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Major depressive disorder in sub-Saharan Africa: findings from the Neuro-GAP-Psychosis study

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Article

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Abstract

Major depressive disorder (MDD) is a significant contributor to the burden of mental disorders in Africa, necessitating an understanding of its prevalence and risk factors across diverse socio-cultural contexts to address health disparities and improve care. This cross-sectional study analyzed 7,073 adult participants from hospital settings in Uganda, Kenya, Ethiopia, and South Africa within the NeuroGAP-Psychosis study. Prevalence estimates, calculated with 95% confidence intervals, revealed overall rates of 0.9% for current MDD and 5.1% for lifetime MDD, with South Africa reporting the highest prevalence (2.1% current, 8.4% lifetime). Multilevel logistic regression identified significant associations between current MDD and negative life events, alcohol use, and Kessler psychological distress scores, while lifetime MDD was linked to age, female sex, chronic pain, frequent headaches, and positive psychosis screening. These findings underscore the need for targeted mental health interventions tailored to the identified risk factors to reduce the burden of MDD in the studied populations.

Introduction

Major depressive disorder (MDD) is a common mental disorder characterized by persistent feelings of sadness, hopelessness and lack of interest in normally pleasurable activities. [1,2]

The global prevalence for MDD has been estimated at 3.4%, accounting for point, 12 month and lifetime prevalence using pooled prevalence ratios[3]. It is estimated that 10–15% of the general population experience clinical depression in their lifetimes with 5% of men and 9% of women experiencing a depressive disorder in a given year.[4] According to the World Health Organisation, MDD was responsible for over 50 million years lived with disability (YLD) in 2015 and can lead to suicide which is responsible for up to 800,000 deaths annually.[5] MDD leads to high levels of morbidity and a 10% increased risk of all-cause mortality.[6]

The burden of MDD has been reported to vary per WHO region and the study population. It has been reported to vary from 3.6% in the Western Pacific region to 5.4% in the African region.[5] Africa accounts for over 9% of the global burden of MDD,[5] yet it is a region where very low treatment rates have been reported for MDD.[7,8]

From existing limited data, in Sub-Saharan Africa (SSA) an age-standardized prevalence of 4.5% has been estimated for MDD.[3] The age-standardized prevalence of MDD has been reported to be higher in SSA than elsewhere globally.[3] In South Africa, a prevalence of 4.6%[9] has been reported among the general population while prevalence rates of 1.9–38% have been reported among small controlled populations. In Uganda, a pooled prevalence of 30.2% has been determined by a systematic review and a meta-analysis among heterogeneous samples[10] while MDD prevalence estimates of 4.2–29.3% have been determined among general populations from various study sites in Uganda.[11–15] In Ethiopia, a prevalence of 4.7% has been reported among the general population while prevalence rates of 4.8–57% have been reported among heterogeneous samples.[16,17] In Kenya, a prevalence of 4.4% has been reported among the general population while prevalence rates of 6.3–72.9% have been reported among heterogeneous samples.[18,19]

Despite accumulating data on MDD prevalence across various regions in SSA, a comprehensive understanding of the disorder's epidemiological landscape remains elusive. Current research shows considerable variability

in MDD prevalence. This suggests that existing studies may not fully capture the nuances of how depression manifests across SSA's varied cultural, economic, and demographic contexts. This may also be attributable to the different methods employed I in assessing for MDD and the different populations being sampled. Additionally, while links between MDD and lifestyle diseases such as diabetes and hypertension, as well as infectious diseases like HIV, Ebola, and COVID-19 have been noted, there is a dearth of studies exploring these relationships. The inconsistent use of diagnostic criteria and potential underdiagnosis due to cultural perceptions of mental health highlight the need for more localized and culturally adapted research methodologies. Also, given the heterogeneous nature of MDD, it is important to know the rates and risk factors for MDD in different populations, to inform policies that target reducing the burden of the disorder. This study aimed to investigate the prevalence and specific risk factors (demographic, social and family dynamics, lifestyle and health behaviours, physical health conditions, psychological and geographical/cultural) for MDD among a cross-sectional sample of participants recruited from hospital settings from Eastern (Uganda, Kenya, Ethiopia) and Southern (South Africa) Africa.

