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Epidemiology of depressive disorders in people living with hypertension in Africa: a systematic review and meta-analysis

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3 1 **Epidemiology of depressive disorders in people living with hypertension in**
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6 2 **Africa: a systematic review and meta-analysis**
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17 **Abstract**

18 **Objectives:** Better knowledge of epidemiology of depressive disorders in people living with
19 hypertension can help to implement pertinent strategies to address its burden. The objective
20 was to estimate the prevalence of depressive disorders and symptoms in people living with
21 hypertension in Africa.

22 **Design:** Systematic review and meta-analysis.

23 **Population:** People living with hypertension in Africa.

24 **Data sources and synthesis:** PubMed, EMBASE, African Index Medicus, Africa Journal
25 Online were searched up to January 31st, 2020; regardless of language of publication. Two
26 independent investigators selected studies, extracted data, and assessed the methodological
27 quality of included studies. Multivariate random-effects meta-analysis served to pool data
28 taking in account the variability between diagnostic tools for identifying patients with
29 depressive disorders or symptoms.

30 **Results:** We included 11 studies with 5,299 participants with hypertension. The mean age
31 varied between 50.3 and 59.6 years. The proportion of males varied between 28% and 54%.
32 Data were collected between 2002 and 2017. Four studies were conducted in South Africa,
33 three studies in Nigeria, one in Ghana, one in both Ghana and Nigeria, one in Ethiopia, and
34 one in Burkina-Faso. The adjusted prevalence of depressive disorders taking in account the
35 variance between diagnostic tools was 17.9% (95% confidence interval [CI]: 13.0-23.4). The
36 prevalence of depressive symptoms and major depressive symptoms was 33.3% (95%CI: 9.9-
37 61.6) and 7.8% (95%CI: 3.0-14.5). There was heterogeneity attributable to the diagnostic
38 tools for depressive disorders and symptoms. There was no publication bias.

39 **Limitation:** All regions of Africa were not represented weakening the generalizability of
40 findings to the entire region.

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3 41 **Conclusion:** Depressive disorders and symptoms are prevalent in people living with
4
5 42 hypertension in Africa, indicating that strategies from clinicians, researchers, and public
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7 43 health makers are needed to reduce its burden in the region.
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14 **Keywords**

15 46
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17 47 Depression; Depressive symptoms; Depressive disorders; Hypertension; Africa
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48 **Strengths and Limitations of this study**

- 49 • Not all sub-regions of Africa were represented in this review
- 50 • This is the first review performed among people living with hypertension Africa to
51 investigate the epidemiology of depressive disorders and symptoms.
- 52 • We found a huge heterogeneity between studies explained by the difference between
53 diagnostic tools for depressive disorders.
- 54 • We were not able to explore all sources of heterogeneity due to scarcity of
55 epidemiological data.

56 Introduction

57 Cardiovascular diseases (CVDs) are the leading killers worldwide with approximately 18
58 million deaths per year,¹ and hypertension is involved in approximately 50% of CVDs.²⁻⁴
59 According to the World Health Organization (WHO), the number of people living with
60 hypertension worldwide is estimated at 1.13 billion, and the African region has the highest
61 prevalence of hypertensive patients (27%).⁴ Hypertension deleterious effects are linked to
62 direct human consequences with increased morbidity and mortality but also harmful economic
63 outcomes pertaining to its management and its invalidating complications.⁵⁻⁷ Detrimental
64 human outcomes related to chronic high blood pressure encompass target organ damage
65 involving cerebrovascular, heart, and kidney diseases;^{4,5} but also mental health repercussions
66 notably anxiety, stress and depression.⁸⁻¹⁰

67 Depressive disorder is recognized to be the most common mental health illness and the
68 second cause of disability worldwide,^{11,12} after cardiovascular diseases. It accounts for 3% of
69 global disability adjusted life years (DALYs).¹² According to the WHO, depressive disorder
70 affects more than 300 million people (4.4% of the world population), and its prevalence in the
71 African region is estimated at 9% (29.9 million of cases).¹³ Some subpopulations have been
72 identified as depression risk groups, including patients with chronic cardiometabolic
73 conditions such as hypertension.^{9,14} A wide range of previously published works have
74 interested on the interaction between hypertension and depression.^{8,10,15,16} Comprehensively,
75 the majority of these studies concluded to the fact that hypertensive disease and depressive
76 disorder share bidirectional interplay with patients with hypertension more likely to develop
77 depression and inversely.^{8,17} As examples of evidence, a meta-analysis of 41 studies
78 (including 31 studies from China and three from Africa) which included 30,796 patients with
79 hypertension found that 26.8% have depression,¹⁰ and another one which included 22,367
80 participants found that depression significantly increase the risk of hypertension incidence

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3 81 with an adjusted relative risk of 1.42.¹⁵ Additionally, it has been reported that hypertensive
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5 82 patients with comorbid depression are more exposed to poor medication adherence with
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7 83 uncontrolled blood pressure as well as chronic vascular complications and cardiovascular
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9 84 disease related mortality.^{8,10,15,16,18} The burden of the depression-hypertension co-occurrence
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11 85 is worsened by the fact that approximately one hypertensive patients on ten have untreated
12
13 86 depression.^{10,19}

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17 87 Considering up-to-date scientific literature, depression is frequent and harmful in hypertensive
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19 88 patients in occidental settings,^{10,20} hypertension and depression are commonly encountered
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21 89 amongst African populations,^{2,4,13} but data summarizing and focusing on the burden of
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23 90 depression among hypertensive Africans are not yet available. Hence, we conducted this
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25 91 systematic review and meta-analysis with the aim to determine the prevalence of depressive
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27 92 disorders/symptoms in people living with hypertension in Africa.
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33 94 **Methods**

34 35 95 **Design**

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38 96 This systematic review and meta-analysis was conducted according to the Joanna Briggs
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40 97 Institute guidelines.²¹ This study was reported according to the preferred reporting items for
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42 98 systematic reviews and meta-analyses (PRISMA) guidelines.²² The protocol of this review
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44 99 was registered in PROSPERO.

45 46 47 100 **Eligibility criteria**

48 49 101 ***Condition***

50
51 102 We considered studies reporting the prevalence (or enough data to compute this estimate) of
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53 103 depressive disorders and symptoms.

54 55 104 ***Context***

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3 105 We considered studies conducted in people living in Africa. Studies conducted in Africans
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5 106 living outside Africa were not considered.
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7 107 ***Population***

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9 108 We considered studies conducted in people with diagnosed hypertension.
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11 109 ***Study design***

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13 110 Cross-sectional, case-control, and cohort studies.
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15 111 **Data sources**

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17 112 We searched PubMed, Excerpta Medica Database (EMBASE), Africa Index Medicus, and
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19 113 Africa Journal Online to identify all relevant records published up to January 31st, 2020; with
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21 114 any language restriction. The search strategy in EMBASE is available in the Appendix
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23 115 (Supplementary Table 1). To supplement the bibliographic database searches and identify
24
25 116 potential additional data sources, we scrutinized the reference list of all relevant original and
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27 117 review papers.
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31 118 **Study selection**

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33 119 Titles and abstracts of articles retrieved from literature search were independently screened by
34
35 120 two investigators (FTE and JJB), and the full-texts of those potentially eligible were obtained
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37 121 and further assessed for final inclusion. Disagreements were resolved through consensus.
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40 122 **Data collection and management**

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42 123 A preconceived and standardized data extraction form was used to collect information on first
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44 124 author's name, study country, year of publication, period of participants' recruitment, study
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46 125 design, setting, sampling method, timing of data collection, response rate, mean or median
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48 126 age of the population, age range, proportion of males, number of participants with
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50 127 hypertension, the number of participants with depressive disorders. In case of multinational
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52 128 studies, data were separated to show the estimate within individual countries. Two
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3 129 investigators (FTE and JJB) independently extracted the data from individual studies, with
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5 130 disagreements being resolved through consensus.
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8 131 Two investigators (FTE and JJB) independently assessed study methodological quality of
9
10 132 included studies with tool developed by Joanna Briggs Institute,²¹ with disagreements being
11
12 133 resolved through discussion and consensus.
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14 134 **Data synthesis and analysis**

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17 135 Meta-analyses were performed with the *meta*, *metafor*, and *dmetar* packages of the statistical
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19 136 software *R* (version 3.6.2). Prevalence estimates were reported with 95% confidence interval
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21 137 (95%CI). Prevalence pooling was done with Freeman-Tukey double arcsine transformation
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23 138 using random-effects meta-analysis model.²³ We adjusted the prevalence in a multivariate
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25 139 meta-analysis to take in account the variance between tools used to identify patients with
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27 140 depressive disorders/symptoms. Egger's test served for detecting the presence of publication
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29 141 bias.²⁴ A p-value < 0.10 on Egger test was considered indicative of statistically significant
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31 142 publication bias. Heterogeneity was evaluated by the χ^2 test on Cochran's Q statistic,²⁵ which
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33 143 was quantified by I^2 values. The I^2 statistic estimates the percentage of total variation across
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35 144 studies due to true between-study differences rather than chance. In general, I^2 values greater
36
37 145 than 60-70% indicate the presence of substantial heterogeneity.²⁶ Inter-rater agreements
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39 146 between investigators for study inclusion and methodological quality assessment were
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41 147 assessed using Kappa Cohen's coefficient.²⁷
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46 148 **Patient and public involvement**

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49 149 Patients or the public were not involved in the design, conduct, reporting, or dissemination of
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51 150 our research.
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55 56 152 **Results**

57 58 153 **The review process and study characteristics** 59 60

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3 154 We initially identified 890 records and finally retained 11 full texts (13 prevalence data) in the
4
5 155 meta-analysis (Supplementary Figure 1).²⁸⁻³⁸ Agreement between investigators on selection
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7 156 based on title and abstract was $\kappa = 0.88$ and $\kappa = 1.0$ for final inclusion.
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10 157 Of the 11 included studies, eight studies used probabilistic sampling while three used non-
11
12 158 probabilistic sampling. All studies prospectively collected and analysed data and used the
13
14 159 same method to identify patients with depressive disorders. Sample size was adequate in nine
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16 160 studies and response rate in two studies (Supplementary Table 2).
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19 161 The characteristics of included studies are presented in the Table 1. All studies were cross-
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21 162 sectional (Table 1). Patient Health Questionnaire-9 was the most used tool, $n = 4$. The mean
22
23 163 age varied between 50.3 and 59.6 years. The proportion of males varied between 28% and
24
25 164 54%. Data on depressive disorders/symptoms were collected between 2002 and 2017. Four
26
27 165 studies were conducted in South Africa, three studies in Nigeria, one study in Ghana, one
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29 166 study in both Ghana and Nigeria, one study in Ethiopia, and one study in Burkina-Faso. None
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31 167 of the study was conducted in Central Africa and North Africa.
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35 168 **Prevalence of depressive disorders/symptoms in people with hypertension in Africa**

36
37 169 In total, 5,299 participants with hypertension were included. There was substantial
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39 170 heterogeneity for all analyses, all $I^2 > 75\%$ (Figure 1). The prevalence of depressive disorders
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41 171 was 18.6% (95%CI: 13.8-23.9; 5 studies) (Figure 1). The adjusted prevalence taking in
42
43 172 account the variance between diagnostic tools was 17.9% (95%CI: 13.0-23.4) with 52.7% of
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45 173 variance due to difference between tools. There was no publication bias ($p = 0.789$). There
46
47 174 was no data on major depressive disorders.
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51 175 The prevalence of depressive symptoms was 37.3% (95%CI: 19.3-57.3; 6 studies). The
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53 176 adjusted prevalence taking in account the variance between diagnostic tools was 33.3%
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55 177 (95%CI: 9.9-61.6) with 74.1% of variance due to difference between tools. There was no
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57 178 publication bias ($p = 0.115$).
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3 179 The prevalence of major depressive symptoms was 7.9% (95%CI: 1.7-17.9; 2 studies). The
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5 180 adjusted prevalence taking in account the variance between diagnostic tools was 7.8%
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7 181 (95%CI: 3.0-14.5) with 43.3% of variance due to difference between tools. The p value on
8
9 182 Egger test was 0.789.
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15 184 **Discussion**

17 185 This meta-analysis of data from 5,299 people with hypertension living in five countries in
18 186 Africa revealed that depressive disorders and symptoms are prevalent in this population with
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20 187 substantial heterogeneity according to the diagnostic tools. The present systematic review
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22 188 suggests that approximately one on five and one-third of patients with hypertension have
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24 189 respectively depression and depressive symptoms.
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29 190 Globally, there are dissimilarities between our findings and the one of previous studies on
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31 191 depression among hypertensive patients. For instance, compared to our findings, a meta-
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33 192 analysis on the prevalence of depression in patients with hypertension and which included 41
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35 193 studies (most of them from China) found higher rates of depression with a summarized
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37 194 prevalence of 26.9% (95%CI: 21.7% - 32.3%).¹⁰ The same meta-analysis found that 28.5%
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39 195 (95% CI: 22.2% - 35.3%) of Chinese patients with hypertension had depression.¹⁰ Our review
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41 196 revealed more cases of depression among patients with hypertension compared to occidental
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43 197 studies. For example, considering data of United States Multi-Disciplinary Group Practice
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45 198 Observational Study which included 4,362 adult patients with hypertension (13% of anxiety
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47 199 and/or depression), our study's prevalence of depressive disorder is higher.³⁹ Also, a cross-
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49 200 sectional study done in Spain among 5,954 hypertensive patients with high cardiovascular risk
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51 201 profile found that 15.6% had depression, of which 61.4% were untreated.¹⁹ This variability in
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53 202 results can be explained by the changeability pertaining to the criteria and/or diagnostic tools
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55 203 used to screen depressive disorder across studies' populations.^{40,41} Noteworthy, Li and
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3 204 colleagues who studied depressive disorder among hypertension in a meta-analysis of 41
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5 205 studies suggested that self-assessed screening tools of depression or depressive symptoms
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7 206 might overestimate the prevalence of depression.¹⁰ Indeed they found a 30% depression
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9 207 prevalence using self-administrated diagnostic scales versus a 21% prevalence using clinical-
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11 208 interviewed tools.¹⁰ This could be link to patients' confusion about depression and
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13 209 hypertension symptoms such as poor appetite, fatigue and sleep disturbances.¹⁰In our review
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15 210 the most used diagnostic tool was the PHQ-9 and another fact to highpoint is that differences
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17 211 in prevalence can also be explained by the cut-off-point used for a same tool to define a
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19 212 positive screening for depression.^{29,42,43} Mahmood and colleagues while assessing depression
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21 213 among 411 hypertensive outpatients in a Pakistan hospital by using PHQ-9 with a score of 10
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23 214 or above as cut-off point found a prevalence of 40.1%,⁴⁴ more than two folds ours. In our
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25 215 study we had a substantial heterogeneity for all analyses which can also be related to the
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27 216 variance between diagnostic tools used for depression assessment. The previously cited meta-
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29 217 analysis of Li and colleagues also showed evidence of high-level heterogeneity.¹⁰
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31 218 This meta-analysis highlights the fact that depressive disorder is frequently encountered
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33 219 among hypertensive patients. This review might substantiate the relevancy to conduct further
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35 220 studies with the aim to investigate on the better diagnosis tool for depression among
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37 221 hypertensive patients in order to reduce heterogeneity of results. Moreover, our review could
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39 222 justify carrying out epidemiological studies on the depression-hypertension comorbidity in
40
41 223 other African regions in order to have more representative regional picture of the evidence.
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43 224 All this might help to establish adapted policies pertaining to the management of hypertensive
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45 225 patients with depression, notably for a tailored pharmacological treatment.^{18,45,46} Nevertheless,
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47 226 our analysis could already draw clinician's awareness on the necessity to assess depression
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49 227 symptoms among hypertensive patients, especially since previously published works found
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51 228 that comorbid depression contribute to more deleterious cardiovascular outcomes.^{8,10,15,16,18}
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3 229 This study should however be interpreted considering some limitations. First and most
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5 230 common to meta-analyses of prevalence studies,⁴⁷ we found a huge heterogeneity between
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7 231 studies for which we undertook adjusted analysis to take account the variance due to
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9 232 diagnostic tools. However, some characteristics that may further explain heterogeneity were
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11 233 not reported or there was no enough study to conduct such analysis including sex, sub-
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13 234 regions, and age groups. Second, the various geographic regions and countries were variably
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15 235 represented and some countries were represented. This may weaken the generalizability of our
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17 236 findings and call for more epidemiological studies in this region.

18
19 237 Despite these limitations, this first systematic review and meta-analysis on depressive
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21 238 disorders/symptoms in people living with hypertension in Africa provided a clear summary of
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23 239 the existing knowledge. A protocol had been registered before, and we used rigorous
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25 240 methodological and statistical procedures to obtain and pool data. Furthermore, we have taken
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27 241 in account the variability due to diagnostic tools. There was no publication bias.

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34 35 243 **Conclusions**

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37 244 Overall, our review found that depression is prevalent among patients with hypertension. This
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39 245 may have significant implications for routine clinical practice while treating and following
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41 246 hypertensive patients. However, since our analysis has limitations pertaining to diagnostic
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43 247 tools consistency within studies and also to the unrepresentative geographic distribution,
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45 248 further studies would be relevant in order to reinforce our findings. All this could be a support
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47 249 for a personalized management of patients with hypertension and depression.

