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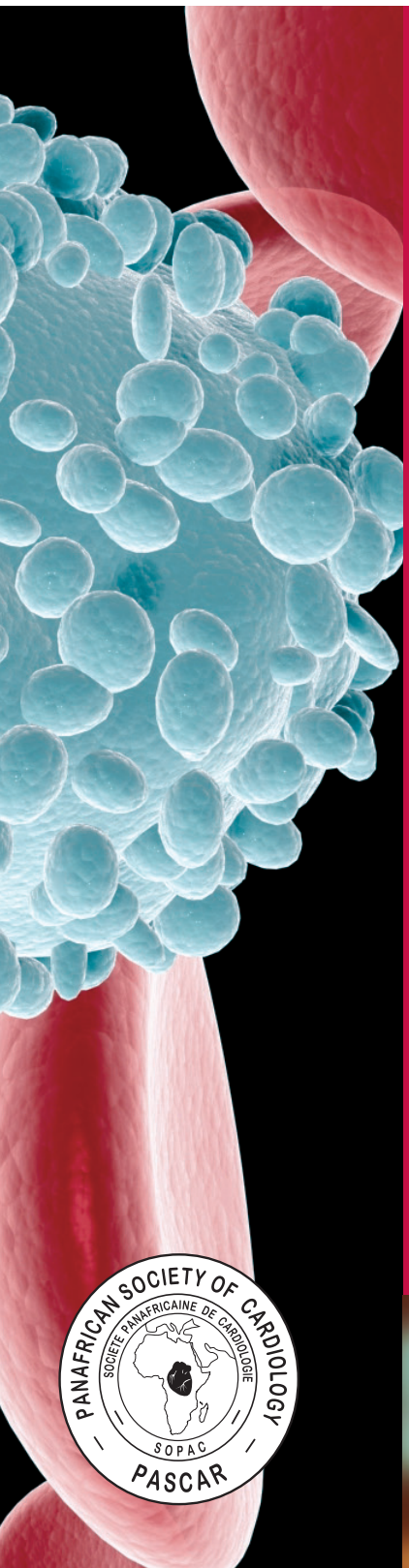

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CONTENTS | Vol 26, No 2, H3Africa Supplement, MARCH/APRIL 2015

EDITORIAL

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Editorial

H3Africa comes of age

George A Mensah, Emmanuel K Peprah, Uchechukwu KA Sampson, Richard S Cooper

With the advent of technology that made possible large-scale sequencing and genotyping studies, it quickly became apparent that the demographic history of our species had been recorded in the genome and we could reconstruct our wanderings across the globe by studying DNA. While the vast majority of genetic variation is shared among continental populations, the most prominent finding from these early surveys of regional populations was the substantially greater degree of heterozygosity found in contemporary African populations.[1] The 'out of Africa' story has long been a central dogma in paleoanthropology, and the rich cultural and linguistic heritage of the continent has also been well documented; yet the implications of this phase of human history for biomedicine had never been fully appreciated.

Major research endeavours, including the HapMap Project,[2] the 1,000 Genomes,[3] and more recently the African Genome Diversity Project,[4] have exhaustively demonstrated that African populations exhibit greater sequence variation, shorter population-shared haplotype lengths, and less linkage disequilibrium than other continental groups, all a result of the long history of human occupation of sub-Saharan Africa (SSA).[2-4] At the same time, the biomedical research community was confronted with the glaring reality that genetic research on both normal phenotypic traits as well as conditions of medical interest had been grossly neglected in Africa. As a result, in 2010, the US National Institutes of Health and the UK Wellcome Trust joined forces to launch an unprecedented research programme, now known as Human Heredity and Health in Africa, or H3Africa.[5]

H3Africa has established an ambitious agenda that includes not only large-scale, disease-specific research projects but training and capacity development as well. In this special issue of *Cardiovascular Journal of Africa,* some of the initial efforts of the disease-oriented programme of H3Africa are described.

The articles document the enormous effort contributed by staff at the NIH and the Wellcome Trust and teams of scientists in Africa and their collaborators in Europe and North America to bring state-of-the art genomic science to Africa. These reports primarily reflect presentations that were made at the 30 May 2014 workshop of the H3Africa cardiovascular disease (CVD) working group held in conjunction with the fourth H3Africa consortium meeting in Cape Town, South Africa.[6]

The primary workshop objectives were to review the burden of CVD in sub-Saharan Africa, advance our understanding of the genetic underpinnings of the major CVDs in Africa, and strengthen collaborations among the H3Africa research teams and other researchers using novel genomic and epidemiological tools in the assessment of CVD in Africa.[6] As is readily apparent, CVD research consortia sponsored by H3Africa are well on their way to becoming mature international collaborations that are capable of coordinating recruitment of participants, phenotype characterisation and analysis of genetic variation and other key physiological traits.

Defining the historical and biomedical contest for H3Africa

H3Africa has taken on a series of daunting challenges. As confirmed above, however, the record of accomplishment on display in the collection of reports in this issue demonstrate that progress is being made – both to create a coherent intellectual framework for the research that has been initiated and to build a structure that can carry out the complex logistical and laboratory tasks that the work scope demands. However H3Africa has set an even higher standard against which it will ultimately be judged. While dedicated to capacity building and the application of the powerful new tools of genomics on the continent, as described in the White Paper,[7] written at the launch of H3Africa, there is also a clear recognition that in a region of the world with limited resources for biomedical research and healthcare delivery, all scientific ventures in SSA must take account of this context of under-development. This perspective was clearly articulated in the final paragraph of the H3Africa White Paper[7]

> *Genomics is under increasing pressure to demonstrate the value of the enormous investment… that have been made (and must) accept a direct comparison to epidemiology and public health as weapons to improve human health… Nowhere will this competition be more difficult than in Africa.*[7]

For research in CVD, the bar in terms of the competition for relative efficacy is raised even higher than for many other diseases. In the last half-century, epidemiology has provided a near-complete description of the environmental factors that cause common CVD, and both preventative and therapeutic measures with great efficacy have been identified.

Wide implementation of these prevention and treatment strategies in most industrialised countries has led to dramatic declines in both coronary heart disease and stroke mortality of 60–80% in the last 50 years.[8,9] At least half of the decline in CVD

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mortality has been accomplished by reducing population levels of risk factors.[8,9] A similarly dramatic decline in CVD mortality resulting from population-level reductions of risk factors cannot be demonstrated for sub-Saharan Africa for a variety of reasons.

First, reliable survey data on CVD risk factors and incidence and mortality are virtually non-existent in sub-Saharan Africa (SSA), with the exception of the Republic of South Africa, Mauritius and the Seychelles.[10] A recent meta-analysis of sample surveys however documented the substantial burden of hypertension, and the all-too-obvious low rates of treatment and control.[11] Likewise, as documented in three articles in this issue, stroke imposes an enormous burden on the population of SSA. Therefore, while the attempt is being made to drive biomedical research forward into wholly unchartered territory through the use of genomic technology, we must not lose sight of the historical context of the evolution of CVD and the requirement in the short run to use what we already know will spare patients premature mortality, morbidity and misery.

For reasons too obvious to require elaboration, the infrastructure of public health surveillance for CVD risk factors and primary care systems that can provide long-term treatment are missing in most of SSA. Establishing these essential components of a healthcare system must therefore rank as the most urgent priority.

How then can we situate the research agenda for genomics and the H3 programme within the real-world context of SSA? As noted above, this question weighed heavily on the minds of the scientists and staff who designed H3Africa, and the White Paper and other related documents provide insightful responses to this question. Science is a broad social movement and consistent improvement in the health and economic opportunity of any country requires a vibrant scientific community.

