

# Risk factors for myocardial infarction and stroke in Africa

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## INTRODUCTION

Cardiovascular disease (CVD) accounted for 30% of all deaths worldwide according to estimates in 2005 and almost half of these deaths were in people under the age of 70 years.<sup>(1)</sup> According to the World Health Organisation (WHO), in 2005, more than 1.1 million deaths in the African region were caused by cardiovascular diseases and more than half of these were due to ischaemic heart disease (IHD) and stroke.<sup>(2)</sup> Projections suggest that this figure will almost double by 2030<sup>(3,2)</sup> and that IHD and stroke will become two of the three leading causes of death in low- and middle-income countries.<sup>(4)</sup>

In African regions IHD is the leading cause of death in men and second leading cause of death in women over the age of 60 years.<sup>(3)</sup> In South Africa approximately 33 and 60 people die per day because of a myocardial infarction or a stroke respectively.<sup>(5)</sup> The underlying pathology for CVD is atherosclerosis, which

## ABSTRACT

**Background:** Definitive information on the strength of association between various risk factors and cardiovascular disease in Africa is lacking.

**Objective:** We conducted a systematic review of studies investigating risk factors for acute myocardial infarction (AMI) and stroke in Africa.

**Data sources:** We searched Medline and Embase as well as the reference lists of the included articles.

**Study eligibility criteria:** We included case-control and cohort studies conducted in an African country, which assessed risk factors for first episodes of (AMI) or stroke in people of any age.

**Methods:** Two independent reviewers screened studies for eligibility, extracted data and assessed study quality. We described measures of association (odds ratios) with confidence intervals of risk factors for AMI and stroke separately.

**Results:** Twelve articles reporting results from five case-control studies met our inclusion criteria but only one study (INTERHEART) investigated risk factors for AMI. No eligible cohort studies were identified. The direction of association for established risk factors for AMI and stroke seem to be similar globally but the strength of association of various risk factors varies between countries and within African ethnic groups. In Africa, diabetes and hypertension had the highest risk associated with AMI and hypertension was the strongest risk factor for stroke. Overall, the quality of the included case-control studies was good.

**Conclusions and implications:** Our results confirm the urgent need for prospective studies investigating risk factors for AMI and stroke in African populations. A few high quality case-control studies exist but these do not adequately represent the cultural and genetic diversity in Africa, or the influence of infections on cardiovascular outcomes. Dynamic risk factors that rely on self-report such as diet, physical activity and stress will be better assessed through longitudinal cohort studies. SAHeart 2011; 8:12-23

develops silently over many years and is usually advanced by the time it becomes symptomatic. IHD and stroke are the main components of CVD and share common risk factors. The progression of atherosclerosis is accelerated by the presence of modifiable risk factors such as tobacco use, obesity, hypertension,

diabetes and dyslipidemia.<sup>(6,7)</sup> Addressing risk factors through primary and secondary prevention strategies have been shown to reduce mortality and morbidity.<sup>(7)</sup>

Major risk factors for CVD in Africa may be similar to those in the Western world, but because African populations are of wide genetic and ethnic diversity, are heavily burdened by infectious diseases and at different stages of epidemiological health transition, it is uncertain whether information from studies in economically more developed countries can be applied to the African context.<sup>(3,8,9)</sup> Definitive information on the strength of association between various risk factors and CVD in Africa is lacking,<sup>(3,8)</sup> primarily due to insufficient research on non-communicable diseases, weak study designs and small sample sizes. In order to improve our understanding of the risk factors most relevant to African populations, to help inform targeted health promotion and primary prevention strategies, and to guide the design of future research we conducted a systematic review of high level epidemiological studies investigating risk factors for myocardial infarction and stroke conducted in Africa.

## MATERIALS AND METHODS

### Study eligibility

We included case-control or cohort studies conducted in African countries that assessed the association of specific risk factors (e.g. socio-demographic, family history, lifestyle, clinical, biochemical or other) for first episodes of acute myocardial infarction (AMI) or stroke. We considered only studies published in English but documented all potentially eligible studies reported in other languages. There was no restriction in terms of the setting in which studies were conducted or age of the participants. We excluded studies that reported on recurrent events or that did not specifically state that only first episode events were investigated. Studies that focused exclusively on women during pregnancy or the puerperium, or on patients with specific underlying cardiac abnormalities such as atrial fibrillation, cardiomyopathies or valvular heart disease were also excluded.

### Search strategy

A broad search strategy was developed with assistance from an experienced information specialist for electronic searches in Medline (1966 to 31 August 2010) and Embase (1972 to 10 September 2010). We used exploded medical subject headings (MeSH) including Cerebrovascular Disorders, Myocardial Ischaemia, Stroke, Myocardial Infarction, and Africa; subject headings for Risk, Cohort or Case-Control, Prospective or Retrospective Studies in combination with text words including Heart Attack, Cerebrovascular Accident, Cerebrovascular Incident; as well as text words for all the African countries individually. The search terms for Africa were adapted from the search strategy developed by Siegfried et al.<sup>(10)</sup> The searches had no language restriction but were limited to humans. The specific search strategies can be found in Appendix I. We searched the reference lists of articles included in this review for additional relevant studies.