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53 54 251 **Author Contributors**

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56 252 Conception: JJB, FTE. Designing of the protocol: FTE, JJB. Literature search: JJB. Studies
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58 253 selection: FTE, JJB. Data extraction: FTE, JJB. Data management: JJB. Data synthesis and
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3 254 analysis: JJB. Writing of the first draft: JJB, FTE. Critical revision: FTE, MNT, JJB.
4
5 255 Approved the final version: FTE, MNT, JJB. Guarantor of the review: JJB.
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17 18 19 261 **Competing interests**

20
21 262 We declare no competing interests.

22 23 24 263 **Patient consent**

25
26 264 Not applicable.

27 28 265 **Data sharing statement**

29
30 266 All data generated for this study are in the manuscript and its supporting files.
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34 35 268 **References**

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410 **Figures legend**

411 Figure 1. Crude prevalence of depressive disorders/symptoms in people living with
412 hypertension in Africa

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413 **Table 1. Characteristics of included studies**

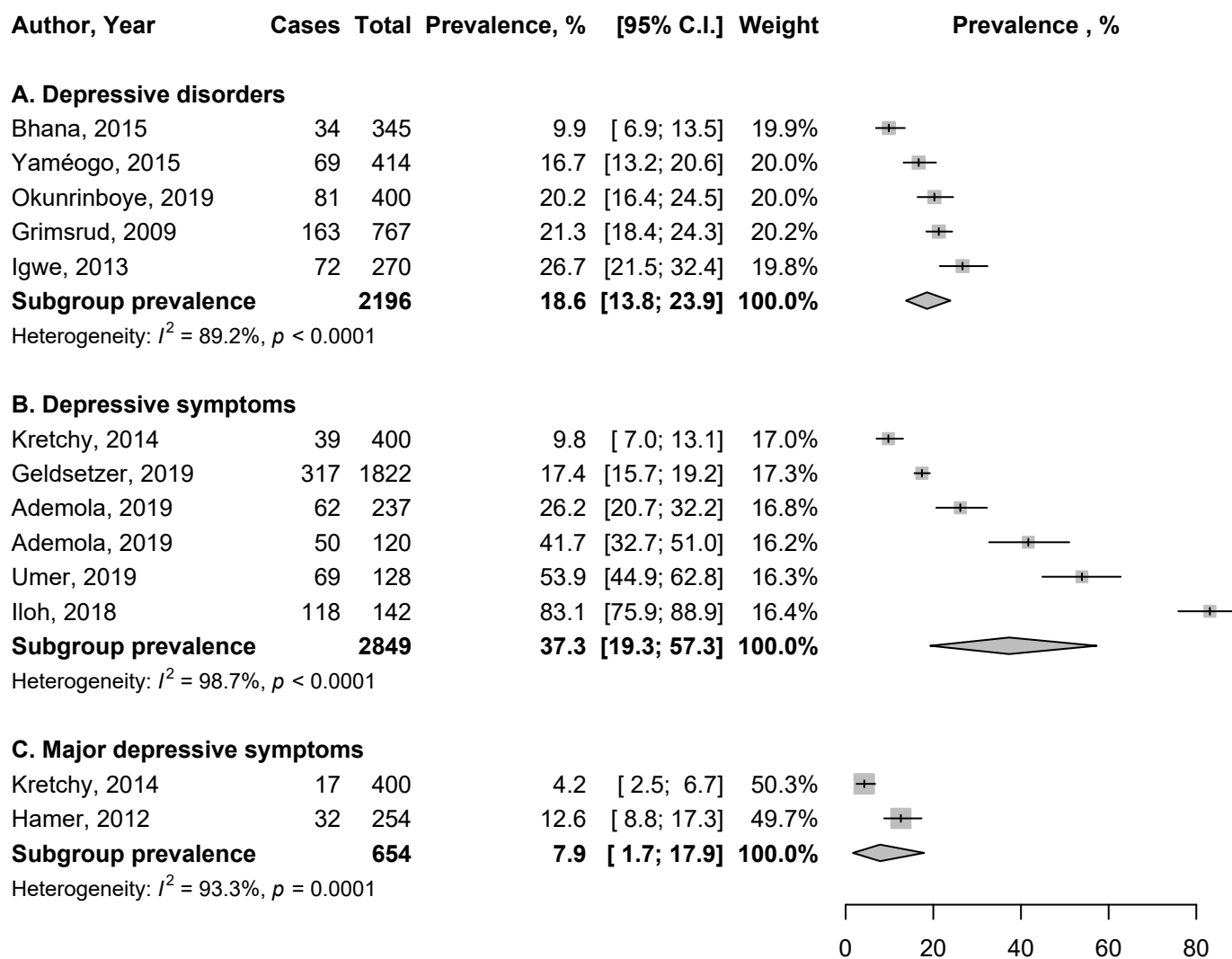
Author	Year	Setting	Diagnosis of conditions	Inclusion criteria	Population	Period of inclusion	Country	Sample
Ademola	2019	Hospital	Patient Health Questionnaire 9 (PHQ-9)	Age \geq 18 y, diagnosis of hypertension, treatment with an antihypertensive medication for at least 12 months	%Males: 41.7; Mean age: 57	2013	Ghana, Nigeria	357
Bhana	2015	Population	Depression module of the Structured Clinical Interview for DSM-IV (SCID)	Age \geq 18 y, clinic attendance for routine chronic disease services (e.g., HIV, hypertension, diabetes) and ability to comprehend and complete study components in Tswana or English.	NR	2014	South Africa	345
Geldsetzer	2019	Population	Center for Epidemiological Studies—Depression (CES-D) screening tool	Age \geq 40 y and continuously living in the area during the 12 months prior to study enrollment	%Males: 37.4	2014-2015	South Africa	1822
Grimsrud	2009	Population	Composite International Diagnostic Interview Version 3.0 (CIDI-3.0)	South Africans \geq 18 years who lived in households and hostels during the field period of the study	%Males: 28; Mean age: 50.3	2002-2004	South Africa	767
Hamer	2012	Population	Patient Health Questionnaire 9 (PHQ-9)	Age: 25-60 y with hypertension	NR	2008-2009	South Africa	254
Igwe	2013	Hospital	Mini International Neuro-psychiatric Interview (MINI)	Age: 18 - 64 years. Hypertension for at least 1 year and stable without need for hospital admission for 3 months prior to assessment	%Males: 53.7; Mean year: 50.4	2010-2011	Nigeria	270
Iloh	2018	Hospital	Patient Health Questionnaire 9 (PHQ-9)	Age \geq 18 years with hypertension	%Males: 40.7	2017	Nigeria	142
Kretchy	2014	Hospital	Depression Anxiety Stress Scale (DASS) – 21	Age \geq 18 y, a diagnosis of hypertension, reporting prescription of at least one antihypertensive medication for a minimum of two months	%Males: 37.25	2012	Ghana	400
Okunrinboye	2019	Hospital	Mini International Neuro-psychiatric Interview (MINI)	Age: 18 and 64 y who were diagnosed by a consultant physician at the Centre as suffering from hypertension and have been on anti-hypertensive medication for at least 6 months, spoke Yoruba or English language fluently	%Males: 38; Mean age: 59.6	2012	Nigeria	400
Umer	2019	Hospital	Patient Health Questionnaire 9 (PHQ-9)	Age \geq 18 y, follow-up for hypertension	%Males: 52.8	2014	Ethiopia	128

Yaméogo	2015	Hospital	Hospital Anxiety and Depression Scale (HADS)	Hypertensive consenting adult outpatients	%Males: 40.1; Mean age: 54.6	2010-2011	Burkina-Faso	414
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414 NR: not reported.

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15 **APPENDIX**
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21 Supplementary Table 1. Search strategy..... 2
22 Supplementary Table 2. Methodological quality of included studies..... 4
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25 Supplementary Figure 1. PRISMA flow diagram 5
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Supplementary Table 1. Search strategy

Search	Search terms
#1	'africa'/exp OR africa OR 'algeria'/exp OR algeria OR 'angola'/exp OR angola OR 'benin'/exp OR benin OR 'botswana'/exp OR botswana OR 'burkina faso'/exp OR 'burkina faso' OR 'burundi'/exp OR burundi OR 'cameroon'/exp OR cameroon OR 'canary islands'/exp OR 'canary islands' OR 'cape verde'/exp OR 'cape verde' OR 'central african republic'/exp OR 'central african republic' OR 'chad'/exp OR chad OR 'comoros'/exp OR comoros OR 'congo'/exp OR congo OR 'democratic republic of congo' OR 'djibouti'/exp OR djibouti OR 'egypt'/exp OR egypt OR 'equatorial guinea'/exp OR 'equatorial guinea' OR 'eritrea'/exp OR eritrea OR 'ethiopia'/exp OR ethiopia OR 'gabon'/exp OR gabon OR 'gambia'/exp OR gambia OR 'ghana'/exp OR ghana OR 'guinea'/exp OR guinea OR 'guinea bissau'/exp OR 'guinea bissau' OR 'ivory coast'/exp OR 'ivory coast' OR 'cote ivoire' OR 'jamahiriya' OR 'kenya'/exp OR kenya OR 'lesotho'/exp OR lesotho OR 'liberia'/exp OR liberia OR 'libya'/exp OR libya OR 'madagascar'/exp OR madagascar OR 'malawi'/exp OR malawi OR 'mali'/exp OR mali OR 'mauritania'/exp OR mauritania OR 'mauritius'/exp OR mauritius OR 'mayotte'/exp OR mayotte OR 'morocco'/exp OR morocco OR 'mozambique'/exp OR mozambique OR 'namibia'/exp OR namibia OR 'niger'/exp OR niger OR 'nigeria'/exp OR nigeria OR 'principe' OR 'reunion'/exp OR reunion OR 'rwanda'/exp OR rwanda OR 'sao tome' OR 'senegal'/exp OR senegal OR 'seychelles'/exp OR seychelles OR 'sierra leone'/exp OR 'sierra leone' OR 'somalia'/exp OR somalia OR 'south africa'/exp OR 'south africa' OR 'st helena'/exp OR 'st helena' OR 'sudan'/exp OR sudan OR 'swaziland'/exp OR swaziland OR 'tanzania'/exp OR tanzania OR 'togo'/exp OR togo OR 'tunisia'/exp OR tunisia OR 'uganda'/exp OR uganda OR 'western sahara'/exp OR 'western sahara' OR 'zaire'/exp OR zaire OR 'zambia'/exp OR zambia OR 'zimbabwe'/exp OR zimbabwe OR 'central africa'/exp OR 'central africa' OR 'central african'/exp OR 'central african' OR 'west africa'/exp OR 'west africa' OR 'west african'/exp OR 'west african' OR 'western africa'/exp OR 'western africa' OR 'western african'/exp OR 'western african' OR 'east africa'/exp OR 'east africa' OR 'east african'/exp OR 'east african' OR 'eastern africa'/exp OR 'eastern africa' OR 'eastern african'/exp OR 'eastern african' OR 'north africa'/exp OR 'north africa' OR 'north african'/exp OR 'north african' OR 'northern africa'/exp OR 'northern africa' OR 'northern african'/exp OR 'northern african' OR 'south african'/exp OR 'south african' OR 'southern africa'/exp OR 'southern africa' OR 'southern african'/exp OR 'southern african' OR 'sub saharan africa'/exp OR 'sub saharan africa' OR 'sub saharan african'/exp OR 'sub saharan african' OR 'subsaharan africa'/exp OR 'subsaharan africa' OR 'subsaharan african'
#2	'depression'/exp OR depression OR 'depressive disorder'/exp OR 'depressive disorder' OR 'depressive symptom'/exp OR 'depressive symptom' OR 'depressive neuros*' OR 'depressive syndrome*'

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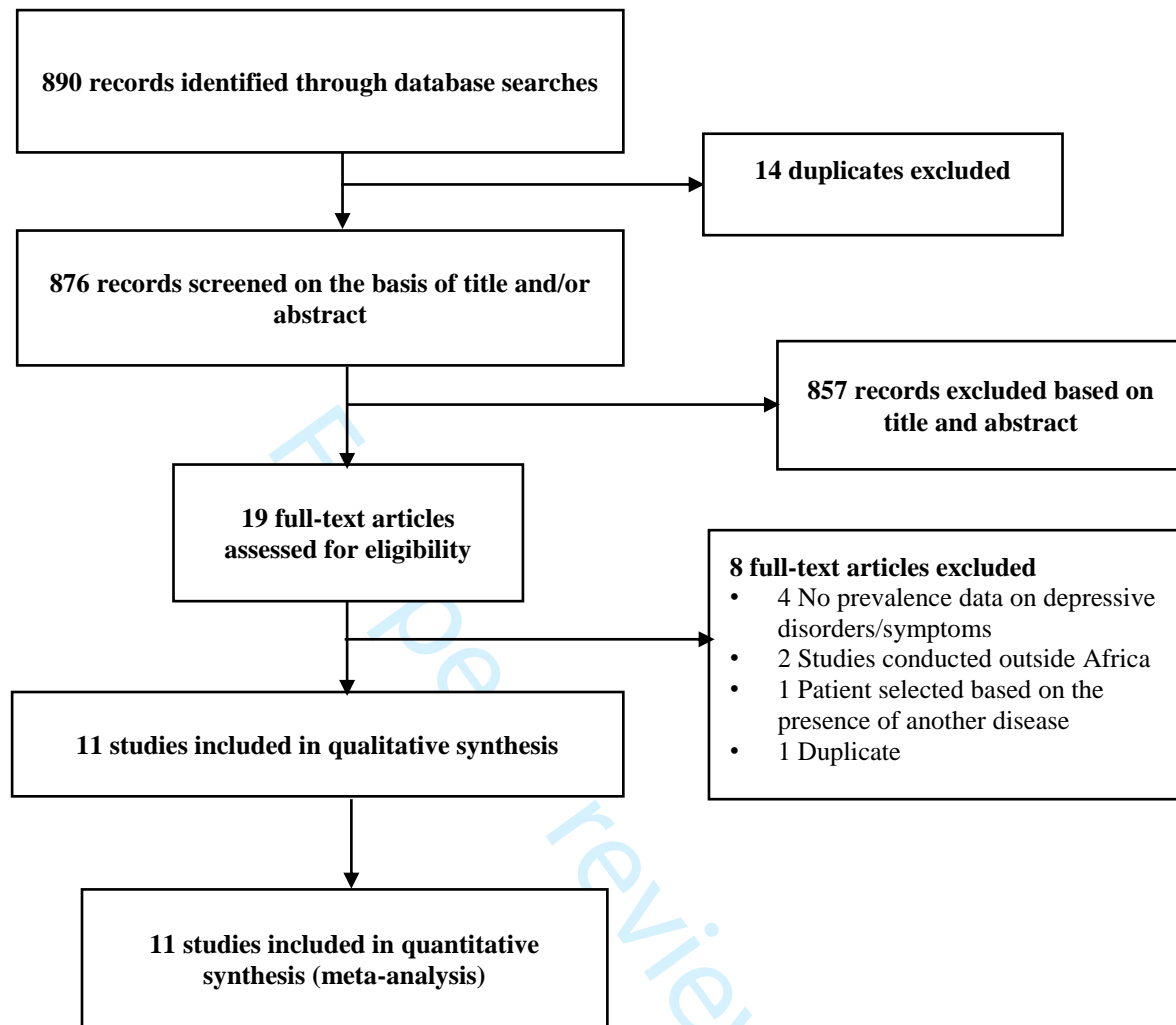
#3	'hypertension'/exp OR hypertension OR 'high blood pressure'/exp OR 'high blood pressure' OR (high AND ('blood'/exp OR blood) AND ('pressure'/exp OR pressure))
#4	#1 AND #2 AND #3

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Supplementary Table 2. Methodological quality of included studies

Author, Year	Sampling method	Timing of data collection	Sample size adequate	Response rate	Same method of data collection for all participants
Ademola, 2019	Convenience	Prospectively	No	Not described	Yes
Bhana, 2015	Convenience	Prospectively	Yes	Not described	Yes
Geldsetzer, 2019	Stratified Random	Prospectively	Yes	Adequate	Yes
Grimsrud, 2009	Stratified Multistage	Prospectively	Yes	Not described	Yes
Hamer, 2012	Convenience	Prospectively	Yes	Not described	Yes
Igwe, 2013	Convenience	Prospectively	Yes	Not described	Yes
Iloh, 2018	Convenience	Prospectively	Yes	Not described	Yes
Kretchy, 2014	Time-Location	Prospectively	Yes	Not described	Yes
Okunrinboye, 2019	Systematic Random	Prospectively	Yes	Not described	Yes
Umer, 2019	Convenience	Prospectively	No	Adequate	Yes
Yaméogo, 2015	Convenience	Prospectively	Yes	Not described	Yes

Supplementary Figure 1. PRISMA flow diagram





PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7, Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8



PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9, Appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9, Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9-10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

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42 From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.
 43 doi:10.1371/journal.pmed1000097

44 For more information, visit: www.prisma-statement.org.

45 For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

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BMJ Open

Epidemiology of depressive disorders in people living with hypertension in Africa: a systematic review and meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-037975.R1
Article Type:	Original research
Date Submitted by the Author:	14-Sep-2020
Complete List of Authors:	Endomba Angong, Francky Teddy; Health Economics and Policy Research and Evaluation for Development Results Group; University of Bourgogne, Psychiatry Internship Program Mazou, Temgoua Ngou ; Health Economics and Policy Research and Evaluation for Development Results Group Bigna, Jean Joel; Centre Pasteur du Cameroun, Department of Epidemiology and Public Health
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Depression & mood disorders < PSYCHIATRY, Hypertension < CARDIOLOGY, EPIDEMIOLOGY

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6 2 **Africa: a systematic review and meta-analysis**
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34 16 **Word count:** 2,692; Abstract: 318 words
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17 **Abstract**

18 **Objectives:** Better knowledge of epidemiology of depressive disorders in people living with
19 hypertension can help to implement pertinent strategies to address its burden. The objective was
20 to estimate the prevalence of depressive disorders and symptoms in people living with
21 hypertension in Africa.