H3Africa has clearly injected tremendous enthusiasm into the biomedical community in Africa and has led to rapid intellectual and technical advances in many areas of biomedicine. As editorialists, we respond to the question 'what role for genomics?' not with skepticism but rather a plea for an appreciation of the full breadth of scientific achievement now available to those who work to reduce the burden of CVD, and a reminder that we must never forget that curiosity and skepticism are co-equal ingredients of the research process.

Progress into the translational sphere is already being made and genomics has led to multiple breakthroughs in CVD research in recent years. The discovery of genetic variants of the gene coding for PCSK9 has led directly to a major new treatment modality for hyperlipidaemia.[12] Notably, the mutation underlying this discovery was found in an Afro-origin population, where it occurs at a frequency of 1–2%, and underscores the importance of genetic research in the highly diverse societies of SSA.

Identification of a variant in APOL1 has greatly improved our understanding of the excess rates of renal failure in Afro-origin populations,[13-15] again based on a mutation occurring primarily in Africans. Genomic research is also generating mounting evidence that levels of high-density lipoprotein (HDL) cholesterol are not causally related to risk of CVD.[16] If fully verified, a demonstration of a non-causal role for HDL cholesterol would have a major impact on the approach of physicians to the treatment of serum lipid levels and re-direct an enormous research effort away from drugs intended to raise levels of this lipoprotein.

We are on the threshold of the discoveries of the molecular mechanisms underlying CVD that can improve the life of patients everywhere, and, although only on the threshold, we can confidently say that the door has been unlocked. For instance, what if in this process we were able to realise a stroke-free generation of individuals living with sickle cell disease?[17] What if we were able to identify genetic or bio-molecular targets that help transform the outcomes of CVD? Compelling research questions such as these must be part of the strategic visioning in biomedical research over the next decade.[17]

Many opportunities for important discoveries of the mechanism of disease in CVD will surely be found in Africa. In the interim, however, we must endeavour to also implement evidence-based interventions that are feasible, affordable and appropriate to implement within the constraints of the SSA setting for the prevention and control of cardiovascular diseases in Africa. A priority among these interventions is those that address hypertension, diabetes, unhealthy diet, physical inactivity and tobacco use. Additionally, investments to improve the systematic collection, analysis and reporting of survey data on CVD incidence, prevalence, magnitude and trends in risk exposure, disease burden and mortality will be necessary.

The current myriad of clinical and public health challenges cannot await the promises of the genomic revolution. Active dissemination and implementation of effective interventions for prevention, treatment and control of CVD and other non-communicable diseases must be prioritised. Herein, the words of Dr Martin Luther King ring loud and true because indeed '… we are confronted with the fierce urgency of now... there is such a thing as being too late… this is a time for vigorous and positive action.'

The views expressed in this article are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute, National Institutes of Health, or the US Department of Health and Human Services.

References

1. Gabriel SB, Schaffner SF, Nguyen H, *et al*. The structure of haplotype blocks in the human genome. *Science* 2002; **296**(5576): 2225–2229.
2. McVean G, Spencer CC, Chaix R. Perspectives on human genetic variation from the HapMap Project. *PLoS Genet* 2005; **1**(4): e54.
3. Abecasis GR, Auton A, Brooks LD, *et al.* An integrated map of genetic variation from 1,092 human genomes. *Nature* 2012; **491**(7422): 56–65.
4. Gurdasani D, Carstensen T, Tekola-Ayele F, *et al.* The African Genome Variation Project shapes medical genetics in Africa. *Nature* 2015; **517**(7534): 327–332.
5. National Institutes of Health. NIH and Wellcome Trust announce partnership to support population-based genome studies in Africa. *NIH News* 2010 June 22; Available at: URL: http://www.nih.gov/news/health/jun2010/nhgri-22.htm.
6. Owolabi MO, Mensah GA, Kimmel PL, *et al.* Understanding the rise in cardiovascular diseases in Africa: harmonising H3Africa genomic epidemiological teams and tools. *Cardiovasc J Afr* 2014; **25**(3): 134–136.
7. H3Africa Working Group. Harnessing genomic technologies toward improving health in Africa: Opportunities and challenges. Recommendations for the Human Heredity and Health in Africa (H3Africa) Initiative to the Wellcome Trust and the National Institutes of Health. National Human Genome Research Institute/National

Institutes of Health 2011 January 31; Available at: URL: http://h3africa.org/images/PDF/h3africa_whitepaper.pdf.
8. Ford ES, Ajani UA, Croft JB, *et al*. Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. *N Engl J Med* 2007; **356**(23): 2388–2398.
9. Capewell S, O'Flaherty M. What explains declining coronary mortality? Lessons and warnings. *Heart* 2008; **94**(9): 1105–1108.
10. Cooper RS, Bovet P. Measures of health and disease in Africa: are current methods giving us useful information about trends in cardiovascular diseases? *Prog Cardiovasc Dis* 2013; **56**(3): 270–277.
11. Ataklte F, Erqou S, Kaptoge S, Taye B, Echouffo-Tcheugui JB, Kengne AP. Burden of undiagnosed hypertension in sub-saharan Africa: a systematic review and meta-analysis. *Hypertension* 2015; **65**(2): 291–298.
12. Kotowski IK, Pertsemlidis A, Luke A, *et al*. A spectrum of PCSK9 alleles contributes to plasma levels of low-density lipoprotein cholesterol. *Am J Hum Genet* 2006; **78**(3): 410–422.
13. Genovese G, Friedman DJ, Ross MD, *et al*. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science* 2010; **329**(5993): 841–845.
14. Genovese G, Friedman DJ, Pollak MR. APOL1 variants and kidney disease in people of recent African ancestry. *Nat Rev Nephrol* 2013; **9**(4): 240–244.
15. Parsa A, Kao WH, Xie D, *et al*. APOL1 risk variants, race, and progression of chronic kidney disease. *N Engl J Med* 2013; **369**(23): 2183–2196.
16. Voight BF, Peloso GM, Orho-Melander M, *et al.* Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet* 2012; **380**(9841): 572–580.
17. Mensah GA, Kiley J, Mockrin SC, *et al*. National Heart, Lung, and Blood Institute Strategic Visioning: Setting an Agenda Together for the NHLBI of 2025. *Am J Public Health* 2015; e1–e4.

Cardiovascular Topics

Mortality from cardiovascular diseases in sub-Saharan Africa, 1990–2013: a systematic analysis of data from the Global Burden of Disease Study 2013

George A Mensah, Gregory A Roth, Uchechukwu KA Sampson, Andrew E Moran, Valery L Feigin, Mohammed H Forouzanfar, Mohsen Naghavi, Christopher JL Murray, for the GBD 2013 Mortality and Causes of Death collaborators

Abstract

Background: Cardiovascular disease (CVD) has been the leading cause of death in developed countries for most of the last century. Most CVD deaths, however, occur in low- and middle-income, developing countries (LMICs) and there is great concern that CVD mortality and burden are rapidly increasing in LMICs as a result of population growth, ageing and health transitions. In sub-Saharan Africa (SSA), where all countries are part of the LMICs, the pattern, magnitude and trends in CVD deaths remain incompletely understood, which limits formulation of data-driven regional and national health policies.

Objective: The aim was to estimate the number of deaths, death rates, and their trends for CVD causes of death in SSA, by age and gender for 1990 and 2013.

Methods: Age- and gender-specific mortality rates for CVD were estimated using the Global Burden of Disease (GBD) 2010 methods with some refinements made by the GBD 2013 study to improve accuracy. Cause of death was estimated as in the GBD 2010 study and updated with a verbal autopsy literature review and cause of death ensemble modelling (CODEm) estimation for causes with sufficient information. For all quantities reported, 95% uncertainty intervals (UIs) were also computed.

