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Genetic factors contributing to hypertension in African-based populations: A systematic review and meta-analysis

Yandiswa Y. Yako PhD[1] | Eric V. Balti MD, PhD[2] | Tandi E. Matsha PhD[3] | Anastase Dzudie MD, PhD[4] | Deirdre Kruger PhD[5] | Eugene Sobngwi MD, PhD[6] | Charles Agyemang PhD[7] | Andre P. Kengne MD, PhD[8]

[1]Department of Human Biology, Faculty of Health Sciences, Walter Sisulu University, Mthatha, South Africa

[2]Diabetes Research Center and Diabetes Clinic, Department of Internal Medicine, Free University of Brussels, Brussels, Belgium

[3]Department of Biomedical Sciences, Faculty of Health and Wellness Science, Cape Peninsula University of Technology, Cape Town, South Africa

[4]Faculty of Medicine and Biomedical Sciences, University of Yaounde 1, Yaounde, Cameroon

[5]Department of Surgery, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa

[6]Department of Internal Medicine and Specialities, Faculty of Medicine and Biomedical Sciences, University of Yaounde 1, Yaounde, Cameroon

[7]Department of Public Health, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

[8]Non-Communicable Diseases Research Unit, South African Medical Research Council, Cape Town, South Africa

Correspondence
Prof Andre Pascal Kengne, MD, PhD, Non-Communicable Diseases Research Unit, South African Medical Research Council, Cape Town, South Africa.
Email: Andre.kengne@mrc.ac.za; apkengne@yahoo.com

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In a systematic review, the authors explored genetic association studies of essential hypertension in African populations. Studies reporting on the association of polymorphism(s) with hypertension in African populations were included. Appropriate studies were pooled using random effects model meta-analysis, under six potential inheritance models. In all, 46 polymorphisms in 33 genes were investigated for their association with hypertension or blood pressure levels. Meta-analysis was possible for three single nucleotide polymorphisms: rs4340, rs699, and rs5186. An association was found between rs5186, rs699, and hypertension under allele contrast and homozygous codominant models (odds ratio, 1.63 [95% confidence interval, 1.04–2.54] and 4.01 [95% confidence interval, 1.17–13.80] for rs5186, respectively; and 1.80 [95% confidence interval, 1.13–2.87] for rs699). Findings were mostly robust in sensitivity analyses. According to the systematic review, there is currently insufficient evidence on the specific polymorphisms that pose the risk of hypertension in African populations. Large-scale genetic studies are warranted to better understand susceptibility polymorphisms that may be specific to African populations.

1 | BACKGROUND

Hypertension was rarely reported in the early 20th century but is now recognized as the leading cardiovascular risk factor in African populations.[1,2] Africa has the highest prevalence of hypertension, particularly among persons 25 years and older, predominantly in sub-Saharan Africa.[1,3] The increasing prevalence rate of hypertension has been particularly evident in this region, from approximately 80 million in 2000 to projections of 150 million by 2025.[4] The burden associated with hypertension relates to cardiovascular[5] and renal complications, which have also increased in African populations. The growing hypertension and related complications are attributed to environmental

and behavioral changes including exposure to air pollution, increased alcohol consumption, tobacco use, sedentary lifestyle, adoption of a high-salt diet,[6] and consumption of refined sugar and unhealthy fats and oils.

Apart from environmental and lifestyle factors, genetics also play a major role in facilitating hypertension occurrence. According to family and twin studies, the heritability of hypertension ranges from 24% to 50%.[7,8] Hypertension exists not only as a monogenic trait but also as the essential type, which accounts for 95% of all cases of hypertension.[9] While monogenic hypertension is well defined with 12 causative genes, essential hypertension involves a complex interaction of multiple polymorphisms in numerous genes. More than 60 single nucleotide polymorphisms (SNPs) have been reported in European populations,[10,11] African Americans,[12] and Asians.[13,14] According to these studies, known loci account for only 2.5% of the phenotypic variance for systolic and diastolic blood pressure (BP). It is speculated that the missing heritability may be elucidated through search for rare and structural sequence variants, epigenetics, and investigating gene-gene and gene-environment interactions.[15] While modifiable risk factors for hypertension are well established in African countries, the contribution of genetic factors remains elusive. The current systematic review focused on collating genetic association studies of hypertension conducted in African populations residing in their respective countries and critically assessing the extent to which these studies were performed.

2 | METHODS

2.1 | Data source and selection of studies

We conducted a systematic review of genetic association studies performed in populations residing in African countries, following the Systematic Reviews of Genetic Association Studies protocol.[16] Four databases (PubMed, Embase, Scopus, and Web of Science) were searched using a combination of terms illustrated in Tables S1 and S2. This was supplemented by searching reference lists for relevant articles. Two investigators independently conducted the literature search to identify all potential studies related to polymorphisms associated with essential hypertension in populations residing in African countries. The last search date was July 21, 2017.