22 **Design:** Systematic review and meta-analysis.

23 **Data sources:** PubMed, EMBASE, African Index Medicus, Africa Journal Online were
24 searched up to January 31, 2020; regardless of the language of publication.

25 **Eligibility criteria:** We included studies conducted among adults (≥ 18 years) living in Africa,
26 and reporting the prevalence of depressive disorders and symptoms.

27 **Data extraction and synthesis:** Two independent investigators selected studies, extracted data,
28 and assessed the methodological quality of included studies by using the tool developed by
29 Joanna Briggs Institute. Multivariate random-effects meta-analysis served to pool data by
30 considering the variability between diagnostic tools for identifying patients with depressive
31 disorders or symptoms.

32 **Results:** We included 11 studies with 5,299 adults with hypertension. The mean age varied
33 between 50.3 and 59.6 years. The proportion of males varied between 28% and 54%. Data were
34 collected between 2002 and 2017. Data were from South Africa, Nigeria, Ghana, Ethiopia, and
35 Burkina-Faso. The adjusted prevalence of depressive disorders taking in account the variance
36 between diagnostic tools was 17.9% (95% confidence interval [CI]: 13.0-23.4). The prevalence
37 of depressive symptoms and major depressive symptoms was 33.3% (95%CI: 9.9-61.6) and
38 7.8% (95%CI: 3.0-14.5). There was heterogeneity attributable to the diagnostic tools for
39 depressive disorders and symptoms. There was no publication bias.

40 **Limitation:** All regions of Africa were not represented weakening the generalizability of
41 findings to the entire region.

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3 42 **Conclusion:** Depressive disorders and symptoms are prevalent in people living with
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5 43 hypertension in Africa, indicating that strategies from clinicians, researchers, and public health
6
7 44 makers are needed to reduce its burden in the region.
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15 47 **Keywords**
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17 48 Depression; Depressive symptoms; Depressive disorders; Hypertension; Africa
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49 **Strengths and Limitations of this study**

- 50 • Not all sub-regions of Africa were represented in this review.
- 51 • This is the first review performed among people living with hypertension Africa to
52 investigate the epidemiology of depressive disorders and symptoms.
- 53 • We found a huge heterogeneity between studies explained by the difference between
54 diagnostic tools for depressive disorders.
- 55 • We were not able to explore all sources of heterogeneity due to scarcity of epidemiological
56 data.

57 **Introduction**

58 Cardiovascular diseases (CVDs) are the leading killers worldwide with approximately 18
59 million deaths per year,[1] and hypertension is involved in approximately 50% of CVDs.[2–4]
60 According to the World Health Organization (WHO), the number of people living with
61 hypertension worldwide is estimated at 1.13 billion, and the African continent has the highest
62 prevalence of hypertensive patients (27%).[4] The deleterious effect of hypertension are linked
63 to direct human consequences with increased morbidity and mortality but also harmful
64 economic outcomes pertaining to its management and the repercussions of its complications.[5–
65 7] Detrimental human outcomes related to chronic high blood pressure encompass target organ
66 damage involving cerebrovascular, heart, and kidney diseases;[4,5] but also mental health
67 repercussions notably anxiety, stress and depression.[8–10]
68 Depressive disorder is recognized to be the most common mental health illness and the second
69 cause of disability worldwide,[11,12] after cardiovascular diseases. It accounts for 3% of global
70 disability adjusted life years (DALYs).[12] According to the WHO, depressive disorder affects
71 more than 300 million people (4.4% of the world population), and its prevalence in the African
72 continent is estimated at 9% (29.9 million of cases).[13] Some subpopulations have been
73 identified as depression risk groups, including patients with chronic cardiometabolic conditions
74 such as hypertension.[9,14] A wide range of previously published works addressed an interest
75 on the interaction between hypertension and depression.[8,10,15,16] Comprehensively, the
76 majority of these studies concluded that hypertensive disease and depressive disorder share
77 bidirectional interplay with patients with hypertension more likely to develop depression and
78 conversely.[8,17] As examples of evidence, a meta-analysis of 41 studies (including 31 studies
79 from China and three from Africa) which included 30,796 patients with hypertension found that
80 26.8% have depression,[10] and another one which included 22,367 participants found that
81 depression significantly increase the risk of hypertension incidence with an adjusted relative

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3 82 risk of 1.42.[15] Additionally, it has been reported that hypertensive patients with comorbid
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5 83 depression are more exposed to poor medication adherence with uncontrolled blood pressure
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7 84 as well as chronic vascular complications and cardiovascular disease related
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9 85 mortality.[8,10,15,16,18] The burden of the depression-hypertension co-occurrence is
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11 86 worsened by the fact that approximately one hypertensive patient in ten has untreated
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13 87 depression.[10,19]

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17 88 Considering up-to-date scientific literature, depression in hypertensive patients is common in
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19 89 western contexts,[10,20] hypertension and depression are commonly encountered amongst
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21 90 African populations,[2,4,13] but data summarizing and focusing on the burden of depression
22
23 91 among hypertensive Africans are not yet available. Hence, we conducted this systematic review
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25 92 and meta-analysis with the aim to explore the prevalence of depressive disorders/symptoms,
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27 93 and major depression in individuals living with hypertension in Africa.
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32 33 95 **Methods**

34 35 96 **Design**

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38 97 This systematic review and meta-analysis was conducted according to the Joanna Briggs
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40 98 Institute guidelines.[21] This study was reported according to the preferred reporting items for
41
42 99 systematic reviews and meta-analyses (PRISMA) guidelines.[22] The protocol of this review
43
44
45 100 was registered in PROSPERO, with the following registration number CRD42020168979.

46 47 101 **Eligibility criteria**

48 49 102 ***Condition***

50
51 103 We considered studies reporting the prevalence (or enough data to compute this estimate) of
52
53 104 depressive disorders and symptoms. We considered depressive disorders (and major depressive
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55 105 disorders) diagnosed according to the Diagnostic and Statistical Manual of Mental Health
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57 106 Disorders IV or V [23,24], or International Statistical Classification of Diseases and Related
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3 107 Health Problems-10 [25]. In studies where depressive disorders were not defined using the
4
5 108 aforementioned criteria, we considered the definition used by authors, including especially
6
7 109 diagnostic scores such as the Patient Health Questionnaire-9. Major depressive symptoms
8
9 110 notably included depressive mood and anhedonia.

111 ***Context***

112 We considered studies conducted in people living in Africa. Studies conducted in Africans
113 living outside Africa were not considered.

114 ***Population***

115 We considered studies conducted in adults (≥ 18 years) living with hypertension, independently
116 of the diagnosis criteria used, of the therapeutic regimen and the control status for the
117 hypertensive disease.

118 ***Study design***

119 Cross-sectional, case-control, and cohort studies.

120 **Data sources**

121 We searched PubMed, Excerpta Medica Database (EMBASE), Africa Index Medicus, and
122 Africa Journal Online to identify all relevant records published up to January 31st, 2020;-without
123 any language restriction. The search strategy in EMBASE is available in the Appendix
124 (Supplementary Table 1). To supplement the bibliographic database searches and identify
125 potential additional data sources, we scrutinized the reference list of all relevant original and
126 review papers.

127 **Study selection**

128 Titles and abstracts of articles retrieved from literature search were independently screened by
129 two investigators (FTE and JJB), and the full-texts of those potentially eligible were obtained
130 and further assessed for final inclusion. Disagreements were resolved through consensus.

131 **Data collection and management**

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3 132 A preconceived and standardized data extraction form was used to collect information on first
4
5 133 author's name, study country, year of publication, period of participants' recruitment, study
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7 134 design, setting, sampling method, timing of data collection, response rate, mean or median age
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10 135 of the population, age range, proportion of males, number of participants with hypertension, the
11
12 136 number of participants with depressive disorders. In case of multinational studies, data were
13
14 137 separated to show the estimate within individual countries. Two investigators (FTE and JJB)
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16 138 independently extracted the data from individual studies, with disagreements being resolved
17
18 139 through consensus.

21 140 Two investigators (FTE and JJB) independently assessed study methodological quality of
22
23 141 included studies with tool developed by Joanna Briggs Institute [21], with disagreements being
24
25 142 resolved through discussion and consensus. Risk of bias was considered low for each criterion
26
27 143 if studies used probabilistic sampling, prospectively collected data, had adequate sample size
28
29 144 (required sample size attained), response rate > 80%, and same method of data collection for
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31 145 participants. Studies with low risk of bias had to have four or more criteria, two or three for
32
33 146 moderate risk of bias, and no or one for low risk of bias.

37 147 **Data synthesis and analysis**

40 148 Meta-analyses were performed with the '*meta*', '*metafor*', and '*dmetar*' packages of the
41
42 149 statistical software *R* (version 3.6.2). Prevalence estimates were reported with 95% confidence
43
44 150 interval (95%CI). Prevalence pooling was done with Freeman-Tukey double arcsine
45
46 151 transformation using random-effects meta-analysis model.[26] We adjusted the prevalence in a
47
48 152 multivariate meta-analysis to take in account the variance between tools used to identify
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50 153 patients with depressive disorders/symptoms. Egger's test served for detecting the presence of
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52 154 publication bias.[27] A p-value < 0.10 on Egger test was considered indicative of statistically
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54 155 significant publication bias. Heterogeneity was evaluated by the χ^2 test on Cochran's Q
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56 156 statistic,[28] which was quantified by I^2 values. The I^2 statistic estimates the percentage of total
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3 157 variation across studies due to true between-study differences rather than chance. In general, I^2
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5 158 values greater than 60-70% indicate the presence of substantial heterogeneity.[29] Inter-rater
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7 159 agreements between investigators for study inclusion and methodological quality assessment
8
9 160 were assessed using Kappa Cohen's coefficient.[30]

12 161 **Patient and public involvement**

14 162 Patients or the public were not involved in the design, conduct, reporting, or dissemination of
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16
17 163 our research.

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22 165 **Results**

24 166 **The review process and study characteristics**

26 167 We initially identified 890 records and finally retained 11 full texts (13 prevalence data) in the
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28 168 meta-analysis (Supplementary Figure 1).[31–41] Agreement between investigators on selection
29
30
31 169 based on title and abstract was $\kappa = 0.88$ and $\kappa = 1.0$ for final inclusion.

33 170 Of the 11 included studies, eight studies used non-probabilistic sampling while three used
34
35 171 probabilistic sampling. All studies prospectively collected and analysed data and used the same
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37
38 172 method to identify patients with depressive disorders. Sample size was adequate in nine studies
39
40 173 and response rate in two studies (Supplementary Table 2). Three studies had low risk of bias
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42 174 and eight moderate risk. None of the studies had high risk of bias.

44 175 The characteristics of included studies are presented in the Table 1. All studies were cross-
45
46 176 sectional. Patient Health Questionnaire-9 was the most used tool, $n = 4$. The mean age varied
47
48 177 between 50.3 and 59.6 years. The proportion of males varied between 28% and 54%. Data on
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50 178 depressive disorders/symptoms were collected between 2002 and 2017. Four studies were
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53 179 conducted in South Africa, three studies in Nigeria, one study in Ghana, one study in both
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56 180 Ghana and Nigeria, one study in Ethiopia, and one study in Burkina-Faso. None of the study
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59 181 was conducted in Central Africa and North Africa. Talking about the language of the tool used
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3 182 to assess depressive status, four studies indicated that they use native/local languages back
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5 183 translated in English for reporting.[32,33,35,36]
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7 184 **Prevalence of depressive disorders/symptoms in people with hypertension in Africa**

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9
10 185 In total, 5,299 participants with hypertension were included. There was substantial
11
12 186 heterogeneity for all analyses, all $I^2 > 75\%$ (Figure 1). The prevalence of depressive disorders
13
14 187 was 18.6% (95%CI: 13.8-23.9; 5 studies) (Figure 1). The adjusted prevalence taking in account
15
16 188 the variance between diagnostic tools was 17.9% (95%CI: 13.0-23.4) with 52.7% of variance
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18 189 due to difference between tools. There was no publication bias ($p = 0.789$). There was no data
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20 190 on major depressive disorders.
21
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23
24 191 The prevalence of depressive symptoms was 37.3% (95%CI: 19.3-57.3; 6 studies). The adjusted
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26 192 prevalence taking in account the variance between diagnostic tools was 33.3% (95%CI: 9.9-
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28 193 61.6) with 74.1% of variance due to difference between tools. There was no publication bias (p
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30 194 = 0.115).
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33 195 The prevalence of major depressive symptoms was 7.9% (95%CI: 1.7-17.9; 2 studies). The
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35 196 adjusted prevalence taking in account the variance between diagnostic tools was 7.8% (95%CI:
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37 197 3.0-14.5) with 43.3% of variance due to difference between tools. The p value on Egger test
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39 198 was 0.789.
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42 199 In subgroup analysis, there was no difference between population-based and hospital-based for
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44 200 all outcomes except for major depressive disorders where the prevalence was higher in
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46 201 population-based study (12.6%; 95%CI: 8.8-17.0; 1 study) compared to hospital-based study
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48 202 (4.2%; 95%CI: 2.5-6.5; 1 study), $p = 0.0001$ (Supplementary Figures 2, 3, and 4). However,
49
50 203 there was low number of studies in compared groups. The prevalence of depressive disorders
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52 204 was higher among women (23.8%; 95%CI: 18.7-29.3; 1 study) compared to men (14.5%;
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54 205 95%CI: 9.3-20.6; 1 study), $p = 0.0227$ (Supplementary Figure 5). There was no difference for
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56 206 depressive symptoms (Supplementary Figure 6).
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6 208 **Discussion**

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8 209 This meta-analysis of data from 5,299 adults with hypertension living in five countries in Africa
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10 210 revealed that depressive disorders and symptoms are prevalent in this population with
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12 211 substantial heterogeneity according to the diagnostic tools. This systematic review suggests that
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14 212 approximately one on five and one-third of patients with hypertension have respectively
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16 213 depression and depressive symptoms.

17
18 214 Globally, there are dissimilarities between our findings and previous studies on depression
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20 215 among adults with hypertension. For instance, in China, compared to our findings, a meta-
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22 216 analysis of 41 studies on the prevalence of depression in patients with hypertension found
23
24 217 higher rates of depression with a pooled prevalence of 26.9% (95%CI: 21.7% - 32.3%) [10].

