1   **Relationship between depressive symptoms and cumulative 24-hour urinary norepinephrine**

2   **excretion level among undergraduate medical students in Uganda**

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Abstract

Background

17 Depression is a serious mental health problem in different parts of the world and has been reported

18 to be rising among undergraduate medical students. The incidence of depression has not only been

19 linked to psychosocial factors but also to biological factors, such as altered urinary levels of

20 norepinephrine. This study was carried out to determine the prevalence of depression among

21 undergraduate medical students in Uganda and examine the relationship between depressive

22 symptoms and 24-hour urinary norepinephrine excretion levels in the participants.

Methods

24 One hundred and sixteen undergraduate medical students (75 males and 41 females) of Kampala

25 International University, in southwestern Uganda were evaluated for depression using the 21-item

26 Beck Depression Inventory-II (BDI) questionnaire. Twenty-four-hour urine collections from each

27 participant were assayed for norepinephrine excretion levels. Descriptive statistics and Pearson

28 correlation coefficient were computed to examine the data obtained.

Results

30 The results of this study showed that, a total of 33 participants (28.4%) have depressive symptoms.

31 Students with depressive symptoms had higher but not significant 24-hour urinary mean

32 norepinephrine excretion levels than those without depressive symptoms (121.97±51.48μg/day Vs

33 87.58±18.64 μg/day, P>0.05). There was a positive weak relationship between BDI scores and 24-

34 hour urinary norepinephrine levels (r= 0.21, p = 0.28). Regression models accounting for socio-

35 demographic characteristics indicated that, type of accommodation, marital status, relationship

36   with parents, educational sponsorship may be risk factors for depressive symptoms observed in

37   the participants.

Conclusions

39   These results suggest that increased urinary norepinephrine excretion and other psychosocial

40   factors may be associated with depressive symptoms. Measurements of 24-hour urinary

41   norepinephrine excretion may serve as an integrative parameter in diagnosing and management of

42   patients with depression.

Introduction

Depression is one of the most common mental disorders affecting people of different ages, gender and socio-cultural settings in both developed and developing countries. It has been declared by the World Health Organization as one of the global leading causes of morbidity and mortality contributing significant economic burden on societies worldwide [1-5]. Studies have suggested that medical students are at high risk of developing depression and this has been associated with significant reduction in productivity, disruption in learning, poor interpersonal relationships with peers and consequently poor academic grades and in some cases termination of schooling which often leads to substance abuse and suicidal behavior [6-8]. Since depression among medical students have such an obvious negative effect on function in medical school and later in clinical practice, it is important to examine the prevalence, causes and diagnosis of the disorder in medical students. The prevalence and risk factors for depression in Ugandan university students has not been well studied in Uganda. The few available studies have examined depression amongst adolescents in secondary schools [9], traumatized individuals [10] and among persons living with human immune deficiency virus (HIV) infection [11]. Although psychosocial problems had been reported among the undergraduate students in Uganda [12], no study has examined the link between socio-demographic factors and biological effects of the disease in this population.

Previous research has suggested that enhanced activity of the hypothalamic–pituitary–adrenal (HPA) axis with concomitant increased concentrations of catecholamines such as serotonin (5-HT), norepinephrine (NE), and dopamine (DA) plays an etiological role in the onset and development of depressive symptoms [13, 14]. Serotonin and DA have been the most studied neurotransmitters in depression, however, converging lines of evidence suggest that the NE pathway is of major importance in the pathophysiology and treatment of depressive disorder [15-

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66   18]. The noradrenergic system uses NE as the main chemical messenger and serves multiple brain

67   functions including arousal, motivation, attention, mood, learning, memory and stress response

68   [19]. Higher NE levels have been linked to low socioeconomic status [20]. Neuroactivities of NE-

69   selective tricyclic antidepressants such as desipramine and nortriptyline indicates that NE could

70   be majorly involved in NE neurotransmission in depression [21]. These studies provide a rationale

71   for measuring NE output in depression and invoke NE as player in etiology of this disorder.

72   Studies have highlighted a need for biomarkers in psychiatry to enhance patient

73   management and ensure treatment success [22, 23]. While urinary measures of neurotransmitters

74   are not a direct assessment of central nervous system activities, urinary excretion of

75   neurotransmitters or their metabolites have been characterized as biomarkers of various

76   neurological conditions [24, 25]. Thus, the urinary excretion of NE may act as a biomarker in

77   diagnosing and management of patients with depression. Given the high prevalence and costs of

78   depression, the impairment associated with depression, and the difficulty in treating depression

79   once it has developed, efforts to improve the early detection of depression and treat it as soon as

80   possible are warranted. This study was therefore, designed to examine the association between

81   prevalence of depressive symptoms and 24-hour (24-h) urinary NE excretion levels in a

82   representative sample of undergraduate medical students in Uganda. The results obtained maybe

83   important in the efforts to identify the causes and diagnosis of the disorder among medical students.

Materials and methods

Participants

86   One hundred and sixteen (116) male and female students were studied in the Faculty of Biomedical

87   Sciences in the School of Health Sciences of Kampala International University, Uganda. The

88   students in biomedical sciences are made up of three group of classes which include students in

89 semesters one to three respectively. Each class was considered to be a cluster and using the

90 appropriate allocation method of sampling, one class was randomly selected from the three classes.

91 Thus, all the 169 students in the selected class constituted the participants of the present study. Of

92 these, the relationship of depressive symptoms with 24-h urinary NE excretion levels was

93 evaluated in 75 males and 41 females (n = 116). These participants returned the questionnaires

94 and their urine samples were verified to meet the collection and storage criteria during the 24-h

95 collection period. All participants had no history of cardiovascular or metabolic diseases.