2.2 | Selection criteria

Studies were included if they met the following criteria: (1) investigated the association between polymorphisms and essential hypertension in Africa-based populations, (2) were original studies containing independent data, (3) were a case-control or cohort design, and (4) contained sufficient data to calculate the odd ratio (OR) with a confidence interval (CI). Studies were excluded if they: (1) were duplicate publications, (2) reported selectively on migrant Africans outside Africa, (3) were family studies, (4) used linkage analysis, (5) were secondary hypertension studies, and (6) analyzed mixed populations of African descent without considering their country of residence.

2.3 | Data extraction

Two reviewers independently extracted the following data from selected studies: first author and year of publication, study setting and design, population characteristics (number of cases and controls, and distribution of various genotypes), genetic models, Hardy-Weinberg equilibrium (HWE) test, and measures of genetic association and adjustment for confounders. Disagreements were resolved by consensus. The presence of bias was assessed by considering the following: case definition, population stratification, and reporting of methods used (sample size, genotyping method and its reliability/accuracy, validation of results, and statistical analyses).

2.4 | Statistical analyses

For polymorphisms assessed by more than two studies, we used random effects model meta-analysis to derive the pooled OR and 95% CIs for the association with prevalent hypertension under six types of inheritance models: contrast, homozygote codominant, heterozygote codominant, dominant, overdominant, and recessive models. The departure from HWE of each study was retested, and credibility of the pooled association was assessed using the Venice interim criteria.[17] Heterogeneity across studies was assessed using the Q-statistic and quantified using the I^2 statistics.[18] The Egger test was used to diagnose publication bias.[19] Potential outliers were investigated in sensitivity analysis by dropping each study at a time. The Duval and Tweedie trim-and-fill method was used to adjust estimates for the effects of publication bias. Data analysis used R version 3.3.3 (2017-03-06; The R Foundation for Statistical Computing) and meta-package. This systematic review is reported according to the recommendation of the HuGE Handbook and Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (checklist available in Table S3).

3 | RESULTS

3.1 | Literature search

Figure 1 summarizes the studies selection process. We retrieved 409 records through searches: PubMed (n = 164), Embase (n = 136), Web of Science (n = 127), Scopus (n = 5), and reference lists (n = 1). After removing duplicates and screening titles and abstracts, the full text of 53 publications was assessed for eligibility. Of these, 15 were excluded for the following reasons: the study population was comprised of family members (n = 5), missing data (n = 1), different study design (eg, investigated the effect of polymorphisms in the plasma renin-angiotensin-aldosterone system in patients with hypertension, assessed the combined effect of multiple genes on hypertension, ecological variability and its relationship with fives genes involved in

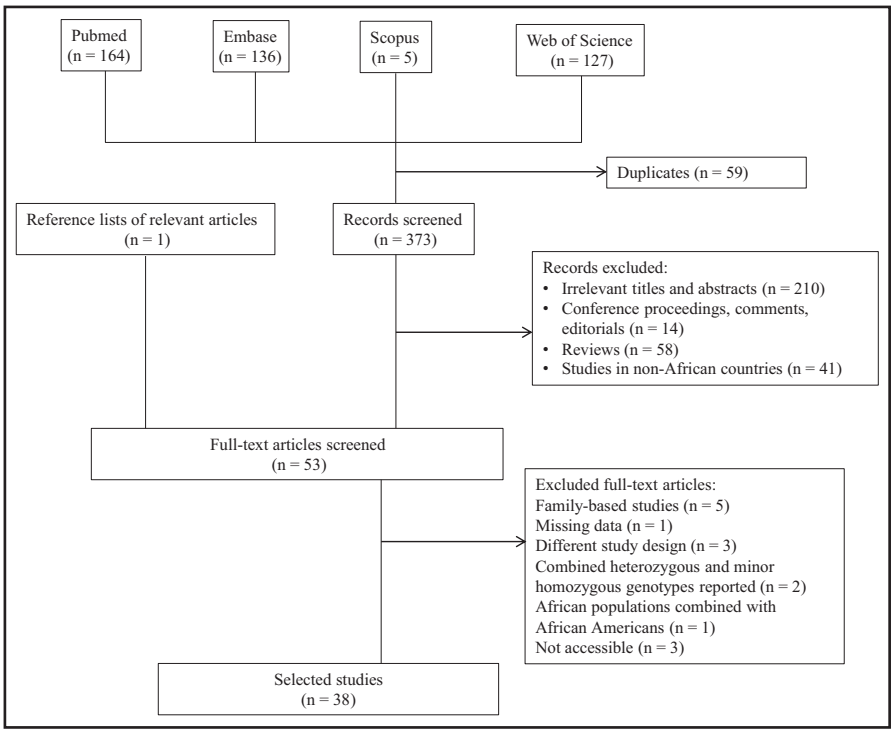

FIGURE 1 Flowchart for the studies selection process

regulation of BP) (n = 3), the frequency of the heterozygous and minor homozygous genotypes were reported as a combined number (n = 2), African populations were analyzed together with African Americans (n = 1), and three articles were not accessible. Finally, 38 studies were included in this review.