25
26 218 Our review revealed a higher prevalence of depression among patients with hypertension
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28 219 compared to occidental studies. For instance, considering data of United States Multi-
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30 220 Disciplinary Group Practice Observational Study which included 4,362 adult patients with
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32 221 hypertension (13% of anxiety and/or depression).[42] A cross-sectional study done in Spain
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34 222 among 5,954 hypertensive patients with high cardiovascular risk profile found that 15.6% had
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36 223 depression.[19] These differences across regions can be explained by the changeability

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38 224 pertaining to the criteria and/or diagnostic tools used to screen depressive disorder across
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40 225 studies.[43,44] Noteworthy, Li and colleagues who studied depressive disorder among
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42 226 hypertension in a meta-analysis of 41 studies suggested that self-assessed screening tools of
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44 227 depression or depressive symptoms might overestimate the prevalence of depression.[10]

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46 228 Indeed they found a 30% depression prevalence using self-administrated diagnostic scales
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48 229 versus a 21% prevalence using clinical-interviewed tools.[10] This could be linked to patients'
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50 230 confusion about depression and hypertension symptoms such as poor appetite, fatigue and sleep
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52 231 disturbances.[10] In our review the most used diagnostic tool was the PHQ-9 and another fact
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3 232 to highpoint is that differences in prevalence can also be explained by the cut-off-point used for
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5 233 a same tool to define a positive screening for depression.[32,45,46] Mahmood and colleagues
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7 234 while assessing depression among 411 hypertensive outpatients in a Pakistan hospital by using
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10 235 PHQ-9 with a score of 10 or above as cut-off point found a prevalence of 40.1%,[47] more than
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12 236 two folds ours. In our study, we had a substantial heterogeneity for all analyses which can also
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14 237 be related to the variance between diagnostic tools used for depression assessment. The
15
16 238 previously cited meta-analysis of Li and colleagues also showed evidence of high-level
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18 239 heterogeneity.[10]
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21 240 In our sub-group analysis, we found that there was no difference between population-based and
22
23 241 hospital-based for all outcomes except for major depressive disorders which prevalence was
24
25 242 higher in population-based study. This result has to be cautiously interpreted regarding the
26
27 243 amount of studies in each group (only one study per group measured with depression
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29 244 investigated with different tools). We also found that the prevalence of depressive disorders
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31 245 was higher for women when compared to men. This finding is in accordance with what is known
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33 246 concerning gender differences in depression. [48–50] This can be linked to hormonal
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35 247 differences between the two genders, and the fact that women experience periods of
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37 248 physiological changes such as menstruation, pregnancy and perimenopause. [49,51,52] There
38
39 249 are growing evidence on the potential positive role of hormone replacement therapy on
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41 250 postmenopausal depression.[51,52] Previous studies on twins revealed that women are more
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43 251 sensitive to interpersonal relationship.[51,53] This could be more pronounced in sub-Saharan
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45 252 African cultures considering the role of ale gender in families, with as consequence a lesser
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47 253 capacity to express their psychological distress.[53–55]
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49 254 This meta-analysis highlights the fact that depressive disorder is frequently encountered among
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51 255 hypertensive patients. This review might substantiate the relevancy to conduct further studies
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53 256 with the aim to investigate on the better diagnosis tool for depression among hypertensive
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3 257 patients in order to reduce heterogeneity of results. Moreover, our review could justify carrying
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5 258 out epidemiological studies on the depression-hypertension comorbidity in other African
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7 259 regions in order to have more representative regional picture of the evidence. Since we were
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10 260 able to identify only 11 studies in the last 20 years our study calls for more primary research on
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12 261 the relationship between hypertension and mental health in the continent, by using homogenous
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14 262 diagnostic tools. Researchers, clinicians, and public health policy makers can also explore
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16
17 263 implementing registries to better measure the burden of mental health disorders in the
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19 264 continent.[56–58] All this might help to establish adapted policies pertaining to the
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21 265 management of hypertensive patients with depression, notably for a tailored pharmacological
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23 266 treatment.[18,59,60] Nevertheless, our analysis could already draw clinician's awareness on the
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26 267 necessity to screen depression symptoms among hypertensive patients, especially since
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28 268 previously published works found that comorbid depression contribute to more deleterious
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30 269 cardiovascular outcomes.[8,10,15,16,18]
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33 270 This study should however be interpreted considering some limitations. First and most common
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35 271 to meta-analyses of prevalence studies [61], we found a huge heterogeneity between studies for
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37 272 which we undertook subgroup analysis to investigate sources of heterogeneity and adjusted
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39 273 analysis to take account the variance due to diagnostic tools. However, some characteristics that
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42 274 may further explain heterogeneity were not reported or there were not enough studies to conduct
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44 275 such analysis including sub-regions and age groups. Second, there was a substantial variability
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46 276 regarding the representativeness of regions and countries, with some ones less or not
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48 277 represented. This may weaken the generalizability of our findings and call for more
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51 278 epidemiological studies in this region. Not all studies had low risk of bias, especially, most of
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53 279 studies used non-probabilistic sampling. However, due to low number of studies included in
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56 280 this meta-analysis, we were not able to perform sensitivity analysis to assess the robustness of
57
58 281 our findings based on methodological quality.
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3 282 Despite these limitations, this first systematic review and meta-analysis on depressive
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5 283 disorders/symptoms in people living with hypertension in Africa provided a clear summary of
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7 284 the existing knowledge. This systematic review is a starting point for understanding the
8
9 285 epidemiology and relationship between mental health and hypertension in African countries
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11 286 where it is challenging to have such data. A protocol had been registered before, and we used
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13 287 rigorous methodological and statistical procedures to obtain and pool data. Furthermore, we
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15 288 have taken in account the variability due to diagnostic tools. There was no publication bias.
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17 289

21 290 **Conclusions**

23
24 291 Overall, our review found that depressive disorders and symptoms are prevalent in people living
25
26 292 with hypertension in select African countries. Including an assessment of mental health in
27
28 293 patients with hypertension seems prudent, with the potential for intervention. However, since
29
30 294 our analysis has limitations pertaining to diagnostic tools consistency within studies and also to
31
32 295 the unrepresentative geographic distribution, further studies would be relevant in order to
33
34 296 reinforce our findings. All this could be a support for a personalized management of patients
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36 297 with hypertension and depression.
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38 298

42 299 **Author Contributors**

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45 300 Conception: JJB, FTE. Designing of the protocol: FTE, JJB. Literature search: JJB. Studies
46
47 301 selection: FTE, JJB. Data extraction: FTE, JJB. Data management: JJB. Data synthesis and
48
49 302 analysis: JJB. Writing of the first draft: JJB, FTE. Critical revision: FTE, MNT, JJB. Approved
50
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52
53

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4
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7
8 309 **Competing interests**

9
10 310 We declare no competing interests.

11
12 311 **Patient consent**

13
14 312 Not applicable.

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17 313 **Data sharing statement**

18
19 314 All data generated for this study are in the manuscript and its supporting files.

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488 **Figures legend**

489 Figure 1. Crude prevalence of depressive disorders/symptoms in people living with
490 hypertension in Africa

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491 **Table 1. Characteristics of included studies**

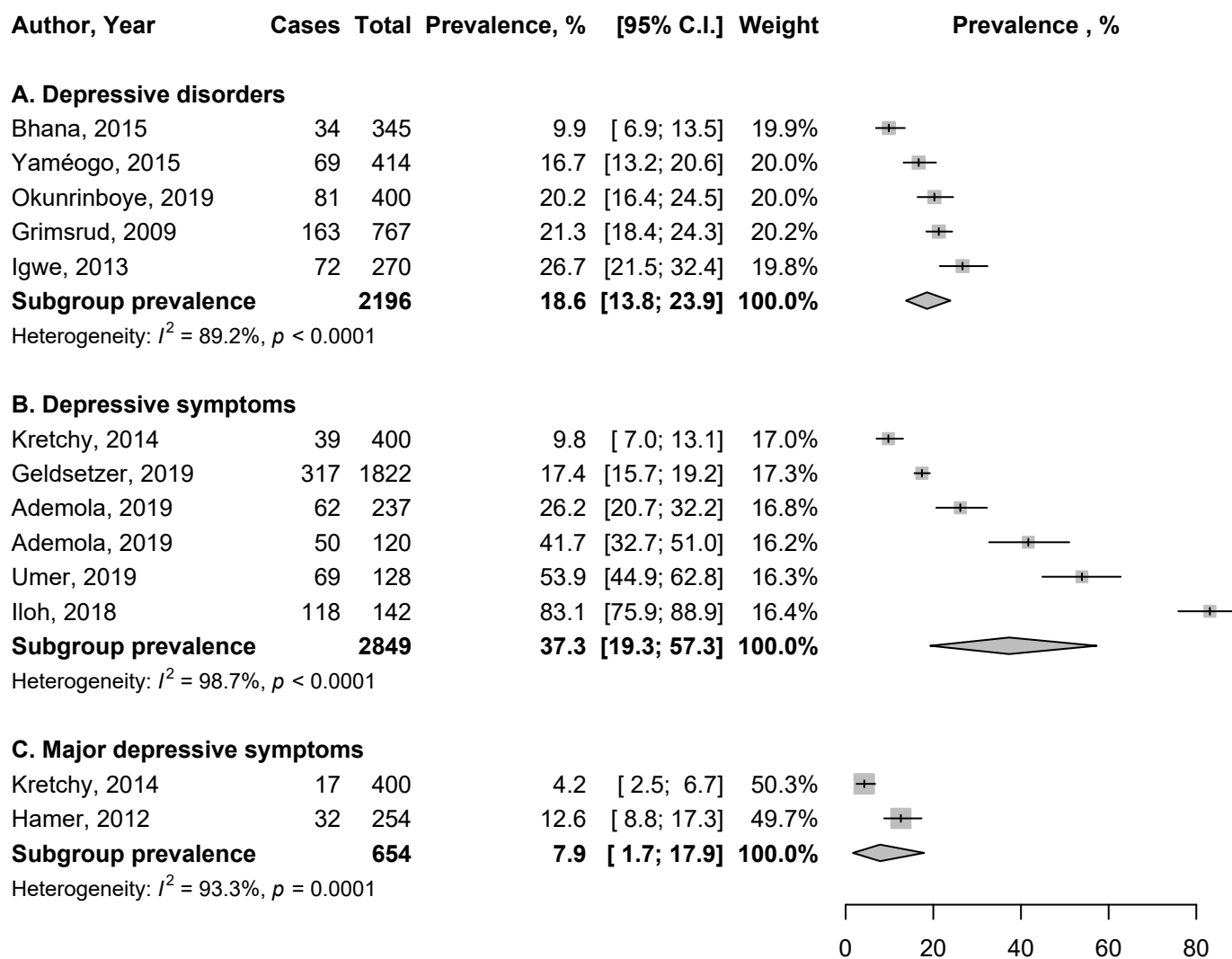
Author	Year	Design, Setting	Diagnosis of conditions	Validity of the tool used	Language of the tool used	Inclusion criteria	Population	Period of inclusion	Country	Sample
Ademola	2019	Cross-sectional, Hospital	Patient Health Questionnaire 9 (PHQ-9)	Validated	NR	Age \geq 18 y, diagnosis of hypertension, treatment with an antihypertensive medication for at least 12 months	%Males: 41.7; Mean age: 57	2013	Ghana, Nigeria	357
Bhana	2015	Cross-sectional, Population	Depression module of the Structured Clinical Interview for DSM-IV (SCID)	NR	English, seTswana	Age \geq 18 y, clinic attendance for routine chronic disease services (e.g., HIV, hypertension, diabetes) and ability to comprehend and complete study components in Tswana or English.	NR	2014	South Africa	345
Geldsetzer	2019	Cross-sectional, Population	Center for Epidemiological Studies—Depression (CES-D) screening tool	NR	English, Shangaan	Age \geq 40 y and continuously living in the area during the 12 months prior to study enrolment	%Males: 37.4 Mean age : NR	2014-2015	South Africa	1822
Grimsrud	2009	Cross-sectional, Population	Composite International Diagnostic Interview Version 3.0 (CIDI-3.0)	NR	NR	South Africans \geq 18 y who lived in households and hostels during the field period of the study	%Males: 28.0; Mean age: 50.3	2002-2004	South Africa	767
Hamer	2012	Cross-sectional, Population	Patient Health Questionnaire 9 (PHQ-9)	Validated	English and local language	Age: 25-60 y with hypertension	NR	2008-2009	South Africa	254
Igwe	2013	Cross-sectional, Hospital	Mini International Neuro-psychiatric Interview (MINI)	NR	NR	Age: 18 - 64 y. Hypertension for at least 1 year and stable without need for hospital admission for 3 months prior to assessment	%Males: 53.7; Mean age: 50.4	2010-2011	Nigeria	270
Iloh	2018	Cross-sectional, Hospital	Patient Health Questionnaire 9 (PHQ-9)	Validated	NR	Age \geq 18 y with hypertension	%Males: 40.7; Mean age : NR	2017	Nigeria	142

Kretchy	2014	Cross-sectional, Hospital	Depression Anxiety Stress Scale (DASS) – 21	NR	NR	Age ≥ 18 y, a diagnosis of hypertension, reporting prescription of at least one antihypertensive medication for a minimum of two months	%Males: 37.3; Mean age : NR	2012	Ghana	400
Okunrinboye	2019	Cross-sectional, Hospital	Mini International Neuro-psychiatric Interview (MINI)	NR	Yoruba, English	Age: 18 and 64 y who were diagnosed by a consultant physician at the Centre as suffering from hypertension and have been on anti-hypertensive medication for at least 6 months, spoke Yoruba or English language fluently	%Males: 38.0; Mean age: 59.6y	2012	Nigeria	400
Umer	2019	Cross-sectional, Hospital	Patient Health Questionnaire 9 (PHQ-9)	Validated	English, Afan Oromo, Amharic	Age ≥ 18 y, follow-up for hypertension	%Males: 52.8; Mean age : NR	2014	Ethiopia	128
Yaméogo	2015	Cross-sectional, Hospital	Hospital Anxiety and Depression Scale (HADS)	NR	NR	Hypertensive consenting adult outpatients	%Males: 40.1; Mean age: 54.6y	2010-2011	Burkina-Faso	414

492 NR: not reported.

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3 **Epidemiology of depressive disorders in people living with hypertension in**
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6 **Africa: a systematic review and meta-analysis**
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15 **APPENDIX**
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Supplementary Table 1. Search strategy

Search	Search terms
#1	'africa'/exp OR africa OR 'algeria'/exp OR algeria OR 'angola'/exp OR angola OR 'benin'/exp OR benin OR 'botswana'/exp OR botswana OR 'burkina faso'/exp OR 'burkina faso' OR 'burundi'/exp OR burundi OR 'cameroon'/exp OR cameroon OR 'canary islands'/exp OR 'canary islands' OR 'cape verde'/exp OR 'cape verde' OR 'central african republic'/exp OR 'central african republic' OR 'chad'/exp OR chad OR 'comoros'/exp OR comoros OR 'congo'/exp OR congo OR 'democratic republic of congo' OR 'djibouti'/exp OR djibouti OR 'egypt'/exp OR egypt OR 'equatorial guinea'/exp OR 'equatorial guinea' OR 'eritrea'/exp OR eritrea OR 'ethiopia'/exp OR ethiopia OR 'gabon'/exp OR gabon OR 'gambia'/exp OR gambia OR 'ghana'/exp OR ghana OR 'guinea'/exp OR guinea OR 'guinea bissau'/exp OR 'guinea bissau' OR 'ivory coast'/exp OR 'ivory coast' OR 'cote ivoire' OR 'jamahiriya' OR 'kenya'/exp OR kenya OR 'lesotho'/exp OR lesotho OR 'liberia'/exp OR liberia OR 'libya'/exp OR libya OR 'madagascar'/exp OR madagascar OR 'malawi'/exp OR malawi OR 'mali'/exp OR mali OR 'mauritania'/exp OR mauritania OR 'mauritius'/exp OR mauritius OR 'mayotte'/exp OR mayotte OR 'morocco'/exp OR morocco OR 'mozambique'/exp OR mozambique OR 'namibia'/exp OR namibia OR 'niger'/exp OR niger OR 'nigeria'/exp OR nigeria OR 'principe' OR 'reunion'/exp OR reunion OR 'rwanda'/exp OR rwanda OR 'sao tome' OR 'senegal'/exp OR senegal OR 'seychelles'/exp OR seychelles OR 'sierra leone'/exp OR 'sierra leone' OR 'somalia'/exp OR somalia OR 'south africa'/exp OR 'south africa' OR 'st helena'/exp OR 'st helena' OR 'sudan'/exp OR sudan OR 'swaziland'/exp OR swaziland OR 'tanzania'/exp OR tanzania OR 'togo'/exp OR togo OR 'tunisia'/exp OR tunisia OR 'uganda'/exp OR uganda OR 'western sahara'/exp OR 'western sahara' OR 'zaire'/exp OR zaire OR 'zambia'/exp OR zambia OR 'zimbabwe'/exp OR zimbabwe OR 'central africa'/exp OR 'central africa' OR 'central african'/exp OR 'central african' OR 'west africa'/exp OR 'west africa' OR 'west african'/exp OR 'west african' OR 'western africa'/exp OR 'western africa' OR 'western african'/exp OR 'western african' OR 'east africa'/exp OR 'east africa' OR 'east african'/exp OR 'east african' OR 'eastern africa'/exp OR 'eastern africa' OR 'eastern african'/exp OR 'eastern african' OR 'north africa'/exp OR 'north africa' OR 'north african'/exp OR 'north african' OR 'northern africa'/exp OR 'northern africa' OR 'northern african'/exp OR 'northern african' OR 'south african'/exp OR 'south african' OR 'southern africa'/exp OR 'southern africa' OR 'southern african'/exp OR 'southern african' OR 'sub saharan africa'/exp OR 'sub saharan africa' OR 'sub saharan african'/exp OR 'sub saharan african' OR 'subsaharan africa'/exp OR 'subsaharan africa' OR 'subsaharan african'
#2	'depression'/exp OR depression OR 'depressive disorder'/exp OR 'depressive disorder' OR 'depressive symptom'/exp OR 'depressive symptom' OR 'depressive neuros*' OR 'depressive syndrome*'