The titles and/or abstracts of all articles identified were screened for eligibility by two independent reviewers (CL and LL) using pre-specified criteria. Any abstract deemed by one of the reviewers as being potentially relevant was reviewed in full text. Any uncertainty or disagreement about eligibility was resolved through discussion and remaining uncertainty was resolved through discussion with a third reviewer (JV).

### Data extraction

CL and LL independently extracted data from the eligible studies using a structured data extraction form with disagreements resolved through consensus and, where necessary, by consultation with JV.

We planned to extract the following data:

- Study design (prospective or retrospective cohort study, nested or other case control study), sample selection and sample size, setting, eligibility criteria, and follow-up or data-collection period.
- Information on pre-specified risk factors (along with potential confounders) as well as the definitions and methods used in

each study. These could include but were not limited to: socio-demographic information (age, gender, ethnicity, employment, education and socio-economic status), family history, lifestyle factors (former or current tobacco use, physical activity, and dietary patterns and alcohol use), personal clinical history (hypertension, diabetes, dyslipidemia, depressive mood or psychological stress), waist circumference (WC) or body mass index (BMI), HIV status and use of ARV treatment and biochemical markers (C-reactive protein, lipid profile, serum glucose, homocysteine, and genetic markers)

- Information about the disease outcome: for each study it was documented how a first episode of acute myocardial infarction or stroke was defined. We also documented the number of fatal and non-fatal episodes when this was reported.

We planned to extract data on relationship of risk factors with disease outcomes using two approaches depending on the two study designs included in this review:

- **Cohort studies:** The number of non-fatal and fatal cases of AMI or stroke for participants with and without the risk factor.
- **Case-control studies:** The number of cases or controls exposed and not exposed to a certain risk factor.

We planned to use this information to calculate a relative risk or odds ratio with a 95% confidence interval for individual studies; and where appropriate conduct meta-analysis. Where only the measure of association for a risk factor was reported this was extracted together with the level of precision (95% confidence interval, standard error or p-value). Where the measure of association was adjusted for potential confounding variables this was noted and the variables recorded.

### Quality Assessment

The quality of included cohort- and case-control studies was rated using adapted versions of the critical appraisal tools developed in the Critical Appraisal Skills Programme (CASP). (<http://www.sph.nhs.uk/what-we-do/public-health-workforce/resources/critical-appraisals-skills-programme>.) Judgements of the methodolo-

gical quality focussed on internal validity and the relevant study design components were rated as adequate, inadequate or unclear according to pre-specified criteria for the two types of designs separately. (Appendix 2)

### Data synthesis and analyses

We described measures of association (odds ratios) with confidence intervals of risk factors for AMI and stroke separately and summarised these in a table. Only one study assessed AMI as the outcome and the studies investigating stroke all assessed different risk factors. We could therefore not pool results or do sub group analyses.

### Results

We identified 862 potentially relevant articles through searching PubMed and EMBASE. A total of 12 articles were included in our review. Figure 1 presents a flowchart showing the process we followed in compiling the final list of articles for inclusion. The majority of articles were excluded because they reported on non-African studies. Seven were excluded because the full text was available in French or Spanish only and eligibility could not be determined from the abstract. We identified no cohort studies that were eligible for inclusion.

The 12 articles considered in this review reported on five separate studies: INTERHEART<sup>(8,11-15)</sup> INTERSTROKE,<sup>(16)</sup> the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception<sup>(17-19)</sup> and two unnamed studies.<sup>(20,21)</sup> Only INTERHEART assessed risk factors for first episode of AMI. Data were separately reported for Africa collectively or for specific African ethnic groups in eight articles from INTERHEART. Two of these papers were excluded,<sup>(22,23)</sup> since the African results they reported were subsequently documented more fully in INTERHEART Africa;<sup>(8)</sup> this more recent report is included. The WHO Collaborative Study included cases with first time diagnosis of both AMI and stroke, but the number of AMI cases from Africa (four cases and eight controls) was too small and therefore only stroke could be assessed. INTERSTROKE and the two remaining studies included first episodes of stroke only.

## RISK FACTORS FOR FIRST EPISODE OF AMI

The main findings for Africa or African ethnic groups from the INTERHEART study are summarised in this section and in Table I. INTERHEART aimed to determine the strength of association between various risk factors and first episode of AMI in an overall global population and within populations defined by ethnic group or geographic region.<sup>(23)</sup>

## SOCIO-DEMOGRAPHIC FACTORS

The mean age of controls and cases from Africa were 52.2 (SD±11.5) years and 54.3 (SD±11.3) years, (p = 0.0017) respectively; African cases were significantly younger than cases in