3.2 | Characteristics of studies

Study characteristics are presented in Table S4. The majority (n = 34, 92%) used a case-control design. Nine studies were conducted in Tunisia; eight in South Africa; six in Egypt; five in Ghana; three in Algeria; and two in Cameroon, Nigeria, and Morocco each; and one in Burkina Faso. Twenty studies (53%) did not report on the ethnicity of the study population. Studies varied according to the number of included participants, which ranged from 65 to 1939. Most studies defined hypertension as systolic BP/diastolic BP (SBP/DBP) ≥140/90 mm Hg or the use of antihypertensive medications at inclusion. Other studies used either auscultatory DBP >90 mm Hg or 24-hour ambulatory DBP >85 mm Hg[20] and auscultatory DBP >95 mm Hg,[21] SBP/DBP >139/89 mm Hg,[22] SBP/DBP >140/90 mm Hg,[2324] SBP/DBP ≥125/80 mm Hg,[25] seated DBP >60 mm Hg,[26] and SBP/DBP >159/94 mm Hg.[27] Ranjith and colleages[28] did not assign any values to define hypertensive status. On the other hand, Kooffreh and coworkers[29] grouped patients with hypertension according to the severity of the disease as prehypertension (SBP/DBP: 120–139/80–89 mm Hg), stage 1 hypertension (SBP/DBP: 140–159/90–99 mm Hg), and stage 2 hypertension (SBP/DBP ≥160/100 mm Hg). AbdRaboh and colleagues[30] included patients who had stage 1 hypertension (SBP/DBP > 140–145/90–95 mm Hg) or were using at least one antihypertensive medication.

3.3 | Genetic assessment and associations

A total of 46 polymorphisms in 33 genes were investigated for their association with prevalent hypertension and/or BP. None of the studies conducted a genome-wide scan; instead a candidate gene approach was used. The polymerase chain reaction–restriction fragment length polymorphism was a genotyping method of choice for most studies (55.3%). Five studies[22,28,30–32] did not provide covariates adjustment, while six[22,27,33–37] reported *P* values without effect estimates (Table S5). Some investigators included multiethnic populations, but participants were stratified by tribes or chiefdoms in only one study.[38]

The widely studied polymorphisms were those in genes of the renin-angiotensin-aldosterone system (RAAS) including angiotensin-converting enzyme (*ACE*) I/D (n = 9 studies), angiotensinogen (*AGT*) M235T (n = 7), and angiotensin II type 1 receptor (*AGTR1*) 1166A>C (n = 7). The SNPs of these genes were included in the meta-analysis. Four of the 30 polymorphisms (*CPS1*-T1405N; *BSND*-43V>I; *SH2B3*-W262R; *GNB3*-825C>T; *AGT*-T174M) that were investigated by one to three studies deviated from HWE. We also observed variable associations of the 30 SNPs in relation to hypertension or its traits (Table S5). For example, *AGT*-T147M was investigated in Algerian[39] and Ghanaian[33] populations, and demonstrated association with both SBP and DBP only in Ghanaians. On the other hand, *MTFHR*-677C>T was studied in Algerians[40] and Cameroonians[37] with no evidence of association in both populations, while in Moroccans an increased risk of hypertension was found in TT carriers.[41] One polymorphism (*NPCR*-55C>A) had low minor allele frequency and could not be assessed for its role in hypertension.[24] Seventeen of the remaining 27 polymorphisms demonstrated statistically significant associations with hypertension, SBP, or DBP (Table S5).

