Review

Methylenetetrahydrofolate Reductase Polymorphism (rs1801133) and the Risk of Hypertension among African Populations: A Narrative Synthesis of Literature

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Abstract: In this review, we have gathered and analyzed the available genetic evidence on the association between the methylenetetrahydrofolate reductase gene (MTHFR), rs1801133 and the risk of Hypertension (HTN) in African populations, which was further compared to the global data evidence. This review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol and Human Genome Epidemiology Network (HuGENet) guidelines. Literature was retrieved through major search databases, including PubMed, Scopus, Web of Science, and African Journal Online. We identified 64 potential studies, of which 4 studies were from the African continent and 60 studies were reported globally. Among the studies conducted in Africa, only two (n = 2) reported a significant association between the MTHFR (rs1801133) and the risk of developing HTN. Only one (n = 1) study population was purely composed of black Africans, while others were of other ethnicities. Among studies conducted in other continents (n = 60), forty-seven (n = 47) studies reported a positive association between MTHFR (rs1801133) and the risk of developing HTN, whereas the remaining studies (n = 14) did not show a significant association. Available literature suggests an apparent association between rs1801133 and HTN in global regions; however, such information is still scarce in Africa, especially in the black African population.

Keywords: Hypertension; methylenetetrahydrofolate reductase gene; MTHFR; single-nucleotide polymorphism; Africa; genetic variation

1. Introduction

Hypertension (HTN) remains a major risk factor for the development of cardiovascular diseases (CVDs), which significantly contributes to high rates of mortality and morbidity worldwide. Globally, HTN affects over 1.4 billion individuals above the age of 18 years and the number is expected to increase to 1.56 billion by 2025 [1–3]. In Africa, HTN...
affects approximately 74.4 million individuals [4,5]. Although there are various treatments available for HTN, it is apparent that patients are now gaining resistance to the treatment, and more severe cases have been recorded, particularly among individuals of African origin [5,6]. Furthermore, the high prevalence and severity of HTN that has been observed across different populations have been attributed to genetic variation [7]. Generally, it has been reported that genetic factors contribute to approximately 30–60% of the blood pressure (BP) variation that has been observed [8,9]. Therefore, it is critical to explore genetic factors with regards to HTN with the aim of understanding their role in the pathogenesis and progression of the disease.

Many approaches have been used to identify genetic variants associated with HTN in various populations [1,10,11]. The most common type of genetic variants are single nucleotide polymorphisms (SNPs), which represent approximately 90% of human genetic variations [12]. Several genome-wide association studies have identified multiple SNPs associated with HTN [13,14]. Amongst the predominantly identified variants is the SNP rs1801133 (position 677 C > T) found in exon 4 of the Methylenetetrahydrofolate reductase gene (MTHFR), which has been reported to be associated with elevated BP in various populations [15,16].

The MTHFR gene sits on the short arm of chromosome 1 (1p36.22), which has 12 exons and encodes for a protein containing 656 amino acids [17,18]. MTHFR is an enzyme that facilitates the production of 5-methyl-tetrahydrofolate, an active form of folate (Vitamin B9) in the body [19]. Previous research has demonstrated that 5-methyl-tetrahydrofolate is a positive allosteric modulator of nitric oxide synthase 3, which plays a significant role in the production of nitric oxide, a potent vasodilator in the regulation of BP [20]. Moreover, the MTHFR gene polymorphism has been suggested to be associated with increased levels of plasma homocysteine (hyperhomocysteinemia), which acts as an independent risk factor for HTN [21,22]. Factors like excessive alcohol consumption and smoking can influence the elevation of homocysteine in blood plasma [23,24]. According to a cross-sectional study conducted among women, the association between folate intake and homocysteine was altered by both alcohol intake and MTHFR rs1801133 [25].

A meta-analysis by Wu et al. [26] already demonstrated that MTHFR gene polymorphisms are linked with a significantly increased risk of HTN in subjects that carry the T allele and TT genotype. Another meta-analysis by Yang et al. [27], which was conducted in Indiana, United States of America, also reported an association between MTHFR (rs1801133) and HTN. However, this association was only significant among Asian and Caucasian populations, while no correlation was observed for Latinos, Africans, and Indians, suggesting the implication of ethnicity in disease susceptibility. Importantly, the authors acknowledged the essential limitations, such as the relatively small sample size and data scarcity for Latinos, Africans, and Indians. Furthermore, studies conducted in Morocco [16] and China [28] suggested that MTHFR (rs1801133) is associated with an increased risk of HTN. Conversely, Amrani-Midoun et al. [15], reported no association in the Algerian population. Thus, information regarding the correlation between MTHFR polymorphism (rs1801133) and HTN remains elusive, especially among black Africans. This review has extracted and critically analyzed the available clinical evidence on the association of MTHFR (rs1801133) and HTN in African populations, and further compared the evidence with studies conducted in other parts of the world.

2. Methods
2.1. Search Strategy

A comprehensive literature search was performed using subject headings or primary search (MeSH) terms such as “Methylenetetrahydrofolate reductase gene”, “MTHFR”, “hypertension”, “genetic”, “single nucleotide polymorphism”, and “pharmacogenomics” (Supplementary File S1) following the Human Genome Epidemiology Network (HuGENet) [29,30] and PRISMA guidelines [31,32] (Tables S1 and S2). The reference lists of included studies were further scanned for additional relevant studies. The search was done using major
search engines and databases, including PubMed, Scopus, Web of Science, and African Journal Online. However, this review was not registered with online registries; therefore, the protocol does not have a registration number. Nevertheless, the aforementioned search engines and databases were thoroughly searched to make sure no other similar studies are currently underway.

2.2. Inclusion Criteria and Data Extraction

Studies included in the current review meet the following requests: (a) only the case-control studies were considered; (b) evaluated the MTHFR gene, rs1801133 polymorphism, and HTN risk; and (c) studies with data on the genotypes among cases and controls [33]. Studies were excluded if (a) conducted before the inception of molecular biology techniques (1983), (b) non-human studies, (c) family studies, and (d) reviews (Table 1). The data were independently and carefully assessed for compliance with the inclusion or exclusion criteria by three authors (S.E.M, K.Z, and C.M) who resolved disagreements and reached a consistent decision with the help of a fourth investigator (B.M). The following information was extracted from each study: the first author, publication year, country, ethnicity, continent, number of cases and controls, source of controls, and Hardy-Weinberg Equilibrium (HWE). Language restriction was applied during the search meaning studies conducted in other languages that could not translate into English were excluded.

Table 1. Inclusion Criteria and Data Extraction.

| Inclusion                                      | Exclusion                                      |
|------------------------------------------------|------------------------------------------------|
| Published from 1984 to 2021                    | Studies conducted before 1983                  |
| Human studies                                  | Non-human studies                             |
| Reported data on the genotypes among cases and controls | No genotypes among cases and controls |
| Studies reporting association between MTHFR polymorphisms (rs1801133) and HTN | Studies in gene expression |
| Studies provided enough data to calculate ORs and 95% confidence interval | Studies provided not enough data to calculate ORs and 95% confidence interval |
| Case-control design                            | Reviews                                        |
| Non-family-based studies                       | Family-based studies                           |

3. Results

There are very limited studies reporting on MTHFR (rs1801133) association and HTN in African populations. Out of all identified relevant studies, only one study population was indigenous African (Cameroon) [34]; others were composed of Caucasian participants (Algeria, Morocco, Egypt) [15,16,35]. For this reason, a narrative synthesis of the findings was performed, instead of a meta-analysis.