96 A coded self-administered questionnaire requesting information on the participant's

97 age, sex, marital status, family type, financial support, parental loss, occupation, type of

98 residence and nationality were filled by all participants. To ensure reliability in the participant's

99 response, validation and reliability studies were done in pre-test on 25 students in another class.

100 Cronbach's alpha was used to measure the reliability of the questions. The results showed that

101 the questionnaire has high validation and reliability scores with a Cronbach's alpha coefficient

102 of 0.8. All experimental protocols were approved by the Institutional Research Ethics

103 Committee (IREC) of Mbarara University of Science and Technology, Uganda. Informed

104 consent was obtained from all participants prior to participation in this study. Confidentiality

105 of information was maintained by ensuring that codes but not names were used to label the

106 study tools.

Determination of depressive symptoms

108 The prevalence of depressive symptoms among participants was determined using the Beck

109 Depression Inventory (BDI) scale-II. The BDI scale is a well-validated and widely used 21-

110 item self-report instrument developed to evaluate the presence and severity of depression in

111 adults and adolescents in non-clinical settings [26-30]. In this study, participants were advised

112   to choose an option for each question that best described their feelings over the preceding week.

113   Responses to the 21 items were summed up to give their depressive status on a 4-point scale

114   giving a maximum score of 63. Participants with BDI score of 0-9 were categorized as normal,

115   scores of 10-18 were indicative of mild mood disturbance, scores of 19-29 were indicative of

116   moderate depression, scores of 30-40 were indicative of severe depression and those with score

117   of 40 and over were categorized as having very severe depression.

118   The prevalence of suicide ideation was measured with a frequency count of "yes"

119   response to each of the following questions: a) Have you ever experienced suicide thoughts

120   along with the wish to end your life by suicide? b) Did you experience suicide thoughts along

121   with the wish to end your life by suicide last week? The participants found to have depressive

122   symptoms or suicide ideation were instructed to discuss these symptoms with a physician for

123   further evaluation and treatment.

24-hour urine collection

125   Participants were provided with 3-liter opaque collection jugs containing a preservative (10 ml

126   of 6N hydrochloric acid, pH < 3.5) and a smaller 100 ml specimen bottles containing no

127   preservative. The 3-litre collection jug was labelled with a code similar to that of the BDI and

128   questionnaire earlier completed by the participant. To ensure urine collection during a typical

129   day under typical conditions, the participants were asked to collect urine in their residential

130   environment during a 24–h period.

131   They were instructed to collect all urine passed during the target period (Saturday to

132   Sunday when there are no scheduled lectures or university activities). The collection of the 24-h

133   urine started with the participant voiding (completely emptying bladder) and discarding the first

134   urine passed on Saturday morning. Thereafter, they were instructed to collect all of the urine

135   passed during that day and night including urine passed during bowel movements, up to and

136   including the first voiding of the following day (Sunday). Each urine sample was first collected

137   into the smaller container for ease of convenience and immediately transferred into the 3-litre

138   collection jug containing preservative. The participants were asked to keep the urine collection

139   jug tightly closed and refrigerated or kept in a cool place throughout the collection period. No

140   dietary restrictions were enforced; however, participants were advised to discontinue taking all

141   medications for an interval of at least 12 hours preceding the urine collection period.

142   To ensure compliance with the collection protocol, mobile phone numbers of every five

143   participants were assigned to a research assistant who sent four reminder messages at different

144   times within the 24-h period to continue with collection and to verifying that the urine jugs were

145   properly stored. If it was discovered that, a participant did not adhere to the collection protocol or

146   if the volume collected was less than 1 litre, the participant was asked to repeat the collection the

147   following weekend. In the laboratory, the volume of cumulative 24-h urine samples was recorded

148   and stirred thoroughly, separated into 10 ml aliquots in a sterile sample bottles, and then stored in

149   the laboratory refrigerator prior to analysis.

Measurement of 24-hour urinary norepinephrine

151   Quantitative measurement of NE in each urine sample was performed by enzyme immunoassay

152   (EIA) following a protocol described in detail by the manufacturer of the assay kit (Abnova, UK).

153   Westermann, et al [25] established the accuracy and reproducibility of the enzyme linked

154   immunoassay methodology for NE as compared to previously validated high-pressure liquid

155   chromatography (HPLC) methodology. The authors concluded that EIA measures for urinary NE

156   are appropriate for clinical applications as they were rapid, accurate, and reproducible.

Sample pre-treatment

157
158   An aliquot (10 µl) of working standard and 10 µl of urine samples were added to borate-coated

159   wells of a macrotiter plate. To these, 250 µl of double distilled deionised water was added. 50µl

160   of assay and extraction buffer (0.1 mol/L Tris-HCL buffer, 0.7 mol/L NaCl, 0.1 mol/L EDTA,

161   0.3 mmol/L $Na_2S_2O_5$, pH 9.3) were added to each well of the plate respectively. The plates were

162   covered with adhesive foil and incubated for 30 min at room temperature on a shaker (approx.

163   600 rpm) after which the plates were emptied and blotted dry by taping the inverted plate on

164   absorbent material. Thereafter, 150 µl of acylation buffer was added to the wells respectively.

165   The plates were incubated for further 15 min at room temperature on a shaker (approx. 600

166   rpm). Wash buffer (1 mL) was pipetted into the wells and the plates incubated for 10 min at

167   room temperature on a shaker (approx. 600 rpm). 150 µl of hydrochloric acid was added into

168   the wells and the plates were covered with adhesive foil. The plates were further incubated for

169   10 min at room temperature on a shaker (approx. 600 rpm) after which the foil was discarded

170   and 20 µl of the supernatant was removed for subsequent norepinephrine EIA.

