (-12.0, + 3.28)	+ 3.10 (-0.89, + 7.11)	+ 3.31 (-0.80, + 7.41)
Age (years)		-0.02 (-0.31, + 0.26)	-0.04(-0.41, + 0.33)	+ 0.13 (-0.10, +0.29)	+ 0.13 (-0.07, 0.33)
Education	No formal	1	1	1	
	Formal	-0.45(-7.79, + 6.89)	-2.96 (-10.64,+ 4.72)	-1.50 (-5.46, + 2.46)	+ 1.36 (-2.81, +5.54)
Relative wealth	Average or above	1	1	1	
	Low or very low	+ 3.75 (-4.39, + 11.88)	+ 2.71 (-5.37, + 10.80)	-0.14 (-4.46, + 4.19)	-0.50 (-4.88, + 3.88)
Marital status	Married	1	1	1	
	Single or formerly married	+ 3.45 (-3.85, 10.75)	+ 7.25 (-1.23, 15.73)	-4.36 (-8.26, -0.46)	-3.97 (-8.63, + 0.69)
Duration of epilepsy (years)		-0.14 (-0.51, +0.23)	-0.23(-0.62, +0.15)	+ 0.15 (-0.04, + 0.35)	+ 0.13 (-0.08, +0.34)
Seizure frequency/month		-1.78 (-2.63, -0.93)	-1.73 (-2.73, -0.74)	0.84 (0.28, 1.39)	0.88 (0.32, 1.44)
OSSS score		+ 1.08(-0.98, +3.14)	+ 1.29 (-0.74, +3.33)	-0.54 (-1.65, + 0.57)	-0.59 (-1.69, +0.50)

*CMD- Common mental disorder, OSSS- Oslo Social Support Scale, QOLIE- Quality of Life in Epilepsy questionnaire, SRQ-20- Self Reported Questionnaire, WHODAS- World Health Organization Disability Assessment Schedule.

Regression analysis: functional disability

CMD symptoms were not significantly associated with a change in functional disability (β coef.= 0.03, 95% CI -0.48, + 0.54). Increased seizure frequency was the only factor significantly associated with a change in functional disability in both univariable and multivariable analysis (adjusted β coef.= +0.88, + 0.32, + 1.44). See Table 2. When the risk of alcohol use was entered into the multivariable model instead of SRQ-20 total score, there was no significant association between moderate to high-risk alcohol use and change in functional disability (β coef.= -1.31, 95% CI -5.89, 3.26) compared to low-risk alcohol use.

Those participants who had good health care engagement (≥ 4 health centre attendance) had a better change in their disability score than those with poor attendance (β coef. =-8.13, 95% CI -14.01, -2.24) in the univariable analysis. Healthcare engagement was not an effect modifier of the association between CMD symptoms (SRQ-20 score) and functional disability (interaction coef.= -0.44, 95% CI -1.50, + 0.62; Likelihood ratio test: χ^2 =4.65, p = 0.10).

Structural equation modelling: quality of life

The fit indices for each measurement model (stigma, CMD symptoms, social support, and quality of life) indicated adequate fit to the data (Additional file 3). The fit indices for the full structural model also indicated adequate fit of the model to the data (χ2 = 1554.2 (degree of freedom = 1072), (p < 0.0001), CFI = 0.97, TLI = 0.97 and RMSEA = 0.06). In the full SEM, QoL at T_1 was significantly predicted by seizure frequency in the 6 month follow-up period (B= -0.91, 95% CI -1.16, -0.66) but not by T_0 CMD symptoms directly (B= -0.14, 95% CI -0.31, + 0.030) or indirectly through the seizure frequency (B= -0.12, 95% CI -0.26, + 0.013). CMD did not have a significant effect on seizure frequency (B = 0.14, 95% CI -0.015, + 0.29). However, the summative (direct + indirect) effect of CMD on QoL was significant (B= -0.27, 95%CI -0.48, -0.056). Baseline stigma (B = 0.83, 95% CI 0.64, 1.03) was a significant predictor of CMD symptoms (Fig. 2).

Structural equation modeling: functional disability

The fit indices for the full structural model indicated adequate fit of the data by χ2 = 1580 (degree of freedom = 1167), (p < 0.0001), CFI = 0.95, TLI = 0.99, and RMSEA = 0.06. Functional disability at T_1 was predicted by baseline (T_0) CMD symptoms (B = 0.24, 95% CI 0.06, 0.41) and seizure frequency (B = 0.67, 95% CI 0.46, 0.87) (Fig. 3). Seizure frequency (B = 0.09, 95% CI -0.01, + 0.05) did not have a mediation effect on the relationship between CMD symptoms and functional disability. The summative (direct plus indirect) effect of CMD symptoms on functional disability was significant (B = 0.34, 95% CI 0.14, 0.52).