3.1. Characteristics of Studies

Using our search strategy (Figure 1), we have identified 1230 related studies, of which four (n = 4) were from the African continent and (n = 60) were from non-African continents (globally). Based on our inclusion and exclusion criteria, there were 321 cases and 308 controls for the African population and 15,865 cases and 28,762 controls for other global populations globally, that were available for this analysis. The study characteristics are described in Table 1. In all the studies reported in Africa [15,16,34,35], HTN was defined as systolic/diastolic BP (SBP/DBP) $\geq 140/\geq 90$ mm Hg. Among the included studies reported in the African region (n = 4), only two (n = 2) studies reported a significant association between the MTHFR (rs1801133) and the risk of developing HTN [16,34]. All African studies, where age was reported, included only patients aged above 40 years, except for Amin et al. [35], which included patients aged $\leq 45$ years. Furthermore, most African studies included more females than males with exception of Amin et al. [35] which
did not report on gender. In studies reported in other continents \( (n = 60) \), forty-seven separate studies showed a significant association between \( MTHFR \) (rs1801133) and the risk to develop HTN Table 2, whereas the remaining studies did not show any significant association \( (n = 14) \).

3.2. Association of \( MTHFR \) (rs1801133) and HTN Reported in African Continent

In this section, we briefly summarize the evidence on \( MTHFR \) (rs1801133) associations based on the four available studies reporting on African populations (Table 2).

The first study was conducted by Amin et al. [35], and it was aimed at evaluating the presence of \( MTHFR \) (rs1801133) polymorphism and its association with HTN and myocardial infarction among participants of Egyptian origin \( (n = 181, \leq 45 \text{ and } \geq 45 \text{ years}) \). The study showed that there was no association between \( MTHFR \) (rs1801133) and HTN. The study further demonstrated that individuals with HTN were smokers and presented with impaired lipid profiles such as significantly raised levels of total cholesterol (TC), triglycerides, low-density lipoprotein-cholesterol (LDL-c), and low high-density lipoprotein cholesterol (HDL-c), in comparison to the control group. The gender of the participants was not reported in this study. The authors clearly stated the guidelines \( (SBP/DBP \geq 140/90 \text{ mm Hg}) \) that were used to define HTN. However, the method used to adjust for patients who were already on treatment was not mentioned.

The second study by Nassereddine et al. [16] was carried out to evaluate the association between \( MTHFR \) (rs1801133) variant and HTN in a Moroccan population \( (n = 203, \text{ range } 40-87 \text{ years}) \). The authors demonstrated a significant association between rs1801133 and HTN. It was further demonstrated that the distribution of demographic and clinical characteristics of patients did not show a significant trend in relation to HTN. Thus, the study did not adjust for confounding factors. The study reported more females \( (n = 77) \) than...
males \((n = 24)\). Lastly, the study defined HTN as SBP/DBP ≥ 140/90 mm Hg. However, the authors did not provide any information about the treatment status of the cohort.

Table 2. Main characteristics of studies included in this review.

| Author, Year | Association | Country | Ethnicity | Cases | Cases with SNP | Control | Controls with SNP | p-Value HWE |
|--------------|-------------|---------|-----------|-------|----------------|---------|------------------|-------------|
| **Africa**   |             |         |           |       |                |         |                  |             |
| Ghogomu et al., 2016 [34] | Yes | Cameroon | Bantu | 41   | 38             | 50      | 5                | Yes         |
| Amrani-Midoun et al., 2016 [15,36] | No | Algeria | Caucasian | 82   | 45             | 72      | 28               | Yes         |
| Nassereddine et al., 2015 [16] | Yes | Morocco | Caucasian | 101  | 54             | 102     | 48               | Yes         |
| Amin et al., 2012 [35] | No | Egypt | Caucasian | 97   | 40             | 84      | 37               | Yes         |
| **Asia**     |             |         |           |       |                |         |                  |             |
| Arina et al., 2019 [37] | Yes | Indonesia | Asian | 53   | 21             | 53      | 10               | Yes         |
| Dwivedi et al., 2017 [38] | Yes | India | Asian | 100  | 29             | 223     | 39               | No          |
| Fan et al., 2016 [28] | Yes | China | Chinese | 214  | 177            | 494     | 375              | Yes         |
| Wen et al., 2015 [39] | Yes | China | Asian | 174  | 129            | 634     | 376              | Yes         |
| Wang et al., 2015 [40] | Yes | China | Asian | 190  | 94             | 287     | 143              | Yes         |
| Cai et al., 2014 [41] | Yes | China | Chinese | 200  | 161            | 200     | 139              | Yes         |
| Xi et al., 2013 [42] | Yes | China | Chinese | 619  | 378            | 2458    | 1376             | Yes         |
| Zhang et al., 2012 [43] | No | China | Asian | 189  | 61             | 165     | 48               | Yes         |
| Cao et al., 2012 [44] | Yes | China | Asian | 223  | 158            | 147     | 98               | Yes         |
| Yin et al., 2012 [45] | Yes | China | Asian | 670  | 426            | 682     | 360              | No          |
| Liu et al., 2011 [46] | No | China | Asian | 155  | 97             | 140     | 66               | No          |
| Cai et al., 2009 [47] | Yes | China | Chinese | 130  | 53             | 39      | 8                | Yes         |
| Lin et al., 2008 [48] | Yes | China | Asian | 50   | 31             | 123     | 50               | Yes         |
| Luo et al., 2008 [49] | Yes | China | Asian | 442  | 182            | 195     | 57               | Yes         |
| Tang et al., 2007 [50] | Yes | China | Asian | 252  | 113            | 195     | 57               | Yes         |
| Markan et al., 2007 [51] | Yes | India | Asian | 153  | 48             | 133     | 28               | Yes         |
| Hui et al., 2007 [52] | No | Japan | Asian | 261  | 178            | 271     | 167              | Yes         |
| Xing et al., 2007 [53] | Yes | China | Asian | 695  | 493            | 509     | 327              | No          |
| Li et al., 2006 [54] | No | China | Asian | 26   | 8              | 30      | 9                | Yes         |
| Hu et al., 2006 [55] | No | China | Asian | 110  | 55             | 115     | 54               | Yes         |
| Kalita et al., 2006 [56] | Yes | India | Asian | 28   | 10             | 32      | 11               | Yes         |
| Lwin et al., 2006 [57] | No | Japan | Asian | 116  | 77             | 219     | 155              | Yes         |
| Liu et al., 2005 [58] | Yes | China | Asian | 100  | 71             | 100     | 69               | Yes         |
| Sun et al., 2003 [59] | Yes | China | Asian | 55   | 49             | 46      | 32               | Yes         |
| Wang et al., 2002 [60] | Yes | China | Asian | 105  | 88             | 46      | 32               | Yes         |
| Zhan et al., 2000 [61] | No | China | Asian | 127  | 83             | 170     | 108              | Yes         |
| Kobashi et al., 2000 [62] | Yes | Japan | Asian | 184  | 120            | 215     | 132              | Yes         |
| Gao et al., 1999 [63] | Yes | China | Asian | 127  | 83             | 170     | 108              | Yes         |
| Nakata et al., 1998 [64] | No | Japan | Asian | 173  | 110            | 184     | 119              | Yes         |
| Nishio et al., 1996 [65] | No | Japan | Asian | 47   | 31             | 82      | 53               | Yes         |
| **Europe**   |             |         |           |       |                |         |                  |             |
| Bayramoglu et al., 2015 [66] | Yes | Turkey | White | 125  | 60             | 99      | 43               | Yes         |
| Husemoen et al., 2014 [67] | Yes | Denmark | White | 4694 | 2463           | 7697    | 3907             | Yes         |
| Ilhan et al., 2008 [68] | Yes | Turkey | Turk | 78   | 42             | 100     | 28               | Yes         |
Table 2. Cont.