Enzyme Immunoassay

172   The enzyme solution (25 µl) was added into all wells of the NE microtiter strips followed by the

173   addition of 20 µl of the extracted standards and urine samples into the appropriate wells. The

174   solution was incubated at 37 °C for 30 min on a shaker. NE antiserum (50 µl) was added to the

175   wells and covered with adhesive foil. The preparation was further incubated for 2 hours at room

176   temperature on a shaker (approx. 600 rpm). Thereafter, the foil was removed and the content of

177   the wells aspirated. The plates were then washed 3x by adding 300 µl of wash buffer (0.02 mol/L

178   Tris-HCl buffer, 0.1 mol/L NaCl, 5 mmol/L KCl, 0.2% Tween 80, pH 7.3) discarding the content

179   and blotting dry each time by tapping the inverted plate on absorbent material. 100 µl of the

180   enzyme conjugate were then added to all the wells. The plates were incubated for 30 min at room

9

181   temperature on a shaker. The contents of the wells were discarded and the plates were washed 3x

182   by adding 300 µl of wash buffer, discarding the content and blotting dry each time by tapping the

183   inverted plate on absorbent material. 100 µL of the substrate was added to all wells and incubated

184   for 25 ± 5 min at room temperature on a shaker. The reaction was stopped when an orange color

185   was developed in positive wells by adding 100 µL of the stop solution to each well.

186   The microtiter plate was shaken to ensure a homogeneous distribution of the solution. The

187   developed color intensity is proportional to the NE concentration in the sample. The absorbance

188   of the solution in the wells were read within 10 minutes, using a microplate reader set to 540 nm.

189   Quantification of unknown samples was achieved by comparing their absorbance with a standard

190   curve prepared with known standard concentrations. The standard curve was obtained by plotting

191   the absorbance readings against the corresponding standard concentrations. The concentrations of

192   NE in the urine samples were read directly from the standard curve. The normal reference range

193   for the assay was < 90 µg/day for norepinephrine.

Statistical analysis

195   Analysis of data was performed with Microsoft Excel for Mac (2016). The Data obtained for socio-

196   demographic characteristics of participants, 24-h NE levels and prevalence of depressive

197   symptoms were expressed as mean ± standard deviation (SD) or number or percentage. Differences

198   in the amount of NE in 24-h urine samples in normal and individuals exhibiting depressive

199   symptoms were analysed using independent t-test. Correlations between depressive symptoms and

200   levels of NE in 24-h urine samples were assessed using Pearson correlation coefficient and Chi-

201   square tests to identify significant predictors of depression. Odds ratios (OR) and 95% confidence

202   intervals were also calculated for each variable. All p-values were two-tailed, with a p-value of <

203   0.05 considered to be of statistical significance.

Results

204

205 The study group included 75 men and 41 women representing 64.7% and 35.3% respectively. The

206 age of participants ranged from 17 to 45 years with a mean (±SD) of 24.6±5.7 years. The socio-

207 demographic data of all 116 participants are shown in Table 1. A total of 20 (17.2%) of the

208 participants are married, 52 (44.8%) are single, 42 (36.2%) are in a relationship and 2 (1.7%) are

209 divorced. Of all the participants, 81 (69.9%) were from a polygamous family and 35 (30.1%) were

210 from a monogamous family. Majority of the participants were Ugandans (78.5%) followed by

211 Kenyans and Nigerians (10%) respectively. They mainly lived in rented-room or house outside the

212 campus (81.9%) while 10.3% and 7.8% were living in the university hostel and with parents or

213 relatives respectively. Among participants that have religion, 80.2% and 16.4% of participants

214 consider themselves as practicing Christians and Muslims respectively. Only 3.4% indicated that

215 they had no religion. Twenty-three participants (19.8%) had paid employment in addition to their

216 studentships. Most of the participants reported that, they were fully supported financially by their

217 relatives (42.2%). Others reported that, they were supported by their parents (19.8%), friends

218 (5.2%) and government scholarship (18.1%). The rest (14.7%) indicated that they were self-

219 sponsored.

220 **Table 1: Socio-demographic Characteristics of Participants** (*n = 116*).

Variable	Number	% or Mean ± SD
Gender		
Male	75	64.70%
Female	41	35.30%
Age (years)		
All	116	24.6 ± 5.7
Male	75	25.7 ± 5.7
Female	41	22.7 ± 5.1
Marital Status		
Married	20	17.20%

Single	52	44.80%
Divorced	2	1.70%
In a Relationship	42	36.20%
Occupation		
Student Only	93	80.20%
Part-time Job	23	19.80%
Practice of Religion		
Christian	93	80.20%
Muslim	19	16.40%
Others	4	3.40%
Residence		
University Hostel	12	10.30%
Renting a room/house	95	81.90%
Living with Parent/Relatives	9	7.80%
Financial Support		
Parents	23	19.80%
Friends	6	5.20%
Relatives	49	42.20%
Government Scholarship	21	18.10%
Self-sponsored	17	14.70%
Nationality		
Uganda	91	78.50%
Kenya	12	10.30%
Nigeria	12	10.30%
Rwanda	1	0.90%
Family Type		
Monogamous	81	69.90%
Polygamous	35	30.10%
Quality of Relation with Parents		
Good	94	81.00%
Moderate	19	16.40%
Poor	3	2.60%
Parental loss		
Both are Alive	48	41.10%
One Parent is Alive	26	22.40%
Orphan	42	36.20%
Age at Parental Loss		
≤ 10 years	12	17.60%
> 10 years	56	82.40%

221

Prevalence of depressive symptom among participants

223   Table 2 shows the proportion of participants whose BDI score indicated depressive symptoms.

224   The results indicated that 33 (28.4%) of the 116 participants exhibited depressive symptoms.

225   According to the cut off scores, those that were detected as having depressive symptoms

226   consisted of 16 (13.8%) cases of mild mood disturbance (BDI score of 10-18), 14 (12.1%) cases

227   of moderate depression (BDI score of 19-29) and 3 (2.6%) cases of severe depression (BDI

228   score of 30-40). There was no reported case of very severe depression (BDI score of >40).