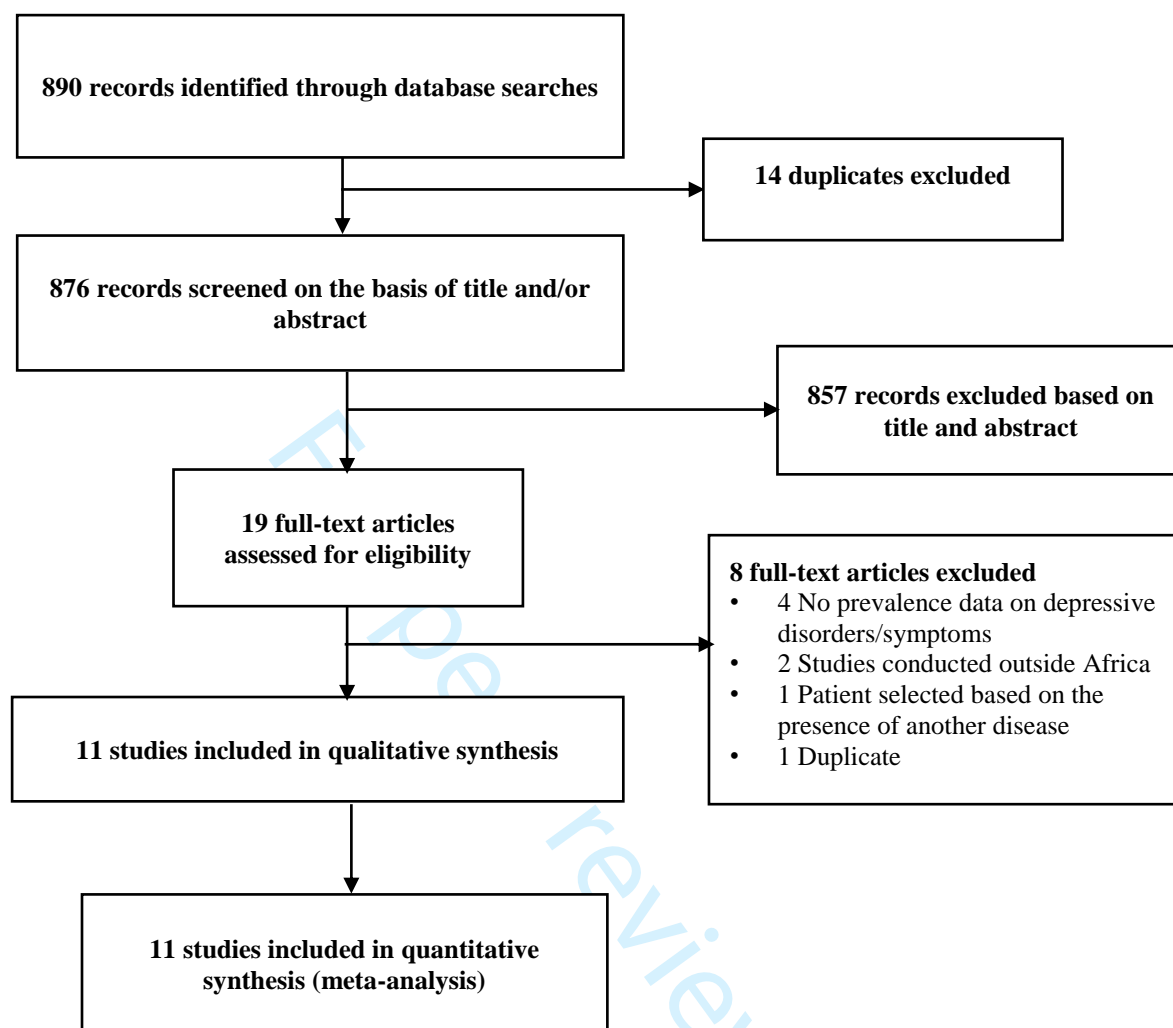
#3	'hypertension'/exp OR hypertension OR 'high blood pressure'/exp OR 'high blood pressure' OR (high AND ('blood'/exp OR blood) AND ('pressure'/exp OR pressure))
#4	#1 AND #2 AND #3

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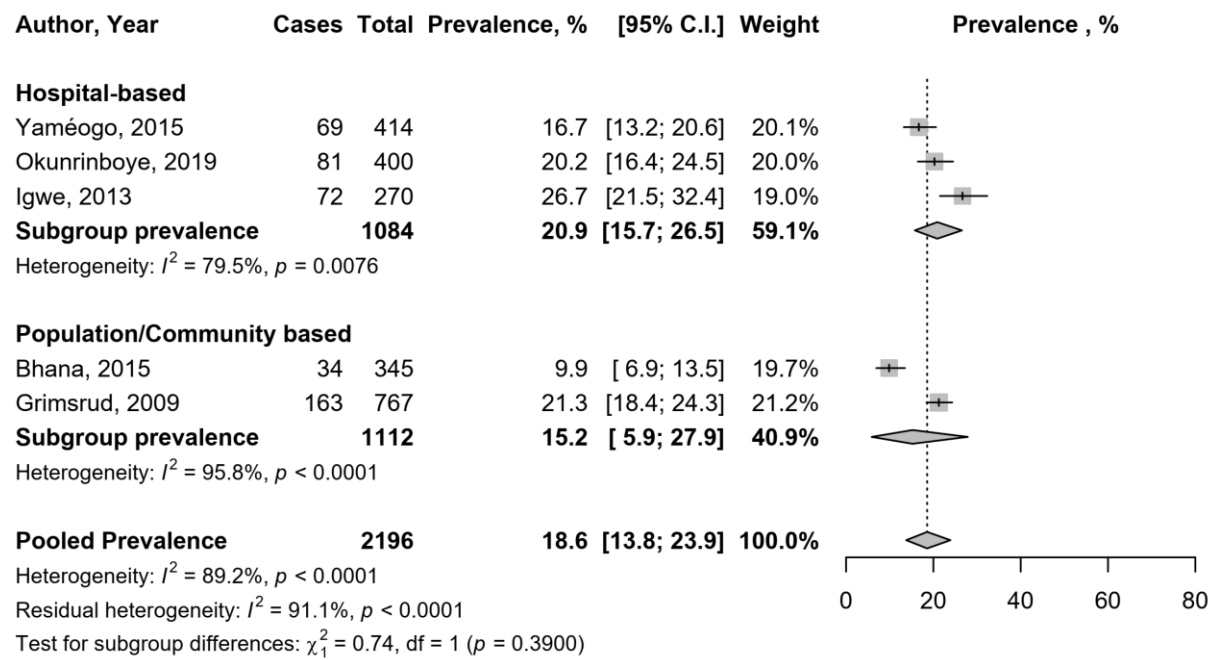
Supplementary Table 2. Methodological quality of included studies

Author, Year	Sampling method	Timing of data collection	Sample size adequate	Response rate	Same method of data collection for all participants	SUMMARY (Risk of bias)
Ademola, 2019	Convenience	Prospectively	No	Not described	Yes	Moderate
Bhana, 2015	Convenience	Prospectively	Yes	Not described	Yes	Moderate
Geldsetzer, 2019	Stratified Random	Prospectively	Yes	Adequate	Yes	Low
Grimsrud, 2009	Stratified Multistage	Prospectively	Yes	Not described	Yes	Low
Hamer, 2012	Convenience	Prospectively	Yes	Not described	Yes	Moderate
Igwe, 2013	Convenience	Prospectively	Yes	Not described	Yes	Moderate
Iloh, 2018	Convenience	Prospectively	Yes	Not described	Yes	Moderate
Kretchy, 2014	Time-Location	Prospectively	Yes	Not described	Yes	Moderate
Okunrinboye, 2019	Systematic Random	Prospectively	Yes	Not described	Yes	Low
Umer, 2019	Convenience	Prospectively	No	Adequate	Yes	Moderate
Yaméogo, 2015	Convenience	Prospectively	Yes	Not described	Yes	Moderate

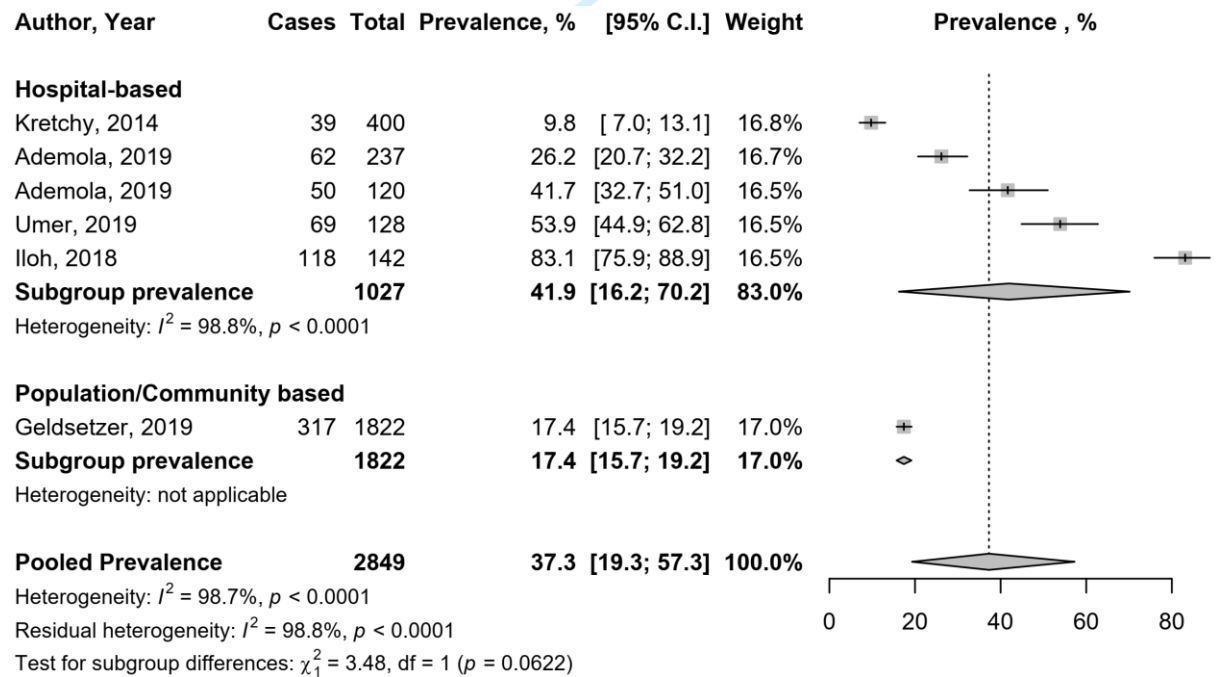
Supplementary Figure 1. PRISMA flow diagram



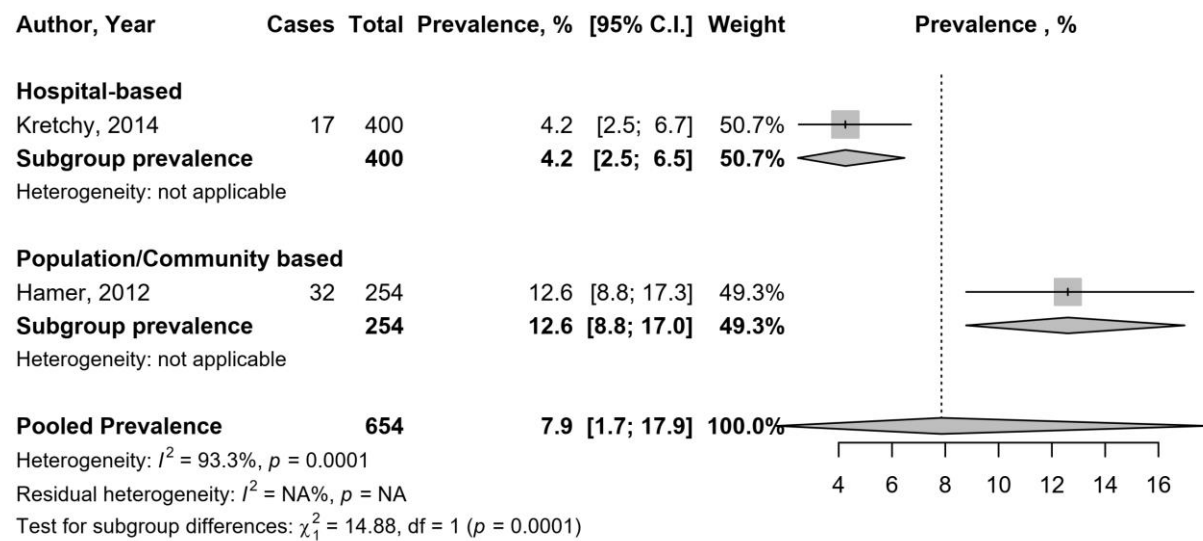
Supplementary Figure 2. Meta-analysis prevalence of depressive disorders by setting



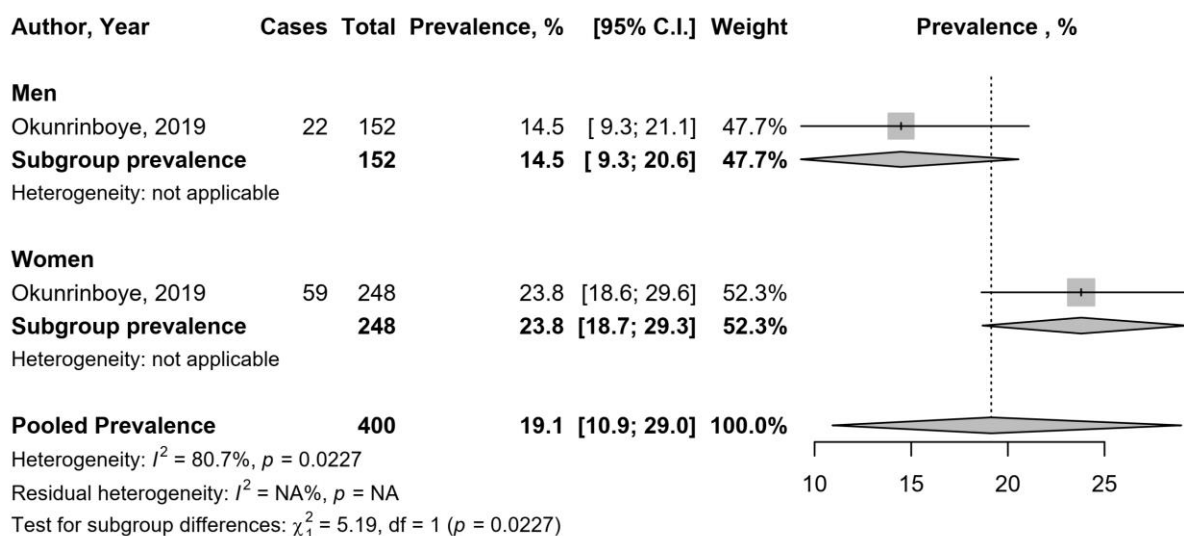
Supplementary Figure 3. Meta-analysis prevalence of depressive symptoms by setting



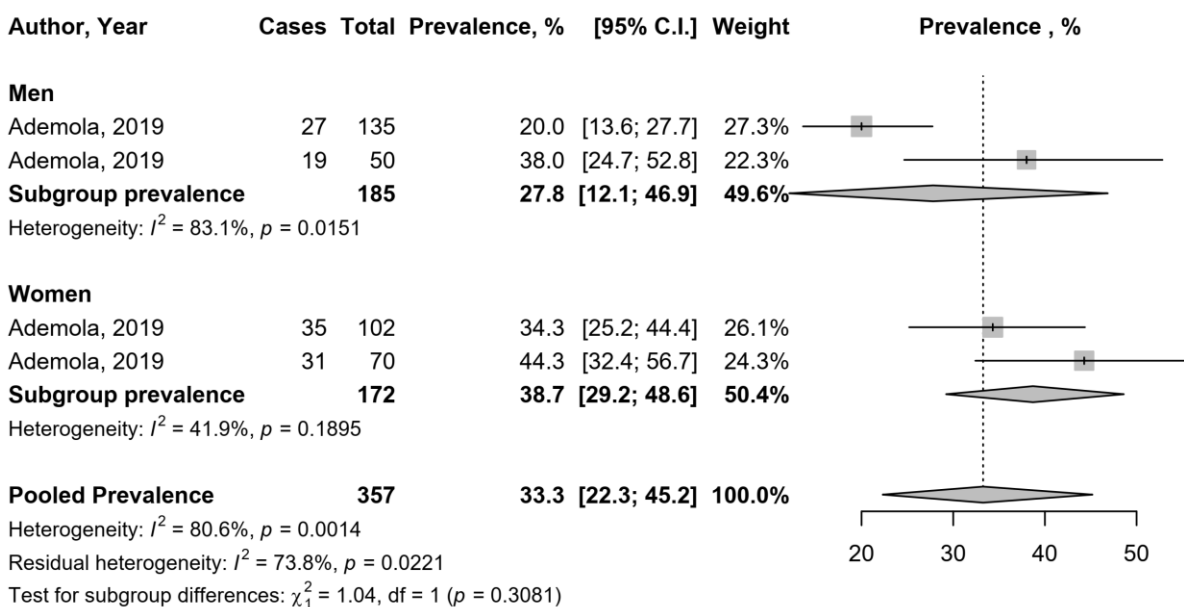
Supplementary Figure 4. Meta-analysis prevalence of major depressive disorders by setting



Supplementary Figure 5. Meta-analysis prevalence of depressive disorders by sex



Supplementary Figure 6. Meta-analysis prevalence of depressive symptoms by sex





PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7, Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8



PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9, Appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9, Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9-10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

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42 From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.
 43 doi:10.1371/journal.pmed1000097

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BMJ Open

Epidemiology of depressive disorders in people living with hypertension in Africa: a systematic review and meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-037975.R2
Article Type:	Original research
Date Submitted by the Author:	12-Nov-2020
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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Depression & mood disorders < PSYCHIATRY, Hypertension < CARDIOLOGY, EPIDEMIOLOGY

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3 1 **Epidemiology of depressive disorders in people living with hypertension in**
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6 2 **Africa: a systematic review and meta-analysis**
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17 **Abstract**

18 **Objectives:** Better knowledge of epidemiology of depressive disorders in people living with
19 hypertension can help to implement pertinent strategies to address its burden. The objective was
20 to estimate the prevalence of depressive disorders and symptoms in people living with
21 hypertension in Africa.