| Author, Year            | Association | Country           | Ethnicity | Cases | Cases with SNP | Control | Controls with SNP | p-Value |
|-------------------------|-------------|-------------------|-----------|-------|----------------|---------|-------------------|---------|
| Marinho et al., 2007    | Yes         | Portugal          | Portuguese| 64    | 49             | 128     | 71                | Yes     |
| Nagy et al., 2007       | Yes         | Hungary           | White     | 101   | 52             | 73      | 41                | Yes     |
| Demir et al., 2006      | Yes         | Turkey            | White     | 100   | 67             | 102     | 59                | Yes     |
| Cesari et al., 2005     | Yes         | Italy             | White     | 90    | 50             | 90      | 48                | Yes     |
| Tylicki et al., 2005    | Yes         | Austria/Poland    | White     | 90    | 50             | 90      | 48                | Yes     |
| Yilmaz et al., 2004     | Yes         | Turkey            | White     | 64    | 35             | 47      | 23                | Yes     |
| Frederiksen et al., 2004| Yes         | Denmark           | White     | 1267  | 691            | 7971    | 4120              | Yes     |
| Rodriguez-Esparragon et al., 2003 | No       | Spain             | White     | 232   | 149            | 215     | 120               | Yes     |
| Kahleova et al., 2002   | Yes         | Czech Republic    | White     | 164   | 82             | 173     | 87                | Yes     |
| Benes et al., 2001      | No          | Czech Republic    | White     | 193   | 120            | 209     | 123               | No      |
| Zusterzeel et al., 2000 | Yes         | Netherlands       | White     | 76    | 44             | 403     | 198               | Yes     |

**Middle East**

| Author, Year            | Association | Country           | Ethnicity | Cases | Cases with SNP | Control | Controls with SNP | p-Value |
|-------------------------|-------------|-------------------|-----------|-------|----------------|---------|-------------------|---------|
| Alghasham et al., 2012  | Yes         | Saudi Arabia      | Qassim    | 123   | 50             | 250     | 65                | Yes     |
| Fakhrzadeh et al., 2009 | Yes         | Iran              | Asian     | 160   | 61             | 76      | 40                | Yes     |

**North America**

| Author, Year            | Association | Country           | Ethnicity | Cases | Cases with SNP | Control | Controls with SNP | p-Value |
|-------------------------|-------------|-------------------|-----------|-------|----------------|---------|-------------------|---------|
| Perez-Razo et al., 2015 | Yes         | Mexico            | Mexican   | 569   | 423            | 590     | 465               | Yes     |
| Vazquez-Alaniz et al., 2014 | Yes       | Mexico            | Mixed     | 194   | 132            | 194     | 140               | Yes     |
| Deshmukh et al., 2009   | Yes         | United States     | White     | 42    | 20             | 118     | 66                | Yes     |
| Canto et al., 2008      | Yes         | Mexico            | White     | 125   | 89             | 274     | 213               | Yes     |
| Rajkovic et al., 2000   | Yes         | United States     | American  | 171   | 29             | 183     | 32                | Yes     |
| Powers et al., 1999     | Yes         | United States     | American  | 122   | 76             | 114     | 60                | Yes     |

**Oceania**

| Author, Year            | Association | Country           | Ethnicity | Cases | Cases with SNP | Control | Controls with SNP | p-Value |
|-------------------------|-------------|-------------------|-----------|-------|----------------|---------|-------------------|---------|
| Powdar et al., 2012     | No          | Australia         | White     | 377   | 207            | 393     | 218               | Yes     |
| Ng et al., 2009         | Yes         | Australia         | White     | 38    | 24             | 80      | 40                | Yes     |
| Heux et al., 2004       | Yes         | New Zealand       | White     | 247   | 160            | 249     | 144               | Yes     |

**South America**

| Author, Year            | Association | Country           | Ethnicity | Cases | Cases with SNP | Control | Controls with SNP | p-Value |
|-------------------------|-------------|-------------------|-----------|-------|----------------|---------|-------------------|---------|
| Rios et al., 2017       | Yes         | Brazil            | American  | 96    | 83             | 85      | 65                | Yes     |
| Fridman et al., 2013    | Yes         | Argentina         | White     | 75    | 46             | 150     | 79                | Yes     |
| Fridman et al., 2008    | No          | Argentina         | White     | 40    | 25             | 86      | 47                | Yes     |
| Soares et al., 2008     | Yes         | Brazil            | American  | 30    | 17             | 16      | 7                 | Yes     |

The third study by Amrani-Midoun et al. [15] reported a lack of association between MTHFR (rs1801133) and HTN in an Algerian population ($n = 154, \geq 42$ years); however, the authors did acknowledge the impact of the small sample size used. Despite the small sample used, this study showed that there were significant differences between participants with HTN and controls with respect to age, SBP, DBP, and family history of HTN. The study was composed of more females ($n = 84$) than males ($n = 70$), and defined HTN as SBP/DBP $\geq 140/90$ mm Hg. However, the method that was used for adjusting for the use...
of antihypertensive medication was not mentioned. Also, the genotyping method used in this study (PCR-RFLP) could be a potential limitation.

The fourth study was conducted by Ghogomu et al. [34], and it reported an association between MTHFR (rs1801133) and HTN in the native Bantu ethnic group of the South-West region of Cameroon (n = 91, range 40–70 years). Of note, this was the only study that sampled participants from an indigenous African population. Lipid profile dispersion for all subjects reported that serum lipid levels were higher in hypertensive patients than in healthy controls. The study further demonstrated that the MTHFR (rs1801133) variant may influence individual susceptibility to HTN through a mechanism that involves an increase in the level of serum LDL-c. However, the sample size was very small and was likely accompanied by biasedness. Furthermore, the study did not report on the number of females/males that were sampled. HTN was defined as having elevated SBP ≥140 mm Hg and DBP of at least ≥90 mm Hg. Patients who were already placed on hypertensive medication were also categorized as hypertensive.

4. Discussion

The MTHFR gene has been among the most studied genes associated with the development and progression of HTN [26,36]. Indeed, numerous genetic studies have investigated the association between the genetic variant of MTHFR (rs1801133) and the risk of developing HTN [36–38]. However, these studies reported conflicting results. In our previous systematic review, the MTHFR gene (rs1801133) was reported as one of the most studied genes associated with HTN among African populations [95]. Thus, in the present review, we gathered and analyzed the available genetic evidence on the association between MTHFR (rs1801133) and HTN among Africans and further compared the evidence with global data.

We reviewed 60 published articles that examined the association between MTHFR (rs1801133) and HTN. Out of 60 published articles, 47 reported a positive association between HTN and the MTHFR variant. However, only 4 studies were conducted in the African continent, of which 2 reported a positive association between rs1801133 and HTN [16,34]. The inconsistencies observed between these studies may be due to: (a) the limited number of relevant African studies and their relatively small sample sizes, which makes comparisons with other studies challenging. Given the small sample size in these studies, many true associations with small effects will not be significant and many suggestive associations may be false. In addition, the use of various cohorts, to maximize sample size and increase statistical power, could interfere with the biased results as some associations may be due to heterogeneity [96]; (b) the low frequency of the MTHFR (rs1801133) T allele observed among the African populations [97], which may be influenced by folate deficiency due to malnutrition and impaired intestinal absorption of folic acid, which are common in Africa [98]. Lastly, a study by Amrani-Midoun et al. [15] also suggested that these differences may be due to the epigenetic mechanisms which are involved in the gene expression predisposed by environmental factors such as lifestyle and diet. All the aforementioned factors may lead to failure to replicate the association of MTHFR (rs1801133) with disease phenotypes.