Results: In 2013, CVD caused nearly one million deaths in SSA, constituting 38.3% of non-communicable disease deaths and 11.3% of deaths from all causes in that region. SSA contributed 5.5% of global CVD deaths. There were more deaths in women (512 269) than in men (445 445) and more deaths from stroke (409 840) than ischaemic heart disease (258 939). Compared to 1990, the number of CVD deaths in SSA increased 81% in 2013. Deaths for all component CVDs also increased, ranging from a 7% increase in incidence of rheumatic heart disease to a 196% increase in atrial fibrillation. The age-standardised mortality rate (per 100 000) in 1990 was 327.6 (CI: 306.2–351.7) and 330.2 (CI: 312.9–360.0) in 2013, representing only a 1% increase in more than two decades.

Conclusions: In SSA, CVDs are neither epidemic nor among the leading causes of death. However, a significant increase in the number of deaths from CVDs has occurred since 1990, largely as a result of population growth, ageing and epidemiological transition. Contrary to what has been observed in other world regions, the age-adjusted mortality rate for CVD has not declined. Another important difference in CVD deaths in SSA is the predominance of stroke as the leading cause of death. Attention to aggressive efforts in cardiovascular health promotion and CVD prevention, treatment and control in both men and women are warranted. Additionally, investments to improve directly enumerated epidemiological data for refining the quantitation of risk exposures, death certification and burden of disease assessment will be crucial.

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Cardiovascular disease (CVD), principally ischaemic heart disease and stroke, constitute the leading cause of global mortality, and accounted for 17.3 million deaths worldwide in 2013.[1] In high-income, developed countries, CVDs have been the

leading cause of death throughout most of the last century. In the United States, for example, heart disease has been the leading cause of death every year since 1918.[2] Currently, however, most CVD deaths occur in low- and middle-income countries (LMIC) and there is growing concern that an epidemic of CVDs is emerging in these countries that must be prevented.[3,4] The World Health Organisation (WHO) and the United Nations have also called attention to a rising burden of CVD and other non-communicable diseases and the need for aggressive measures to forestall this epidemic in these countries[5,6]

In sub-Saharan Africa (SSA), where all countries are part of the developing world, the magnitude of and trends in CVD deaths remain incompletely understood. The African regional office of the WHO has stated that CVDs are 'increasing rapidly in Africa, and it is now a public health problem throughout the African region'.[7] However, a systematic analysis of estimates for CVD mortality in the Global Burden of Disease (GBD) 2010 study showed no significant rise in age-standardised mortality rates for CVD in SSA for the period of 1990–2010.[8,9] Similarly, recent data from the INDEPTH Health and Demographic Surveillance System show little evidence of NCD mortality rates increasing over time.[10,11] However, data on CVDs are limited in the region,[12-14] and novel methods are required in order to make meaningful estimates.

Clarifying the epidemiology of CVD in SSA is essential for the formulation of regional and national health policies. Accordingly, we explored as a primary objective, estimates of the number of deaths, age-standardised and age- and gender-specific mortality rates, and their trends in SSA, by age and gender, for the period 1990–2013 for total CVD, rheumatic heart disease (RHD), ischaemic heart disease (IHD), cerebrovascular disease (including ischaemic and haemorrhagic stroke), hypertensive heart disease, cardiomyopathy and myocarditis, atrial fibrillation and flutter, aortic aneurysm, peripheral arterial disease (PAD) and endocarditis. These data for SSA were also compared to data for developing and developed countries.

Methods

Age and gender year-specific mortality rates for CVD were estimated using the methods as published in the GBD 2013 study.[1] In brief, the GBD 2013 study collected all available data on mortality, including vital registration and verbal autopsy. Raw data were corrected to account for outliers and non-specific causes of death (i.e. 'garbage' codes).

Modelling was performed using a custom ensemble-model approach (CODem) to estimate deaths for each country, including countries without data.[15] CODem employs Gaussian process regression and spatio-temporal modelling, as well as cardiovascular-specific covariates, such as systolic blood pressure, to produce consistent estimates.[1] Estimates were adjusted to fit an envelope of all-cause mortality and all-cardiovascular mortality to ensure that no strata contained more deaths that occurred for any of its parent categories.

For SSA, mortality data for the years 1980–2011 were used from Madagascar, Ethiopia, Mauritius, Seychelles, South Africa, Zambia, Mozambique, Kenya, Tanzania, Burkino Faso, Zimbabwe, Mali and Ghana. For all quantities reported, 95% uncertainty intervals (UIs) were also computed using 1 000 draws from the posterior distribution of each age–gender–country–year-specific set of estimates. Death numbers from each country and each cause were summed to produce estimates for the entire region of SSA.

Results

As shown in Table 1, CVDs caused nearly one million deaths in SSA in 2013. The number of deaths in women (512 269) exceeded those in men (445 445) for total CVDs and also for all cardiovascular causes of death except ischaemic heart disease, aortic aneurysms and peripheral vascular disease. There were more deaths from stroke (409 840) than ischaemic heart disease (258 939). Compared to 1990, CVD deaths increased 81% in 2013. Similarly, deaths for all component CVDs also increased, ranging from a 7% increase in rheumatic heart disease to a 196% increase in atrial fibrillation. The age-standardised mortality rate (per 100 000) for total CVD in 1990 was 327.6 (CI: 306.2–351.7) and 330.2 (CI: 312.9–360.0) in 2013, representing a 1% increase.

As previously demonstrated, SSA experiences the world's lowest IHD death rates, and IHD ranks below stroke as a leading cause of CVD death in the region.[12] On average, SSA experienced no significant change in age-standardised IHD mortality rate

Table 1. Total number of deaths and age-standardised mortality rates for component cardiovascular causes of death in 1990 and 2013 and the respective percentage changes

Cause	*Number of deaths, 1990*	*95% UI*	*Number of deaths, 2013*	*95% UI*	*% Change*	*Age-standardized death rate (per 100 000), 1990*	*95% UI*	*Age-standardized death rate (per 100 000), 1990*	*95%UI*	*% Change*
Ischaemic heart disease	138 308	(116 618–153 645)	258 939	(232 158–305 680)	87	91.4	(76.9–101.7)	92.9	(82.8–110.2)	2
Ischaemic stroke	101 040	(77 903–117 660)	206 439	(139 860–242 225)	104	75.0	(57.2–87.5)	81.5	(55.0–95.7)	9
Hemorrhagic stroke	125 603	(103 055–147 517)	203 401	(173 620–262 418)	62	72.2	(57.1–87.6)	64.7	(54.0–87.5)	–10
Hypertensive heart disease	37 525	(29 485–49 443)	86 035	(62 970–111 978)	129	26.8	(21.0–36.5)	32.8	(24.2–44.0)	22
Cardiomyopathy	28 917	(23 557–36 082)	53 742	(44 926–65 634)	86	12.7	(10.6–17.0)	14.5	(11.9–18.2)	14
Rheumatic heart disease	23 625	(17 644–31 608)	25 239	(20 478–40 444)	7	10.3	(7.5–13.7)	6.5	(5.3–10.1)	–37
Atrial fibrillation	414	(331–509)	1 227	(959–1 558)	196	0.4	(0.3–0.5)	0.6	(0.5–0.8)	50
Aortic aneurysm	5 150	(3 370–6 714)	9 854	(7 809–12 840)	91	3.3	(2.2–4.3)	3.4	(2.7–4.5)	3
Peripheral vascular disease	469	(371–580)	1 338	(1 122–1 618)	185	0.4	(0.3–0.5)	0.6	(0.5–0.7)	50
Endocarditis	9 622	(6 339–15 825)	13 868	(10 967–18 524)	44	4.7	(3.0–8.6)	3.7	(2.9–5.3)	–21
Other cardiovascular diseases	59 206	(48 291–74 859)	98 632	(77 904–138 971)	67	30.3	(24.8–41.1)	29.1	(22.7–42.8)	–4
Total cardiovascular diseases	529 880	(492 351–568 410)	958 713	(909 427–1 049 606)	81	327.6	(306.2–351.7)	330.2	(312.9–360.0)	1