22 **Design:** Systematic review and meta-analysis.

23 **Data sources:** PubMed, EMBASE, African Index Medicus, Africa Journal Online were
24 searched up to January 31, 2020; regardless of the language of publication.

25 **Eligibility criteria:** We included studies conducted among hypertensive adult patients (≥ 18
26 years) living in Africa and reporting the prevalence of depressive disorders and symptoms.

27 **Data extraction and synthesis:** Two independent investigators selected studies, extracted data,
28 and assessed the methodological quality of included studies by using the tool developed by
29 Joanna Briggs Institute. Multivariate random-effects meta-analysis served to pool data by
30 considering the variability between diagnostic tools used to identify patients with depressive
31 disorders or symptoms.

32 **Results:** We included 11 studies with 5,299 adults with hypertension. Data were collected
33 between 2002 and 2017, from South Africa, Nigeria, Ghana, Ethiopia, and Burkina-Faso. The
34 mean age varied between 50.3 and 59.6 years. The proportion of males ranged from 28% to
35 54%. The adjusted prevalence of depressive disorders taking into account the variance between
36 diagnostic tools was 17.9% (95% confidence interval [CI]: 13.0-23.4). The prevalence of
37 depressive symptoms and major depressive symptoms was 33.3% (95%CI: 9.9-61.6) and 7.8%
38 (95%CI: 3.0-14.5). There was heterogeneity attributable to the diagnostic tools for depressive
39 disorders and symptoms. There was no publication bias.

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3 41 **Conclusion:** Notwithstanding the representativeness lack of some (sub) regions of Africa,
4
5 42 weakening the generalizability of findings to the entire region; depressive disorders and
6
7 43 symptoms are prevalent in people living with hypertension in Africa, indicating that strategies
8
9 44 from clinicians, researchers, and public health makers are needed to reduce its burden in the
10
11 45 region.
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22 49 **Keywords**
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24 50 Depression; Depressive symptoms; Depressive disorders; Hypertension; Africa
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Keywords

Depression; Depressive symptoms; Depressive disorders; Hypertension; Africa

51 **Strengths and Limitations of this study**

- 52 • Not all sub-regions of Africa were represented in this review.
- 53 • This is the first review performed among people living with hypertension Africa to
54 investigate the epidemiology of depressive disorders and symptoms.
- 55 • We found a huge heterogeneity between studies explained by the difference between
56 diagnostic tools for depressive disorders.
- 57 • We were not able to explore all sources of heterogeneity due to scarcity of epidemiological
58 data.

59 Introduction

60 Cardiovascular diseases (CVDs) are the leading cause of deaths worldwide with approximately
61 18 million deaths per year [1]. Hypertension is involved in approximately 50% of CVDs [2–4].
62 According to the World Health Organization (WHO), the number of people living with
63 hypertension worldwide is estimated at 1.13 billion, and Africa has the highest prevalence of
64 people with hypertension (27%) [4]. In addition to high morbidity and mortality, hypertension
65 is also associated with high socio-economic burden related to its management and
66 complications [5–7]. Detrimental outcomes related to chronic high blood pressure encompass
67 target organ damage involving cerebrovascular, heart, and kidney diseases [4,5]; but also,
68 mental health repercussions including anxiety, stress and depression [8–10].
69 Depressive disorder is the most common mental health disease and the second cause of
70 disability worldwide after cardiovascular diseases [11,12]. It accounts for 3% of the global
71 disability adjusted life years (DALYs) [12]. According to the WHO, depressive disorder affects
72 more than 300 million people (4.4% of the global population), and its prevalence in the African
73 continent is estimated at 9% (29.9 million of cases) in the general population [13]. Some
74 subpopulations have been identified as higher risk of depression, including patients with
75 chronic CVDs such as hypertension [9,14]. A wide range of previously published studies
76 addressed the interaction between hypertension and depression [8,10,15,16]. Most of these
77 studies concluded that hypertension and depressive disorder share bidirectional interplay where
78 patients with hypertension were more likely to develop depression and conversely [8,17]. As
79 examples of evidence, a meta-analysis of 41 studies (including 31 studies from China and three
80 from Africa) which included 30,796 patients with hypertension found that 26.8% have
81 depression, and another one which included 22,367 participants found that depression
82 significantly increases the risk of hypertension incidence [10,15] Additionally, it has been
83 reported that patients living with hypertension with comorbid depression are at higher risk of

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3 84 suboptimal medication adherence with uncontrolled blood pressure, complicated by chronic
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5 85 vascular complications and cardiovascular disease related mortality [8,10,15,16,18]. The
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7 86 burden of the depression-hypertension co-occurrence is worsened by the fact that
8
9 87 approximately one hypertensive patient in ten has untreated depression [10,19].
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12 88 Considering up-to-date scientific literature, depression in hypertensive patients is common in
13
14 89 western contexts [10,20], hypertension and depression are commonly encountered amongst
15
16 90 African populations [2,4,13], but data summarizing and focusing on the burden of depression
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18 91 among hypertensive Africans are not yet available. Hence, we conducted this systematic review
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20 92 and meta-analysis with the aim to explore the prevalence of depressive disorders/symptoms,
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22 93 and major depression in people living with hypertension in Africa.
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28 95 **Methods**

30 96 **Design**

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33 97 This systematic review and meta-analysis was conducted according to the Joanna Briggs
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35 98 Institute guidelines [21]. This study was reported according to the preferred reporting items for
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37 99 systematic reviews and meta-analyses (PRISMA) guidelines [22]. The protocol of this review
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39
40 100 was registered in PROSPERO with the following registration number: CRD42020168979.

42 101 **Eligibility criteria**

44 102 ***Condition***

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47 103 We considered studies reporting the prevalence (or enough data to compute this estimate) of
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49 104 depressive disorders and symptoms. We considered depressive disorders (and major depressive
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51 105 disorders) diagnosed according to the Diagnostic and Statistical Manual of Mental Health
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53 106 Disorders IV or V [23,24], or International Statistical Classification of Diseases and Related
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55 107 Health Problems-10 [25]. In the studies where depressive disorders were not defined using the
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57
58 108 aforementioned criteria, we considered the definition used by authors, including especially
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3 109 diagnostic scores such as the Patient Health Questionnaire-9. Major depressive symptoms
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5 110 notably included depressive mood and anhedonia.
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7 111 ***Context***

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10 112 We considered studies conducted in people living in Africa. Studies conducted in Africans
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12 113 living outside Africa were not considered.
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14 114 ***Population***

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17 115 We considered studies conducted in adults (≥ 18 years) living with hypertension regardless of
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19 116 the diagnosis criteria used, of the therapeutic regimen and the control status for the hypertensive
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21 117 disease.
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23 118 ***Study design***

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26 119 Cross-sectional, case-control, and cohort studies.
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28 120 **Data sources**

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31 121 We searched PubMed, Excerpta Medica Database (EMBASE), Africa Index Medicus, and
32
33 122 Africa Journal Online to identify all relevant records published up to January 31st, 2020;-without
34
35 123 any language restriction. The search strategy in EMBASE is available in the Appendix
36
37 124 (Supplementary Table 1). To supplement the bibliographic database searches and identify
38
39 125 potential additional data sources, we scrutinized the reference list of all relevant original and
40
41 126 review papers.
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44 127 **Study selection**

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47 128 Titles and abstracts of articles retrieved from literature search were independently screened by
48
49 129 two investigators (FTE and JJB), and the full-texts of those potentially eligible were obtained
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51 130 and further assessed for final inclusion. Disagreements were resolved through consensus.
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53 131 **Data collection and management**

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56 132 A preconceived and standardized data extraction form was used to collect information on first
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58 133 author's name, study country, year of publication, period of participants' recruitment, study
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3 134 design, setting, sampling method, timing of data collection, response rate, mean or median age
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5 135 of the population, age range, proportion of males, number of participants with hypertension, the
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7 136 number of participants with depressive disorders. In case of multinational studies, data were
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10 137 separated to show the estimate within individual countries. Two investigators (FTE and JJB)
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12 138 independently extracted the data from individual studies, with disagreements being resolved
13
14 139 through consensus.

16
17 140 Two investigators (FTE and JJB) independently assessed study methodological quality of
18
19 141 included studies with tool developed by Joanna Briggs Institute [21], with disagreements being
20
21 142 resolved through discussion and consensus. Risk of bias was considered low for each criterion
22
23 143 if studies used probabilistic sampling, prospectively collected data, had adequate sample size
24
25 144 (required sample size attained), response rate > 80%, and same method of data collection for
26
27 145 participants. Studies with low risk of bias had to have four or more criteria, two or three for
28
29 146 moderate risk of bias, and no or one for low risk of bias.

32 33 147 **Data synthesis and analysis**

35 148 Meta-analyses were performed with the '*meta*', '*metafor*', and '*dmetar*' packages of the
36
37 149 statistical software *R* (version 3.6.2). Prevalence estimates were reported with 95% confidence
38
39 150 interval (95%CI). Prevalence pooling was done with Freeman-Tukey double arcsine
40
41 151 transformation using random-effects meta-analysis model [26]. We adjusted the prevalence in
42
43 152 a multivariate meta-analysis to take in account the variance between tools used to identify
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45 153 patients with depressive disorders/symptoms. Egger's test served for detecting the presence of
46
47 154 publication bias [27]. A p-value < 0.10 on Egger test was considered indicative of statistically
48
49 155 significant publication bias. Heterogeneity was evaluated by the χ^2 test on Cochran's Q statistic
50
51 156 [28], which was quantified by I^2 values. The I^2 statistic estimates the percentage of total
52
53 157 variation across studies due to true between-study differences rather than chance. In general, I^2
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55 158 values greater than 60-70% indicate the presence of substantial heterogeneity [29]. Inter-rater
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3 159 agreements between investigators for study inclusion and methodological quality assessment
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5 160 were assessed using Kappa Cohen's coefficient [30].
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8 161 **Patient and public involvement**

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10 162 Patients or the public were not involved in the design, conduct, reporting, or dissemination of
11
12 163 our research.
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16 165 **Results**

17 166 **The review process and study characteristics**

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20 167 We initially identified 890 records and finally retained 11 full texts (13 prevalence data) in the
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22 168 meta-analysis (Supplementary Figure 1) [31–41]. Agreement between investigators on
23
24 169 selection based on title and abstract was $\kappa = 0.88$ and $\kappa = 1.0$ for final inclusion.
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29 170 Of the 11 included studies, eight studies used non-probabilistic sampling while three used
30
31 171 probabilistic sampling. All studies prospectively collected and analysed data and used the same
32
33 172 method to identify patients with depressive disorders. Sample size was adequate in nine studies
34
35 173 and response rate in two studies (Supplementary Table 2). Three studies had low risk of bias
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37 174 and eight moderate risk. None of the studies had high risk of bias.
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40 175 The characteristics of included studies are presented in the Table 1. All studies were cross-
41
42 176 sectional. Patient Health Questionnaire-9 was the most used tool, $n = 4$. The mean age varied
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44 177 between 50.3 and 59.6 years. The proportion of males varied between 28% and 54%. Data on
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46 178 depressive disorders/symptoms were collected between 2002 and 2017. Four studies were
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48 179 conducted in South Africa, three studies in Nigeria, one study in Ghana, one study in both
49
50 180 Ghana and Nigeria, one study in Ethiopia, and one study in Burkina-Faso. None of the study
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52 181 was conducted in Central Africa and North Africa. Talking about the language of the tool used
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54 182 to assess depressive status, four studies indicated that they use native/local languages back
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56 183 translated in English for reporting [32,33,35,36].
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184 **Prevalence of depressive disorders/symptoms in people with hypertension in Africa**

185 In total, 5,299 participants with hypertension were included. There was substantial
186 heterogeneity for all analyses, all $I^2 > 75\%$ (Figure 1). The prevalence of depressive disorders
187 was 18.6% (95%CI: 13.8-23.9; 5 studies) (Figure 1). The adjusted prevalence taking into
188 account the variance between diagnostic tools was 17.9% (95%CI: 13.0-23.4) with 52.7% of
189 variance due to difference between tools. There was no publication bias ($p = 0.789$). There was
190 no data on major depressive disorders.

191 The prevalence of depressive symptoms was 37.3% (95%CI: 19.3-57.3; 6 studies). The adjusted
192 prevalence taking into account the variance between diagnostic tools was 33.3% (95%CI: 9.9-
193 61.6) with 74.1% of variance due to difference between tools. There was no publication bias (p
194 = 0.115).

195 The prevalence of major depressive symptoms was 7.9% (95%CI: 1.7-17.9; 2 studies). The
196 adjusted prevalence taking into account the variance between diagnostic tools was 7.8%
197 (95%CI: 3.0-14.5) with 43.3% of variance due to difference between tools. The p value on
198 Egger test was 0.789.

199 In subgroup analysis, there was no difference between population-based and hospital-based for
200 all outcomes except for major depressive disorders where the prevalence was higher in
201 population-based study (12.6%; 95%CI: 8.8-17.0; 1 study) compared to hospital-based study
202 (4.2%; 95%CI: 2.5-6.5; 1 study), $p = 0.0001$ (Supplementary Figures 2, 3, and 4). However,
203 there was low number of studies in compared groups. The prevalence of depressive disorders
204 was higher among women (23.8%; 95%CI: 18.7-29.3; 1 study) compared to men (14.5%;
205 95%CI: 9.3-20.6; 1 study), $p = 0.0227$ (Supplementary Figure 5). There was no difference for
206 depressive symptoms (Supplementary Figure 6).

208 **Discussion**

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3 209 This meta-analysis of data from 5,299 adults with hypertension living in five countries in Africa
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5 210 revealed that depressive disorders and symptoms are prevalent in this population with
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7 211 substantial heterogeneity according to the diagnostic tools. This systematic review suggests that
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9 212 approximately one on five and one-third of patients with hypertension have respectively
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11 213 depression and depressive symptoms.

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13
14 214 Globally, there are dissimilarities between our findings and previous studies on depression
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16 215 among adults with hypertension. For instance, in China, a meta-analysis of 41 studies on the
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18 216 prevalence of depression in patients with hypertension found higher rate of depression with a
19
20 217 pooled prevalence of 26.9% (95%CI: 21.7% - 32.3%) [10]. Our review revealed a higher
21
22 218 prevalence of depression among patients with hypertension compared to occidental studies. For
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24 219 instance, considering data of United States Multi-Disciplinary Group Practice Observational
25
26 220 Study which included 4,362 adult patients with hypertension, 13% had anxiety and/or
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28 221 depression [42]. A cross-sectional study done in Spain among 5,954 hypertensive patients with
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30 222 high cardiovascular risk factors found that 15.6% of them had depression [19]. These
31
32 223 differences across regions can be explained by the changeability pertaining to the criteria and/or
33
34 224 diagnostic tools used to screen depressive disorder [43,44]. Noteworthy, Li and colleagues who
35
36 225 studied depressive disorder among patients with hypertension in a meta-analysis of 41 studies
37
38 226 suggested that self-assessed screening tools of depression or depressive symptoms might
39
40 227 overestimate the prevalence of depression [10]. Indeed, they found a 30% depression
41
42 228 prevalence using self-administrated diagnostic scales versus a 21% prevalence using clinical-
43
44 229 interviewed tools [10]. This could be linked to patients' confusion about symptoms possibly
45
46 230 encountered in both depression and hypertension such as poor appetite, fatigue and sleep
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48 231 disturbances [10]. In our review, the most used diagnostic tool was the PHQ-9 and another fact
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50 232 to highpoint is that differences in prevalence can also be explained by the cut-off-points used
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52 233 for a same tool to define a positive screening for depression [32,45,46]. Mahmood and
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3 234 colleagues while assessing depression among 411 hypertensive outpatients in a Pakistan
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5 235 hospital by using PHQ-9 with a score of 10 or above as cut-off point found a prevalence of
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7 236 40.1% [47], more than two folds compared to our findings. In our study, we had a substantial
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10 237 heterogeneity for all analyses which can also be related to the variance between diagnostic tools
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12 238 used for depression assessment. The previously cited meta-analysis of Li and colleagues also
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14 239 showed evidence of high-level heterogeneity due to diagnostic tools considered in original
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16 240 studies [10].