Although all included African studies [15,16,34,35] defined HTN as SBP/DBP ≥140/90 mm Hg, there were great differences in these studies, partly because of the criteria used in selecting participants and methods applied in each study. A study by Ghogomu et al. [34] and Nassereddine et al. [16] reported an association between MTHFR (rs1801133) polymorphism and HTN. However, these studies did not adjust for confounding factors such as gender, age, and smoking status. This may introduce bias, thus making it difficult to compare the findings with other studies. Furthermore, the age inconsistencies among the four African studies [15,16,34,35] may impose challenges when comparisons are made with other studies. For instance, a study by Nassereddine et al. [16], included 101 outpatients with a mean age of 61.6 ± 9 (range 40–87 years) and 102 age and sex-matched unrelated healthy control subjects with a mean age of 59.24 ± 10.7 (range 40–87 years); whereas a study that was conducted by Amin et al. [35] sampled young adults aged <45 years and older adults aged ≥45 years. The use of antihypertensive medication
was reported by African studies \[15,16,34,35\]; however, the methods used for adjustments were not mentioned. This may introduce bias when making comparisons across studies, as studies that make adjustments would not be comparable to studies that did not make adjustments. Ghogomu et al. \[34\] was the only study that was composed of participants from an indigenous African population \[15,16,35\], thus limiting comparisons across different racial groups, since the genetics of HTN vary across different populations and geographical regions \[17,99\].

Nonetheless, a recent systematic review and meta-analysis comprising of 57 studies with 14,378 patients and 25,795 control subjects examined the association between \textit{MTHFR} (rs1801133) and HTN and revealed that the major reason for equivocal results might be the racial differences observed across the different studies \[36\]. In comparison with that study, the present review had the following advantages: First, there were 64 eligible studies with 16,186 hypertensive cases and 29,070 controls, which could provide more reliable conclusions. Second, since none of the previous systematic reviews and meta-analyses \[26,27,100–102\] focused on the indigenous African populations, we assessed the comparison among studies reported on other cohorts with the ones reported on African populations. Therefore, future studies should pay more attention to the differences in the genetic background of indigenous African populations. For this reason, our review updates information from the previous systematic reviews \[26,27,100–102\] with additional supplements and adjustments, which makes it a comprehensive study regarding the association between \textit{MTHFR} (rs1801133) and HTN.

**Strengths and Limitations of This Study**

It must be pointed out that this is the first review that specifically assessed the effect of \textit{MTHFR} (rs1801133) on HTN in Africa, as well as performing comparisons between African studies and available global data, which opens the door for future research. However, it should be noted that there were certain limitations to the present analysis, which inevitably prevented more in-depth analyses. First, the sample size of some of the selected studies was relatively small. Second, variations between population characteristics, phenotypic measures, and genotypic analyses could cause bias when comparing the current findings with previous reports. Third, literature was surveyed globally; unfortunately, in Africa, we were able to identify only four studies, which suggests that there is a lack of information regarding the black African ethnic groups in relation to genetic association studies. Furthermore, out of those identified studies \((n = 4)\), only one study by Ghogomu et al. \[34\] was composed of a purely black African population and the remaining three studies were composed of other ethnicities \[15,16,35\]. Thus, our meta-analysis only included a few numbers of participants who were of African origin. As such, the analysis was unlikely to produce valid results (Figure 2), thus we conducted a narrative synthesis of the results. This indicates that there is an urgent need to carefully plan African-specific studies with large sample sizes in order to be able to draw conclusions on the association between \textit{MTHFR} (rs1801133) and HTN.
Figure 2. Forest plot of the evaluation for the association between the MTHFR (rs1801133) and HTN in the dominant genetic model (Africa). We evaluated the risk of the TT or CT genotype on HTN compared with the CC genotypes. Then, pooled Odds ratios (OR) with 95% confidence intervals (CI) and z score were performed to estimate associations. All analyses were performed using R software (Version 3.3.3, using R package meta) [15,16,34,35,103].

5. Conclusions

Although the association between rs1801133 and HTN was predominantly reported in other global regions, the result from the current review opened avenues to further explore a possible association between rs1801133 and HTN among individuals of African origin. Furthermore, this study has demonstrated the need to generate African-specific genomic data. Such data could provide insights into human evolution and the role of genetic variants in disease phenotypes. These data could also increase our understanding of African population genomics and highlight its potential impact on biomedical research and genetic susceptibility to disease. Thus, future studies should sample a fair number of participants that completely represent the African population. Since African populations are well known to have high genetic diversity, because of their deep evolutionary history, and genetic differences, it is of utmost importance for future association studies to pay more attention to African genetic studies and to understand the functional and biological relevance of associated rs1801133. Moreover, improved methods need to be developed to understand and compare heritability across populations and study participants from different parts of the African continent. It is also imperative for all studies to report more detail in the protocols used to enable better replication and minimize bias between studies.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/genes13040631/s1, Supplementary File S1: Publication Search, Table S1: PRISMA abstract check list, Table S2: PRISMA manuscript check list.

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References

1. Sombié, H.K.; Koloğlo, J.K.; Tchelougou, D.; Ouedraogo, S.Y.; Ouattara, A.K.; Compaoré, T.R.; Nagalo, B.M.; Sorgho, A.P.; Nagabila, I.; Soubeiga, S.T. Positive association between ATP2B1 rs17249754 and essential hypertension: A case-control study in Burkina Faso, West Africa. *BMC Cardiovasc. Disord.* 2019, 19, 155. [CrossRef] [PubMed]

2. World Health Organization. *Global Status Report on Noncommunicable Diseases 2014*; World Health Organization: Geneva, Switzerland, 2014.

3. World Health Organization. *Primary Health Care on the Road to Universal Health Coverage: 2019*; Global Monitoring Report; World Health Organization: Geneva, Switzerland, 2021.

4. Woodward, R.; Mgaya, E.; Mwanansao, C.; Peck, R.N.; Wu, A.; Sun, G. Retinopathy in adults with hypertension and diabetes mellitus in Western Tanzania: A cross-sectional study. *Trop. Med. Int. Health* 2020, 25, 1214–1225. [CrossRef] [PubMed]

5. Opie, L.H.; Seedat, Y.K. Hypertension in Sub-Saharan African Populations. *Circulation* 2005, 112, 3562–3568. [CrossRef]

6. Mengesha, H.G.; Petrucka, P.; Spence, C.; Tafesse, T.B. Effects of angiotensin converting enzyme gene polymorphism on hypertension in Africa: A meta-analysis and systematic review. *PLoS ONE* 2019, 14, e0211054. [CrossRef] [PubMed]

7. Pinto, I.C.; Martins, D. Prevalence and risk factors of arterial hypertension: A literature review. *J. Cardiovasc. Med. Ther.* 2017, 1, 1–7.

8. Timberlake, D.S.; O’Connor, D.T.; Parmar, R.J. Molecular genetics of essential hypertension: Recent results and emerging strategies. *Curr. Opin. Nephrol. Hypertens.* 2001, 10, 71–79. [CrossRef]

9. Morgado, J.; Sanches, B.; Anjos, R.; Coelho, C. Programming of Essential Hypertension: What Pediatric Cardiologists Need to Know. *Pediatr. Cardiol.* 2015, 36, 1327–1337. [CrossRef] [PubMed]

10. Amrani-Midoun, A.; Kiando, S.R.; Treard, C.; Jeunemaitre, X.; Bouatia-Naji, N. Genetic association study between T-786C NOS3 polymorphism and essential hypertension in a sample of an Algerian population of Oran city. *Int. J. Cardiol.* 2016, 225, 408–411. [CrossRef] [PubMed]

11. Kayima, J.; Liang, J.; Natanzon, Y.; Nankabirwa, J.; Ssinabulya, I.; Nakibuuka, J.; Katamba, A.; Mayanja-Kizza, H.; Miron, A.; Li, C. Association of genetic variation with blood pressure traits among East Africans. *Clin. Genet.* 2017, 92, 487–494. [CrossRef] [PubMed]

12. Palmer, L.J.; Cardon, L.R. Shaking the tree: Mapping complex disease genes with linkage disequilibrium. *Lancet* 2005, 366, 1223–1234. [CrossRef]

13. Wang, Y.; Wang, J.-G. Genome-Wide Association Studies of Hypertension and Several Other Cardiovascular Diseases. *Heart Genom.* 2018, 16, 1–29. [CrossRef]