229   **Table 2: Percentages of participants whose BDI Score indicated depression by gender (Mean =**
230   **9.04, SD = 7.4, Range: 1 – 45)**

BDI score	Male (n = 75)	Female (n = 41)	Total (n = 116)
Normal (0-9)	56 (48.3%)	27 (23.2%)	83 (71.6%)
Mild Mood Disturbance (10 -18)	10 (8.6%)	6 (5.2%)	16 (13.8%)
Moderate Depression (19-29)	8 (6.9%)	6 (5.2%)	14 (12.1%)
Severe Depression (30- 40)	1 (0.9%)	2 (1.7%)	3 (2.6%)

231

232   The incidence of depression was found to be more among male participants (16.4%)

233   when compared to female participants (12.1%) as shown in Fig 1. There were no significant

234   differences in mean depression scores in relation to age, sex, marital status, financial support or

235   type of residence (p >0.05). Among the depressed participants, 9 (7.8%) reported having

236   suicidal ideation over the past 2 weeks as compared to 8 (6.8%) of participants without

237   depressive symptoms (Table 3).

238   **Figure 1: Prevalence of Depression among Participants (*n = 116*)**

239   **Table 3: Bivariate Analysis of Risk Factors for Depressive Symptoms**

Variable	Depressive Symptoms	Non-Depressive Symptoms	X^2 (df)	P-value
	n (%)	n (%)		
Suicidal Ideation (n=116)				
Yes	9 (7.6)	8 (6.8)	17.005 (1)	0.0003
No	24 (20.7)	75 (64.5)		
Age Group in years (n =116)				
< 20	3 (2.6)	5 (4.3)	1.974 (3)	0.578
20 - 29	25 (21.6)	63 (54.3)		
30 - 39	3 (2.6)	13 (11.2)		
40 - 49	2 (1.7)	2 (1.7)		
Gender (n=116)				
Male	19 (16.4)	56 (48.3)	1.011 (1)	0.315
Female	14 (12.1)	27 (23.3)		
Residence (n=116)				
University Hostel	5 (4.3)	7 (6)	1.376 (2)	0.307
Renting a room/house	27 (23.3)	68 (58.6)		
Living with Parents or Relatives	1 (0.9)	8 (6.9)		
Financial Support (n=116)				
Friends	2 (1.7)	4 (3.4)	1.818 (4)	0.769
Government Scholarship	8 (6)	13 (12.1)		
Parents	3 (3.4)	20 (16.4)		
Relatives	15 (12.9)	34 (29.3)		
Self-sponsored	5 (4.3)	12 (10.3)		
Marital Status (n=116)				
Single	16 (13.8)	36 (31.0)	7.418 (3)	0.058
In a relationship	9 (7.8)	33 (28.4)		
Married	6 (5.1)	14 (12.3)		
Divorced	2 (1.7)	0 (0)		
Occupation (n=116)				
Student only	24 (20.7)	69 (59.5)	1.608 (1)	0.205
Part-time job	9 (7.8)	14 (12.1)		
Family Type (n=116)				
Monogamous	22 (19)	59 (50.9)	0.219 (1)	0.640
Polygamous	11 (9.5)	24 (20.7)		
Parent Loss (n=116)				
Both are alive	12 (10.3)	36 (31.0)	0.905 (2)	0.636
Only one is alive	7 (6.0)	19 (16.4)		
Orphan	14 (12.1)	28 (24.1)		
Quality of Relationship with Parents (n=116)				

Good	23 (19.8)	71 (61.2)		
Moderate	9 (7.6)	10 (8.6)	7.042 (2)	0.0296
Poor	1 (0.9)	2 (1.7)		

240

Relationship between depression and associated risk factors

242 The association between BDI scores with different psychosocial and demographic variables

243 was determined by bivariate and multivariate analysis. The results obtained for the bivariate

244 analysis are displayed in Table 3. The analysis did not indicate significant differences in

245 participants with depressive symptoms when compared to those without symptoms of

246 depression in relation to gender ($X^2 = 1.011$, df = 1, p = 0.315), age ($X^2 = 1.974$, df = 3, p =

247 0.578), type of residence ($X^2 = 1.376$, df = 2, p = 0.307), type of financial support ($X^2 = 1.818$,

248 df = 4, p = 0.769) and family type ($X^2 = 0.219$, df = 1, p = 0.640). However, there was a weak

249 and significant association of depressive symptoms with marital status ($X^2 = 7.418$, df = 3, p =

250 0.058) and the thoughts of committing suicide ($X^2 = 17.005$, df = 1, p = 0.0003); and relationship

251 with parents ($X^2 = 7.042$, df = 2, p = 0.0296) respectively.

252   Results from multivariate analysis indicates that, the type of residence where the

253 participant is staying in (OR 1.94, 95 % CI 0.57 - 6.61, p < 0.05), the thoughts of committing

254 suicide (OR 15.19, 95 % CI 3.07 - 75.11, p < 0.05), and the source of financial support the

255 individual is receiving (OR 1.33, 95 % CI 0.48 - 3.65, p < 0.05) were each independently

256 associated with significant depressive symptoms.

Mean levels of 24-hour urinary norepinephrine excretion

258 The mean 24-h NE excretion levels of all the depressed participants (121.97 ± 51.48 µg/day)

259 was higher when compared to participants without depressive symptoms (87.58 ± 18.64 µg/day)

260 but the difference was not statistically significant (P > 0.05, Fig 2). 24-h urinary NE

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261   concentrations in females and males were not remarkably different in participants with or

262   without depressive symptoms (p > 0.05). However, 29 of the 33 participants with depressive

263   symptoms showed NE levels above the reference range. In addition, the mean amount of NE

264   excreted by participants with depressive symptoms was not related with the severity of

265   depression (MMD = 118.13±38.99 µg/day, MD = 124.79±36.48 µg/day, SD = 129.33±39.56

266   µg/day) respectively (Fig 3).