INTERHEART overall (p <0.0001).<sup>(6)</sup> Among the black African population, a higher socioeconomic status as measured by the degree of formal education and higher income was associated with an increased risk of AMI. The odds ratio (OR) and 95% confidence interval (CI) for participants with tertiary education compared to those with less than eight years of schooling, was 1.86; 95% CI: 1.06 to 3.25.<sup>(6)</sup> By contrast the study found no association for coloured Africans (OR 0.71; 95%CI 0.30 to 1.68) and a decreased risk among Africans of European descent or other Africans (OR 0.30; 95%CI 0.15 to 0.58).<sup>(6)</sup> In this study coloured Africans included a group of mixed race ancestry descending from the first South African nations, the Koi and San people, as well as European, African and Malaysian people that were mainly from South Africa.<sup>(8)</sup>

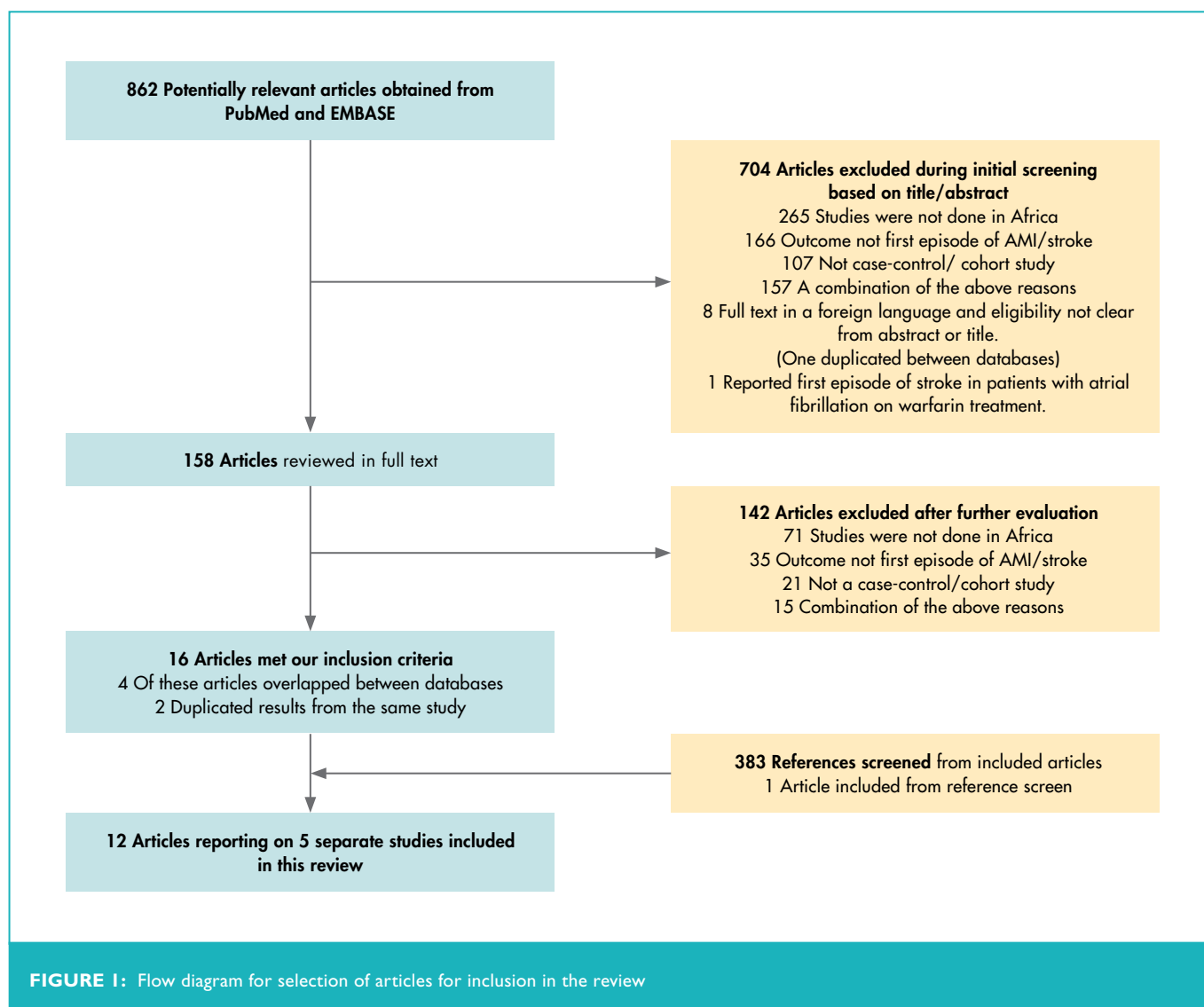


FIGURE 1: Flow diagram for selection of articles for inclusion in the review



**TABLE 1:** Risk factors for first episode of AMI: The INTERHEART study continued

| Author (publication year)                  | Sample size in Africa*<br>(Cases: Controls)                | Risk factor (Definition)   | Population group/<br>ethnicity | Odds ratio<br>(95% or 99%<br>Confidence interval) | Statistical analysis<br>(variables<br>adjusted for)                     |
|--|--|--|--------------------------------|---|---|
| Yusuf S, et al. (2005) <sup>(14)</sup>     | Africa: 1367 (578:789)<br>BMI: (543:771)<br>WHR: (528:737) | BMI (1 SD increase)  | Black African                  | 1.29 (1.10-1.52)                                  | Unconditional<br>logistic regression<br>(Age, sex)                      |
|  |  | Waist circumference (1 SD increase)  | Coloured African               | 1.07 (0.94-1.22)                                  |   |
|  |  |  | Black African                  | 1.57 (1.31-1.88)                                  |   |
|  |  | WHR (1 SD increase)  | Coloured African               | 1.16 (0.99-1.34)                                  |   |
|  |  |  | Black African                  | 1.36 (1.09-1.69)                                  |   |
|  |  | Overweight (BMI>25)  | Coloured African               | 2.25 (1.79-2.84)                                  |   |
|  |  |  | Black African                  | 2.33 (1.49-3.66)                                  |   |
|  |  | Obese (BMI>30)   | Coloured African               | 1.62 (1.16-2.27)                                  |   |
| Black African                              | 2.23 (1.45-3.45)   |  |                                |   |   |
| Rosengren A, et al. (2004) <sup>(15)</sup> | Africa: 1259   | High general stress (Several periods<br>of or permanent stress at work,<br>home or both.)                  | Africa (Combined)              | 1.51 (1.07-2.12)                                  | Unconditional<br>logistic regression<br>(Age, sex, region,<br>smoking.) |
|  |  |  | Black African                  | 1.64 (0.91-2.95)                                  |   |
|  |  |  | Coloured African               | 2.09 (1.25-3.50)                                  |   |