14. Rhodes, C.J.; Batai, K.; Bleda, M.; Haimel, M.; Southgate, L.; Germain, M.; Pauciolo, M.W.; Hadinnapola, C.; Aman, J.; Girerd, B. Genetic determinants of risk in pulmonary arterial hypertension: International genome-wide association studies and meta-analysis. *Lancet Respir. Med.* 2018, 7, 227–238. [CrossRef]

15. Amrani-Midoun, A.; Kiando, S.R.; Treard, C.; Jeunemaître, X.; Bouatia-Naji, N. The relationship between MTHFR C677T gene polymorphism and essential hypertension in a sample of an Algerian population of Oran city. *Int. J. Cardiol.* 2016, 225, 408–411. [CrossRef] [PubMed]

16. Nassereddine, S.; Kassogue, Y.; Korchì, F.; Habbal, R.; Nadifi, S. Association of methyleneetetrahydrofolate reductase gene (C677T) with the risk of hypertension in Morocco. *BMC Res. Notes* 2015, 8, 775. [CrossRef] [PubMed]

17. Liew, S.-C.; Gupta, E.D. Methyleneetetrahydrofolate reductase (MTHFR) C677T polymorphism: Epidemiology, metabolism and the associated diseases. *Eur. J. Med. Genet.* 2015, 58, 1–10. [CrossRef]

18. Tisato, V.; Silva, J.A.; Longo, G.; Gallo, I.; Singh, A.V.; Milani, D.; Gemmati, D. Genetics and Epigenetics of One-Carbon Metabolism Pathway in Autism Spectrum Disorder: A Sex-Specific Brain Epigenome? *Genes* 2021, 12, 782. [CrossRef] [PubMed]

19. Ferrarazzi, E.; Tiso, G.; Di Martino, D. Folic acid versus 5- methyltetrahydrofolate supplementation in pregnancy. *Unpublished*. [CrossRef] [PubMed]

20. McMahon, A.; McNulty, H.; Hughes, C.F.; Strain, J.J.; Ward, M. Novel Approaches to Investigate One-Carbon Metabolism and Related B-Vitamins in Blood Pressure. *Nutrients* 2016, 8, 720. [CrossRef] [PubMed]

21. Cao, C.; Hu, J.; Dong, Y.; Zhan, R.; Li, P.; Su, H.; Peng, Q.; Wu, T.; Lei, L.; Huang, X. Gender Differences in the Risk Factors for Endothelial Dysfunction in Chinese Hypertensive Patients: Homocysteine Is an Independent Risk Factor in Females. *PLoS ONE* 2015, 10, e0118686. [CrossRef] [PubMed]

22. Rodrigo, R.; Passalacqua, W.; Araya, J.; Orellana, M.; Rivera, G. Homocysteine and Essential Hypertension. *J. Clin. Pharmacol.* 2003, 43, 1299–1306. [CrossRef]
23. Gibson, A.; Woodside, J.V.; Young, I.S.; Sharpe, P.C.; Mercer, C.; Patterson, C.C.; McKinley, M.C.; Kluitjmans, L.A.J.; Whitehead, A.S.; Evans, A. Alcohol increases homocysteine and reduces B vitamin concentration in healthy male volunteers—A randomized, crossover intervention study. *JQM Int. J. Med.* 2008, 101, 881–887. [CrossRef] [PubMed]

24. Omoike, O.E.; Paul, T.K.; Ridner, S.; Awasthi, M.; Harirforoosh, S.; Mamudu, H.M. Association between smoking status and homocysteine levels and possible effect modification by cholesterol and oestradiol. *Biomarkers* 2019, 25, 126–130. [CrossRef] [PubMed]

25. Puri, M.; Kaur, L.; Walia, G.K.; Mukhopadhyay, R.; Sachdeva, M.P.; Trivedi, S.S.; Ghosh, P.K.; Saraswathy, K.N. MTHFR C677T polymorphism, folate, vitamin B12 and homocysteine in recurrent pregnancy losses: A case control study among north Indian women. *J. Périnat. Med.* 2013, 41, 549–554. [CrossRef]

26. Wu, Y.-L.; Hu, C.-Y.; Lu, S.-S.; Gong, F.-F.; Feng, F.; Qian, Z.-Z.; Ding, X.-X.; Yang, H.-Y.; Sun, Y.-H. Association between methylenetetrahydrofolate reductase (MTHFR) C677T/A1298C polymorphisms and essential hypertension: A systematic review and meta-analysis. *Metabolism* 2014, 63, 1503–1511. [CrossRef]

27. Yang, B.; Fan, S.; Zhi, X.; Li, Y.; Liu, Y.; Wang, D.; He, M.; Hou, Y.; Zheng, Q.; Sun, G. Associations of MTHFR Gene Polymorphisms with Hypertension and Hypertension in Pregnancy: A Meta-Analysis from 114 Studies with 15411 Cases and 21970 Controls. *PLoS ONE* 2014, 9, e87497. [CrossRef]

28. Fan, S.; Yang, B.; Zhi, X.; Wang, Y.; Wei, J.; Zheng, Q.; Sun, G. Interactions of Methylenetetrahydrofolate Reductase C677T Polymorphism with Environmental Factors on Hypertension Susceptibility. *Int. J. Environ. Res. Public Health* 2016, 13, 601. [CrossRef] [PubMed]

29. Khoury, M.J.; Dorman, J.S. The Human Genome Epidemiology Network. *Am. J. Epidemiol.* 1998, 148, 1–4. [CrossRef]

30. Sagoo, G.; Little, J.; Higgins, J. Systematic Reviews of Genetic Association Studies. *PLoS Med.* 2009, 6, e1000028. [CrossRef] [PubMed]

31. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Int. J. Surg.* 2021, 88, 105906. [CrossRef]

32. Subirana, M.; Solá, I.; Garcia, J.M.; Gich, I.; Urrúitia, G. A nursing qualitative systematic review required MEDLINE and CINAHL for study identification. *J. Clin. Epidemiol.* 2005, 58, 20–25. [CrossRef] [PubMed]

33. Field, A.P.; Gillett, R. How to do a meta-analysis. *Br. J. Math. Stat. Psychol.* 2010, 63, 665–694. [CrossRef]

34. Ghogomu, S.; Ngolle, N.; Mouliom, R.; Asa, B. Association between the MTHFR C677T gene polymorphism and essential hypertension in South West Cameroon. *Genet. Mol. Res.* 2016, 15, 28. [CrossRef] [PubMed]

35. Amin, H.A.; Aziz, H.F.A.; Leheta, O.F.; Kamal, H. Methylenetetrahydrofolate Reductase (677C/T) Polymorphism in Myocardial Infarction and hypertension. *Am. J. Biochem. Biotechnol.* 2012, 8, 150–156. [CrossRef]

36. Fu, L.; Li, Y.; Luo, D.; Deng, S.; Wu, B.; Hu, Y. Evidence on the causal link between homocysteine and hypertension from a meta-analysis of 40 173 individuals implementing Mendelian randomization. *J. Clin. Hypertens.* 2019, 21, 1879–1894. [CrossRef] [PubMed]

37. Arina, C.A.; Amir, D.; Siregar, Y.; Sembiring, R.J. The Role of Polymorphism Gen Methylene Tetra Hydrofolate Reductase (MTHFR) C677T in Ischaemic Stroke Patients with and without Hypertension. *Open Access Maced. J. Med. Sci.* 2019, 7, 29–32. [CrossRef] [PubMed]

38. Dwivedi, M.K.; Sinha, D. Role of MTHFR 677 C > T Polymorphism on Blood Homocysteine and Susceptibility to Hypertension. *Int. J. Hum. Genet.* 2017, 17, 118–125. [CrossRef]

39. Wen, C.; Lv, J.-F.; Wang, L.; Zhu, W.-F.; Fan, F.-S.; Wang, X.-Z. Association of a Methylene Tetrahydrofolate Reductase C677T Polymorphism with Several Blood Chemical Levels in a Chinese Population. *Genet. Test. Mol. Biomark.* 2015, 19, 24–29. [CrossRef]