267   **Figure 2: Mean (± SD) 24 – h of urinary excretion (µg/ml) of norepinephrine of the study**

268   **population (n= 116).**

269   **Figure 3: Mean (± SD) 24 – h of urinary excretion (µg/ml) of norepinephrine of the study**

270   **population according to Beck Depression Inventory (BDI) score (n= 116).** *Mild Mood*

271   *Disturbance (MMD), Moderate Disturbance (MD), Severe Depression (SD)*

272   A simple linear regression analysis was done to determine the relationship between the

273   level of NE and the occurrence of depressive symptomatology. The results showed that there was

274   a weak non-significant correlation between the BDI and the 24-h urinary NE level [coefficient of

275   correlation (r^2 = 0.2059, P > 0.05; Fig 4). In the calculated relative risk analysis, males were 1.2

276   (95% CI 0.612 – 2.423) times more likely to have higher urinary NE excretion levels compared to

277   females.

278   **Figure 4: Linear regression coefficient of the relation between 24-h urine norepinephrine**

279   **(NE) concentrations and the presence of depressive symptoms**

Discussion

281   To the best of our knowledge, this is the first study to estimate the prevalence of depression and

282   examine the association with socio-demographic and biological determinants of the disease among

283   undergraduate medical students in Uganda. Only one previous study has determined the prevalence

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284   of depression among university students in Uganda without examining the underlying cause of the

285   observed rate of depression [12]. The results of our study indicated that, 28.4% and 14.4% of

286   undergraduate medical students of Kampala International University, Uganda, exhibited

287   depressive symptoms and suicide ideation respectively. No significant changes in mean depression

288   scores were observed among male and female participants even though prevalence was slightly

289   higher in males. The participants with depressive symptoms were more likely than those without

290   symptoms to have increased levels of 24-h mean NE excretion above the normal range (<90

291   μg/day).

292   The rate of depression of 28.4% is much higher than the 16.24% reported earlier among

293   the first-year students of Makerere University Kampala, Uganda [12] but closely aligned with the

294   results obtained from meta-analysis of 195 studies involving 129,123 medical students in 47

295   countries which demonstrated that 27.2% of medical students (range, 9.3% - 55.9%) screened

296   positive for depression and that 11.1% (range, 7.4% - 24.2%) reported suicidal ideation [31]. The

297   prevalence of depression and percentage of individuals with suicide ideation observed in this study

298   is concerning given that the development of depression and suicidality has been linked to an

299   increased short-term risk of suicide as well as a higher long-term risk of future depressive episodes

300   and morbidity [32, 33]. Also, depressive and suicidal symptoms in medical trainees may adversely

301   affect the long-term health of physicians as well as the quality of care [34].

302   The concept that depression can be caused only by psychosocial or biological factors have

303   been suggested but their causal links still remain unclear. We found that depression rates were

304   higher among students within the age group of 20 – 29 years (21.6%), those renting a room/house

305   outside the university (23.3%), those who are full-time students (20.7%), those whose financial

306   support comes from relatives (12.9%), and surprisingly those who claimed to have good quality

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307 relationship with parents (21.6%) when compare to other variables in the same category (Table 3).

308 When these variables were examined as risk factors for depression in the bivariate analysis, marital

309 status, relationship with parents and suicide ideation prove significant. In Multivariate analysis,

310 the type of residence, source of financial support and suicide ideation were each independently

311 associated with significant depressive symptoms. We observed no interactions between depressive

312 symptoms and the other variables that were entered in our logistic model (all p values for

313 interaction > 0.05). Similar studies elsewhere indicated problems linked with accommodation,

314 very large family size, financial hardships, difficulties in relationships, heavy cigarette smoking

315 and high level of alcohol consumption, and fear of examinations were significantly associated with

316 depressive disorders [35-37]. Although studies involving similarly aged members in the general

317 population have reported a higher prevalence of depression among women compared to men

318 [38,39], we found no evidence that women were more likely than men to experience depression as

319 our results indicated that depressive symptoms were slightly higher in males than females. This is

320 similar to the observations of Bostanci et al., and Bayram et al., [40, 41] who reported no difference

321 between depression and gender.

322   While urinary measures are not a direct assessment of central activity, studies have

323 characterized urinary neurotransmitters as biomarkers of various conditions linked to the

324 disruptions within the central nervous system [25, 42]. The causal direction between BDI scores

325 and NE levels was assessed in this study. The results showed a positive non-significant correlation

326 between the BDI scores and 24-h urinary NE level ($r^2 = 0.2059$, $P > 0.05$). In stepwise multiple

327 linear regression tests, 24-h urinary NE concentration was not influenced by age or any of our

328 predetermined associated risk factors. Other studies have consistently show significant

329 relationship of depression disorders with urinary NE excretion levels [43, 44). The observed

330   elevated NE levels may be associated with increased HPA- axis activity as previously reported

331   [45]. An increase in hypothalamic–pituitary–adrenal (HPA) activity has been observed in 20% to

332   40% of depressed outpatients and in 40% to 60% of depressed inpatients [46]. Since all the

333   participants in the present study were not suffering from any diseases associated with the

334   cardiovascular or the endocrine systems, the elevated NE levels in the integrated 24-h urine

335   samples indicates a plausible causative role of NE in increasing the risk of developing depressive

336   symptoms. These findings argue for assessment of urinary NE excretion in the diagnosis of

337   depressive disorders in the context of a detailed patient history.