|  |  | Depressive mood (Feeling sad, blue or<br>depressed for ≥2 consecutive weeks<br>during the past 12 months.) | Africa (Combined)              | 1.69 (1.20-2.39)                                  |   |
| Black African                              | 1.63 (0.91-2.93)   |  |                                |   |   |
|  |  |  | Coloured African               | 1.72 (1.03-2.88)                                  |   |

\*In total 12 461 cases and 14 637 controls were recruited from 262 centres in 52 countries including 578 cases and 789 controls from sub-Saharan Africa.<sup>(23)</sup> African countries included Benin, Botswana, Cameroon, Kenya, Mozambique, Nigeria, Seychelles, South Africa and Zimbabwe. More than 80% of participants were recruited from South Africa.<sup>(8,23)</sup>

<sup>‡</sup>The World Health Organisation (WHO) and International Diabetes Federation (IDF) defines metabolic syndrome as: self-reported diabetes mellitus or HbA1c ≥ 6.5%, self-reported hypertension or use of prescribed antihypertensive medication, abdominal obesity defined by waist-to-hip ratio (WHR) ≥0.9 for males or WHR ≥0.85 for females (WHO definition) or a waist circumference (WC) ≥94cm for males or WC ≥80cm for females (IDF definition) and an abnormal lipid profile defined by HDL-cholesterol <0.9mmol/L for males or HDL-cholesterol <1.03 mmol/L for females (WHO definition) OR HDL-cholesterol <1.03mmol/L for males or HDL-cholesterol <1.29mmol/L for females (IDF definition) or the use of fibrates/niacin. With the WHO definition MS is defined as diabetes mellitus plus 2 or 3 of the other factors and with the IDF definition MS is defined as abdominal obesity plus 2 or 3 of the other factors.<sup>(11)</sup>

<sup>§</sup>The odds ratio associated with one standard deviation (SD) change (increase) in each of the lipid measures.<sup>(12)</sup> \*Food items that were considered predictive of CVD (meat, salty snacks, and fried foods) or protective (fruits and vegetables) were used to generate a dietary risk score (DRS). By using a point system each participant was assigned a total score. Dietary patterns were classified as “western”, referring to high loadings of fried food, salty snacks and meat, and “prudent” referring to high loadings of fruit and vegetables.<sup>(13)</sup>

## LIFESTYLE FACTORS

AMI risk in current or former smokers was higher than in non-smokers in the overall African population (OR 2.17; 95%CI 1.70 to 2.77) while regular alcohol users had lower risk (OR 0.66; 95% CI 0.50 to 0.87) than non-users.<sup>(6)</sup> No statistically significant association was demonstrated for other lifestyle factors, including physical activity and daily fruit and vegetable intake in the African population. The risk associated with different dietary patterns was assessed using the information gathered through a 19-item qualitative food group frequency questionnaire to generate a dietary risk score (DRS).<sup>(13)</sup> Food items that were considered to be predictive of CVD (meat, salty snacks, and fried foods) or protective (fruits and vegetables) were used to generate the DRS. Intake of food items was grouped into quartiles (Q1 - Q4) and reference values were determined for intake comparisons. Although there was a positive relationship between the DRS and risk of AMI in the INTERHEART global population (Q4 vs Q1: OR 1.92; 95%CI