Results

The socio-demographic characteristics and clinical variables of the study participants are shown in Table 1.

Table 1
description of the socio-demographic characteristics and clinical variables of the study participants. SD = standard deviation.

Factor	Level	Frequency (Percentage) n = 7,073
Sex at birth	Female	2,259 (31.9%)
	Male	4,814 (68.1%)
Age	Mean (SD)	37.1 (11.5)
Marital status	Married/living together	3,504 (49.6%)
	Widowed/divorced/separated	822 (11.6%)
	Single	2,744 (38.8%)
Current living arrangement	Lives alone	1,077 (15.3%)
	Lives with family & friends	5,978 (84.7%)
Highest level of education	Primary or less	1,710 (24.2%)
	Secondary	3,219 (45.5%)
	Tertiary	2,141 (30.3%)
Study country	South Africa	1,805 (25.5%)
	Kenya	682 (9.6%)
	Uganda	2,283 (32.3%)
	Ethiopia	2,303 (32.6%)
Current use of tobacco products	No	4,803 (67.9%)
	Yes	2,270 (32.1%)
Current use of alcoholic beverages	No	2,593 (36.7%)
	Yes	4,480 (63.3%)
Current use of substances	No	4,996 (70.6%)
	Yes	2,077 (29.4%)
Blood pressure	Normal	5,050 (71.4%)
	High	2,023 (28.6%)
Body mass index	Mean (SD)	23.9 (4.9)

Prevalence of Major Depressive Disorder

As shown in Table 2, the overall prevalence of current and lifetime MDD from this study was 0.9 and 5.1% respectively. For current MDD at country level, South Africa had the highest prevalence (2.1%) followed by Uganda (0.7%), Ethiopia (0.5%) and Kenya (0.1%). For lifetime MDD at the country level, South Africa still had the highest prevalence (8.4%) followed by Uganda (7.9%), Ethiopia (1.2%) and the lowest being Kenya (0.3%).

Table 2
Prevalence of major depressive disorder among the study participants. MDD = major depressive disorder, CI = confidence interval.

Study Site	Number of participants	Number of MDD cases	Prevalence (95% CI)
a) Current major depressive disorder			
South Africa	1,805	37	2.1% (1.5, 2.8)
Uganda	2,283	16	0.7% (0.4, 1.1)
Ethiopia	2,303	12	0.5% (0.3, 0.9)
Kenya	682	01	0.1% (0.02, 1.0)
Combined in all 4 countries	7,073	66	0.9% (0.7, 1.2)
b) **Lifetime major depressive disorder**			
South Africa	1,805	151	8.4% (7.2, 9.7)
Uganda	2,283	180	7.9% (6.8, 9.1)
Ethiopia	2,303	27	1.2% (0.08, 1.7)
Kenya	682	2	0.3% (0.07, 1.2)
Combined in all 4 countries	7,073	360	5.1% (4.6, 5.6)

Factors associated with current major depressive disorder

In the multilevel models, male sex at birth was marginally significantly associated with current MDD (aOR = 0.47 [95% CI: 0.22; 1.02]). Level of education did not show strong or consistent associations with MDD, as neither secondary nor tertiary education was significantly linked to MDD in any of the models. Living arrangements and marital status were similarly not associated with significant changes in the odds of MDD across the models. Several behavioural and health-related factors were significantly associated with MDD. Current use of alcohol was strongly associated with MDD (aOR = 6.07 [95% CI: 1.89; 19.46]). On the other hand, current substance use and tobacco consumption were not significantly associated with MDD. Experiencing traumatic life events was significantly associated with MDD (aOR = 2.16 [95% CI: 1.00; 4.66]). Among chronic conditions, frequent headaches were significantly associated with MDD (aOR = 1.89 [95% CI: 1.02; 3.50]), while other chronic conditions such as arthritis and chronic back/neck pain did not show significant associations. Higher scores on the Kessler psychological distress scale (K10) were significantly associated with MDD (aOR = 1.26 [95% CI: 1.21; 1.31]). The geographical location, represented by living in Eastern Africa compared to Southern Africa, was not significantly associated with MDD. The ICC for the fully

adjusted model (model 3) was 0.14 (95% CI: 0.09; 0.32), indicating that 14% of the variance in MDD was attributable to differences between countries. These results are summarized in Table 3a.