338   From the foregoing, the findings of this study indicate that biological and psychosocial

339   factors may be considered as risk factors within a larger framework for explaining the etiology of

340   depression. The study is limited by its cross-sectional nature and the fact that only one medical

341   school out of the five in the country at the time of the study was represented. In addition, the study

342   variables were measured by self-report questionnaires, which do not allow diagnostic conclusions

343   since there was no secondary screening such as a clinical interview. However, these self-reported

344   inventories are essential tools for accurately measuring depression because they protect anonymity

345   in a manner that is not possible through formal diagnostic interviews [47]. Due to budget constrain,

346   this study was only able to assess the biomedical student population neglecting students in the

347   clinical years. As a result, there was no comparison with students of other academic years in the

348   University or with another University in different part of the country. The strength of our study

349   was in it being the first to examine the prevalence of depression and 24-h urinary NE level among

350   university students in Uganda.

Conclusions

In conclusion, we found that the prevalence of depression or depressive symptoms among Kampala International University medical students was 28.4% which was within the rates reported from other countries. Increased levels of NE excretion and psychosocial factors may contribute to an increased risk of developing depressive symptoms in the population studied. Because of the high prevalence of depressive and suicidal symptomatology observed among medical students, it is important for medical schools to recognize and support all students experiencing depression, but in particular to consider how best to encourage this group to seek help. Further research is needed to identify strategies for preventing, identify causes of emotional distress and treating these disorders.

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Supporting information

496   S1 Fig 1.

497   S2 Fig 2.

498   S3 Fig 3.

499   S4 Fig 4.

500   S5 Table 1.

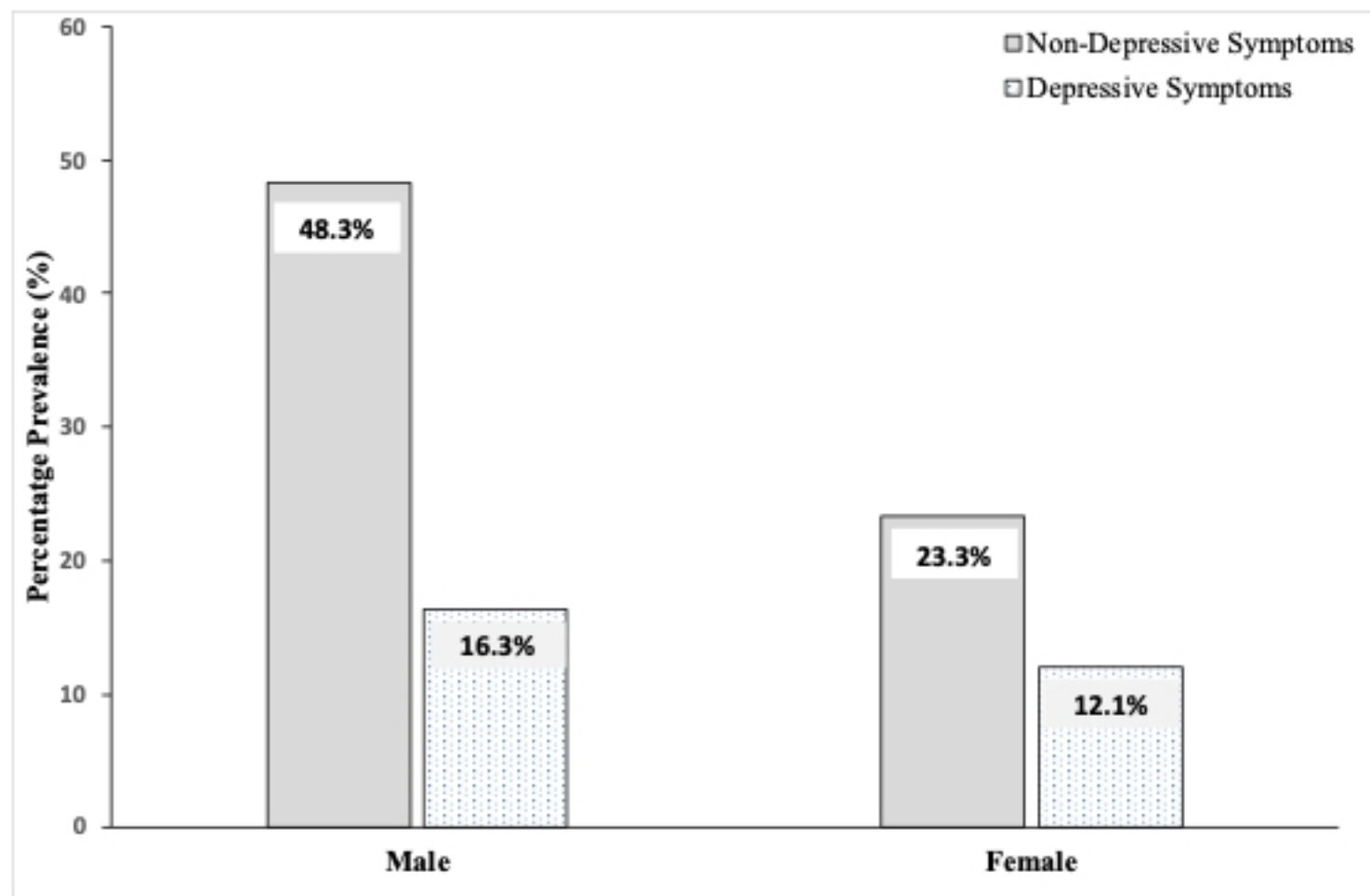501   S6 Table 2.