1.74 to 2.11) this association was weaker and not statistically significant in Africa (Q4 vs Q1: OR 1.22; 95%CI 0.66 to 2.23). Similarly, a prudent dietary pattern (defined as a high intake of fruit and vegetables) was associated with a reduced risk of AMI in the global population (Q4 vs Q1: OR 0.67; 95%CI 0.59 to 0.76) but in Africa this association was not statistically significant (Q4 vs Q1: OR 0.73; 95%CI 0.37 to 1.46).<sup>(13)</sup>

## CLINICAL HISTORY AND EXAMINATION

In Africa, self-reported hypertension (OR 3.44; 95%CI 2.64 to 4.48) and abdominal obesity (OR 2.99; 95%CI 2.20 to 4.07) were both associated with a higher AMI risk.<sup>(6)</sup> These associations were stronger than in INTERHEART as a whole (p-values for test of heterogeneity of effects 0.0023 and <0.0001, respectively). The risks associated with metabolic syndrome defined by the World Health Organisation (WHO) and the International Diabetes Federation (IDF) were similar for all geographic regions and all

ethnic groups. For the African population, the risk associated with metabolic syndrome was higher when using the WHO definition (OR 3.29; 99% CI 2.21 to 4.89) compared to the IDF definition (OR 2.48; 99% CI 1.77 to 3.47) and with both definitions the risk was higher in Africa compared to the global population (OR 2.69; 99% CI 2.45 to 2.95 and OR 2.20; 99% CI 2.03 to 2.38, respectively).<sup>(11)</sup> Three physical measurements were evaluated as potential risk factors for AMI: body mass index (BMI), waist-to-hip ratio (WHR) and waist circumference (WC).<sup>(14)</sup> In the global population one standard deviation (SD) increase in WHR showed the strongest association with AMI (OR 1.37; 95%CI 1.34 to 1.41) and a similar increase in BMI the weakest association (OR 1.10; 95%CI 1.07 to 1.13). Similarly in the black and the coloured African groups one SD increase in WC (OR 1.57; 95%CI 1.31 to 1.88) and one SD increase in WHR (OR 2.25; 95%CI 1.79 to 2.84) showed the strongest associations with AMI, respectively.<sup>(14)</sup> Thus markers of abdominal obesity (WHR or WC) were found to be better predictors of AMI than BMI in the INTERHEART study.<sup>(14)</sup>

General stress and depressive mood were assessed as psychosocial risk factors for AMI.<sup>(15)</sup> The association between high stress levels and AMI was similar in Africa (OR 1.51; 99%CI 1.07 to 2.12) and the overall population (OR 1.55; 99%CI 1.42 to 1.68). The association between depressive mood and AMI was slightly stronger in Africa (OR 1.69; 99%CI 1.20 to 2.39) compared to the overall population (OR 1.55; 99% CI 1.42 to 1.69).<sup>(15)</sup>

### BIOLOGICAL MARKERS

For the assessment of risk associated with lipids, lipoproteins and apolipoproteins non-fasting blood samples were available from 405 black African participants and 510 coloured African participants.<sup>(12)</sup> The Apolipoprotein B100/Apolipoprotein A1 ratio (ApoB/Apo A1) was the most powerful lipid marker for increased risk of AMI. In the global population one SD increase in the ApoB/Apo A1 ratio was a stronger predictor (OR 1.59; 95% CI 1.52 to 1.64) than a similar increase in the Total/HDL cholesterol ratio (OR 1.17;

95% CI 1.13 to 1.20).<sup>(12)</sup> Similarly, one SD increase in the ApoB/Apo A1 ratio was a stronger predictor among the coloured African group, but not among the black African group.<sup>(12)</sup>

### RISK FACTORS FOR FIRST EPISODE OF A STROKE

The main findings for stroke in Africa or African ethnic groups from studies included in this review are summarised in this section and in Table 2.

### SOCIO-DEMOGRAPHIC FACTORS

The objective of the INTERSTROKE study was to determine the strength of association between various risk factors and the first episode of stroke and primary stroke subtypes in high, middle and low income countries.<sup>(24)</sup> In this study the mean age of cases from Africa was 57.7 (SD  $\pm$ 15.3) years compared to a mean age of 61.1 (SD  $\pm$ 12.7) years in the global population.<sup>(24)</sup> Twenty-two percent (71 of 323) of strokes in Africa were fatal compared to only 9% (260 of 3 000) in the global population.<sup>(24)</sup> Stroke was defined by brain CT or MRI in all cases from Africa in the INTERSTROKE study,<sup>(24)</sup> in contrast to the WHO collaborative study where 83% of stroke cases from Africa were not classified into subtypes due to the absence of definitive diagnostic evaluation.<sup>(25)</sup>

The WHO collaborative study aimed to determine the association between current oral contraceptive use and cardiovascular diseases and cases from Africa included women aged 15 to 49 years.<sup>(26)</sup> Chang et al. used the data collected in this study to assess the association between socio-economic status (SES) and AMI or stroke. SES was defined by the level of educational attainment, stratified into high (beyond secondary schooling), secondary and low (primary or no schooling).<sup>(17)</sup> There was a statistically significant inverse relationship between educational attainment and all stroke types combined in all countries, except in Africa. However, after adjustment for other risk factors SES was not a statistically significant factor overall or in Africa.<sup>(17)</sup>