40. Wang, Y.; Xu, X.; Huo, Y.; Liu, D.; Cui, Y.; Liu, Z.; Zhao, Z.; Xu, X.; Liu, L.; Li, X. Predicting Hyperhomocysteinemia by Methylenetetrahydrofolate Reductase C677T Polymorphism in Chinese Patients with Hypertension. *Clin. Appl. Thromb.* 2014, 21, 661–666. [CrossRef] [PubMed]

41. Cai, W.; Yin, L.; Yang, F.; Zhang, L.; Cheng, J. Association between Hcy levels and the CBS844ins68 and MTHFR C677T polymorphisms with essential hypertension. *Biomol. Rep.* 2014, 2, 861–868. [CrossRef]

42. Xi, B.; Zhao, X.; Chandak, G.R.; Shen, Y.; Cheng, H.; Hou, D.; Wang, X.; Mi, J. Influence of Obesity on Association Between Genetic Variants Identified by Genome-Wide Association Studies and Hypertension Risk in Chinese Children. *Am. J. Hypertens.* 2013, 26, 990–996. [CrossRef] [PubMed]

43. Zhang, Y.; Wang, H.; Zhang, X.; Wang, L.; Wu, G. Relationship between homocysteine, methylene tetrahydrofolate reductase C677T polymorphisms and essential hypertension in Kazak nationality in Xinjiang. *J. Clin. Cardiol.* 2012, 28, 570–573. [CrossRef] [PubMed]

44. Cao, Z.Y. The relationship between MTHFR C677T polymorphism and H type hypertension with acute myocardial infarction in elderly population. *Chin. J. Gerontol.* 2012, 32, 5118–5120. [CrossRef]

45. Yin, R.-X.; Wu, J.-Z.; Liu, W.-Y.; Wu, N.-F.; Cao, X.-L.; Miao, L.; Aung, L.H.H.; Zhang, L.; Long, X.-J.; Li, M. Association of Several Lipid-Related Gene Polymorphisms and Blood Pressure Variation in the Bai Ku Yao Population. *Am. J. Hypertens.* 2012, 25, 927–936. [CrossRef] [PubMed]

46. Liu, C.; Li, H.; Qi, Q.; Lu, L.; Gan, W.; Loos, R.J.; Lin, X. Common variants in or near FGFI5, CYP17A1 and MTHFR genes are associated with blood pressure and hypertension in Chinese Hans. *J. Hypertens.* 2011, 29, 70–75. [CrossRef] [PubMed]
47. Cai, Y.; Gong, W. Linkage study in methylenetetrahydrofolate reductase single nucleotide polymorphisms and methotrexate-related adverse effects in patients with rheumatoid arthritis. Chin. J. Prim. Med. Pharm. 2009, 16, 1153–1157.

48. Lin, P.T.; Cheng, C.H.; Wei, J.C.-C.; Huang, Y.C. Low Plasma Pyridoxal 5'-phosphate Concentration and MTHFR 677C→T Genotypes Are Associated with Increased Risk of Hypertension. Int. J. Vitam. Nutr. Res. 2008, 78, 33–40. [CrossRef]

49. Luo, J.W.; Tang, Y.; Chen, H.; Wu, X.Y.; Wu, Y.A.; Deng, Y.L. Study on MTHFR C677T polymorphism in hypertensive subjects with blood stasis syndrome. J. Beijing Univ. Tradit. Chin. Med. 2008, 31, 351–354.

50. Tang, Y.; Chen, H.; Wu, X.Y.; Luo, J.W. The C677T point mutation of N5, 10-methylenetetrahydrofolate reductase (MTHFR) and essential hypertension. Mol. Cardiol. China 2007, 7, 205–207.

51. Markan, S.; Sachdeva, M.; Sehrawat, B.S.; Kumari, S.; Jain, S.K.; Khullar, M. MTHFR 677 CT/MTHFR 1298 CC genotypes are associated with increased risk of hypertension in Indians. Mol. Cell. Biochem. 2007, 302, 125–131. [CrossRef]

52. Hui, P.; Nakayama, T.; Morita, A.; Sato, N.; Hishiki, M.; Saito, K.; Yoshikawa, Y.; Tamura, M.; Sato, I.; Takahashi, T. Common Single Nucleotide Polymorphisms in Japanese Patients with Essential Hypertension: Aldehyde Dehydrogenase 2 Gene as a Risk Factor Independent of Alcohol Consumption. Hypertens. Res. 2007, 30, 585–592. [CrossRef] [PubMed]

53. Xing, X.; Hua, Q. Relationships between the polymorphism of methylenetetrahydrofolate reductase gene C677T and hypertension, cardiac structure and function. Med. J. Chin. People’s Lib. Army 2007, 32, 741–744.

54. Li, C.-M.; Zhang, C.; Lu, X.-L.; Feng, H.-Y.; Su, Q.-X.; Zeng, Y.; Zhang, H.-L.; Qiu, S.-L. Relationship between methylenetetrahydrofolate reductase gene and ischemic stroke. Zhongguo Weizhongbing Ji Jiu Yi Xue = Chin. Crit. Care Med. = Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 2006, 18, 264–267.

55. Hu, D.; Wang, J.; Yao, H.; Lin, J.; Liao, Y.; Jiang, S.; Wang, Y.; Xing, H.; Wang, B.; Huo, Y. Methylenetetrahydrofolate reductase C677T polymorphism, hypertension, and risks of stroke: A prospective nested case-control study. Int. J. Cardiol. 2009, 137, S67. [CrossRef]

56. Misra, U.K.; Kalita, J.; Srivastava, R.; Bansal, V.; Agarwal, S. Methylenetetrahydrofolate reductase gene polymorphism in Indian stroke patients. Neuro. India 2006, 54, 260. [CrossRef] [PubMed]

57. Lwin, H.; Yokoyama, T.; Yoshiike, N.; Saito, K.; Yamamoto, A.; Date, C.; Tanaka, H. Polymorphism of Methylenetetrahydrofolate Reductase Gene (C677T MTHFR) Is Not a Confounding Factor of the Relationship Between Serum Uric Acid Level and the Prevalence of Hypertension in Japanese Patients. J. Clin. 2006, 70, 83–87. [CrossRef] [PubMed]

58. Liu, J.W.; Ye, L.; Liu, J.; Li, X.Y. Study on homocysteine metabolism-related enzymes gene polymorphisms in elderly essential hypertension patients with peripheral arterial occlusive disease. Chin. J. Geriatr. 2005, 24, 332–335.

59. Sun, X.; Li, Y.; Guo, H. The gene polymorphisms of homocysteine metabolism-related enzymes and the associated factors in isolated systolic hypertension. Zhonghua Xin Xue Guan Bing Za Zhi 2003, 31, 269–273.

60. Wang, L.-D.; Guo, R.-F.; Fan, Z.-M.; He, X.; Gao, S.-S.; Guo, H.-Q.; Matsuo, K.; Yin, L.-M.; Li, J.-L. Association of methylenetetrahydrofolate reductase and thymidylate synthase promoter polymorphisms with genetic susceptibility to esophageal and cardiac cancer in a Chinese high-risk population. Dis. Esophagus 2005, 18, 177–184. [CrossRef]

61. Zhan, S.; Gao, Y.; Yin, X.; Huang, Y.; Hu, Y.; Li, L. A case-control study on the relationship between abnormal homocysteine metabolism and essential hypertension. Zhonghua Liu Xing Bing Xue Za Zhi = Zhonghua Liuxingbingxue Zazhi 2000, 21, 194–197. [PubMed]

62. Kobashi, G.; Yamada, H.; Asano, T.; Nagano, S.; Hata, A.; Kishi, R.; Fujimoto, S.; Kondo, K. Absence of association between a common mutation in the methylenetetrahydrofolate reductase gene and preeclampsia in Japanese women. Am. J. Med. Genet. 2000, 93, 122–125. [CrossRef]

63. Gao, Y.; Zhan, S.; Yin, X.; Hu, Y.; Li, L. The relationship between methylenetetrahydrofolate reductase polymorphism and risk of essential hypertension. Beijing Yi Ke Da Xue Xue Bao = J. Beijing Med. Univ. 1999, 31, 370–372.