Table 3

a: Results of fitting multilevel logistic regression model for factors associated with current major depressive disorder. CI = confidence intervals, aOR = adjusted odds ratios, ICC = intraclass correlation coefficient, *p < 0.05.

Factor	Model 1 aOR (95% CI)	Model 2 aOR (95% CI)	Model 3 aOR (95% CI)
Age	**1.00 (0.97; 1.02)**	**0.98 (0.95; 1.01)**	**0.98 (0.95; 1.02)**
Sex at birth			
Female (reference)	1.00	1.00	1.00
Male	0.55 (0.31; 1.00)	0.44 (0.20; 0.94)	0.47 (0.22; 1.02)
Highest level of education			
Primary or less (reference)	1.00	1.00	1.00
Secondary	0.74 (0.38; 1.44)	0.71 (0.33; 1.52)	0.88 (0.40; 1.96)
Tertiary	0.99 (0.47; 2.07)	1.57 (0.66; 3.77)	1.70 (0.71; 4.09)
Current living arrangement			
Lives alone (reference)	1.00	1.00	1.00
Lives with family & friends	1.61 (0.74; 3.54)	2.00 (0.76; 5.22)	2.09 (0.79; 5.50)
Marital status			
Married/Living Together (reference)	1.00	1.00	1.00
Widowed/Divorced/Separated	2.07 (1.03; 4.12)	1.54 (0.66; 3.58)	1.61 (0.69; 3.75)
Single	1.13 (0.59; 2.15)	0.88 (0.42; 1.84)	0.97 (0.46; 2.05)
Use of alcoholic beverages			
No (reference)		1.00	1.00
Yes		5.51 (1.76; 17.20)	**6.07 (1.89; 19.46)***
Substance use			
No (reference)		1.00	1.00
Yes		0.66 (0.32; 1.36)	0.68 (0.33; 1.40)
Use of tobacco products			
No (reference)		1.00	1.00
Yes		1.75 (0.80; 3.81)	2.19 (0.97; 4.95)
Blood pressure			
Normal (reference)		1.00	1.00

Factor	Model 1 aOR (95% CI)	Model 2 aOR (95% CI)	Model 3 aOR (95% CI)
Age	**1.00 (0.97; 1.02)**	**0.98 (0.95; 1.01)**	**0.98 (0.95; 1.02)**
Sex at birth			
High		1.71 (0.91; 3.21)	1.89 (0.99; 3.61)
Body mass index		0.97 (0.92; 1.02)	0.97 (0.93; 1.03)
Negative life events			
No (reference)		1.00	1.00
Yes		1.90 (0.89; 4.03)	**2.16 (1.00; 4.66)***
Chronic conditions			
Arthritis		0.88 (0.34; 2.25)	0.91 (0.36; 2.33)
Chronic back/neck pain		0.91 (0.45; 1.85)	0.91 (0.45; 1.85)
Frequent headaches		1.86 (1.01; 3.43)	**1.89 (1.02; 3.50)***
Cancer		0.39 (0.04; 3.73)	0.40 (0.04; 3.76)
Kessler psychological distress score		1.25 (1.20; 1.30)	**1.26 (1.21; 1.31)***
Psychosis screening			
Past year		0.88 (0.31; 2.45)	0.89 (0.32; 2.49)
Lifetime		1.91 (0.80; 4.55)	1.97 (0.82; 4.72)
Country geographical location			
Southern Africa (reference)			1.00
Eastern Africa			2.12 (0.88; 5.09)
ICC	0.18 (0.03; 0.59)	0.15 (0.09 ; 0.36)	0.14 (0.09 ; 0.32)