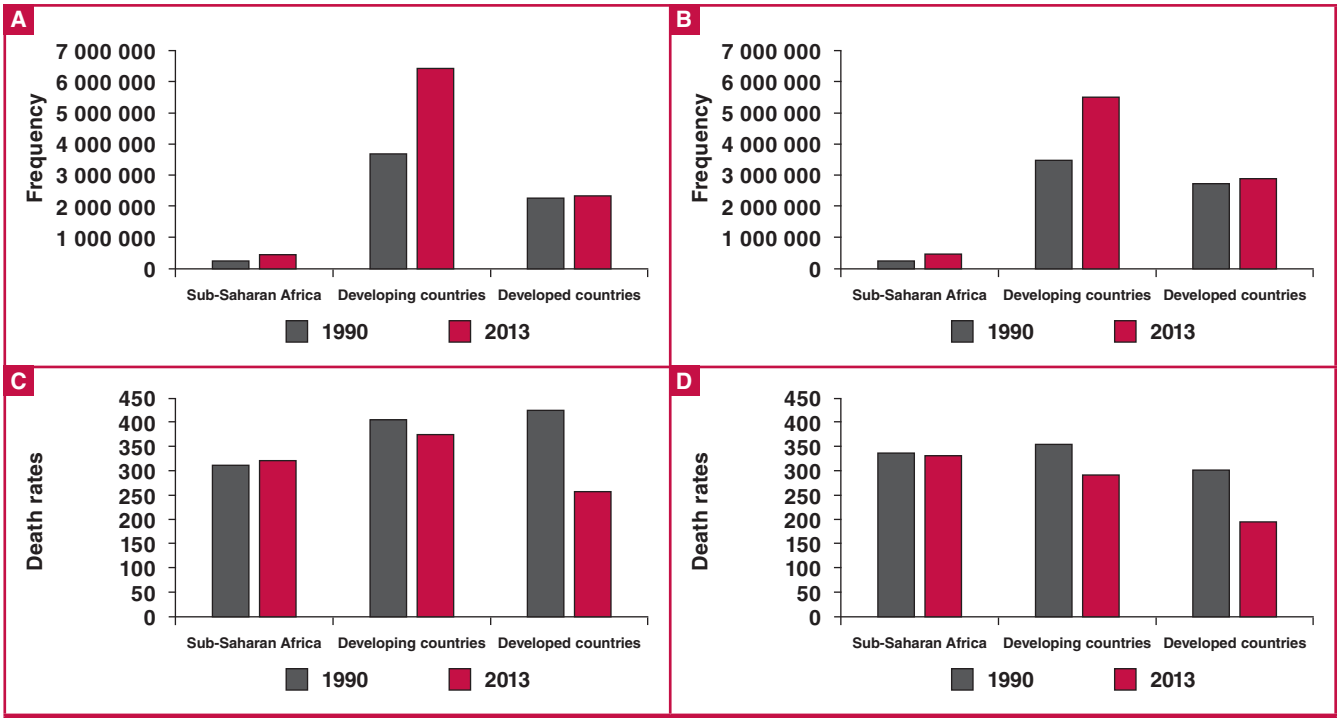

Fig. 1. Number of CVD deaths in men (A) and women (B) in 1990 and 2013 in sub-Saharan Africa, developing countries, and in developed countries. Age-standardised CVD death rates per 100 000 population are shown for men (C) and women (D) in 1990 and 2013 in sub-Saharan Africa, developing countries, and in developed countries.

between 1990 and 2013, however, likely due to aging and growth of the SSA population, the number of IHD deaths increased by 87% over the same interval (Table 1).

As shown in Fig. 1 for both men and women, the number of CVD deaths in SSA was substantially lower than that seen for either the developed or developing countries. Contrary to the pattern seen for developed and developing countries (as a whole), the age-standardised mortality rate for CVD in both men and women in SSA did not decline during the period from 1990 to 2013 (Fig. 1). In fact, the age-standardised mortality rate for women in SSA, which was lower than the corresponding rate in women in developing countries in 1990, is now higher than the rate seen for women in developing countries, and substantially higher than the corresponding rates for both men and women in the developed world (Fig. 1).

The number of deaths from stroke in SSA nearly doubled from 1990 to 2013, but overall age-adjusted stroke mortality rates decreased by 1% (increased by 9% for ischaemic stroke and decreased by 10% for haemorrhagic stroke). The increase in number of stroke deaths in SSA was particularly noticeable for ischaemic stroke (104% increases in 2013 compared to 1990), although age-adjusted stroke mortality rates in SSA regions were one of the lowest in LMIC and only slightly higher than that in developed countries, compared with GBD 2010 stroke mortality estimates. Although the majority of deaths from stroke in SSA in 1990 were due to haemorrhagic strokes (55%), in 2013 the proportional frequency of deaths from haemorrhagic stroke was slightly lower (49.6%) than that from ischaemic stroke. Compared to GBD 2010 stroke mortality estimates, the mean age at death from stroke in SSA was the lowest among all LMIC.

In 1990 the total number of deaths from PAD was 469 (CI: 371–580) compared with 1 338 (CI: 1 122–1 618) in 2013, representing a 185% increase. There were 277 (CI: 204–366) deaths due to PAD among men, which was higher than the 192 (CI: 145–271) deaths observed among women. Similarly, in 2013, the number of PAD deaths among men was 728 (CI: 578–902), which was also higher than the 610 (CI: 480–817) deaths observed among women. The combined age-standardised death rates per 100 000 were 0.4 (CI: 0.3–0.5) and 0.6 (CI: 0.5–0.7) in 1990 and 2013, respectively, representing a 50% increase during the 23-year period. The age-standardised death rates for men were 0.5 (CI: 0.3–0.6) in 1990 and 0.6 (CI: 0.5–0.8) in 2013, which represents a 20% increase. However, women had a 66% increase in age-standardised death rates, as evidenced by the change from 0.3 (CI: 0.2–0.5) in 1990 to 0.5 (CI: 0.4–0.7) in 2013.

The total number of deaths from atrial fibrillation was 414 (331–509) in 1990, compared with 1 227 (CI: 959–1 558) in 2013, representing an increase of 196%. However, the age-standardised death rates (per 100 000) increased by 50% during the study period from 0.4 (CI: 0.3–0.5) in 1990 to 0.6 (CI: 0.5–0.8) in 2013. In 1990 there were 148 (CI: 106–193) deaths due to atrial fibrillation among men, which was less than the 266 (CI: 201–347) deaths observed among women. In 2013 there was a similar pattern of fewer AFIB deaths in men compared with women: 378 (CI: 295–490) vs 848 (CI: 605–1 170). The age-standardised death rates for men were 0.3 (CI: 0.2–0.4) in 1990 and 0.4 (CI: 03–0.5) in 2013. The corresponding rates for women were 0.5 (CI: 0.3–0.7) and 0.7 (CI: 0.5–1.0), respectively.