64. Nakata, Y.; Katsuya, T.; Takami, S. A common mutation or methylenetetrahydrofolate reductase gene is a risk factor for myocardial infarction? J. Hypertens. 1998, 16, S56.

65. Nishio, H.; Lee, M.J.; Fujii, M.; Kario, K.; Kayaba, K.; Shimada, K.; Matsuo, M.; Sumino, K. A common mutation in methylenetetrahydrofolate reductase gene among the Japanese population. J. Hum. Genet. 1996, 41, 247–251. [CrossRef]

66. Bayramoglu, A.; Urban Kucuk, M.; Guler, H.I.; Abaci, O.; Kucukkaya, Y.; Colak, E. Is there any genetic predisposition of MMP-9 gene C1562T and MTHFR gene C677T polymorphisms with essential hypertension? Cytotechnology 2015, 67, 115–122. [CrossRef]

67. Husemoen, L.L.N.; Skaaby, T.; Jørgensen, T.; Thuesen, B.; Fenger, M.; Grarup, N.; Sandholt, C.H.; Hansen, T.; Lindberg, A. MTHFR C677T genotype and cardiovascular risk in a general population without mandatory folic acid fortification. Eur. J. Nutr. 2014, 53, 1549–1559. [CrossRef] [PubMed]

68. Ilhan, N.; Kucukus, M.; Kaman, D.; Ilhan, N.; Ozbay, Y. The 677 C/T MTHFR polymorphism is associated with essential hypertension, coronary artery disease, and higher homocysteine levels. Arch. Med. Res. 2008, 39, 125–130. [CrossRef] [PubMed]

69. Marinho, C.; Alho, I.; Arduini, D.; Falcão, L.M.; Brás-Nogueira, J.; Bicho, M. GST M1/T1 and MTHFR gene polymorphisms as risk factors for hypertension. Biochem. Biophys. Res. Commun. 2007, 353, 344–350. [CrossRef] [PubMed]

70. Nagy, B.; Hupuczi, P.; Papp, Z. High frequency of methylenetetrahydrofolate reductase 677TT genotype in Hungarian HELLP syndrome patients determined by quantitative real-time PCR. J. Hum. Hypertens. 2006, 21, 154–158. [CrossRef]

71. Demir, S.C.; Evruke, C.; Ozgunen, T.; Kadayifci, O.; Altintas, U.; Kokangul, S. The relationship between pregnancy induced hypertension and congenital thrombophilia. Saudi Med. J. 2006, 27, 1161. [PubMed]
72. Cesari, M.; Zanchetta, M.; Burlina, A.; Pedon, L.; Maioilino, G.; Sticchi, D.; Pessina, A.C.; Rossi, G.P. Hyperhomocysteinemia Is Inversely related to Left Ventricular Ejection Fraction and Predicts Cardiovascular Mortality in High-Risk Coronary Artery Disease Hypertensives. *Arter. Thromb. Vasc. Biol.* 2005, 25, 115–121. [CrossRef]

73. Tyllick, L.; Födinger, M.; Puttng, H.; Rutkowski, P.; Strocezki, P.; Tyszko, S.; Rutkowski, B.; Hörl, W.H. Methylene tetrahydrofolate Reductase Gene Polymorphisms in Essential Hypertension Relation with the Development of Hypertensive End-Stage Renal Disease. *Am. J. Hypertens.* 2005, 18, 1442–1448. [CrossRef]

74. Yilmaz, H.; Ünlüçerçi, Y.; Gurdol, F.; Isbilen, E.; Isbir, T. Association of pre-eclampsia with hyperhomocysteinemia and methylenetetrahydrofolate reductase gene C677T polymorphism in a Turkish population. *Aust. N. Z. J. Obstet. Gynaecol.* 2004, 44, 423–427. [CrossRef] [PubMed]

75. Frederiksen, J.; Juul, K.; Grande, P.; Jensen, G.B.; Schroeder, T.V.; Tybjærg-Hansen, A.; Nordestgaard, B.G.; Ingram, D.A.; Mead, L.E.; Tanaka, H. Methylene tetrahydrofolate reductase polymorphism (C677T), hyperhomocysteinemia, and risk of ischemic cardiovascular disease and venous thromboembolism: Prospective and case-control studies from the Copenhagen City Heart Study. *Blood* 2004, 104, 3046–3051. [CrossRef]

76. Rodríguez-Esparrong, F.; Hernández-Perera, O.; Rodríguez-Pérez, J.C.; Anabitarte, A.; Díaz-Cremades, J.M.; Losada, A.; Fiúza, D.; Hernández, E.; Yunis, C.; Ferrario, C.M. The Effect of Methylene tetrahydrofolate Reductase R677T Common Variant on Hypertensive Risk Is Not Solely Explained by Increased Plasma Homocysteine Values. *Clin. Exp. Hypertens.* 2005, 25, 209–220. [CrossRef] [PubMed]

77. Kahleová, Ž.; Palhyzová, D.; Zvára, K.; Zvarova, J.; Hrach, K.; Novákova, I.; Hyánek, J.; Bendllová, B.; Kozich, V. Essential hypertension in adolescents: Association with insulin resistance and with metabolism of homocysteine and vitamins. *Am. J. Hypertens.* 2002, 15, 857–864. [CrossRef]

78. Beneš, P.; Kančová, K.; Mužik, J.; Groch, L.; Benedik, J.; Elbl, L.; Izakovcová-Hollá, L.; Vašků, A.; Znojil, V.; Vácha, J. Methylenetetrahydrofolate Reductase Polymorphism, Type II Diabetes Mellitus, Coronary Artery Disease, and Essential Hypertension in the Czech Population. *Mol. Genet. Metab.** 2001, 73, 188–195. [CrossRef]

79. Zusterzeel, P.L.; Visser, W.; Bolm, H.J.; Peters, W.H.; Heil, S.G.; Steegers, E.A. Methylene tetrahydrofolate Reductase Polymorphisms in Preeclampsia and the Heli Syndrome. *Hypertens. Pregnancy** 2000, 19, 299–307. [CrossRef] [PubMed]

80. Alghasham, A.; Settín, A.A.; Ali, A. Association of MTHFR C677T and A1298C Gene Polymorphisms with Hypertension. *Int. J. Health Sci.* 2012, 6, 3–11. [CrossRef] [PubMed]

81. Fakhrzadeh, H.; Mirarefin, M.; Sharifi, F.; Ghotbi, S.; Amoli, M.; Pourebrabrahim, R.; Nouri, M.; Larijani, B. Association of methylenetetrahydrofolate reductase gene C677T polymorphism with metabolic syndrome in an Iranian population: Tehran homocysteine survey. *J. Diabetes Metab. Disord.* 2009, 8, 6.