Sensitivity analysis

Similar model fit indices were obtained after imputation of missing data. However, in the imputed model, CMD symptoms directly predicted seizure frequency (B = 0.17, 95% CI 0.3, 0.31), and the indirect (B=-0.15, 95% CI -0.27, -0.03) and total effect B=-0.28, 95%CI -0.48, -0.07) of CMD symptoms on quality of life through seizure frequency also became significant (See Additional file 4).

Discussion

In this prospective cohort study, we investigated the impact of having comorbid CMD symptoms in people with epilepsy living in rural Ethiopia on quality of life and functional disability. In hypothesis-driven regression analyses, neither baseline CMD nor risky alcohol use were associated with a change in functional disability or quality of life, nor moderated by treatment engagement. However, structural equation modelling indicated that baseline CMD had a significant direct impact on functional disability at follow-up. Only the summative effect of CMD on quality of life was significant.

The lack of a prospective association between co-morbid CMD symptoms and change in QoL (in the linear regression model) contrasted with the SEM finding of a significant summative effect of baseline CMD on quality of life at 6 months. The SEM complete case analysis did not find CMD to be associated either directly or indirectly (via seizure control) but sensitivity analysis with multiple imputations of missing data indicated that CMD affected QoL through the mediator of seizure frequency. Our study was likely to have been underpowered and affected by attrition bias which may mean the findings from the multiple imputation analysis are more valid. Cross-sectional analyses of the same cohort at baseline (31) and cross-sectional studies of the association in other LMIC settings (19) showed strong associations between CMD and QoL but are more susceptible to negative recall bias (56) than prospective studies and do not illuminate the potential mechanism of any association and, indeed, its temporal relationship. Furthermore, CMD symptoms may have been managed by PHC workers between baseline and follow-up, supported by the reduced total score of SRQ-20 over time, although there was no evidence of effect modification by treatment engagement.

The association of increased seizure frequency with poor QoL is consistent with the results of studies from high-income countries and from Africa (11, 57, 58). As QoL measurement was also related to the subjective experience of being satisfied and fulfilled in life (56), the direct social and cultural effect of increased seizure frequency on their overall life could be the most troublesome problem for these participants. The SEM sensitivity analysis indicated that seizure frequency may mediate the association between CMD symptoms and QoL and the direct association between CMD and seizure frequency was significant. Previous studies have shown that people with CMD symptoms are less likely to be seizure free (8, 59). Common mental health conditions like depression have been found to contribute to treatment resistance epilepsy (59), poor treatment adherence (17, 18), and increased anti-seizure medication side effects (7). Therefore, comorbid CMD symptoms could have directly contributed to poor anti-seizure medication adherence and side effects which then affected achieving seizure control. Unfortunately, these factors (adherence and anti-seizure medication side effects) were not measured in our study which has limited our findings. We found that only half of the participants were seizure-free at the end of the cohort rather than 70% which is expected for the first-line treatment of generalised tonic-clonic (GTC) seizure with anti-seizure medication (60). Beyond the potential impacts of CMD symptoms, this may also reflect the scarcity and high cost of the alternative classes of anti-seizure medications in this low socio-economic status setting.

For the outcome of functioning, there was also a discrepancy between findings from the linear regression and SEM. However, SEM provided strong evidence of a direct effect of co-morbid CMD symptoms on functional impairment. The global burden and disability associated with depression is substantial (61), compounding disability associated with the underlying chronic neurologic disorder (epilepsy). Meeting basic needs, like food and shelter, is often given highest value by people with chronic mental health conditions in the same setting (62). Therefore, being functional and thus better able to meet basic needs could be more important than satisfaction with life and could explain the stronger prospective associations between CMD and functional disability compared to QoL. The impact of seizure frequency on functional disability was also significant, in keeping with other studies (15, 63), but there was no evidence of CMD symptoms indirectly affecting functioning through seizure frequency similar to QoL.

There was also significant association of epilepsy-related stigma and CMD symptoms on the SEM analysis.

Risky alcohol use was not associated with a change in QoL or functioning. Levels of risky alcohol use were high at baseline, with 14.4% of people with epilepsy having high-risk use of alcohol. This decreased substantially (to 1.7%) over the 6-month follow-up period and could explain why baseline risky alcohol use was not associated with either outcome. At baseline alcohol withdrawal could have been the primary cause of seizures (and/or epilepsy) or alcohol use disorder could be comorbid with epilepsy (10). Evidence from high-income countries indicates a higher prevalence of alcohol use in PWE compared to the general population (4) which is associated with a higher rate of mortality of PWE (9, 10).