The mortality rate from PAD in SSA has increased over the last 23 years. Furthermore, the relative increase in PAD mortality rate among women has been more dramatic than among men. Similar findings are noted for AFIB, wherein we actually observed a higher number of deaths and age-standardised death rates among women compared with men.

Discussion

The most prominent finding in this study was that the age-standardised mortality rate for CVD has not declined in SSA, in sharp contrast to the dramatic declines that have been documented in other world regions, especially in the high-income, developed world. It is of concern that the age-standardised mortality rate for CVD in SSA women, which was lower than the corresponding rate in women in developing countries in 1990, is now higher than in developing countries, and substantially higher than corresponding rates in the developed world. In fact, a previous analysis of the GBD 2013 data on demographic and epidemiological drivers of global CVD mortality suggested that age-specific death rates for western sub-Saharan Africa may have increased.[16] These findings have significant implications for effective prevention and treatment of CVD in SSA.

A second important observation from this study was that although most CVD deaths occur in developing countries, the overall number of CVD deaths in SSA is substantially lower than seen in the rest of the developed and developing world, and amounts to 5.5% of global CVD deaths. In addition, these CVD deaths in SSA constitute 38.3% of non-communicable disease deaths and 11.3% of deaths from all causes in that region.[1] Therefore the assertion that CVD deaths represent an emerging epidemic may be unwarranted. Importantly, however, the approximately one million deaths in 2013 in SSA represent a near doubling of the deaths a decade earlier. Roth *et al*.[16] have showed that population growth and ageing accounted for the increase in the number of global deaths due to CVD between 1990 and 2013, despite an overall decrease in age-specific death rates for most regions.[16]

A careful analysis of the data from SSA to determine the role that population growth, ageing and health transitions play in these deaths is needed. Uniformly however, component CVD deaths increased by a range from 7% for RHD to nearly a three-fold increase in atrial fibrillation and peripheral arterial disease. The good news from the data is the relative decline in the age-standardised mortality rates for RHD, haemorrhagic stroke and endocarditis.

This study has several limitations. Some cardiovascular causes of death are less commonly reported as an underlying cause of death. These diseases include rheumatic heart disease, atrial fibrillation, peripheral vascular disease, endocarditis and aortic aneurysms. Changes over time in the detection and reporting of these conditions most likely reflect not just epidemiological changes but changes in diagnostics and the ways that these diagnoses are attributed to deaths by physicians. Rheumatic heart disease-related mortality may be particularly difficult to attribute as a cause of death, which increases uncertainty for estimates of this condition.

Importantly, data sources on disease burden in SSA are among the most limited in the world, despite several comprehensive networks for data collection related to maternal and child mortality. Unfortunately a functioning vital records system can only be built in a society with a functioning primary health system that provides broad access – a concept that remains a serious challenge for most of SSA within the foreseeable future. Verbal autopsy and sample vital registration will likely expand as countries expand their investment in health system infrastructure.

Efforts should focus on improving comparability across countries and regions within SSA. Increased attention to non-communicable diseases will help highlight the important role of routine surveillance, rather than one-off research studies, as an important source of descriptive statistics related to CVD in SSA.

Conclusions

SSA has seen no significant decline in age-standardised CVD mortality rates, whereas these rates continue to fall dramatically in most of the high- and middle-income world. Without further investment in the prevention and treatment of CVD and other NCDs and their risk factors in SSA, the continent risks being left behind at a time when improved detection, prevention, treatment and control of these diseases and risk factors are leading to longevity and improved quality of life in other world regions. These decisions should be informed ideally by reliably accurate, directly enumerated data, rather than estimates such as those presented in this study.

The relative lack of directly enumerated epidemiological data, coupled with the absence of vital registration systems in 42 of the 46 SSA countries, presents major challenges in mortality and burden of disease data for this region. The estimates of mortality presented here must therefore be interpreted with caution. Nevertheless, we found no evidence to support a rapidly rising epidemic or an impending pandemic of CVD in SSA. However, the consistency of the directional changes in CVD deaths, disability and risk-factor trends observed in GBD 2010, and the mortality trends seen in GBD 2013, together with the young average age at time of death from CVDs in SSA, compel attention to aggressive efforts at CVD risk-factor prevention, treatment and control in both women and men. Coordinated partnerships between ministries of health, other government agencies, non-governmental organisations, and the private sector will be essential in order to mount a targeted response to the observed challenges.

Interventions at the individual and population levels as well as improved systems of healthcare will be required. In addition, investments to improve local-level directly enumerated epidemiological data and refinement of the quantitation of risk exposure, death certification and burden of disease assessment will be crucial. Further research is needed to identify ideal dissemination and implementation strategies for CVD risk reduction in the SSA setting.

Until then, finding ways to implement interventions that are feasible, affordable and acceptable to the local population and are appropriate to implement in low-resource settings for the prevention and control of CVD in Africa should be a priority.[17] This strategy is particularly relevant for the clinical and public health approaches for addressing hypertension, diabetes, unhealthy diet, physical inactivity and tobacco use. Improving access to directly enumerated epidemiological data for the region would also go a long way towards appropriately informed healthcare policy and practice.

References

1. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; **14**: 10–6736.
2. National Center for Health Statistics. National Vital Statistics System HIST290A: Deaths for selected causes by 10-year age groups, race, and sex: Death registration states, 1900–32, and United States, 1933–98. *NCHS*/*NVSS* 15 A.D. January 18; Available at: URL: http://www.cdc.gov/nchs/nvss/mortality/hist290a.htm.
3. Institute of Medicine. *Promoting Cardiovascular Health in the Developing World: A Critical Challenge to Achieve Global Health*. Washington, DC: National Academies Press, 2010.
4. Institute of Medicine. *Preventing the Global Epidemic of Cardiovascular Disease: Meeting the Challenges in Developing Countries*. Washington, DC: National Academies Press, 2010.
5. World Health Organization. Prevention and control of non-communicable diseases – Report of the Secretary-General. *World Health Organization* 2011; 1–18. Available at: URL: http://www.un.org/ga/search/view_doc.asp?symbol=A/66/83&Lang=E.
6. World Health Organization, World Economic Forum. From burden to 'best buys': reducing the economic impact of non-communicable diseases in low- and middle-income countries. WHO 2011; Available at: URL: http://www.who.int/nmh/publications/best_buys_summary.pdf.
7. World Health Organization African Regional Office. Cardiovascular diseases in the African region: current situation and perspectives. http://www.afro.who.int/rc55/documents/afr_rc55_12_cardiovascular.pdf 2004.
8. Lozano R, Naghavi M, Foreman K, *et al*. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**(9859): 2095–2128.
9. Roth GA, Murray CJ. The Global Burden of Disease Study 2010 does not show a rise in the age-standardized mortality rate for cardiovascular disease in sub-Saharan Africa. *Prog Cardiovasc Dis* 2013; **56**(3): 278–280.
10. Oti SO, van de Vijver S, Kyobutungi C. Trends in non-communicable disease mortality among adult residents in Nairobi's slums, 2003–2011: applying InterVA-4 to verbal autopsy data. *Glob Health Action* 2014; **7**: 25533. doi: 10.3402/gha.v7.25533. eCollection@2014.:25533.
11. Sankoh O, Byass P. Cause-specific mortality at INDEPTH Health and Demographic Surveillance System Sites in Africa and Asia: concluding synthesis. *Glob Health Action* 2014; **7**: 25590. doi: 10.3402/gha.v7.25590. eCollection@2014.:25590.
12. Moran AE, Forouzanfar MH, Roth GA, *et al.* The global burden of ischemic heart disease in 1990 and 2010: the global burden of disease 2010 study. *Circulation* 2014; **129**(14): 1493–1501.
13. Krishnamurthi RV, Feigin VL, Forouzanfar MH, *et al*. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet Glob Health* 2013; **1**(5): e259–e281.
14. Moran A, Forouzanfar M, Sampson U, Chugh S, Feigin V, Mensah G. The epidemiology of cardiovascular diseases in sub-Saharan Africa: the global burden of diseases, injuries and risk factors 2010 study. *Prog Cardiovasc Dis* 2013; **56**(3): 234–239.
15. Foreman KJ, Lozano R, Lopez AD, Murray CJ. Modeling causes of death: an integrated approach using CODEm. *Popul Health Metr* 2012; **10**: 1.:1.
16. Roth GA, Forouzanfar MH, Moran AE, *et al*. Demographic and epidemiologic drivers of global cardiovascular mortality. *N Eng J Med* 2015; **372**: 1333–1341. DOI: 10.1056/NEJMoa1406656.
17. Stewart S, Sliwa K. Preventing CVD in resource-poor areas: perspectives from the 'real-world'. *Nat Rev Cardiol* 2009; **6**(7): 489–492.