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19 241 In our sub-group analysis, we found that there was no difference between population-based and
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21 242 hospital-based for all outcomes except for major depressive disorders which prevalence was
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23 243 higher in population-based study. This result has to be cautiously interpreted regarding the
24
25 244 amount of studies in each group (only one study per group measured with depression
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27 245 investigated with different tools). We also found that the prevalence of depressive disorders
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29 246 was higher among women compared to men. This finding is in accordance with what is known
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31 247 concerning gender differences in depression [48–50]. This can be linked to hormonal
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33 248 differences between the two genders, and the fact that women experience periods of
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35 249 physiological changes such as menstruation, pregnancy and perimenopause [49,51,52]. There
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37 250 are growing evidence on the potential positive role of hormone replacement therapy on
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39 251 postmenopausal depression [51,52]. This could be more pronounced in sub-Saharan African
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41 252 cultures considering the role of male gender in families, with as consequence a lesser capacity
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43 253 to express their psychological distress [53–55].

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45 254 This meta-analysis highlights the fact that depressive disorder is frequently encountered among
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47 255 hypertensive patients compared to the general population. This review might substantiate the
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49 256 relevancy to conduct further studies with the aim to investigate on the better diagnosis tool for
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51 257 depression among hypertensive patients in order to reduce heterogeneity of results. Moreover,
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53 258 our review could justify carrying out epidemiological studies on the depression-hypertension
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3 259 comorbidity in other African regions in order to have more representative regional picture of
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5 260 the evidence. Since we were able to identify only 11 studies in the last 20 years our study calls
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7 261 for more primary research on the relationship between hypertension and mental health in the
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9 262 continent, by using homogenous diagnostic tools. Researchers, clinicians, and public health
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11 263 policy makers can also explore implementing registries to better measure the burden of mental
12
13 264 health disorders in the continent [56–58]. All this might help to establish adapted policies
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15 265 pertaining to the management of hypertensive patients with depression, notably for a tailored
16
17 266 pharmacological treatment [18,59,60]. Nevertheless, our analysis could already draw
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19 267 clinician’s awareness on the necessity to screen depression symptoms among hypertensive
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21 268 patients, especially since previously published works found that comorbid depression
22
23 269 contribute to more deleterious cardiovascular outcomes [8,10,15,16,18]. A meta-analysis of
24
25 270 prospective cohort studies suggested that people with depressive disorders had higher risk of
26
27 271 hypertension [61]. Therefore, implementing strategies to reduce the burden of depressive
28
29 272 disorders could help to reduce the prevalence of hypertension. Although pharmacological
30
31 273 interventions can help to reduce the burden of depressive disorders [62], cost-effective non-
32
33 274 pharmacological interventions should be explored first in a context of resources limited setting
34
35 275 like most of countries in Africa [63, 64].

36
37 276 This study should however be interpreted considering some limitations. First and most common
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39 277 to meta-analyses of prevalence studies [65], we found a huge heterogeneity between studies for
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41 278 which we undertook subgroup analysis to investigate sources of heterogeneity and adjusted
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43 279 analysis to take account the variance due to diagnostic tools. However, some characteristics that
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45 280 may further explain heterogeneity were not reported or there were not enough studies to conduct
46
47 281 such analysis including sub-regions and age groups. Second, there was a substantial variability
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49 282 regarding the representativeness of regions and countries, with some ones less or not
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51 283 represented. This may weaken the generalizability of our findings and call for more
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3 284 epidemiological studies in this region. Not all studies had low risk of bias, especially, most of
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5 285 studies used non-probabilistic sampling. However, due to low number of studies included in
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7
8 286 this meta-analysis, we were not able to perform sensitivity analysis to assess the robustness of
9
10 287 our findings based on methodological quality.

11
12 288 Despite these limitations, this first systematic review and meta-analysis on depressive
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14 289 disorders/symptoms in people living with hypertension in Africa provided a clear summary of
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16
17 290 the existing knowledge. This systematic review is a starting point for understanding the
18
19 291 epidemiology and relationship between mental health and hypertension in African countries
20
21 292 where it is challenging to have such data. A protocol had been registered before, and we used
22
23
24 293 rigorous methodological and statistical procedures to obtain and pool data. Furthermore, we
25
26 294 have taken in account the variability due to diagnostic tools. There was no publication bias.

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30 296 **Conclusions**

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32
33 297 Overall, our review found that depressive disorders and symptoms are prevalent in people living
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35 298 with hypertension in select African countries. Including an assessment of mental health in
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38 299 patients with hypertension seems prudent, with the potential for intervention. However, since
39
40 300 our analysis has limitations pertaining to diagnostic tools consistency within studies and also to
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42 301 the unrepresentative geographic distribution, further studies would be relevant in order to
43
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45 302 reinforce our findings. All this could be a support for a personalized management of patients
46
47 303 with hypertension and depression.

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51 305 **Author Contributors**

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54 306 Conception: JJB, FTE. Design of the protocol: FTE, JJB. Literature search: JJB. Studies'
55
56 307 selection: FTE, JJB. Data extraction: FTE, JJB. Data management: JJB. Data synthesis and
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1
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3 308 analysis: JJB. Writing of the first draft: JJB, FTE. Critical revision: FTE, MNT, JJB. Approved
4
5 309 the final version: FTE, MNT, JJB. Guarantor of the review: JJB.
6

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19 315 **Competing interests**

21 316 We declare no competing interests.

24 317 **Patient consent**

26 318 Not applicable.

28 319 **Data sharing statement**

30 320 All data generated for this study are in the manuscript and its supporting files.
31
32 321

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3 504 **Figures legend**
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5 505 Figure 1. Crude prevalence of depressive disorders/symptoms in people living with
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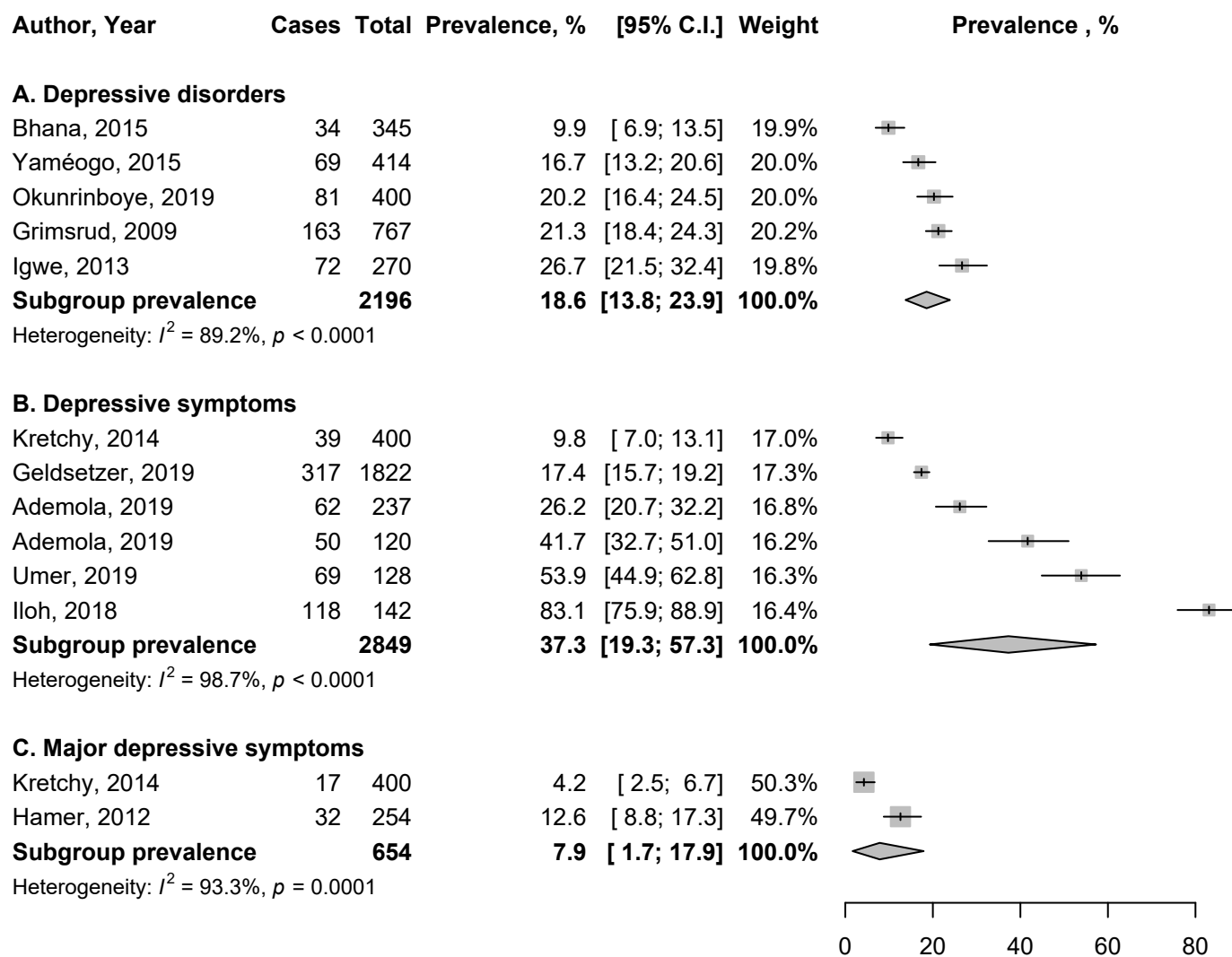
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507 **Table 1. Characteristics of included studies**

Author	Year	Design, Setting	Diagnosis of conditions	Validity of the tool used	Language of the tool used	Inclusion criteria	Population	Period of inclusion	Country	Sample
Ademola	2019	Cross-sectional, Hospital	Patient Health Questionnaire 9 (PHQ-9)	Validated	NR	Age \geq 18 y, diagnosis of hypertension, treatment with an antihypertensive medication for at least 12 months	%Males: 41.7; Mean age: 57	2013	Ghana, Nigeria	357
Bhana	2015	Cross-sectional, Population	Depression module of the Structured Clinical Interview for DSM-IV (SCID)	NR	English, seTswana	Age \geq 18 y, clinic attendance for routine chronic disease services (e.g., HIV, hypertension, diabetes) and ability to comprehend and complete study components in Tswana or English.	NR	2014	South Africa	345
Geldsetzer	2019	Cross-sectional, Population	Center for Epidemiological Studies Depression (CES-D) screening tool	NR	English, Shangaan	Age \geq 40 y and continuously living in the area during the 12 months prior to study enrolment	%Males: 37.4 Mean age : NR	2014-2015	South Africa	1822
Grimsrud	2009	Cross-sectional, Population	Composite International Diagnostic Interview Version 3.0 (CIDI-3.0)	NR	NR	South Africans \geq 18 y who lived in households and hostels during the field period of the study	%Males: 28.0; Mean age: 50.3	2002-2004	South Africa	767
Hamer	2012	Cross-sectional, Population	Patient Health Questionnaire 9 (PHQ-9)	Validated	English and local language	Age: 25-60 y with hypertension	NR	2008-2009	South Africa	254
Igwe	2013	Cross-sectional, Hospital	Mini International Neuro-psychiatric Interview (MINI)	NR	NR	Age: 18 - 64 y. Hypertension for at least 1 year and stable without need for hospital admission for 3 months prior to assessment	%Males: 53.7; Mean age: 50.4	2010-2011	Nigeria	270
Iloh	2018	Cross-sectional, Hospital	Patient Health Questionnaire 9 (PHQ-9)	Validated	NR	Age \geq 18 y with hypertension	%Males: 40.7; Mean age : NR	2017	Nigeria	142

Kretchy	2014	Cross-sectional, Hospital	Depression Anxiety Stress Scale (DASS) – 21	NR	NR	Age \geq 18 y, a diagnosis of hypertension, reporting prescription of at least one antihypertensive medication for a minimum of two months	%Males: 37.3; Mean age : NR	2012	Ghana	400
Okunrinboye	2019	Cross-sectional, Hospital	Mini International Neuro-psychiatric Interview (MINI)	NR	Yoruba, English	Age: 18 and 64 y who were diagnosed by a consultant physician at the Centre as suffering from hypertension and have been on anti-hypertensive medication for at least 6 months, spoke Yoruba or English language fluently	%Males: 38.0; Mean age: 59.6y	2012	Nigeria	400
Umer	2019	Cross-sectional, Hospital	Patient Health Questionnaire 9 (PHQ-9)	Validated	English, Afan Oromo, Amharic	Age \geq 18 y, follow-up for hypertension	%Males: 52.8; Mean age : NR	2014	Ethiopia	128
Yaméogo	2015	Cross-sectional, Hospital	Hospital Anxiety and Depression Scale (HADS)	NR	NR	Hypertensive consenting adult outpatients	%Males: 40.1; Mean age: 54.6y	2010-2011	Burkina-Faso	414

508 NR: not reported.



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3 **Epidemiology of depressive disorders in people living with hypertension in**
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6 **Africa: a systematic review and meta-analysis**
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15 **APPENDIX**
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Supplementary Figure 5. Meta-analysis prevalence of depressive disorders by sex.....	8
Supplementary Figure 6. Meta-analysis prevalence of depressive symptoms by sex.....	8

Supplementary Table 1. Search strategy

Search	Search terms
#1	'africa'/exp OR africa OR 'algeria'/exp OR algeria OR 'angola'/exp OR angola OR 'benin'/exp OR benin OR 'botswana'/exp OR botswana OR 'burkina faso'/exp OR 'burkina faso' OR 'burundi'/exp OR burundi OR 'cameroon'/exp OR cameroon OR 'canary islands'/exp OR 'canary islands' OR 'cape verde'/exp OR 'cape verde' OR 'central african republic'/exp OR 'central african republic' OR 'chad'/exp OR chad OR 'comoros'/exp OR comoros OR 'congo'/exp OR congo OR 'democratic republic of congo' OR 'djibouti'/exp OR djibouti OR 'egypt'/exp OR egypt OR 'equatorial guinea'/exp OR 'equatorial guinea' OR 'eritrea'/exp OR eritrea OR 'ethiopia'/exp OR ethiopia OR 'gabon'/exp OR gabon OR 'gambia'/exp OR gambia OR 'ghana'/exp OR ghana OR 'guinea'/exp OR guinea OR 'guinea bissau'/exp OR 'guinea bissau' OR 'ivory coast'/exp OR 'ivory coast' OR 'cote ivoire' OR 'jamahiriya' OR 'kenya'/exp OR kenya OR 'lesotho'/exp OR lesotho OR 'liberia'/exp OR liberia OR 'libya'/exp OR libya OR 'madagascar'/exp OR madagascar OR 'malawi'/exp OR malawi OR 'mali'/exp OR mali OR 'mauritania'/exp OR mauritania OR 'mauritius'/exp OR mauritius OR 'mayotte'/exp OR mayotte OR 'morocco'/exp OR morocco OR 'mozambique'/exp OR mozambique OR 'namibia'/exp OR namibia OR 'niger'/exp OR niger OR 'nigeria'/exp OR nigeria OR 'principe' OR 'reunion'/exp OR reunion OR 'rwanda'/exp OR rwanda OR 'sao tome' OR 'senegal'/exp OR senegal OR 'seychelles'/exp OR seychelles OR 'sierra leone'/exp OR 'sierra leone' OR 'somalia'/exp OR somalia OR 'south africa'/exp OR 'south africa' OR 'st helena'/exp OR 'st helena' OR 'sudan'/exp OR sudan OR 'swaziland'/exp OR swaziland OR 'tanzania'/exp OR tanzania OR 'togo'/exp OR togo OR 'tunisia'/exp OR tunisia OR 'uganda'/exp OR uganda OR 'western sahara'/exp OR 'western sahara' OR 'zaire'/exp OR zaire OR 'zambia'/exp OR zambia OR 'zimbabwe'/exp OR zimbabwe OR 'central africa'/exp OR 'central africa' OR 'central african'/exp OR 'central african' OR 'west africa'/exp OR 'west africa' OR 'west african'/exp OR 'west african' OR 'western africa'/exp OR 'western africa' OR 'western african'/exp OR 'western african' OR 'east africa'/exp OR 'east africa' OR 'east african'/exp OR 'east african' OR 'eastern africa'/exp OR 'eastern africa' OR 'eastern african'/exp OR 'eastern african' OR 'north africa'/exp OR 'north africa' OR 'north african'/exp OR 'north african' OR 'northern africa'/exp OR 'northern africa' OR 'northern african'/exp OR 'northern african' OR 'south african'/exp OR 'south african' OR 'southern africa'/exp OR 'southern africa' OR 'southern african'/exp OR 'southern african' OR 'sub saharan africa'/exp OR 'sub saharan africa' OR 'sub saharan african'/exp OR 'sub saharan african' OR 'subsaharan africa'/exp OR 'subsaharan africa' OR 'subsaharan african'
#2	'depression'/exp OR depression OR 'depressive disorder'/exp OR 'depressive disorder' OR 'depressive symptom'/exp OR 'depressive symptom' OR 'depressive neuros*' OR 'depressive syndrome*'

#3	'hypertension'/exp OR hypertension OR 'high blood pressure'/exp OR 'high blood pressure' OR (high AND ('blood'/exp OR blood) AND ('pressure'/exp OR pressure))
#4	#1 AND #2 AND #3