Factors associated with lifetime major depressive disorder

In the multilevel models, age and sex were significant predictors of lifetime MDD. Increased age was negatively associated with MDD (adjusted odds ratio (aOR) of 0.98 [95% CI: 0.97; 0.99]) in the fully adjusted model). Males had significantly lower lifetime MDD compared to females (OR of 0.69 [95% CI: 0.50; 0.94]). Education, living arrangements and marital were not significantly associated with MDD. Several behavioural and health-related factors were also significantly associated with MDD. Alcohol consumption was also associated with MDD (aOR of 1.41 [95% CI: 1.03; 1.93]), while substance and tobacco use were not significantly associated with MDD. Experiencing negative life events was strongly associated with MDD, with those reporting such events having more than twice the odds (aOR = 2.32, [95% CI: 1.72; 3.13]) compared to

those who did not. Among chronic conditions, chronic back/neck pain (aOR = 1.53 [95% CI: 1.15; 2.04]) and frequent headaches (aOR = 1.63 [95% CI: 1.25; 2.12]) were significantly associated with MDD, while other chronic conditions like arthritis and cancer were not. Higher scores on the K10 were also asspciated with MDD (aOR = 1.17 [95% CI: 1.14; 1.19]). Additionally, psychosis screening results showed that both past-year psychosis experiences (aOR = 0.49 [95% CI: 0.30; 0.79]), and lifetime psychosis experiences were associated with MDD (aOR = 2.92 [95% CI: 2.11; 4.03]). Geographical location was not a significant factor, as odds of MDD did not statistically differ between individuals from Eastern Africa and those from Southern Africa. The ICC for the fully adjusted model was 0.24 [95% CI: 0.05; 0.64], indicating that 24% of the variance in MDD was attributable to differences between countries. These results are summarized in Table 3b.

Table 3

b: Results of fitting multilevel logistic regression model for factors associated with lifetime major depressive disorder. CI = confidence intervals, aOR = adjusted odds ratios, ICC = intraclass correlation coefficient, *p < 0.05.

Factor	**Model 1**	**Model 2**	**Model 3**
	aOR (95% CI)	**aOR (95% CI)**	**aOR (95% CI)**
Age	**0.99 (0.98; 1.00)**	**0.98 (0.97; 0.99)**	**0.98 (0.97; 0.99)***
Sex at birth			
Female (reference)	1.00	1.00	1.00
Male	0.66 (0.51; 0.55)	0.69 (0.50; 0.95)	**0.69 (0.50; 0.94)***
Highest Level of Education			
Primary or less (reference)	1.00	1.00	1.00
Secondary	0.84 (0.63; 1.13)	1.00 (0.73; 1.38)	1.00 (0.72; 1.38)
Tertiary	1.17 (0.84; 1.62)	1.63 (1.13; 2.36)	1.63 (1.13; 2.36)
Current Living Arrangement			
Lives alone (reference)	1.00	1.00	1.00
Lives with family or friends	1.09 (0.79; 1.51)	1.02 (0.72; 1.46)	1.02 (0.72; 1.46)
Marital Status			
Married/living together (reference)	1.00	1.00	1.00
Widowed/divorced/separated	1.49 (1.07; 2.08)	1.36 (0.94; 1.97)	1.36 (0.94; 1.97)
Single	0.92 (0.69; 1.22)	0.90 (0.66; 1.23)	0.90 (0.66; 1.22)
Use of alcoholic beverages			
No (Ref)		1.00	1.00
Yes		1.41 (1.03; 1.94)	**1.41 (1.03; 1.93)***
Substance use			
No (reference)		1.00	1.00
Yes		1.12 (0.81; 1.55)	1.12 (0.80; 1.55)
Use of tobacco products			
No (reference)		1.00	1.00
Yes		1.37 (0.97; 1.94)	1.37 (0.97; 1.93)
Blood pressure			
Normal (reference)		1.00	1.00

Factor	Model 1 aOR (95% CI)	Model 2 aOR (95% CI)	Model 3 aOR (95% CI)
Age	**0.99 (0.98; 1.00)**	**0.98 (0.97; 0.99)**	**0.98 (0.97; 0.99)***
Sex at birth			
High		0.95 (0.72; 1.25)	0.95 (0.72; 1.25)
Body mass index		1.01 (0.99; 1.04)	1.01 (0.99; 1.04)
Negative life events			
No (reference)		1.00	1.00
Yes		2.33 (1.73; 3.14)	**2.32 (1.72; 3.13)***
Chronic conditions			
Arthritis		0.91 (0.58; 1.43)	0.91 (0.58; 1.43)
Chronic back/neck pain		1.53 (1.15; 2.04)	**1.53 (1.15; 2.04)***
Frequent headaches		1.63 (1.25; 2.12)	**1.63 (1.25; 2.12)***
Cancer		0.53 (0.16; 1.70)	0.53 (0.16; 1.70)
Kessler psychological distress score		1.17 (1.14; 1.19)	**1.17 (1.14; 1.19)***
Psychosis screening			
Past year		0.49 (0.30; 0.79)	**0.49 (0.30; 0.79)***
Lifetime		2.92 (2.11; 4.04)	**2.92 (2.11; 4.03)***
Country Geographical location			
Southern Africa (reference)			1.00
Eastern Africa			0.63 (0.05; 7.13)
ICC	0.39 (0.12; 0.75)	0.24 (0.05; 0.65)	0.24 (0.05; 0.64)