Familial clustering of risk factors for cardiovascular disease among first-degree relatives of patients with chronic kidney disease in a sub-Saharan African population

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Abstract

Objective: To determine the prevalence of risk factors for cardiovascular disease (CVD) in first-degree relatives (FDRs) of patients with chronic kidney disease (CKD) in a sub-Saharan African population.

Methods: This was a cross-sectional survey of 460 subjects (230 FDRs of patients with CKD and 230 healthy controls). Anthropometrics and blood pressures were measured. Spot urine and fasting venous blood samples were obtained for biochemical analysis.

Results: The prevalence of hypertension, diabetes mellitus, obesity and dyslipidaemia were significantly higher in FDRs of patients with CKD compared with the controls: 56 (24.3%) vs 29 (12.6%), $p = 0.01$; 20 (8.7%) vs 6 (2.6%), $p = 0.01$; 40 (17.4%) vs 24 (10.4%), $p = 0.03$ and 171 (74.3%) vs 138 (60.0%), $p = 0.01$, respectively. Hypertension (OR, 1.65), dyslipidaemia (OR, 1.72) and albuminuria (OR, 1.61) were independently associated with being a FDR of patients with CKD.

Conclusion: In this sub-Saharan African population, risk factors for CVD were more prevalent in the FDRs of patients with CKD than in healthy controls.

Keywords: cardiovascular disease, chronic kidney disease, first-degree relatives, risk factors, sub-Saharan Africa

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Cardiovascular disease (CVD) is receiving global attention because of its rising prevalence and its resultant high morbidity and mortality rate and the huge economic burden. It was responsible for one-third of global deaths in 2005 and it is projected that it will account for three-quarters of the deaths worldwide by 2030.[1-3] In sub-Saharan Africa, a region undergoing an epidemiological transition,[2,4] recent reports have suggested that CVD may be the leading cause of death.[3,5]

CVD is particularly prevalent among patients with chronic kidney disease (CKD). In fact, patients with CKD are more likely to die from cardiovascular diseases than from progression of renal disease.[6] The risk of cardiovascular death in patients with end-stage renal disease (ESRD) is 10 to 100 times that in the healthy population,[6,7] and many researchers consider CKD an independent risk factor for CVD in view of the changes in the cardiovascular system associated with CKD, such as endothelial dysfunction, arterial stiffening, left ventricular hypertrophy (LVH), and vascular calcification.[8]

It has been suggested that the higher prevalence of cardiovascular disease seen in patients with CKD may in part be as a result of risk factors for CVD being more prevalent in those individuals. Evidence suggests that both traditional and non-traditional cardiovascular risk factors are more common among patients with CKD than in the general population.[9,10]

Relatives of patients with CKD are themselves at increased risk of developing CKD.[11] This increased risk has been hypothesised to be due to shared genetic and environmental factors.[12] Most of these shared factors are cardiovascular risk factors, such as hypertension, diabetes, obesity and dyslipidaemia.[11,13] Inserra *et al.* reported a high prevalence of common CVD risk factors among 810 first-degree relatives (FDRs) of patients with CKD; with hypertension being present in 41.8%, overweight or obesity in 62.1%, hypercholesterolaemia in 42.9%, hyperglycaemia in 5.2%, and cigarette smoking in 34.8%.[13] Tsai *et al.* and Wei *et al.* both reported the prevalence of CVD risk factors to be significantly higher in FDRs of patients with CKD compared to healthy and spousal controls.[14,15]

FDRs of patients with CKD are not only at increased risk of developing CKD but are also at increased risk of experiencing an adverse cardiovascular event. Because many of the CVD risk factors are modifiable, identifying individuals with a higher prevalence of these risk factors would be a cost effective way of reducing the burden of cardiovascular disease, especially in resource-poor settings.[16-18] FDRs of patients with CKD appear to be one such group.

There is a paucity of data, however, on the prevalence of CVD risk factors in FDRs of patients with CKD from sub-Saharan Africa. The aim of this study was to determine the prevalence of CVD risk factors in a sub-Saharan African population of FDRs of patients with CKD and compare it with a cohort of individuals with no family history of CKD.

Methods

This was a cross-sectional study of a cohort of 460 subjects (230 FDRs of patients with CKD and 230 age- and gender-matched controls with no personal or family history of CKD) carried out between January and June 2011. The FDRs were parents, siblings or offspring of 106 consecutively presenting and consenting patients with CKD who were receiving care

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at the Lagos University Teaching Hospital, Lagos, south-west Nigeria. The study protocol was approved by the health research and ethics committee of the hospital and each participating individual gave written informed consent.

Recruitment into the FDR arm of the study was carried out in two phases. In the first phase of recruitment, we enrolled 106 probands who were consecutively presenting and consenting patients with CKD attending the nephrology out-patient clinic of our teaching hospital. To be eligible for recruitment in this phase, a patient had to be 18 years of age or older and give informed consent. Patients with CKD from autosomal dominant polycystic kidney disease (ADPKD) were excluded. In the second phase, we recruited FDRs of the 106 probands with CKD.

A minimum of one and a maximum of four FDRs were selected from the family of each proband. Where there were four or less eligible FDRs in the family of a proband, all of them were recruited into the study. However, where there were more than four eligible FDRs in the family of a proband, four were selected by balloting.

Individuals were eligible for recruitment into the FDR arm of the study if they were: a parent, sibling or offspring of one of the probands, were 18 years of age or older, and gave informed consent. Exclusion criteria included: age less than 18 years, presence of symptomatic urinary tract infection, on-going febrile illness, presence of heart failure, severe current illness or malignancy, and a family history of ADPKD.

For the control arm of the study, individuals who were age and gender matched with subjects in the FDR arm, and had no family or personal history of CKD were enrolled. Inclusion criteria for subjects in the control arm were: age 18 years or older, absence of personal or family history of CKD and giving informed consent. The exclusion criteria were: age less than 18 years, presence of symptomatic urinary tract infection, on-going febrile illness, heart failure, or other severe current illness or malignancy.

Information was retrieved from the study participants using an interviewer-administered structured questionnaire. Information obtained included: socio-demographic data, personal and family history of kidney disease, a history of diabetes and hypertension, current or past use of medications including herbal preparations and over-the-counter drugs. Information regarding social habits such as cigarette smoking and alcohol consumption were also retrieved.