502   S7 Table 3.
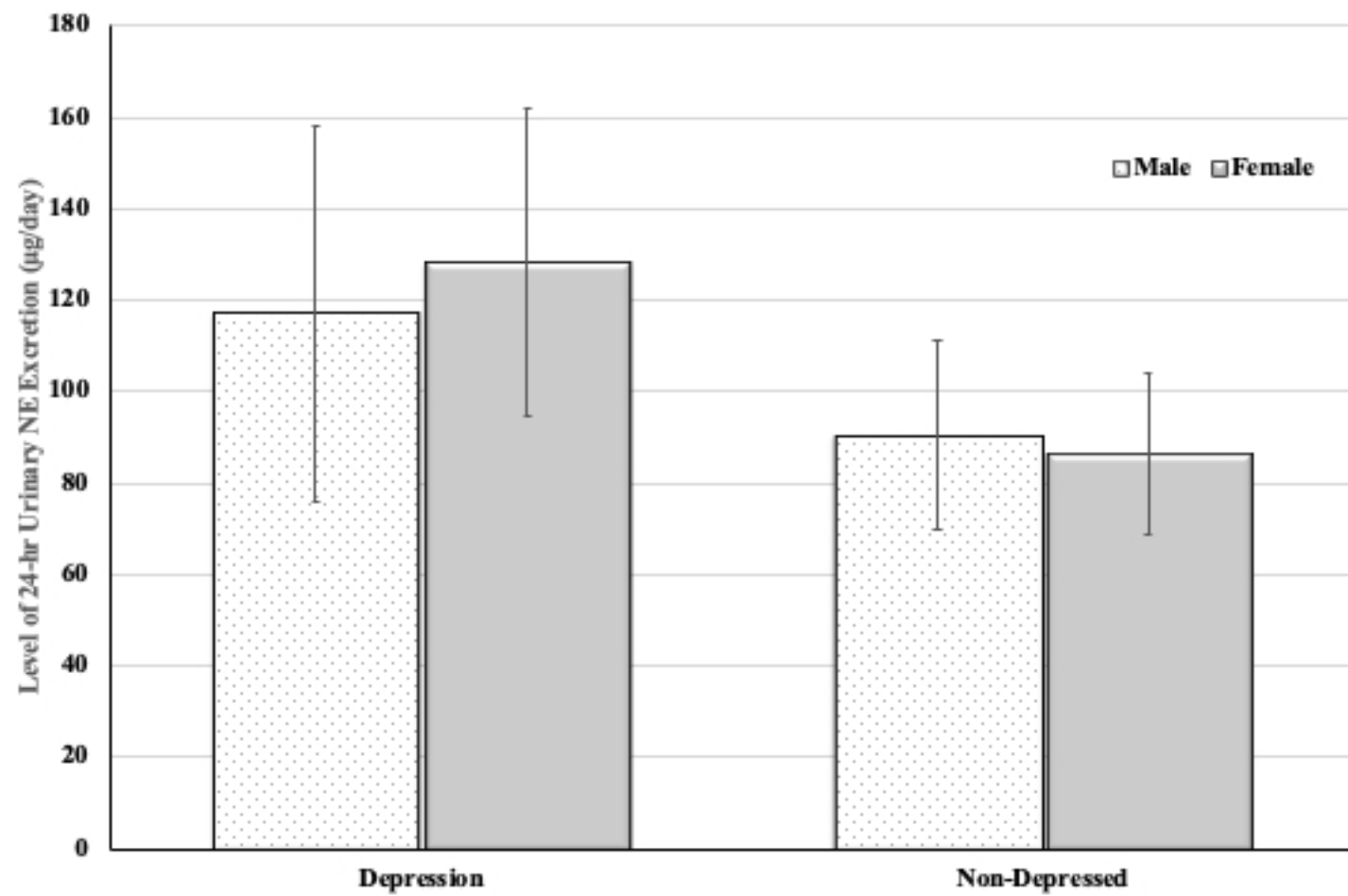
Funding Statement

Competing interests

506   None of the authors have any competing interests.