Discussion

Prevalence

An overall prevalence of 0.9% was observed for current MDD and prevalence of 0.1–2.1% were observed across all the study countries. The observed overall prevalence was lower than the estimated global current prevalence of 3.4% MDD.[3] The overall prevalence of lifetime MDD in this study was 5.1%. This prevalence is lower than the estimated lifetime prevalence of 14.6% and 11.1% which has been reported for MDD in high and low- and middle-income countries respectively.[20] However, this prevalence is comparable to the prevalence of 4.5% which has been reported in SSA for MDD[3] and similar to the prevalence of 5.4% which has been reported

for Africa.[5] The low prevalence for MDD in SSA could be due to several factors which often involve a complex interplay of cultural, social and methodological issues. In many cultures across SSA, MDD may not be recognized in the same way MDD presents in other contexts. The diagnostic tools developed primarily in Western contexts may not be sensitive to the cultural expression of depression in African populations leading to misdiagnosis. This can be exacerbated by the immense cultural and linguistic diversity which exist in Africa. There might also exist unique resilience factors and coping mechanisms which could be protective against the development or recognition of depressive symptoms. This is need to understand how this factors interact to influence the development of MDD in Africa. Also, lifetime MDD prevalence are higher than current MDD prevalence due to the broader time frame which captures any instance of MDD throughout a person's life and the episodic nature of MDD.

For South Africa, the observed current and lifetime prevalence of MDD (2.1% and 8.4% respectively) are less than the prevalence of 4.9% and 9.8% which have been reported for point and lifetime MDD respectively in South Africa.[21,22] For Uganda, the observed current and lifetime prevalence of MDD (0.7% and 7.9 respectively) are much lower than the pooled prevalence of 20.8% which was reported among general populations in Uganda by a systematic review and meta-analysis.[10] For Ethiopia, the observed current and lifetime prevalence of MDD (0.5% and 1.2% respectively) are much lower than the prevalence of 5.3% and 17.4% which have been reported for current and lifetime MDD respectively.[23] For Kenya, the observed current and lifetime prevalence of MDD (0.5% and 1.2% respectively) are much lower than the prevalence of 4.4% which has been reported among general populations in Kenya.[9]

The variations of prevalence by study country is intriguing and could be due to several factors such as socioeconomic factors, cultural differences and stigma and awareness. Higher prevalence for South Africa and Uganda might correlate with socioeconomic stressors such as poverty, unemployment, and social inequality that can contribute to higher rates of depression. For example, South Africa has been reported to have a significant income inequality and high levels of unemployment.[24] Ethiopia and Kenya, with lower rates, might have different socioeconomic dynamics, or there may be other protective factors at play, such as stronger community and family support systems. Cultural norms can influence how individuals express emotions or depression. In some cultures, it's common to express MDD through physical symptoms rather than psychological terms, which could lead to underdiagnosis of MDD. There is need to understand potential ecological factors responsible for variations in the prevalence of MDD across various regions in SSA.

Factors associated with major depressive disorder

Per year increase in age was associated with lower odds for lifetime MDD. Directions of associatons between age and depression have been inconsistent. A large literature review and meta-analysis has reported depression to be more prevalent among elderly populations [25] while analysis of large national health data from the United States has reported MDD to be more prevalent among young adults aged 18–29 years.[26] There is no clear explanation for the association between increasing age and lower odds for MDD in our study participants. However, several factors such as ocio-cultural differences, socioeconomic, demographic and access to mental health services could be responsible. For example, there may be better economic conditions and pension schemes for older adults, there may be more awareness and access to mental health care for old as compared to young adults. Younger adults in SSA may face more socioeconomic hardships and

unemployment. There is need to understand how these factors may influence the risk for MDD across the lifespan in SSA in order to inform targeted mental health interventions.