To the best of our knowledge, this study was the first in Ethiopia or any other low-income country setting to investigate prospectively the impact of comorbid mental health conditions in people with epilepsy on QoL and functional disability. It also used appropriate analyses to investigate the direct and indirect impacts of psychosocial and epilepsy-related factors in an effort to better understand mechanisms underlying associations. The setting reflected the normal routine care of people with epilepsy at primary health care level in contrast to the many studies based in tertiary referral facilities. Alongside these strengths, there were however some limitations of the study. Even though the epilepsy definitions used by WHO's mhGAP and ILAE (International League Against Epilepsy) are similar, diagnostic tools like EEG were not used in this study. This limited the possibility of confirmatory diagnosis of focal seizures by the PHC workers. Though the percentage of people who were lost to follow-up was minimal (7%), there was evidence of selective attrition by people who had higher CMD symptoms at baseline and differences in the final result of the SEM between the complete and imputed data. This suggests potential selection bias which may have reduced the association between CMD symptoms and the outcomes considered in our analysis. We were not able to recruit to the proposed sample size and the analysis was underpowered. We operationalized the definition of treatment engagement as the attendance of participants to the health centre considering it to be a good proxy measurement of treatment adherence due to the concerning health problems. However, treatment engagement is a complex and multi-dimensional construct (64), and the attitudinal and behavioural component was not measured in this

study. This, alongside the sample size, could explain the absence of significant effect modification by treatment engagement in the association between CMD symptoms and the outcomes. We were not able to assess the cognitive function of the participants which could have contributed to poor quality of life and decreased functioning.

In conclusion, comorbid CMD symptoms and seizure frequency had independent negative impacts on functional disability. Seizure frequency also predicted poor quality of life and the sensitivity analyses indicated a possible mechanism linking CMD symptoms with poor quality of life through seizure frequency. Therefore, strengthening the existing integrated mental and physical care of people with epilepsy should include screening and management of the highly prevalent comorbid mental health conditions like depression. Though pharmacological management was frequently practiced by the PHC workers, the social and emotional recovery of people with epilepsy in this context tends to be neglected (65). Hence, it is highly recommended for clinicians to examine the number of psychosocial problems contributing to poor mental health of people with epilepsy alongside the prescription of anti-seizure medications. Cost-effective psychosocial interventions delivered by non-mental health specialists could also be beneficial in the management of common mental health conditions (66). Future research with a larger sample size and longer periods of follow-up are needed to examine the association of comorbid mental health conditions and QoL. Research on interventions that address mental, social, and physical health adversities should be adapted, implemented, and evaluated in this rural community. The availability and sustainable provision of not only the older anti-seizure medications but also the newly available anti-seizure medications is important to achieve good control of seizures and thus improve QoL and functioning. Stigma reduction programs and interventions at the community level are also highly recommended to support social inclusion of people with epilepsy and minimize the impact on mental health (67).

Abbreviations

ASSIST- Alcohol smoking and substance involvement screening tool, CFA – confirmatory factor analysis, CFI-Comparative Fit Index CMD- common mental disorders, CI-confidence interval, ES- effect size, FIS-Family interview schedule, GTC – generalized tonic clonic, HEW- health extension workers, HIC – high income countries, IQR – Interquartile range, LMIC – low and middle income countries, mhGAP- mental health Gap Action Programme, OSSS--Oslo-3 item Social Support scale, , PHC- Primary Health care, PRIME- **PR**ogramme for **I**mproving **M**ental Health Car**E** PWE- people with epilepsy, QoL – quality of life, QOLIE- Quality of life for epilepsy, RMSEA-Root Mean Square Error Approximation SD- standard deviation, SEM – Structural equation modelling, SNNPR - Southern Nations, Nationalities, and Peoples' Region, SRQ – Self reported questionnaire, TLI- Tucker-Lewis Index, WHODAS- World Health Organization disability assessment schedule

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Institutional Review Board of the College of Health Sciences, Addis Ababa University, and the Research Ethics Committee of King's College London (HR-15/16-2434). Informed consent and witnessed verbal consent (for non-literate participants) were sought after adequate information was provided.

Consent for publication – not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are included in the article as additional file 5.