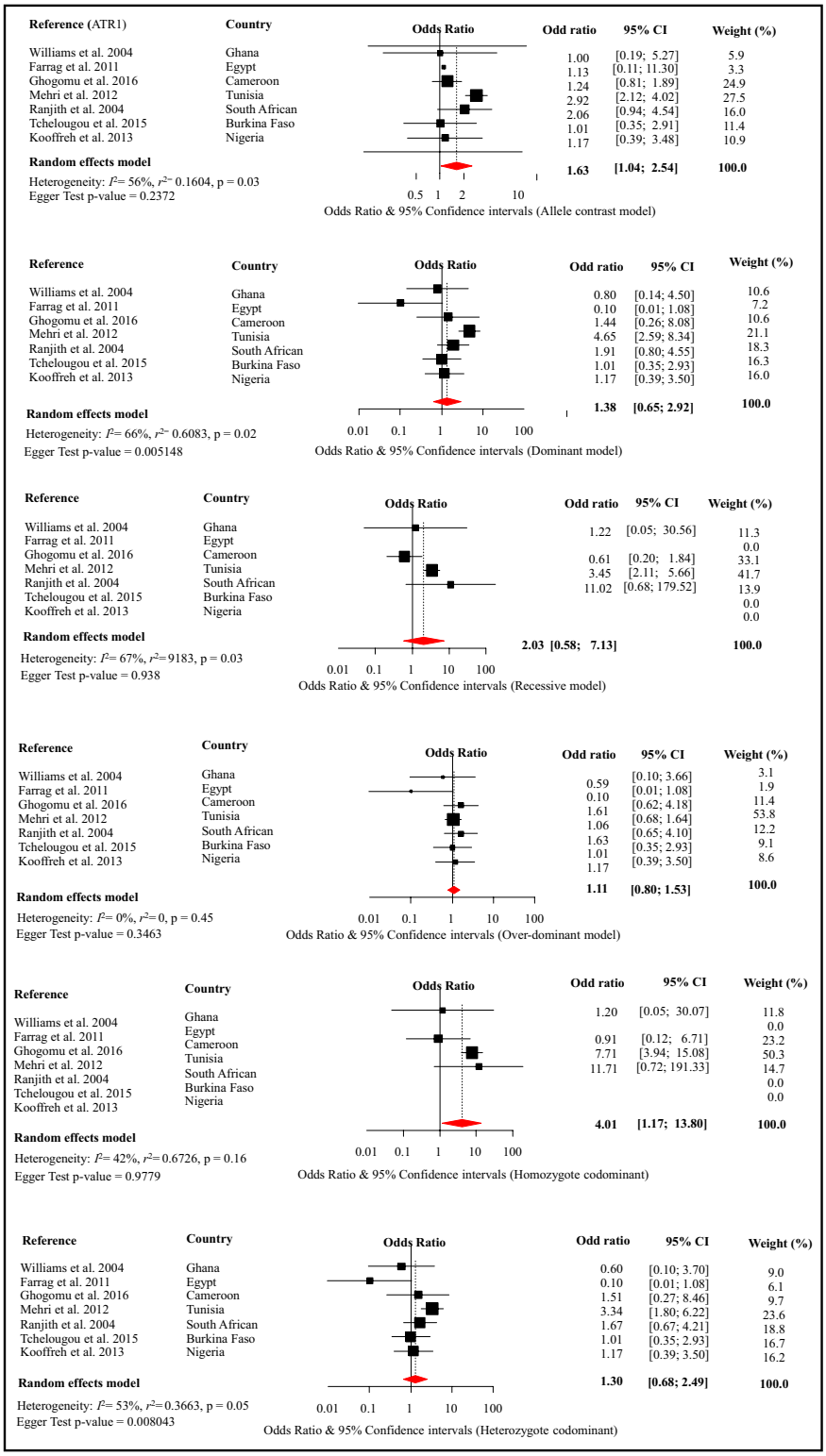

FIGURE 2 Forest plot for the effects of rs5186 from different genetic models on the risk of hypertension across studies in Africa. Figures panels (top to bottom) are for the "alleles contrast," "dominant," and "recessive" models of genetic associations, respectively, for the first column, and "overdominant," "homozygote codominant," and "heterozygote codominant" models for the second column. For each figure panel, the black boxes are for the effect estimates (odd ratio) of the association, and the horizontal bars are for the 95% confidence interval (CI). The sizes of the boxes are proportional to the inverse variance of the effect estimates. The diamond beneath the black boxes is for the overall effect estimates across studies, from random effects model meta-analysis. A dotted vertical line centered on the diamond has been added to assist visual interpretation. For each contributing study, the odd ratio and 95% CI are also shown, together with the weight (in percentage), reflecting the contribution of the study to the overall estimates. The horizontal bar (x-axis) is on log scale to allow a balanced distribution of the CIs around the effect estimates. The heterogeneity statistics are also shown. ATR1 indicates angiotensin II type 1 receptor