**TABLE 2:** Risk factors for first episode of stroke

| Author (publication year)<br>Name of study                           | Sample size in Africa*<br>(Cases: Controls)             | Stroke subtype  | Risk factor (Definition)   | Population group/ethnicity | Number of Cases  | Number of Controls                   | Odds ratio (95% or 99% Confidence interval)  | Statistical analysis (variables adjusted for)  |
|--|---|---|--|----------------------------|--|--------------------------------------|--|--|
| O'Donnell MJ, et al. (2010)<br>INTERSTROKE (Phase I) <sup>(24)</sup> | Africa:646*<br>(323: 323)                               | Subtypes combined   | HPT (Self-reported or BP > 160/90mmHg)<br>Current smoker (Tobacco use in past 12 months)<br>WHR (Textile 3 compared to textile 1)  | African (Combined)         | Not reported separately for these risk factors in Africa |                                      | 4.96 (3.11-7.91)<br>2.18 (1.07-4.43)<br>1.73 (0.99-3.02)   | Unconditional logistic regression (age, sex, region, HPT, smoking status, WHR)   |
| Saidi S, et al. (2009) <sup>(21)</sup><br>Study Unnamed              | Africa: 551<br>(228:323)                                | Ischaemic   | Apo E-genotype: <sup>‡</sup><br>Apo E3/E3<br>Apo E3/E4<br>Apo E4/E4<br>Apo E4-containing<br>Apo E in combination with ACE Del/Del genotype: <sup>‡</sup><br>Apo E4-containing +ACE Del/Del genotype (Overall)<br>Apo E4-containing +ACE Del/Del genotype (>50y cases compared to <50y) | Tunisian Arabs             | 74<br>87<br>28<br>140                                    | 187<br>71<br>10<br>109               | 0.35 (0.25-0.50)<br>2.19 (1.50-3.17)<br>4.38 (2.05-8.80)<br>3.13 (2.18-4.50)   | Unadjusted odds ratio  |
| Okubadejo NU, et al. (2008) <sup>(20)</sup><br>Study Unnamed         | Africa: 155 (69:86)                                     | Ischaemic   | Hyperhomocysteinemia (Plasma homocysteine level above the 90th percentile for the control group which was > 14.2µmol/L in women and > 14.6µmol/L in men.)  | Nigerians                  | 7  | 11                                   | 0.77(0.27-2.12)  | Unadjusted odds ratio  |
| Chang CL, et al. (2002) <sup>(17)</sup><br>WHO collaborative study   | Africa:722 <sup>§</sup><br>Stroke: (198:524)            | Subtypes combined<br><br>Ischaemic: 16 of 198 (8%)<br><br>Unspecified: 165 of 198 (83%) | Secondary educational level**<br>Low educational level<br>Secondary educational level<br>Low educational level<br>Secondary educational level<br>Low educational level   | African (Combined)         | 38<br>145<br>5<br>7<br>28<br>120                         | 139<br>356<br>11<br>20<br>113<br>299 | 0.55 (0.23-1.31)<br>0.79 (0.32-1.93)<br>0.55 (0.05-5.86)<br>0.53 (0.09-3.00)<br>0.40 (0.14-1.11)<br>0.56 (0.19-1.65) | Conditional logistic regression. (Area of residence, history of high blood pressure, diabetes, high blood pressure in pregnancy, number of live births, use of COC, marital status, smoking, alcohol use, blood fats, family history of premature stroke or AMI) |
| Poulter NR, et al. (1996) <sup>(18)</sup><br>WHO collaborative study | Africa: 56 <sup>§</sup><br>Ischaemic stroke: (16:40)    | Ischaemic stroke  | Current use of combined oral contraceptives (COC) compared to non-users. <sup>#</sup>  | African (Combined)         | 3  | 9                                    | 1.21 (0.24-6.05)   | Conditional logistic regression (History of hypertension, rheumatic heart disease and smoking)   |
| Poulter NR, et al. (1996) <sup>(19)</sup><br>WHO collaborative study | Africa: 62 <sup>§</sup><br>Haemorrhagic stroke: (17:45) | Haemorrhagic  | Current use of COC compared to non-users. <sup>#</sup>   | African (Combined)         | 3  | 7                                    | 1.31 (0.29-5.96)   | Conditional logistic regression (History of hypertension and smoking)  |

\*In the first phase of the INTERSTROKE study 3000 case-control pairs were recruited from 84 centres in 22 countries, including 5 African countries (Mozambique, Nigeria, South Africa, Sudan, and Uganda). <sup>‡</sup>The presence of the Apolipoprotein E (Apo E) and Angiotensin-Converting Enzyme (ACE) insertion-deletion (Ins/Del) genotypes were assessed individually and in combination as risk factors for ischaemic stroke. <sup>§</sup>In the WHO collaborative study a total of 2162 stroke cases and 5984 controls were recruited from 21 centres in 17 countries, including 3 African countries (Kenya, Zambia, Zimbabwe). \*\*Level of educational attainment was stratified into high (beyond secondary schooling), secondary and low (primary or no schooling) with high education used as reference group. <sup>#</sup>Current use of COC: Use of an OC at any time in the 3 months before the stroke for cases or before hospital admission for controls. Non-user was defined as past-users or never-users, or women who used progesterogen-only contraceptives or combined injectable contraceptives.