The weight, height, waist and hip circumferences, and blood pressure were measured in each study participant. Ten millilitres each of early morning spot urine and venous blood were obtained from all participants following an overnight fast for the determination of levels of serum creatinine, fasting plasma glucose, fasting lipids and serum uric acid, and urine albumin:creatinine ratio. Glomerular filtration rate was estimated from serum creatinine using a four-variable version of the modification of diet in renal disease (MDRD) study equation.[19]

Diabetes mellitus was defined as a fasting plasma glucose level > 126 mg/dl (7 mmol/l), or diabetes mellitus diagnosed previously by a physician, or use of insulin or oral hypoglycaemic medications.[20] Hypertension was defined as systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg, hypertension previously diagnosed by a physician, or use of antihypertensive medications.[21] Overweight was defined as body mass index (BMI) 25–29.5 kg/m^2 and obesity was defined as BMI ≥ 30kg/m^2.[22] Truncal obesity was defined as waist circumference ≥ 102 cm in males and ≥ 88 cm in females.[23] Hyperuricaemia was defined as a serum uric acid level of ≥ 7 mg/dl.[24] Dyslipidaemia was defined as a ratio of plasma total cholesterol and high-density lipoprotein cholesterol (TC/HDL-C) > 5.[25]

Moderate alcohol drinking was defined as consumption of one drink (14 g) per day.[26] Moderate-to-heavy cigarette smoking was defined as smoking at least six cigarettes per day.[27]

Statistical analysis

Statistical analyses were carried out using the statistical package for social sciences (SPSS), version 17.0 (SPSS Inc, Chicago, IL). Continuous data are presented as mean ± SD and categorical variables are expressed as proportions or percentages. Independent samples *t*-tests were used for comparison of group means, while the chi-square test (χ^2 tests) was applied for comparison of categorical variables in FDRs and controls. Multiple logistic regression analysis was used to determine CVD risk factors that were independently associated with being a FDR of a patient with CKD. Significance was set at a *p*-value less than 0.05.

Results

The 230 FDRs comprised 25 parents (10.8%), 78 siblings (34%) and 127 offspring (55.2%). The parents were seven fathers (3.0%) and 18 mothers (7.8%), the siblings were 39 brothers (17%) and 39 sisters (17%), while the offspring were 69 sons (30.0%) and 58 daughters (25.2%). Age- and gender-matched 230 healthy adults were recruited into the control arm of the study. Table 1 shows the clinical and biochemical characteristics of the FDRs and controls. FDRs of the patients with CKD had significantly higher mean systolic blood pressure, mean diastolic blood pressure, mean body mass index, mean waist circumference and urine albumin:creatinine ratio than the controls.

Table 2 shows a comparison of the prevalence of risk factors for CVD between the FDRs of patients with CKD and the control group. The prevalence of hypertension, diabetes, obesity, dyslipidaemia, hyperuricaemia, albuminuria and reduced estimated glomerular filtration rate (eGFR) were all significantly higher among the FDRs than in the control subjects. Hypertension (OR, 1.65), dyslipidaemia (OR, 1.72) and albuminuria (OR, 1.61) are CVD risk factors that were independently associated with being a FDR of a patient with CKD (Table 3).

Discussion

Our study showed that among our sub-Saharan African cohort, as was previously reported in other populations, risk factors for cardiovascular disease were more prevalent in the FDRs of patients with CKD compared to healthy control subjects. This finding supports the phenomenon of a clustering of CVD risk factors in families of patients with CKD.

Hypertension and diabetes are two of the most important CVD risk factors worldwide. In this study, the prevalence of both conditions was significantly higher among FDRs of patients with CKD than in the control group. However, the picture was slightly different when the prevalence was compared with the

Table 1. Comparison of measured clinical and laboratory parameters of the FDRs of patients with chronic kidney disease and the controls

Variables	*FDRs (n = 230)*	*Controls (n = 230)*	p-*value*
Mean age (years)	33.49 ± 12.0	33.67 ± 12.2	0.87
Mean SBP (mmHg)	116.5 ± 22.5	112.1 ± 18.1	0.02*
Mean DBP (mmHg)	74.9 ± 12.7	71.4 ± 10.5	0.01*
Mean BMI (kg/m^2)	25.5 ± 5.3	23.8 ± 4.0	0.01*
Mean WC (cm)	81.8 ± 13.3	79.3 ± 11.3	0.03*
Mean HC (cm)	100.0 ± 11.3	98.4 ± 11.5	0.13
Mean SCr (µmol/l)	89.9 ± 23.4	88.3 ± 21.1	0.42
Mean FPG (mmol/l)	4.3 ± 1.1	4.3 ± 0.9	0.79
Mean SUA (µmol/l)	239.9 ± 99.4	237.4 ± 81.3	0.85
Mean TC (mg/dl)	146.5 ± 51.0	147.8 ± 40.1	0.24
(mmol/l)	(3.79 ± 1.32)	(3.83 ± 1.04)	
Mean HDL-C (mg/dl)	30.8 ± 10.5	34.7 ± 12.6	0.10
(mmol/l)	(0.8 ± 0.27)	(0.9 ± 0.33)	
Mean LDL-C (mg/dl)	106.7 ± 42.3	107 ± 38.2	0.41
(mmol/l)	(2.76 ± 1.10)	(2.77 ± 0.99)	
Mean TG (mg/dl)	95.1 ± 22.8	92.3 ± 24.3	0.06
(mmol/l)	(1.07 ± 0.26)	(1.04 ± 0.27)	
Mean eGFR (ml/min/1.73 m^2)	106.6 ± 28.3	102.3 ± 25.0	0.09
Mean urine ACR	22.1 (0.5–1.406)	18.2 (0.6–1.296)	0.02*

ACR, albumin:creatinine ratio; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FDRs, first-degree relatives of patient with chronic kidney disease; FPG, fasting plasma glucose; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SCr, serum creatinine; SUA, serum uric acid; TG, triglyceride; WC, waist circumference.

national average. While the prevalence of diabetes in the FDRs in this study was significantly higher than the national average, 8.7 vs 2.3%,[28] the prevalence of hypertension in FDRs in the study was similar to the national average values.[29]

The high prevalence of obesity among the FDRs of patients with CKD is another important CVD risk factor that deserves attention. Some communities in sub-Saharan Africa regard being overweight or obese as a sign of affluence,[30] and so a lot of people are motivated to gain weight. The contribution of obesity to cardiovascular morbidity and mortality is significant[22] and with the epidemiological transition taking place in sub-Saharan Africa, strategies to reduce the burden of obesity are urgently needed.

Table 2. A comparison of the frequency of risk factors for cardiovascular disease among the FDRs of patients with chronic kidney disease and the controls

CVD risk factors	*FDRs (n = 230)* n *(%)*	*Controls (n = 230)* n *(%)*	*Odds ratio*	*95% CI*	p-*value*
Presence of hypertension	56 (24.3)	29 (12.6)	2.23	1.33–3.76	0.01*
Presence of diabetes	20 (8.7)	6 (2.6)	3.56	1.32–10.10	0.01*
Presence of obesity	40 (17.4)	23 (10.0)	1.89	1.06–3.40	0.02*
Significant history of cigarette smoking	14 (6.1)	6 (6.2)	2.42	0.85–7.20	0.07
Presence of truncal obesity	46 (20.0)	39 (17.0)	1.22	0.74–2.02	0.40
Significant history of alcohol use	58 (25.2)	41 (17.8)	1.55	0.97–2.50	0.05
Presence of hyperuricaemia	14 (6.1)	4 (1.7)	3.66	1.10– 3.39	0.02*
Presence of dyslipidaemia	171 (74.3)	138 (60.0)	1.93	1.28–2.93	0.01*
Presence of reduced eGFR	13 (5.7)	4 (1.7)	3.38	1.01–12.50	0.03*
Presence of albuminuria	85 (37.0)	51 (22.2)	2.06	1.34–3.17	0.01*

CI, confidence interval; CVD, cardiovascular disease; FDRs, first-degree relatives of patients with chronic kidney disease; eGFR, estimated glomerular filtration rate. Moderate alcohol drinking was defined as consumption of one drink (14 g) per day. Moderate-to-heavy cigarette smoking was defined as smoking at least six cigarettes per day.