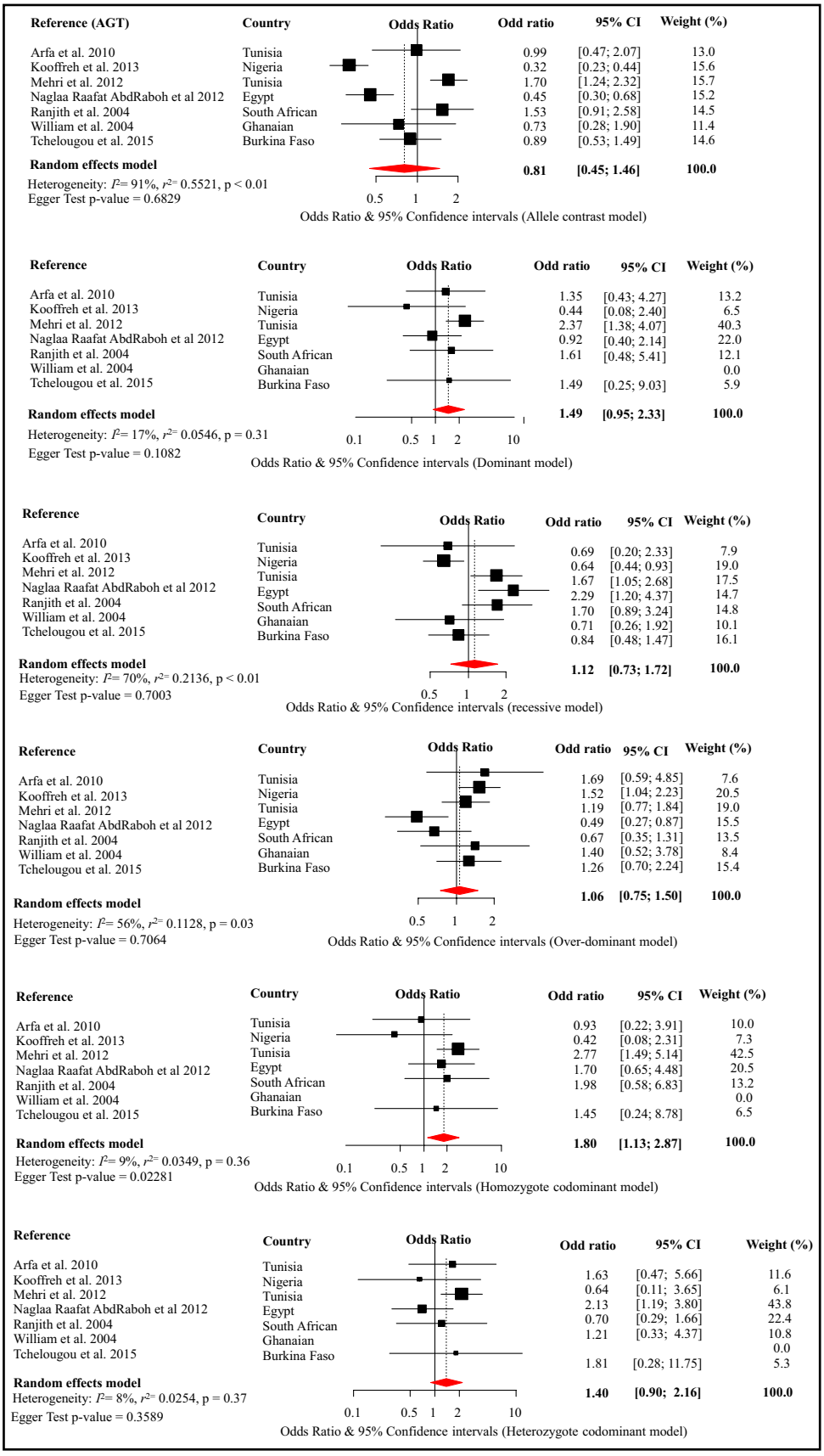

FIGURE 3 Forest plot for the effects of rs699 from different genetic models on the risk of hypertension across studies in Africa. Conventions are as per Figure 2