## CLINICAL HISTORY AND EXAMINATION

INTERSTROKE confirmed that hypertension was a strong risk factor for stroke overall (OR 3.89; 99% CI 3.33 to 4.54) and this association was higher in Africa (OR 4.96; 99%CI 3.11 to 7.91).<sup>(24)</sup> Globally, the association of hypertension was stronger for participants younger than 45 years (OR 8.53; 99%CI: 5.39 to 13.49), which is important considering that Africa had the highest proportion of cases  $\leq 45$  years (77 of 323; 24%).<sup>(24)</sup>

Two earlier reports from the WHO collaborative study investigated current use of combined oral contraceptives (COC) as a risk factor for stroke.<sup>(18,19)</sup> Current use of COC increased the risk of haemorrhagic stroke in all countries, except in Africa and Europe, where no statistically significant association was found (adjusted OR for Africa: 1.31; 95%CI: 0.29 to 5.96).<sup>(19)</sup> Similarly, the adjusted OR for ischaemic stroke was significantly raised for current users of COC in all countries except in Africa where this association was not significant (OR 1.21; 95%CI: 0.24 to 6.05).<sup>(18)</sup>

## BIOLOGICAL MARKERS

Okubadejo et al. investigated the risk associated with hyperhomocysteinemia in 69 cases of ischaemic stroke compared to 86 controls in Nigeria and found no significant difference between the mean homocysteine level in acute stroke cases and controls ( $P = 0.88$ ).<sup>(20)</sup> Furthermore, hyperhomocysteinemia was not found to be risk factor for ischaemic stroke in this population (OR 0.77; 95%CI: 0.27 to 2.12).<sup>(20)</sup>

The only study that investigated genetic risk factors specifically for first episode of stroke was Saidi et al.<sup>(21)</sup> These researchers studied the association of the apolipoprotein E and the angiotensin-converting enzyme (ACE) insertion-deletion (Ins/Del) genotypes individually and in combination as risk factors for ischaemic stroke.<sup>(21)</sup> Their study of 551 Tunisian Arabs found a higher frequency of a combination of the Apo E4-containing and ACE Del/Del genotype in cases than controls (OR 2.67, 95%CI 1.66 to 4.30;  $p$ -value  $< 0.001$ ) and this association was more pronounced

among cases over the age of 50 years (OR 3.04; 95%CI 1.32 to 6.70).<sup>(21)</sup> The Apo E4-containing genotypes were significantly more prevalent among cases than controls ( $p < 0.001$ ) and the homozygous E4/E4 genotype was associated with the highest risk (OR 4.38; 95%CI 2.05 to 8.80).<sup>(21)</sup>

## RISK OF BIAS IN INCLUDED STUDIES

In general, the quality of the five case-control studies included in this review is good. (Appendix 3). All the studies addressed a research question that was clearly defined in terms of the population, the risk factors and the outcome under investigation. Cases were defined precisely in all studies. INTERHEART and INTERSTROKE did not clearly indicate their target geographic populations in Africa. The controls were selected in an acceptable way in all studies, except in the studies of Okubadejo et al.<sup>(20)</sup> and Saidi et al.<sup>(21)</sup> where it was unclear whether the controls were selected from the same study base as the cases. The exposures were clearly defined and measured in an objective manner and in a similar way among cases and controls in all studies. All the studies reported baseline characteristics for cases compared to controls. Most authors applied restrictions in the design through matching for age, gender and region, and adjusted for potential confounders in their analyses. However, Saidi et al. did not adjust their analyses for potential confounding resulting from significant differences in blood pressure and biological markers of cases compared to controls.<sup>(21)</sup> Okubadejo et al. used matching in their study design but it was not clear if they had adjusted for significant differences in hypertension and diabetes between cases and controls.<sup>(20)</sup>

## DISCUSSION

We have conducted a thorough and systematic search for case-control and cohort studies investigating risk factors for first episode of AMI and stroke in Africa. Our results indicate that there is no data available from cohort studies in the African population. To date INTERHEART is the only study to investigate risk factors associated with first episode of AMI in Africa. Despite being the largest study of its kind<sup>(8)</sup> to have included sub-Saharan African

countries, participants from Africa still represented only 5% of the total study population. More than 80% of the African sample was drawn from South Africa, and thus low-income countries in Africa are poorly represented in this study.<sup>(23)</sup> Similarly, in INTERSTROKE and the WHO Collaborative Study less than 11% of the total sample was from Africa. Data from these global studies do not adequately reflect the diversity found in Africa. Furthermore, the small numbers of participants from Africa preclude firm conclusions regarding disease-exposure associations as studies carry the risk of spurious findings due to chance.