Male sex at birth was associated with lower odds for MDD. This finding is in line with findings from a large systematic analysis of the global burden of MDD in 2014 between 1990–2019, which reported MDD burden to be more among females as compared with males [3]. Additionally, a large systematic review and meta-analysis of the epidemiology of MDD among people living with HIV in SSA, also reported the prevalence of MDD to be much higher among women as compared to men.[27] Although underlying biological mechanisms for sex disparity in MDD are not well known, sex hormones have been postulated to play a role. In addition to the role of genetics and environmental factors like stress, sex hormone status has been postulated to be a third factor which contributes to changes in the epigenome, whose effect may translate into changes in gene expression and brain structure and function,[28] thus resulting in increased vulnerability for MDD in women.

Alcohol use was associated with higher odds for MDD. This finding is in line with findings from a large systematic review and meta-analysis of cohort studies which reported an association between alcohol use and MDD.[29] However, it was observed that this association became nonsignificant when confounders were controlled for, suggesting that alcohol use could be leading to MDD through confounders. For example, unemployed individuals are more likely to abuse drugs and be heavy alcohol users and to suffer from MDD.[30]

Witnessing or experiencing traumatic life events was associated with higher odds for MDD. This finding is in agreement with findings from previous studies which reported traumatic life events to have a strong relationship with depression[31] including studies in Uganda that found an increased risk of MDD with increasing negative life events.[12,32] Previous studies have also found that recent traumatic life events play a key role in the onset of MDD.[33] However, onset of MDD and the timing of the negative life events were not determined by the parent study and so this could not be properly investigated in this study.

Chronic neck or back pain was associated with higher odds for MDD. This finding is in line with previous studies which have reported associations between chronic pain and depression and have proposed that this could be mediated through altered neuroplasticity.[34] This relationship has been found to be influenced by anomalies in neurological function that lead to chronic pain preceding depression and depressive symptoms.[34] Back pain in general has been associated with increased risk for MDD among middle aged adults in six countries including Ghana and South Africa.[35] Additionally, a study in southwestern Uganda also found an association between reported back pain and MDD among elderly persons living with HIV/AIDS.[36]

Frequent headaches were associated with higher odds for MDD. This finding is in agreement with findings from a systematic review and meta-analysis which reported migraines (frequent headaches) to be a risk factor for incident cases of MDD in both cross-sectional and cohort studies.[37] However, this relationship could be bidirectional as MDD has also been found to be causal to different forms of frequent headaches by a Mendelian randomization study [38]. Frequent headaches have been suggested to lead to or exacerbate MDD through neurotransmitter imbalances, particularly serotonin and norepinephrine which affect both pain perception and mood.[39] Chronic pain from headaches can impact daily life and contribute to the development or worsening of MDD.

Per unit increase in K10 score was associated with higher odds for both current and lifetime MDD. This is not surprising as the K10 score measures psychological distress and the K10 tool has items which assess for both depression and anxiety symptoms a person has experienced in the most recent 4 week period.[40] The K10 score could be used as tool which can identify people who are at risk of developing MDD in SSA for early intervention to reduce the overall burden of MDD on individuals and healthcare systems.

Lifetime positive screening for psychosis was associated with higher odds for MDD. This could could be due to a fact that some people who suffer from MDD normally report symptoms of psychosis such as delusions and hallucinations.[41] The form of MDD with psychotic features is termed psychotic depression according to the International Classification of Diseases 11th revision.[42] Psychotic depression has been reported to be a risk factor for psychosis in patients whose index depression had psychotic features [43] hence the need for effective preventative treatments. Psychotic depression is hard to treat and has been reported to be unresponsive to an antidepressant alone.[41] Elevated levels of cortisol have been suggested to be responsible for this form of depression.[44,45] Paradoxically, a past year positive screening for psychosis was associated with lower odds for MDD. There is no direct explanation for this observation. However, acute management and treatment could mitigate the symptoms of MDD. Indeed, atypical antipsychotics have been reported to have a direct preventive effect on the development of depressive symptoms during management of acute psychosis.[46]