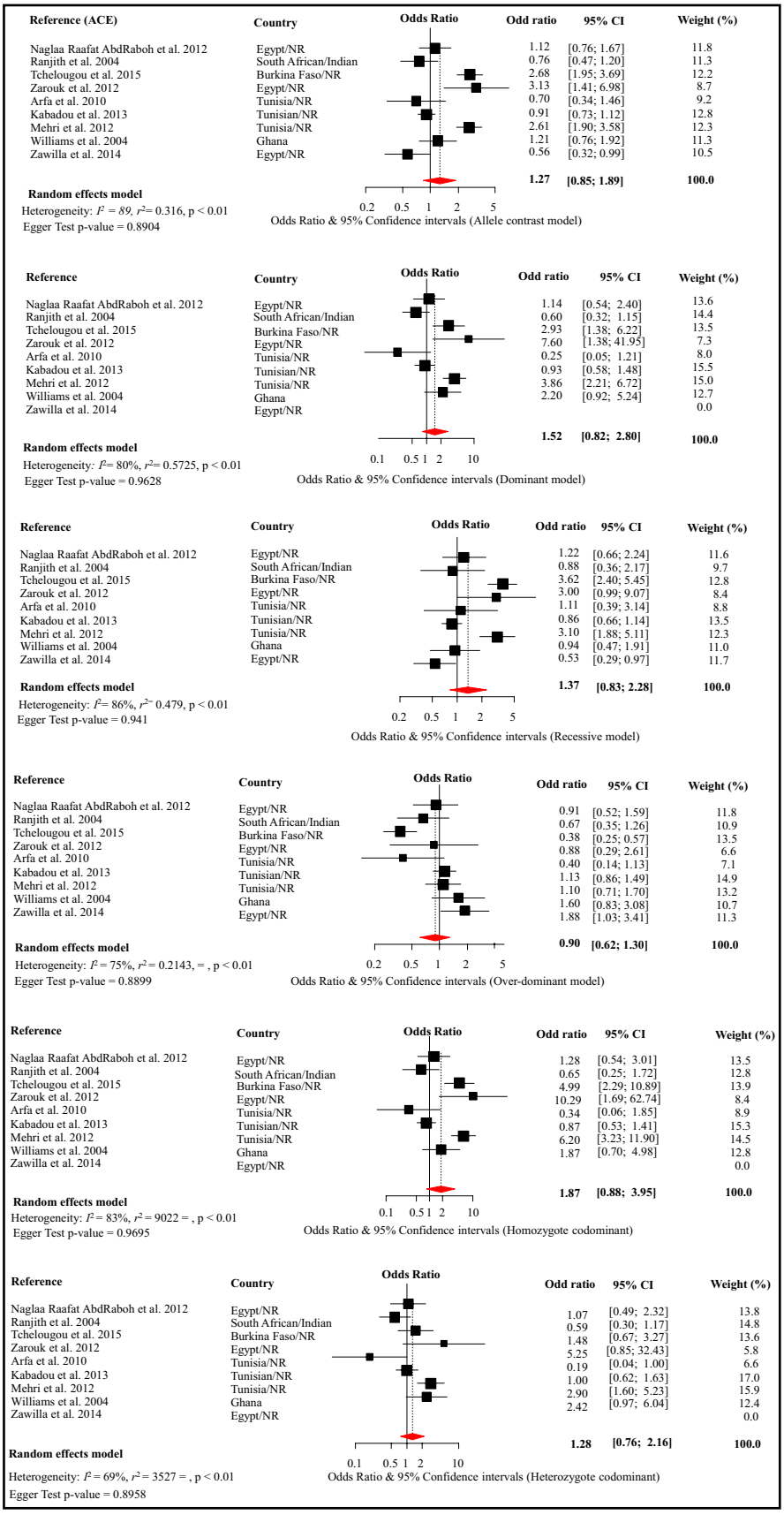

FIGURE 4 Forest plot for the effects of rs4340 from different genetic models on the risk of hypertension across studies in Africa. Conventions are as per Figure 2

3.4 | Meta-analysis

Meta-analysis was possible for only three SNPs within the *ACE*, *AGT*, and *AGTR1*, respectively, rs4340, rs699, and rs5186 (Figures 2–4). These are the SNPs that were investigated by more than three different studies (Table 1). Details of these studies are summarized in Table 1 and Table S4.

Meta-analysis of rs5186 included seven studies totaling the number of cases and controls to 1229 and 1626, respectively. There was evidence of an association between rs5186 and hypertension under allele contrast (OR, 1.63; 95% CI, 1.04–2.54) and homozygous codominant (OR, 4.01; 95% CI, 1.17–13.80) models (Figure 2). Sensitivity analyses suggested that these significant pooled estimates were driven by the effects of Mehri[42] and Ranjith[28] and colleagues since the pooled estimates for both models were nonsignificant each time one of the two studies was omitted (Figure S1). There was evidence of substantial heterogeneity for the alleles contrast (P = .03) and dominant models (P < .01), driven by the study by Mehri and associates[42] (Figure S1), and for the recessive model (P = .03), driven by the study by Goghomu and coworkers[36] The Egger test was in favor of significant publication bias for the dominant model (P = .005) and heterozygote codominant model (P = .008). For both models, the trim-and-fill method imputed four studies with unrealistic effect estimates (OR ranging from 5.65 to 106.2) (Figure S4). There was a lack of information about genotyping quality control and controlling for population stratification and therefore likelihood of bias. The significant deviation from HWE of the distribution of genotypes (P < .0001 in Ghanaian and Cameroonian populations) indicates an existence of genotyping error. We provided Venice grading ABB or moderate epidemiological credibility for this meta-analysis (Table 2).

The rs699 meta-analysis included seven studies with a total of 1257 cases and 1710 controls. An association between rs699 and hypertension was observed for the homozygous codominant model (OR, 1.80; 95% CI, 1.13–2.87), with no evidence of statistical heterogeneity

TABLE 1 Genotype frequency distribution of the rs4340, rs5186, and rs699 in African populations