Current evidence suggests that the direction of association for established risk factors for AMI<sup>(8,11-15)</sup> and stroke<sup>(24)</sup> are similar across countries but that the strength of association of particular risk factors varies between countries and within African ethnic groups. Hypertension and diabetes were found to be stronger risk factors for AMI in Africa than in the global INTERHEART population, with the risk being almost two-fold higher for the black African group.<sup>(8)</sup> Similarly, abdominal obesity and an elevated ApoB /ApoA-I ratio show a stronger association in Africa and are the most pronounced among the coloured and European African groups.<sup>(8,12,14)</sup> Hypertension was the predominant risk factor for all stroke subtypes and the association was the strongest in Africa.<sup>(24)</sup>

Higher socio-economic status defined by increasing levels of education and higher income was associated with higher risk of AMI in the black African group, in contrast to the other African groups.<sup>(8)</sup> Women with the highest level of education were at the highest risk of all types of stroke in Africa in contrast to the other countries.<sup>(17)</sup>

This variation in the direction of association may represent differences in stages of epidemiologic transition, differences in lifestyle and perhaps underlying genetic differences within African populations and between continents. Only one study assessing a genetic risk factor met our inclusion criteria<sup>(21)</sup> indicating that there is a lack of research investigating possible genetic risk factors for first episode of AMI and stroke. There have been no major epidemiological studies investigating the potential influence of infectious

diseases on the risk of first episodes of AMI and stroke, which is concerning given the high burden of infectious diseases in Africa.

## STRENGTHS AND LIMITATIONS OF OUR REVIEW

We are not aware of previous systematic reviews addressing our research question and believe that our review gives the most comprehensive result on the topic to date. We used systematic methods to reduce bias in the identification of studies, extraction of relevant data, appraisal of study quality and synthesis of information. However, there are limitations to our work; although a comprehensive search strategy without language restrictions was used in our review only two databases were searched. Seven articles were excluded because the full text was only available in a language other than English and eligibility could not be determined from the abstract. A future update of this review should include translations of reports published in languages other than English. We could not conduct meta-analysis as planned since there was only one study assessing risk factors for AMI and the studies investigating stroke all assessed different risk factors.

## FUTURE RESEARCH

The importance of various risk factors can be determined either through prospective cohort studies in which exposures are measured in a large group of participants who are then followed up over time until an adequate number develop the outcome of interest or through case-control studies in which the distribution of exposures between cases and controls are compared retrospectively. The need for large prospective studies has been recognised internationally.<sup>(27,28)</sup> The Prospective Urban Rural Epidemiology (PURE) study was initiated in 2002 and plans to recruit 157 000 participants from 17 countries worldwide, in order to investigate societal, lifestyle and cardiovascular risk factors for chronic non-communicable diseases (CNCDs).<sup>(28)</sup> Target recruitment goals from Africa (including South Africa and Zimbabwe) are 3 000 participants, i.e. two percent of the total sample.<sup>(28)</sup> The Global Epidemiology Initiative established at the Harvard School of Public Health aims to address the need for cohort studies in

Africa by establishing a Partnership for Cohort research and Training (PaCT), an ambitious project which will investigate CNCDs among 500 000 people from four African countries over the next decade.

Cohort studies have certain strengths compared to case-control studies:

- Temporal and causal relationships between exposures and outcomes can be investigated.
- Multiple outcomes of a particular exposure can be assessed which is important for chronic diseases that share common risk factors.
- The incidence of disease and changes in risk factors over time can be monitored.
- A cohort can provide a study population for embedded randomised controlled trials of interventions.
- The potential for recall bias and selection bias are limitations of case-control studies and these can be reduced in a prospective cohort study. This is particularly important when measuring subjective factors, such as lifestyle (including diet and physical activity) and psychosocial factors (including stress and depressive mood). Since these risk factors are also dynamic, they will be better assessed during prospective follow-up. The main drawbacks of cohort studies are that they cost more and take longer to complete. Successful follow-up of participants also presents a substantial challenge. In developing countries, innovative measures such as the use of cell phones are being considered to ensure high levels of participant retention in long-term cohort studies.<sup>(29)</sup>

### CONCLUSIONS AND RECOMMENDATIONS

Our review highlights the complete lack of data from cohort studies investigating risk factors for first episode of AMI or stroke in Africa. A few high quality case-control studies exist but these do not adequately represent the cultural and genetic diversity in Africa or the influence of infections on cardiovascular outcomes. Dynamic risk factors that rely on self-report such as diet, physical activity and

stress will be better assessed through longitudinal cohort studies. Large cohort studies investigating established and new risk factors for cardiovascular diseases among African populations are urgently needed in order to prepare for the rising burden imposed by these diseases.

### ACKNOWLEDGEMENTS

We thank Elizabeth Pienaar, Senior Scientist, South African Medical Research Council for her assistance in developing the search strategy for this review.

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