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

RT, CH and CN participated in the writing of the research proposal. RT contributed to the collection of the data. RT, GM, MB, and CH analysed the data. RT drafted the manuscript. RT, CH, GM, MB and CN made an intellectual contribution and revised the draft. All the authors have read and approved the final manuscript

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Figures

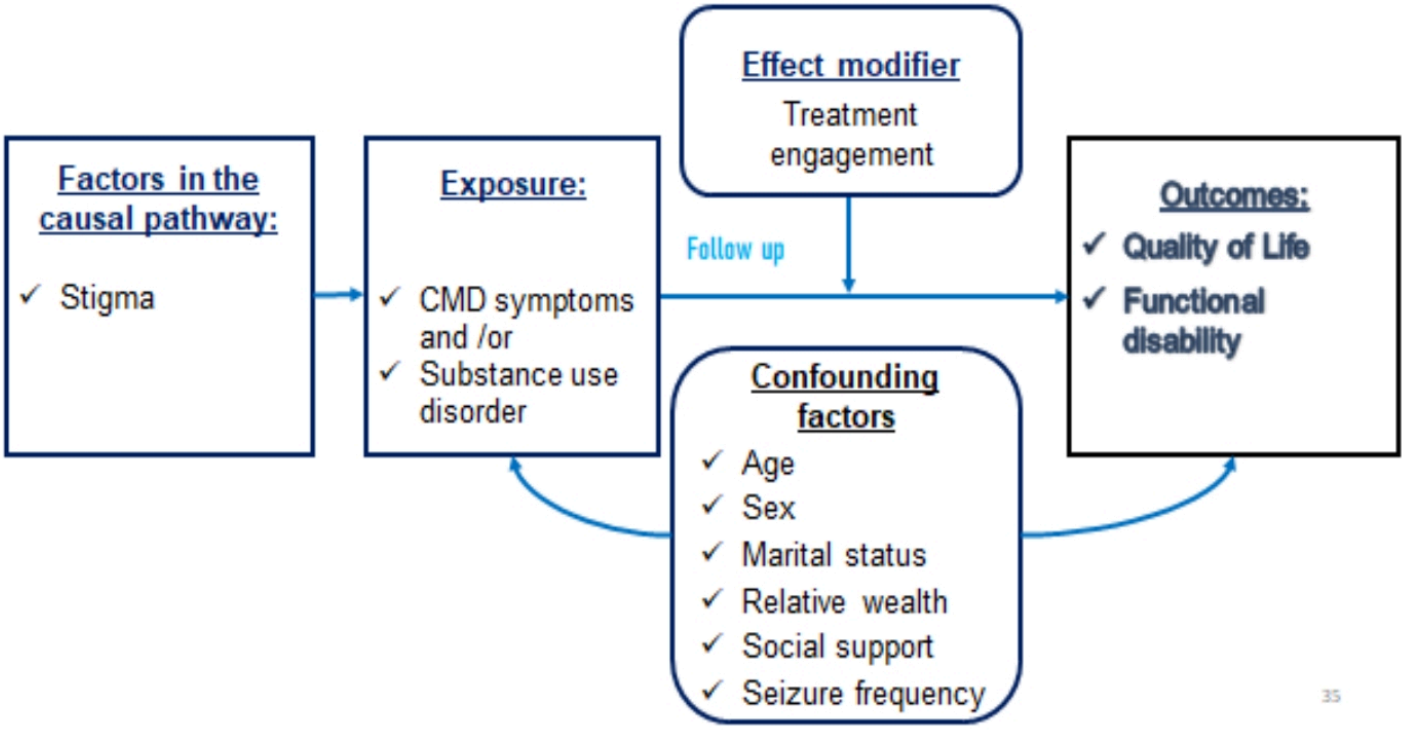

Figure 1

Conceptual model

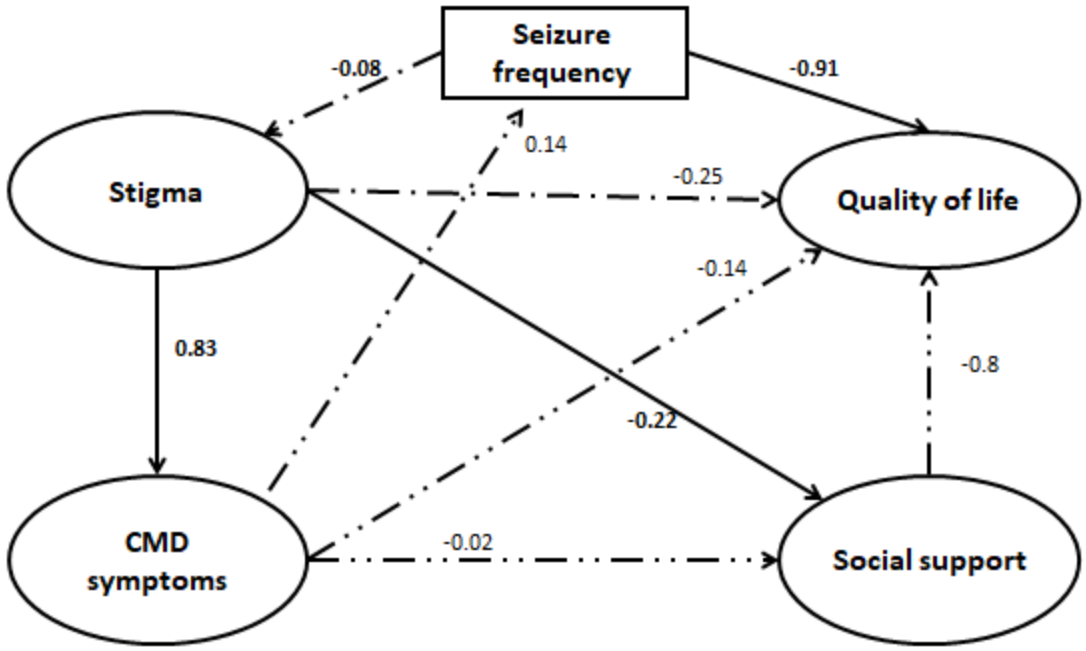

Figure 2

Structural equation model of end line quality of life regressed onto the latent constructs of baseline stigma, CMD symptoms, and social support (CMD- Common mental disorder symptoms, QOL- quality of life). The displayed estimates for regression weights are unstandardized path coefficients (B). Significant weights are indicated by the solid-line arrow. The measurement model was not included for the simplicity of the figure.