82. Pérez-Razo, J.C.; Cano-Martínez, L.J.; Alarcon, G.V.; Canizales-Quinteros, S.; Martínez-Rodriguez, N.; Canto, P.; Roque-Ramírez, B.; Palma-Flores, C.; Esteban-Martínez, R.; López-Hernández, L.B. Functional Polymorphism rs13306560 of the MTHFR Gene Is Associated with Essential Hypertension in a Mexican-Mestizo Population. *Circ. Cardiovasc. Genet.* 2015, 8, 603–609. [CrossRef]

83. Vázquez-Alaniz, F.; Lumbraeras-Marquez, M.I.; Carrillo, A.S.; Aguilar-Duran, M.; Méndez-Hernández, E.M.; Barraza-Salas, M.; Castellanos-Juárez, F.X.; Salas-Pacheco, J.M. Association of COMT G675A and MTHFR C677T polymorphisms with hypertensive disorders of pregnancy in Mexican mestizo population. *Pregnancy Hypertens.* Int. J. Women’s Cardiovasc. Health 2014, 4, 59–64. [CrossRef] [PubMed]

84. Deshmukh, A.; Rodrigue, K.M.; Kennedy, K.M.; Land, S.; Jacobs, B.S.; Raz, N. Synergistic effects of the MTHFR C677T polymorphism and hypertension on spatial navigation. *Biol. Psychol.* 2009, 79, 240–245. [CrossRef] [PubMed]

85. Canto, P.; Canto-Cetina, T.; Juárez-Velázquez, R.; Rosas-Vargas, H.; Rangel-Villalobos, H.; Canizales-Quinteros, S.; Velázquez-Wong, A.C.; Villarreal-Molina, M.T.; Fernández, G.; Coral-Vázquez, R. Methylene tetrahydrofolate Reductase C677T and Glutathione S-Transferase P1 A131G Are Associated with a Reduced Risk of Preeclampsia in Maya-Mestizo Women. *Hypertens. Res.* 2008, 31, 1015–1019. [CrossRef] [PubMed]

86. Rajkovic, A.; Mahomed, K.; Rozen, R.; Malinow, M.; King, I.B.; Williams, M.A. Methylenetetrahydrofolate Reductase 677 C → T Polymorphism, Plasma Folate, Vitamin B12 Concentrations, and Risk of Preeclampsia among Black African Women from Zimbabwe. *Mol. Genet. Metab.* 2000, 69, 33–39. [CrossRef] [PubMed]

87. Powers, R.W.; Minish, L.A.; Lykins, D.L.; Ness, R.B.; Crombleholme, W.R.; Roberts, J.M. Methylenetetrahydrofolate reductase polymorphism, folate, and susceptibility to preeclampsia. *J. Soc. Gynecol. Investig.* 1999, 6, 74–79. [CrossRef]

88. Fowdar, J.; Lason, M.V.; Szvetko, A.L.; Lea, R.A.; Griffiths, L.R. Investigation of Homocysteine-Pathway-Related Variants in Essential Hypertension. *Int. J. Hypertens.* 2012, 2012, 190923. [CrossRef] [PubMed]

89. Ng, X.; Boyd, L.; Dufficy, L.; Naumovski, N.; Blades, B.; Travers, C.; Lewis, P.; Sturm, J.; Yates, Z.; Townley-Jones, M. Folate Nutritional Genetics and Risk for Hypertension in an Elderly Population Sample. *J. Nutr. Nutr.* 2009, 2, 1–8. [CrossRef] [PubMed]

90. Heux, S.; Morin, F.; Lea, R.A.; Ovcaric, M.; Tajouri, L.; Griffiths, L.R. The Methylene tetrahydrofolate Reductase Gene Variant (C677T) as a Risk Factor for Essential Hypertension in Caucasians. *Hypertens. Res.* 2004, 27, 663–667. [CrossRef]

91. Rios, D.R.; Alpoin, P.N.; Godoi, L.C.; Mendes, F.S.; Iwaleed, B.; Sousa, L.P.; Perucci, L.O.; Carvalho, M.G.; Borges, K.B.; Dusse, L. Is there a link among thrombophilia factors and preeclampsia foci and preeclampsia? *J. Thromb. Thrombolysis** 2017, 44, 516–518. [CrossRef]

92. Fridman, O.; Porcile, R.; Morales, A.V.; Gariglio, L.O.; Potenzoni, M.A.; Noceto, P.C. Association of Methylene tetrahydrofolate Reductase Gene 677C>T Polymorphism with Hypertension in Older Women in a Population of Buenos Aires City. *Clin. Exp. Hypertens.* 2012, 35, 159–166. [CrossRef] [PubMed]
93. Fridman, O.; Porcile, R.; Vanasco, V.; Junco, M.N.; Gariglio, L.; Potenzoni, M.A.; Bañes, I.; Morales, A. Study on Homocysteine Levels and Methylenetetrahydrofolate Reductase Gene Variant (C677T) in a Population of Buenos Aires City. *Clin. Exp. Hypertens.* **2008**, *30*, 574–584. [CrossRef]

94. Soares, A.L.; Fernandes, A.P.; Cardoso, J.E.; Sousa, M.O.; Lasmar, M.C.; Novelli, B.A.; Lages, G.F.; Dusse, L.; Vieira, L.M.; Lwaleed, B.A. Plasma Total Homocysteine Levels and Methylenetetrahydrofolate Reductase Gene Polymorphism in Patients with Type 2 Diabetes Mellitus. *Pathophysiol. Haemost. Thromb.* **2007**, *36*, 275–281. [CrossRef]

95. Mabhuda, S.; Mashatola, L.; Kaur, M.; Sharma, J.; Apalata, T.; Muhamed, B.; Benjeddou, M.; Johnson, R. Hypertension in African Populations: Review and Computational Insights. *Genes* **2021**, *12*, 532. [CrossRef]

96. Zhong, S.; Xu, J.; Li, W.; Chen, Z.; Ma, T.; Zhao, J. Methionine synthase A2756G polymorphism and breast cancer risk: An up-to-date meta-analysis. *Gene* **2013**, *527*, 510–515. [CrossRef]

97. Rosenberg, N.; Murata, M.; Ikeda, Y.; Opare-Sern, O.; Zivelin, A.; Geffen, E.; Seligsohn, U. The Frequent 5,10-Methylenetetrahydrofolate Reductase C677T Polymorphism Is Associated with a Common Haplotype in Whites, Japanese, and Africans. *Am. J. Hum. Genet.* **2002**, *70*, 758–762. [CrossRef]

98. Atadzhanov, M.; Mwaba, M.H.; Mukomena, P.N.; Lakhi, S.; Mwaba, P.; Rayaprolu, S.; Meschia, J.F.; Ross, O.A. Frequency of APOE, MTHFR and ACE polymorphisms in the Zambian population. *BMC Res. Notes* **2014**, *7*, 194. [CrossRef] [PubMed]

99. Wolf-Maier, K.; Cooper, R.S.; Kramer, H.; Banegas, J.R.; Giampaoli, S.; Joffres, M.R.; Poulter, N.; Primatesa, P.; Stegmayr, B.; Thamm, M. Hypertension Treatment and Control in Five European Countries, Canada, and the United States. *Hypertension* **2004**, *43*, 10–17. [CrossRef] [PubMed]

100. Kosmas, I.P.; Tatsioni, A.; Ioannidis, J.P. Association of C677T polymorphism in the methylenetetrahydrofolate reductase gene with hypertension in pregnancy and pre-eclampsia: A meta-analysis. *J. Hypertens.* **2004**, *22*, 1655–1662. [CrossRef] [PubMed]

101. Yang, K.-M.; Jia, J.; Mao, L.-N.; Men, C.; Tang, K.-T.; Li, Y.-Y.; Ding, H.-X.; Zhan, Y.-Y. Methylenetetrahydrofolate reductase C677T gene polymorphism and essential hypertension: A meta-analysis of 10,415 subjects. *Biomed. Rep.* **2014**, *2*, 699–708. [CrossRef]

102. Qian, X.; Lu, Z.; Tan, M.; Liu, H.; Lu, D. A meta-analysis of association between C677T polymorphism in the methylenetetrahydrofolate reductase gene and hypertension. *Eur. J. Hum. Genet.* **2007**, *15*, 1239–1245. [CrossRef]

103. Balduzzi, S.; Rücker, G.; Schwarz, G. How to perform a meta-analysis with R: A practical tutorial. *Evid. Based Ment. Health* **2019**, *22*, 153–160. [CrossRef] [PubMed]