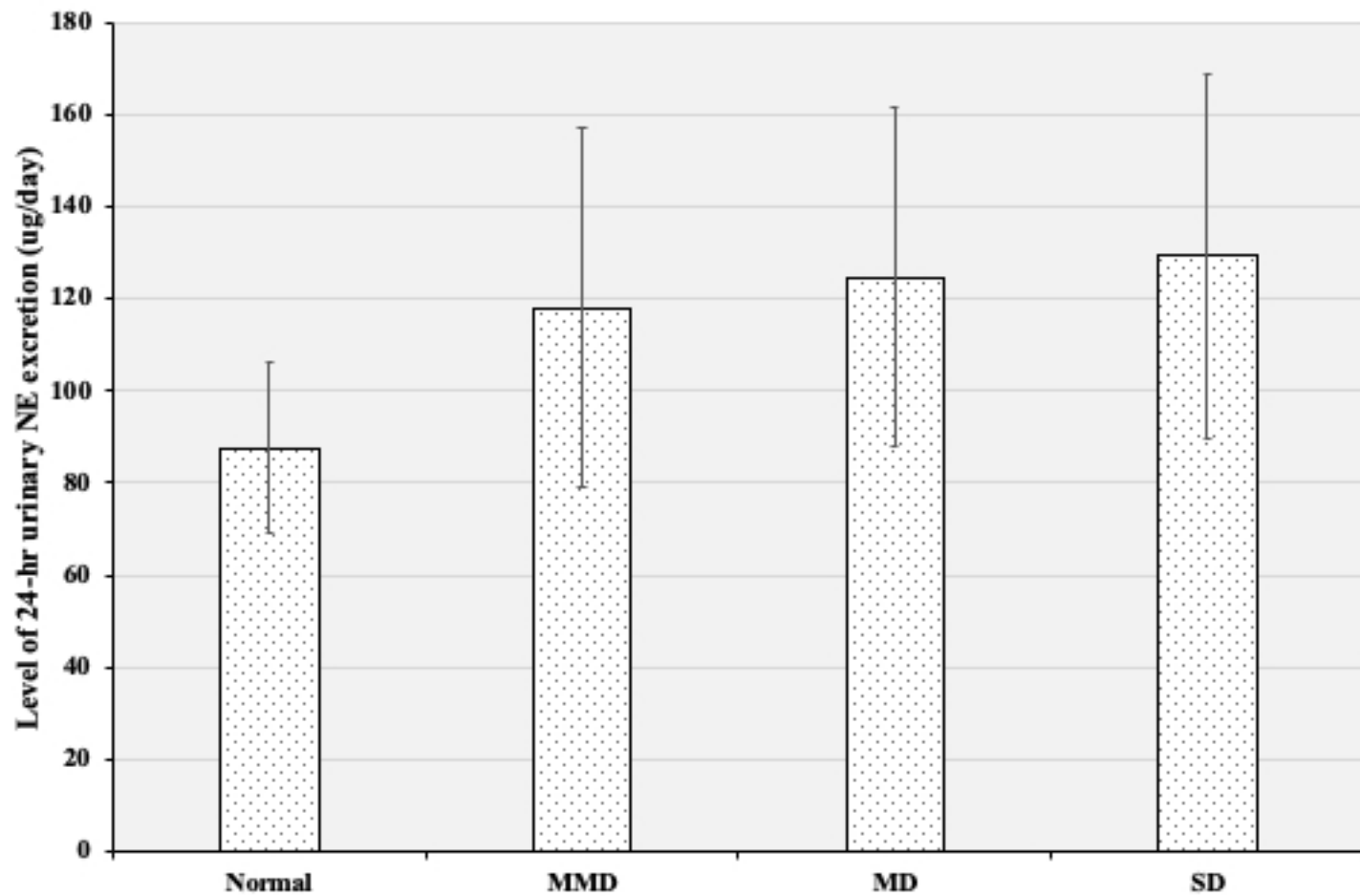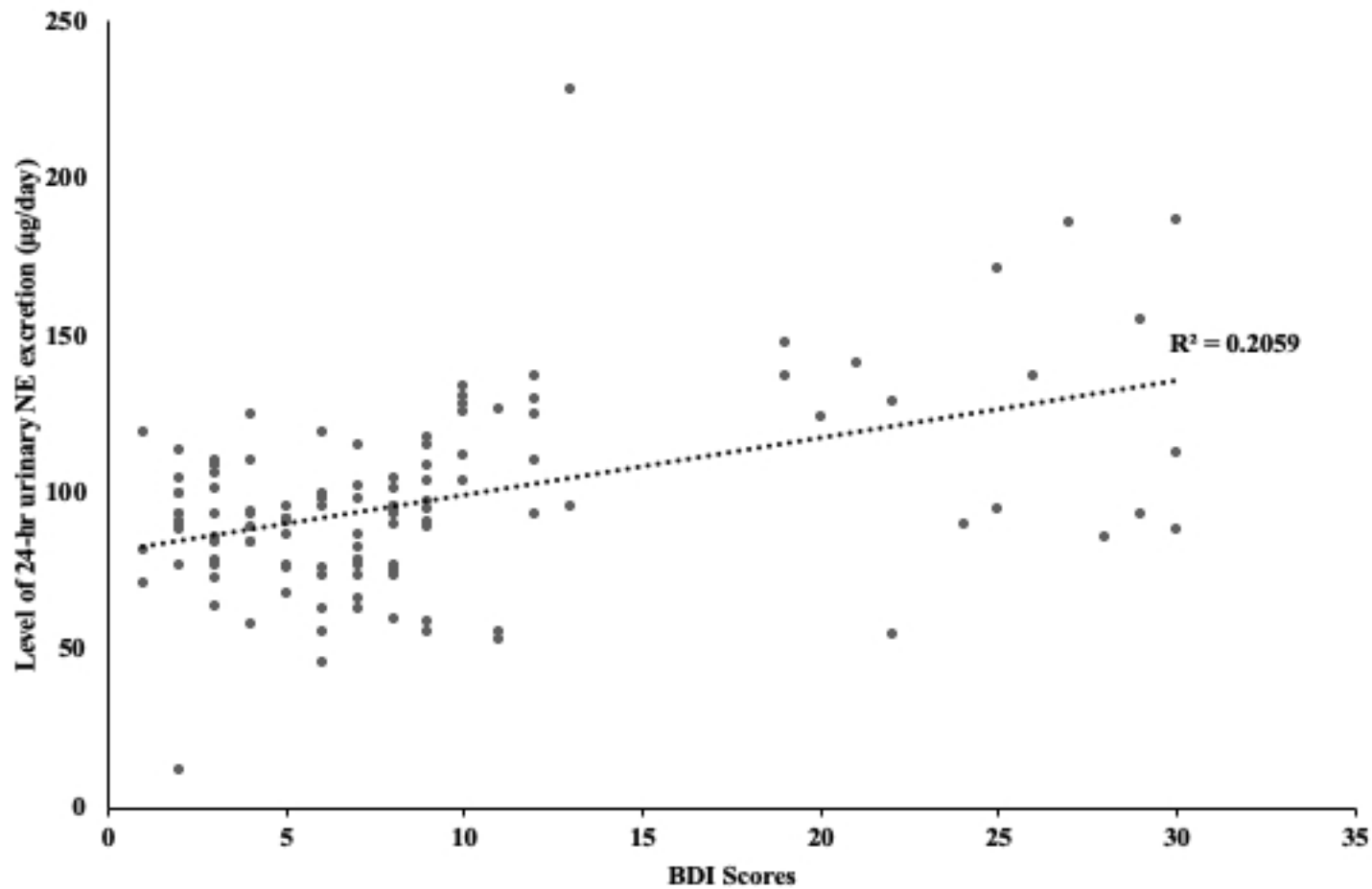
Data availability

508   All relevant data are within the paper.

27

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