Reference	Country	Genotypes, hypertension, No.			HWE (P value)	Genotypes, no hypertension, No.			HWE (P value)
rs5186		**AA**	**AC**	**CC**		**AA**	**AC**	**CC**	
Williams et al[27]	Ghana	113	3	1	<.0001	45	2	0	.882
Farrag et al[34]	Egypt	39	1	0	.936	12	3	0	.667
Ghogomu et al[36]	Cameroon	2	67	5	<.0001	4	89	11	<.0001
Mehri et al[42]	Tunisia	17	63	62	.871	74	82	35	.151
Ranjith et al[28]	South African	35	6	1	.268	410	42	1	.950
Tchelougou et al[58]	Burkina Faso	195	7	0	.802	197	7	0	.803
Kooffreh et al[59]	Nigeria	605	7	0	.887	606	6	0	.906
rs699		**MM**	**MT**	**TT**		**MM**	**MT**	**TT**	
Arfa et al[32]	Tunisia	10	21	8	.618	7	9	6	.398
Kooffreh et al[29]	Nigeria	4	67	541	.232	2	52	642	.391
Mehri et al[60]	Tunisia	23	67	52	.856	60	82	49	.056
AbdRaboh et al[30]	Egypt	14	57	39	.330	11	64	18	.0002
Ranjith et al[28]	South African	3	14	25	.599	50	193	210	.573
William et al[27]	Ghana	0	18	92	.350	0	6	43	.648
Tchelougou et al[58]	Burkina Faso	2	29	171	.541	3	24	177	.051
rs4340		**II**	**ID**	**DD**		**DD**	**DI**	**II**	
AbdRaboh et al[30]	Egypt	17	59	34	.299	25	52	16	.214
Ranjith et al[28]	South African	18	18	6	.666	72	240	141	.071
Tchelougou et al[58]	Burkina Faso	10	57	135	.225	73	104	27	.289
Zarouk et al[61]	Egypt	2	14	24	.982	7	8	6	.279
Arfa et al[32]	Tunisia	14	16	19	.017	8	12	2	.402
Kabadou et al[23]	Tunisian	39	176	173	.553	205	180	40	.957
Mehri et al[60]	Tunisia	20	65	57	.832	34	83	74	.208
William et al[27]	Ghana	14	74	38	.014	16	24	11	.723
Zawilla et al[62]	Egypt	NA	21	78	.238	244	35	NA	.264

HWE, Hardy-Weinberg equilibrium.

between studies (I^2 = 9%) (Figure 3). In sensitivity analyses, this effect estimate was enhanced when findings reported by Arfa[32] or Kooffreh[29] and colleagues were omitted (Figure S2). In similar analyses, omitting AbdRaboh and colleagues[30] led to a significant pooled estimate for the dominant model (OR, 1.83; 95% CI, 1.20–2.81 [I^2 = 0]), for the overdominant model (OR, 1.26; 95% CI, 1.00–1.58 [I^2 = 0]), and for the heterozygote codominant model (OR, 1.75; 95% CI, 1.11–2.75 [I^2 = 0]) (Figure S2). There was significant publication bias (P = .023) for the homozygous codominant model. The trim-and-fill methods imputed three studies with effect size (OR) ranging from 3.76 to 12.94 and a resulting pooled estimate of 2.27 (1.33–3.85, heterogeneity P = .14)) (Figure S5). The significant P value of the Egger test and lack of reporting on adjusting for population stratification prompted us to grade this meta-analysis AAB or moderate epidemiological credibility (Table 2). No deviation from HWE was found in studies included in this meta-analysis (P > .2).

Pooled data on rs4340 included 1198 cases and 1740 controls and suggested no evidence of association with hypertension across the six genetic models (Figure 4). There was substantial heterogeneity across studies in all models (all heterogeneity P < .01), not accounted for by a particular study in sensitivity analysis (Figure S3). For the homozygote codominant models, the pooled estimate reached statistical significance when Kabadou and colleagues[23] was dropped, with an OR of 2.14 (95% CI, 1.01–4.77; I^2 = 0.84) (Figure S3). There was no evidence of publication bias (all P > .890 for the Egger test). The trim-and-fill methods imputed two studies (OR ranging from 3.13 to 3.35) for the overdominant model, and one study (OR, 0.28) for the homozygote codominant model, but the resulting pooled estimates were always nonsignificant (Figure S6). Although there was no evidence of publication bias, these studies failed to report on the quality control of genotyping methods, and the population stratification was not accounted for, thus the weak (ACA) Venice interim grading. Deviation from HWE was found in the Tunisian and Ghanaian hypertension groups (P = .017) that were included in the studies by Arfa[32] and Williams[27] and colleagues, respectively.

4 | DISCUSSION

Heterogeneous susceptibility to hypertension among different populations has been largely documented. This has been particularly noted in the United States, with studies demonstrating that African Americans generally have higher BP levels and are characterized by early-onset hypertension compared with other ethnic groups.[43] Susceptibility to hypertension is influenced, in part, by variations in regulation of body salt and water among many population groups. One of the well-studied pathways involved in regulation of thirst and sodium homeostasis is the RAAS, and genetic variants have been extensively investigated in relation to hypertension.[44,45]

Studies conducted in Africa so far generally lack the power to detect statistically significant association between SNPs and complex diseases, as we observed in this review. We conducted meta-analyses of

TABLE 2 Venice interim assessments of the credibility of each meta-analysis

SNP	Phenotype	Studies, No.	Pooled sample size	Genotyping quality control	Deviation from HWE	Risk of population stratification	Venice interim rating	Overall rating
rs5186	Hypertension (SBP >140 mm Hg and/or DBP >90 mm Hg, doctor diagnosis)	7	2855	Not reported	Yes (two studies)	Yes	ABB	Moderate
rs699	Hypertension (SBP >140 mm Hg and/or DBP >90 mm Hg, doctor diagnosis)	7	2967	Not reported	No	Yes	AAB	Moderate
rs4340	Hypertension (SBP >140 mm Hg and/or DBP >90 mm Hg, doctor diagnosis)	9	2938	Not reported	Yes (two studies)	Yes	ACA	Weak