The proportion of variance in the prevalence of MDD across the study countries was moderate (14%) for current MDD and moderately large (24%) for lifetime MDD. There is thus a need to understand the specific risk factors for MDD across different groups or communities in Africa. Also, given that moderately large proportion of variance is contributed by country level factors, country level intervention strategies could be effective in mitigating MDD rather than individual level strategies – which would likely be less feasible. In addition, the higher proportion in variance for lifetime MDD potentially suggests that persistent regional-level factors are influential and perhaps reflect long-standing regional-level characteristics, cultural factors or structural factors that affect MDD over the lifespan.

Limitations

We could not elucidate the causation of MDD given the cross-sectional nature of the study. Also, in assessing life-time MDD, we relied on the respondents' memory and recall bias which may potentially have resulted in a systematic bias against the recall of temporally distant events. In addition, given the selection criteria for the participants from the hospital settings, our study participants may not truly represent a general population. Additionally, given that participation was volunteer based, we may not have captured people the most severely affected by MDD hence the likelihood of underrepresentation of the most disadvantaged people in the communities studies. Also, since the diagnostic tool used was developed in Western contexts, this could be less sensitive to the cultural expression of MDD in African populations hence leading to misdiagnosis.

Conclusions

This study investigated several factors associated with MDD in participants present at general medical facilities from a majorly African ancestry population. The main findings from the phenotypic analysis were that among the study participants, being female, using alcohol, experiencing or witnessing negative life events, having higher levels of psychological distress and suffering from chronic conditions of either chronic back or neck pain were associated with higher odds for MDD while per year increase in age was associated with lower odds for depression among the study participants. These results suggest that psychosocial factors as well as psychosomatic complaints and physical comorbidities are important risk factors for MDD among the participants for this study.

Methods

Study design

This study was undertaken using data collected by the NeuroGAP-Psychosis study. Details about the NeuroGAP-Psychosis study, the data variables collected and the tools used have been reported by Stevenson and colleagues.[47] In brief, the NeuroGAP-Psychosis study recruited a total of 42,953 participants (21,715 cases of psychosis, 21,238 psychosis-free controls) from four African countries of Uganda, Kenya, Ethiopia, and South Africa over a 5-year period (2018–2023). The aim of the NeuroGAP-Psychosis study is to investigate the genetic risk for psychosis. Each study participant provided a saliva sample from which DNA was extracted and shipped to the Broad Institute in the United States, from where the DNA was sequenced. Out of the 21,715 NeuroGAP-Psychosis study's control participants, a total of 7,073 adult participants were assessed for current and lifetime MDD using the Mini-International Neuropsychiatric Interview (MINI, standard version 7.0.2)[48] and are included in this analysis. The NeuroGAP-Psychosis study's control participants were ascertained from persons who presented at University-affiliated general medical hospitals that draw from similar catchement areas to the psychiatric facilities where the psychosis cases for the NeuroGAP-Psychosis study were recruited. NeuroGAP-Psychosis study control participants were 1) caretakers who had accompanyed someone else to an appointment, 2) students/workers at the hospital/clinic or 3) someone who had visited for a prescription refill or doctor's appointment.

Clinical investigations

A questionnaire (module A of the MINI) was administered by trained research assistants onto the study participants at each of the study sites. Assessment of MDD based on presence of at least one of symptoms of either a depressed mood or loss of interest in pleasurable activities and any other four symptoms which may include significant weight change or apetite disturbance, sleep disturbances, psychomotor agitation or retardation, fatigue, feelings of worthlessness or excessive guilt, diminished ability to think or concentrate and recurrent thoughts of death or suicidal ideation. Additionally, these symptoms had to cause significant distress or impairment in social, occupational or other important areas of functing and were not a result of physiological effects of a substance or another medical condition. For current MDD, presence of symptoms in the last two weeks was assessed while for lifetime MDD, the presence of these symptoms in a participant's lifetime was assessed. The five-item version of the psychosis screening questionnaire (PSQ)[49] was used to screen for psychosis symptoms. The Kessler psychological distress scale (K10)[40] was used to assess for