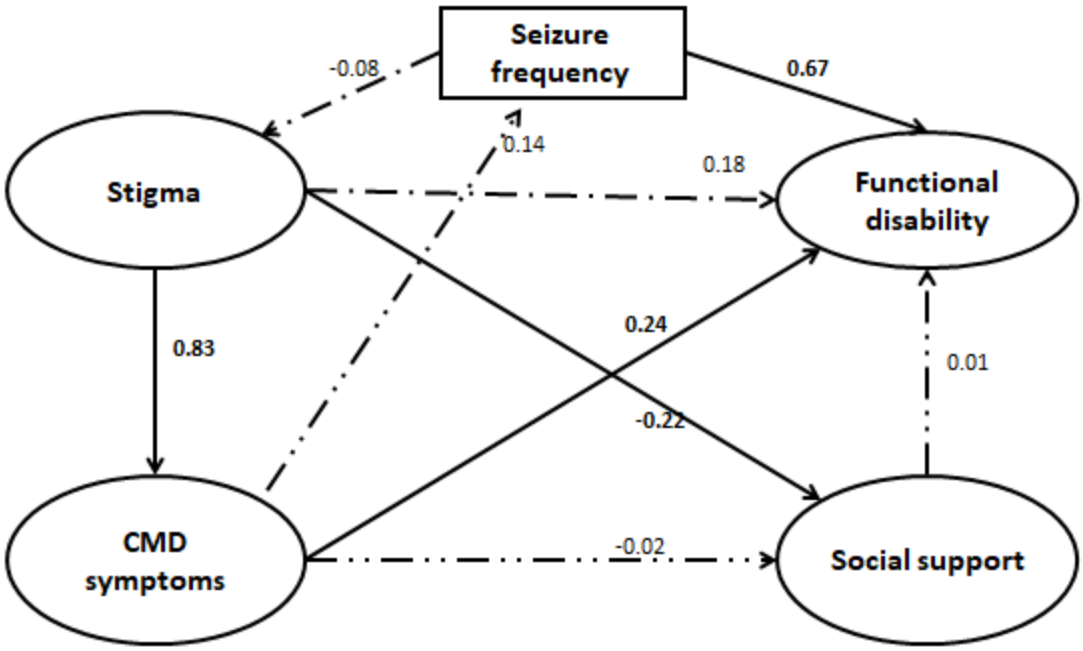

Figure 3

Structural equation model of end-line functional disability regressed on the latent construct of baseline stigma, CMD symptoms, and social support (CMD- Common mental disorder symptoms). The displayed estimates for regression weights are unstandardized (B). Significant weights are indicated by the solid-line arrow. The measurement model was not included for simplicity of the figure

Supplementary Files

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- Additionalfile1conceptualmodelforSEM.pdf
- Additionalfile2Baselinecharacteristics.pdf
- Additionalfile3measurementmodel.pdf
- Additionalfile4SEMafterimputation.pdf
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