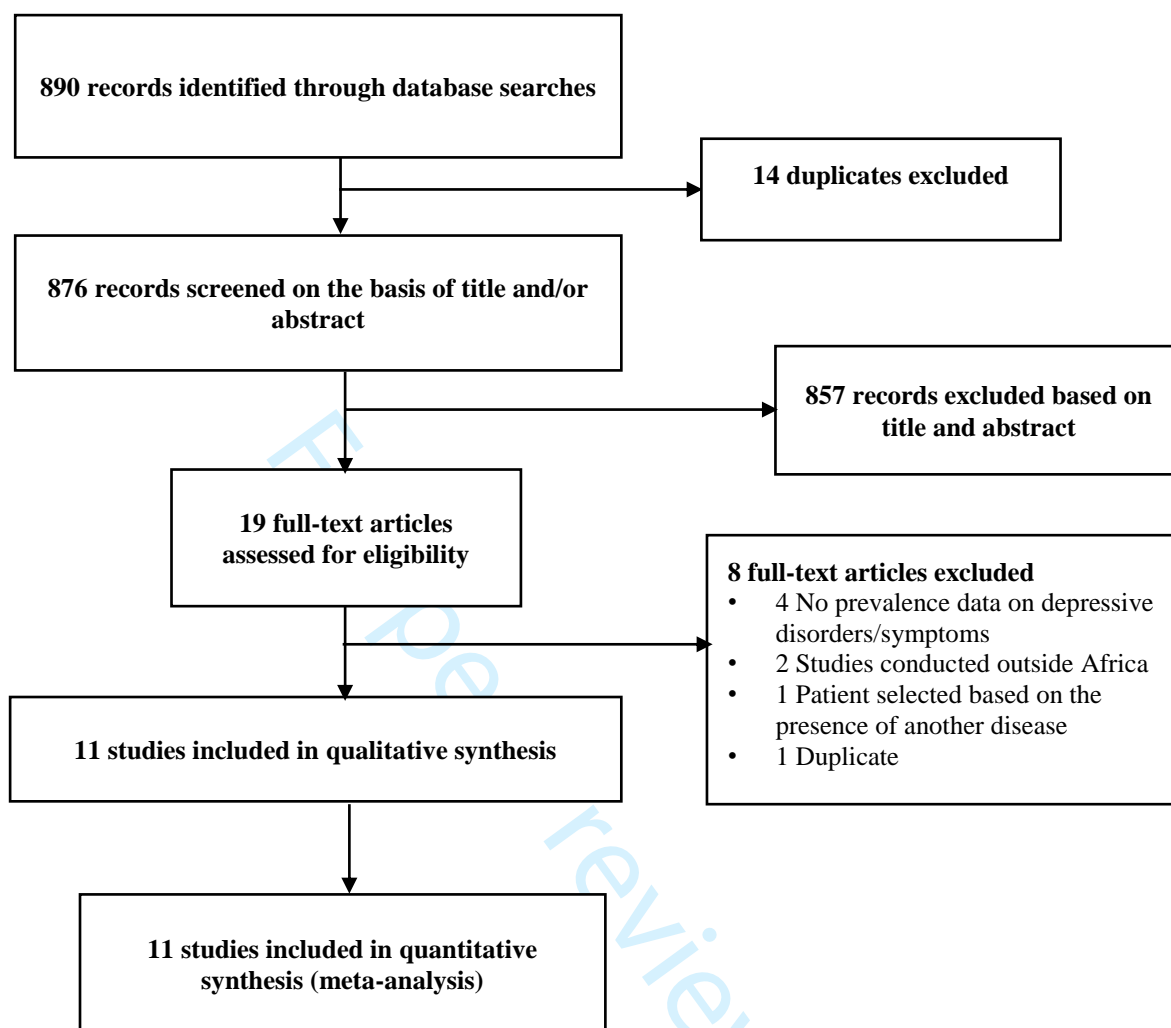
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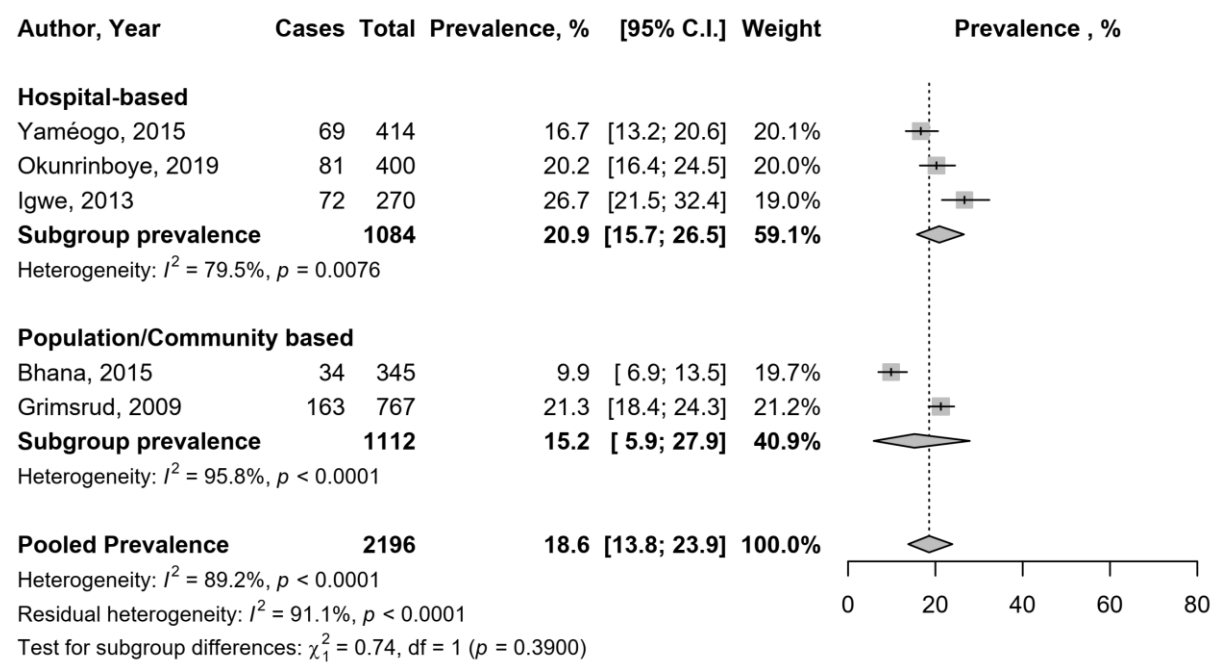
Supplementary Table 2. Methodological quality of included studies

Author, Year	Sampling method	Timing of data collection	Sample size adequate	Response rate	Same method of data collection for all participants	SUMMARY (Risk of bias)
Ademola, 2019	Convenience	Prospectively	No	Not described	Yes	Moderate
Bhana, 2015	Convenience	Prospectively	Yes	Not described	Yes	Moderate
Geldsetzer, 2019	Stratified Random	Prospectively	Yes	Adequate	Yes	Low
Grimsrud, 2009	Stratified Multistage	Prospectively	Yes	Not described	Yes	Low
Hamer, 2012	Convenience	Prospectively	Yes	Not described	Yes	Moderate
Igwe, 2013	Convenience	Prospectively	Yes	Not described	Yes	Moderate
Iloh, 2018	Convenience	Prospectively	Yes	Not described	Yes	Moderate
Kretchy, 2014	Time-Location	Prospectively	Yes	Not described	Yes	Moderate
Okunrinboye, 2019	Systematic Random	Prospectively	Yes	Not described	Yes	Low
Umer, 2019	Convenience	Prospectively	No	Adequate	Yes	Moderate
Yaméogo, 2015	Convenience	Prospectively	Yes	Not described	Yes	Moderate

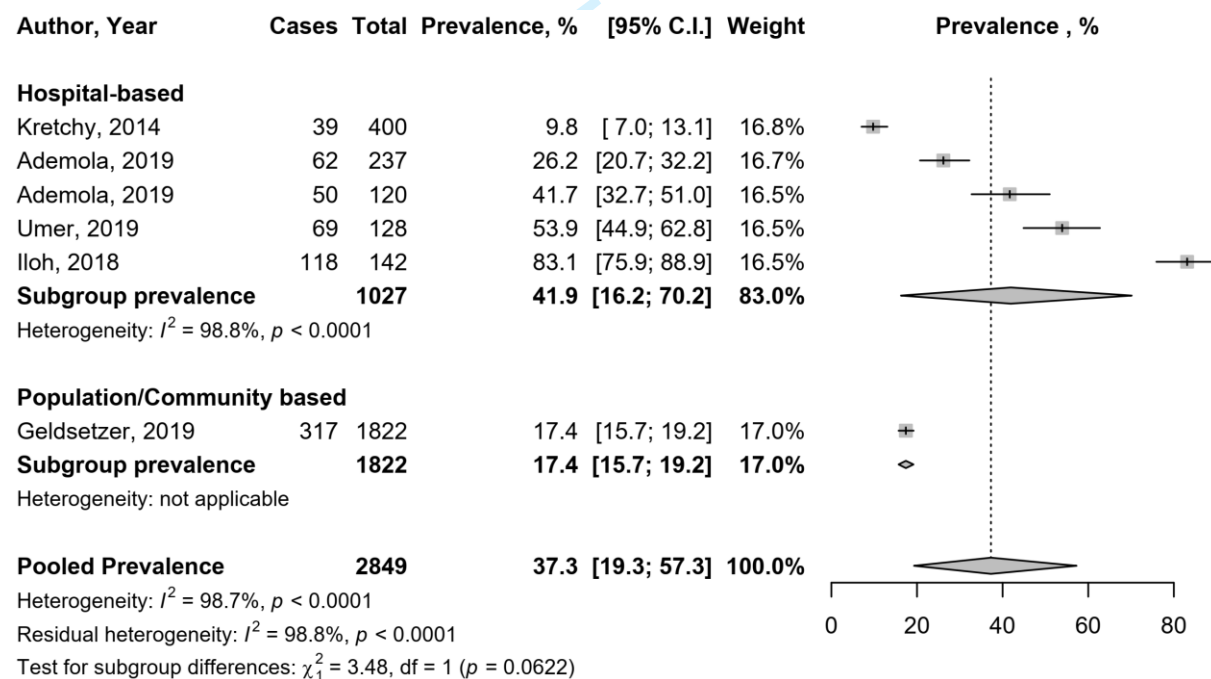
Supplementary Figure 1. PRISMA flow diagram



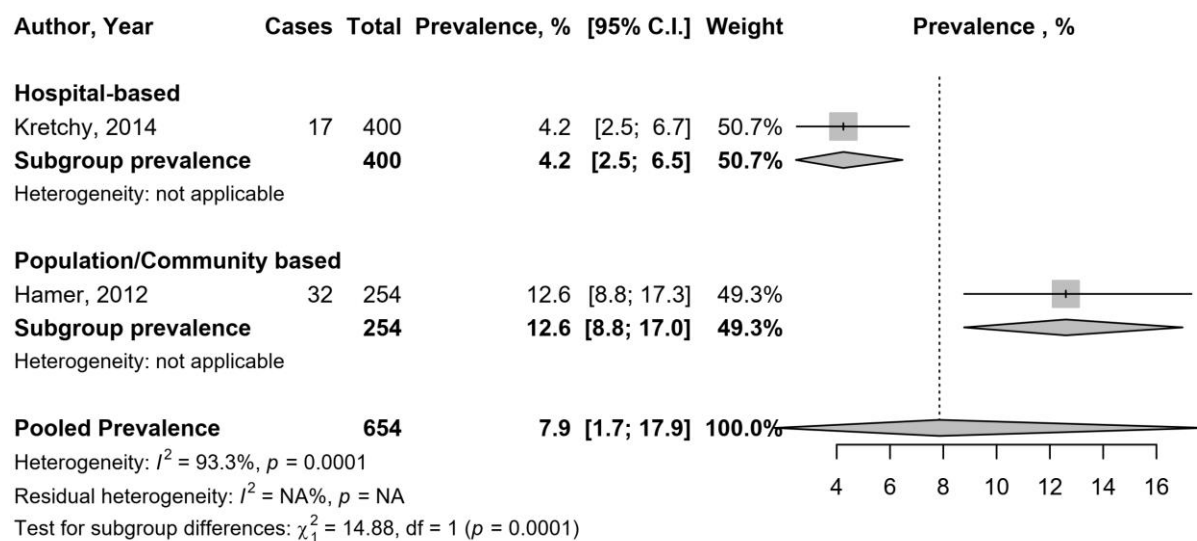
Supplementary Figure 2. Meta-analysis prevalence of depressive disorders by setting



Supplementary Figure 3. Meta-analysis prevalence of depressive symptoms by setting

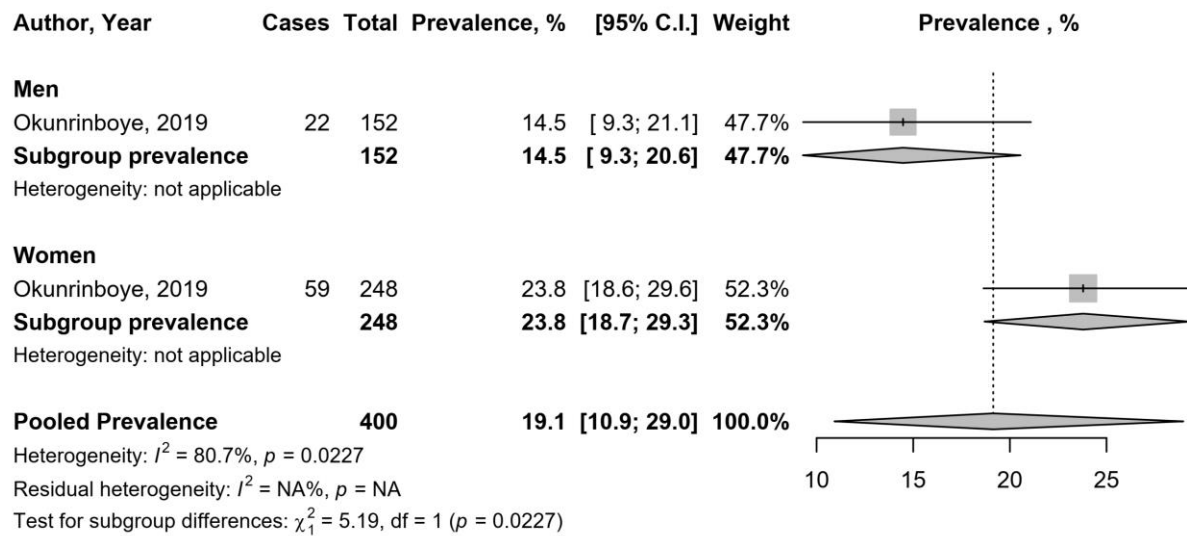


Supplementary Figure 4. Meta-analysis prevalence of major depressive disorders by setting

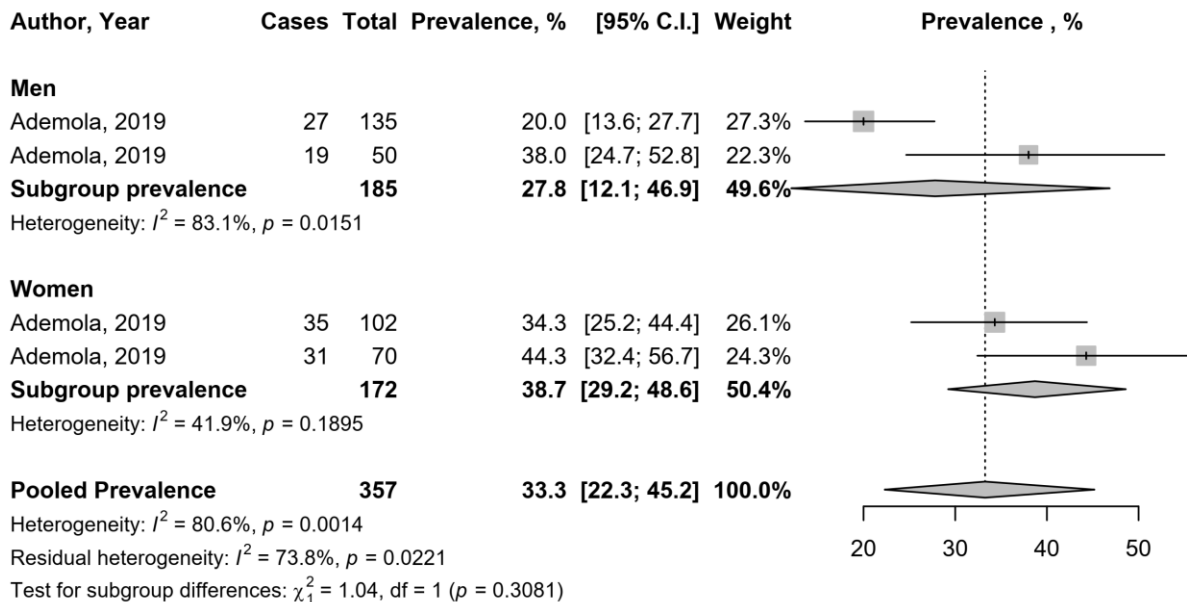


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Supplementary Figure 5. Meta-analysis prevalence of depressive disorders by sex



Supplementary Figure 6. Meta-analysis prevalence of depressive symptoms by sex





PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7, Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8



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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9, Appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9, Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9-10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

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42 From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.
 43 doi:10.1371/journal.pmed1000097

44 For more information, visit: www.prisma-statement.org.

45 For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

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