DBP, diastolic blood pressure; HWE, Hardy-Weinberg equilibrium, SBP, systolic blood pressure.

three SNPs in three genes of the RAAS: *ACE I/D* (rs4340), *AGT M235T* (rs699), and *AGTR1* 1166A>C (rs5186) to achieve an optimum power. We observed an association between rs5186 and hypertension, which is in contrast to findings from a meta-analysis by Liu and coworkers[46] in African Americans. Instead, Liu and associates[46] observed the rs5186-hypertension association in Asians and Caucasians in support of findings reported elsewhere.[45,47] Our meta-analysis also suggests an association of rs699 with hypertension, similar to studies conducted in Asians,[48,49] while no association between any of the common SNPs found in RAAS genes and hypertension has been reported by other authors.[50] The inconsistent findings may be attributable to differences in study design, specifically generalization of hypertension by some studies as hypertension,[45–47] while Sun and colleagues[50] investigated the salt-sensitive hypertension phenotype. Regulation of BP in the presence or absence of salt sensitivity varies considerably among individuals within the same or in different ethnic population groups, and this may also contribute to the lack of consistent associations reported by many studies.

The role of *AGTR1* and *AGT* in hypertension has also been highlighted in patients with renal cell cancer, in whom a significant interaction with hypertension was observed.[51] Similar to many studies,[52] our meta-analysis found no association between rs4340 and hypertension. In contrast, other studies have reported the association of rs4340 with hypertension.[53] Decker and coworkers[51] on the other hand found an interaction between *ACE* and sodium intake, an association that may also be involved in hypertension occurrence. In light of these findings, the role of *ACE* in hypertension may not be ruled out in African populations, as our meta-analysis considered one *ACE* SNP but not its interaction with sodium intake.

The mechanism underlying rs5186-hypertension association is unclear as the SNP is located within the 3′ untranslated region of *AGTR1*. It is possible that rs5186 is in linkage disequilibrium with other functional polymorphisms. Alternatively, this SNP may be involved in regulation of *AGTR1* expression. Despite the elusive function of the rs5186 SNP, the AGTR1 has been selected as the potential treatment target for hypertension because of its evident association with hypertension in certain population groups[46] and effectiveness of its antagonists as antihypertensive therapy.[54] However, BP-lowering efficacy of RAAS inhibitors is not evident in African Americans, probably because of their low renin profile and sensitivity to salt intake.[55] Similarly, black populations in Africa have a characteristic salt-sensitive hypertension[56] and may be less responsive to RAAS inhibitors. It is also important to consider that antihypertensive therapy may be influenced by the presence or absence of polymorphisms in RAAS genes. For example, Woodiwiss and coworkers[57] demonstrated that genotypes of the functional SNPs in *AGT* contributed to the variability of antihypertensive responses to ACE inhibitors in individuals of African ancestry. This study, therefore, highlights the importance of investigating sequence variations in the RAAS genes that may be involved in hypertension occurrence and those that may affect response to treatments in African populations.

5 | STUDY LIMITATIONS AND STRENGTHS

We found moderate heterogeneity among studies included in our meta-analysis, particularly for the rs5186 SNP. This may be attributable to heterogeneous populations of the studies included in the meta-analysis, which included Arabs, Indians, and black and Caucasian Africans. Furthermore, deviation from HWE in two population groups might have contributed to the existing heterogeneity. The studies included and our meta-analysis did not address the presence of population stratification. Our review has other limitations, such as selective reporting of methodological aspects. Not all of the studies included reported sample size calculation, HWE, and adjustment of confounders. The sample sizes of selected studies were relatively small. Furthermore, the definition of hypertension varied among studies. This may have hampered identification of small effects of other polymorphisms investigated. Our meta-analysis was also hindered by the small number of genetic association studies conducted in Africa. Only three SNPs have been investigated by more than three African studies. Our study also has several strengths. This is the first systematic review and meta-analysis of genetic association studies conducted in African populations residing in Africa. We extensively appraised the existing studies using appropriate protocols designed for genetic association studies. We increased the likelihood of detecting significant effects across studies by conducting a meta-analysis under several genetic models, using the Venice interim criteria to assess the quality of studies included.

6 | CONCLUSIONS

Our study findings suggest that, to date, only two SNPs of the *AGT* (rs699) and *AGTR1* (rs5186) are likely to predispose African populations to hypertension, necessitating further investigation in larger-scale genetic studies so that more susceptibility polymorphisms specific to African populations can be discovered.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

ORCID

Andre P. Kengne http://orcid.org/0000-0002-5183-131X

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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