psychological this. This is a ten-item questionnaire based on questions about symptoms for anxiety and depression. The Life events checklist for DSM-5 (LEC-5)[50] was used to assess for negative life events. This checklist assesses exposure to sixteen events known to potentially results in post-traumatic stress disorder or distress. The World Health Organization Alcohol, Smoking and Substance Involvement Screening Test (ASSIST, version3)[51] was used to assess for lifetime use of alcohol, tobacco and other substances. The Composite International Diagnostic Interview (CIDI) screener[52] was used to assess for chronic conditions such as arthritis or rheumatism, chronic back or neck pain, frequent or severe headaches, cancer, among others.

Ethical considerations

The NeuroGAP-Psychosis study was conducted in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Ethical and scientific clearance for the NeuroGAP-Psychosis study was obtained from each of the study sites as shown in the following sentences; Uganda: The Makerere University School of Medicine Research and Ethics Committee (SOMREC #REC REF 2016-057) and the Uganda National Council for Science and Technology (UNCST #HS14ES); Kenya: Moi University College of Health Sciences/Moi Teaching and Referral Hospital Institutional Research and Ethics Committee (IREC) (#IREC/2016/145, approval number: IREC 1727), Kenya National Council of Science and Technology (#NACOSTI/P/17/56302/19576), KEMRI Centre Scientific Committee (CSC#KEMRI/CGMRC/CSC/070/2016), KEMRI Scientific and Ethics Review Unit (SERU# KEMRI/SERU/CGMR-C/070/3575); Ethiopia: Addis Ababa University College of Health Sciences (#014/17/Psy) and the Ministry of Science and Technology National Research Ethics Review Committee (#3.10/14/2018); South Africa: The University of Cape Town Human Research Ethics Committee (#466/2016); and USA: The Harvard T.H. Chan School of Public Health (#IRB17-0822). Participants provided written informed consent for their genetic and health information to be used in future research. Participants' priorities and experiences were taken into consideration during the design of the NeuroGAP-Psychosis study.

Data analysis

All statistical analyses were conducted using STATA version 18.0. Descriptive statistics were used to summarize socio-demographic characteristics, including sex, age, marital status, living arrangement, education level, study country, and body mass index, as well as clinical characteristics such as tobacco use, alcohol use, substance use, and blood pressure. Categorical variables were summarized using frequencies and percentages, while continuous variables were reported as medians with interquartile ranges (IQR). The prevalence of both current and lifetime MDD was estimated for each study country, along with corresponding 95% confidence intervals.

To examine factors associated with MDD, we employed a multilevel logistic regression model to account for the hierarchical structure of the data, with individuals nested within four different countries. Model selection was guided by the likelihood ratio test (LRT) to ensure that only variables that significantly improved model fit were retained. The modeling process followed a sequential approach. First, model 1 included key socio-demographic variables (age, sex, education level, living arrangement, and marital status), selected a priori based on theoretical and empirical evidence. Model 2 extended model 1 by incorporating individual-level

behavioral and clinical characteristics, including alcohol use, substance use, history of traumatic life events, and current physical illness. Variables were retained only if their inclusion significantly improved model fit based on LRT. Finally, model 3 introduced country-level characteristics, such as geographical location, to assess their influence while controlling for individual-level factors.

The intraclass correlation coefficient (ICC) was calculated for each model to quantify the proportion of total variance attributable to between-country differences. A variable was considered to be meaningfully associated with MDD only if it remained statistically significant in the final model and contributed to model fit as determined by LRT. To assess the robustness of the findings, a sensitivity analysis was performed by systematically excluding individual countries and re-estimating the models. A two-sided p-value < 0.05 was considered statistically significant.

Declarations

Data availability

The data that support the findings of this study are available via the National Institute of Mental Health Data Archive. Data are also available from the authors upon reasonable request and with permission of the NeuroGAP-Psychosis study consortium.

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Competing interests

We declare no competing interests.

Author contributions

Conceptualization: AK, DHA, EK, SF; Statistical analysis: WS, AK; First draft: AK; Critical review & Final draft: All authors. All authors approved the final manuscript. All authors had full access to all the data and had final responsibility for the decision to submit for publication. RES, SF and DHA accessed and verified the data.

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