Table 3. Logistic regression of cardiovascular risk factors among FDRs of patients with chronic kidney disease

CVD risk factors	*Odds ratio*	*95% CI*	z-*statistic*	p-*value*
Presence of hypertension	1.65	1.05–2.84	1.82	0.04*
Presence of diabetes	2.37	0.89–0.50	1.72	0.08
Presence of hyperuricaemia	2.76	0.86–8.84	1.71	0.09
Presence of dyslipidaemia	1.73	1.15–2.60	2.62	0.01*
Presence of reduced eGFR	2.12	0.64–6.99	1.23	0.21
Presence of albuminuria	1.62	1.05–2.50	2.17	0.03*

FDRs, first-degree relatives; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate.

Of particular concern is the high prevalence of dyslipidaemia found in this study. Although the prevalence of dyslipidaemia was significantly higher in the FDRs of patients with CKD, the prevalence of more than 60% found in the control arm of the study suggests that this risk factor for CVD, which is not frequently assessed in resource-poor settings because of cost, may be a more serious problem than previously anticipated.

The higher prevalence of albuminuria and reduced eGFR observed in the FDRs in this study was in keeping with findings from similar studies.[11-15] The higher prevalence of CVD risk factors among the FDRs of patients with CKD in this population has highlighted the need to consider this population as having an increased risk of experiencing adverse cardiovascular events, and there is a need for targeted interventions.

Our study had some limitations, including the fact that it was a cross-sectional survey, which has its own inherent weakness, such as difficulty in interpreting associations between outcome and exposure, and lack of long-term monitoring. Also, a history of hypertension and diabetes were self-reported, which may be subject to recall bias.

Conclusion

In this sub-Saharan African population, risk factors for CVD were more prevalent in the FDRs of patients with CKD than in healthy controls.

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References

1. World Health Organization, 2009. Cardiovascular Diseases. http://www.who.int/mediacentre/factsheets/fs317/en/. Accessed Dec 20, 2014.
2. World Health Organization 2005. Preventing chronic diseases: a vital investment. http://www.who.int/chp/chronic_disease_report/contents/en. Accessed Dec 20, 2014.
3. Gaziano TA. Economic burden and the cost-effectiveness of treatment of cardiovascular disease in Africa. *Heart* 2008; **94**(2): 140–144.
4. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006; **367**(9524): 1747–1757.
5. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006; **3**(11): e442.
6. Manjunath G, Tighiouart H, Coresh J, Macleod B, Salem DN, Griffith JL, *et al*. Level of kidney function as a risk factor for cardiovascular

outcomes in the elderly. *Kidney Int* 2003; **63**(3): 1121–1129.
7. Keith DS, Nicholas GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 2004; **164**(6): 659–663.
8. Mathew S, Tustison KS, Sugatani T, Chaudhary LR, Rifas L, Hruska KA. The mechanism of phosphorus as a cardiovascular risk factor in CKD. *J Am Soc Nephrol* 2008; **19**: 1092–1105.
9. Mann JF, Gerstein HC, Yi QL, Lonn EM, Hoogwerf BJ, Rashkow A, *et al.* Development of renal disease in people at high cardiovascular risk: Results of the HOPE randomized study. *J Am Soc Nephrol* 2003; **14**: 641–647.
10. Menon V, Sarnak MJ. The epidemiology of chronic kidney disease stages 1 to 4 and cardiovascular disease: A high risk combination. *Am J Kidney Dis* 2005; **45**: 223–232.
11. Satko SG, Sedor JR, Iyengar SK, Freedman BI. Familial clustering of chronic kidney disease. *Semin Dial* 2007; **20**(3): 229–236.
12. Satko SG, Freedman BI, Moossavi S. Genetic factors in end-stage renal disease. *Kidney Int Suppl* 2005; **94**: S46–49.
13. Inssera FDG, Alpino AMS. Relatives of dialysis patients with increased risk of renal failure. *Medicina* (Beunos Aires) 2007; **67**(1): 8–18.
14. Tsai JC, Chen SC, Hwang SJ, Chang JM, Lin MY, Chen HC. Prevalence and risk factors for CKD in spouses and relatives of haemodialysis patients. *Am J Kidney Dis* 2010; **55**(3): 78–104.
15. Wei X, Li Z, Chen W, Mao H, Li Z, Dong X, *et al.* Prevalence and risk factors of chronic kidney disease in first-degree relatives of chronic kidney disease patients in southern, China. *Nephrol Carlton* 2012; **17**(2): 123–130.
16. Salkeld G, Phongsavan P, Oldenburg B, Johannesson M, Convery P, Graham Clarke P, *et al*. The cost-effectiveness of a cardiovascular risk reduction program in general practice. Health policy (New York). Ireland: Elsevier Sci Ltd, 1997; **41**(2): 105–119.
17. Brunner E, Cohen D, Toon L. Cost effectiveness of cardiovascular disease prevention strategies: a perspective on EU food based dietary guidelines. *Public Health Nutr* 2001; **4**(2B): 711–715.
18. Chamnan P, Simmons RK, Khaw K-T, Wareham NJ, Griffin SJ. Estimating the population impact of screening strategies for identifying and treating people at high risk of cardiovascular disease: modelling study. *Br Med J* 2010; **340**: c1693.
19. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999; **130**(6): 461–470. http://www.qxmd.com/calculate-online/nephrology/mdrd-egfr. Accessed September 24, 2014.
20. WHO guideline on prevention, detection and treatment of diabetes mellitus, 2007. http://www.who.int/diabetes/publications/en/. Accessed September 12, 2014.
21. WHO/ISH Hypertension guidelines, 2005. http://www.who.int/cardiovascular_diseases/guidelines/hypertension/en/. Accessed September 12, 2014.
22. WHO | Obesity and overweight [Internet]. World Health Organisation Media Centre fact sheet No. 311. 2012. http://www.who.int/mediacentre/factsheets/fs311/en. Accessed October 18, 2014.
23. Waist circumference and waist–hip ratio. Report of a WHO expert consultation, 2008. http://www.who.int/nutrition/publications/obesity/WHO_report_waistcircumference_and_waisthip_ratio/en/. Accessed October 18, 2014.
24. Conen D, Wietlisbach V, Bovet P, Shamlaye C, Riesen, W, Paccaud F, *et al*. Prevalence of hyperuricemia and relation of serum uric acid with cardiovascular risk factors in a developing country. *BMC public Health* 2004; **34**: 1473–1482.
25. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *J Am Med Assoc* 2001; **285**(19): 2486–2497.
26. Morse RM, Flavin DK. The definition of alcoholism. The Joint Committee of the National Council on Alcoholism and Drug Dependence and the American Society of Addiction Medicine to Study the Definition and Criteria for the Diagnosis of Alcoholism. *J Am Med Assoc* 1992; **268**: 1012.
27. Husten CG. How should we define light or intermittent smoking? Does it matter? *Nicotine Tob Res* 2009; **11**: 111–121.
28. Oyegbade OO, Abioye-Kuteyi EA, Kolawole BA, Ezeoma IT, Bello IS. Screening for Diabetes mellitus in a Nigerian family practice population. *SA Fam Pract* 2007; **49**(8): 15–21.
29. Ogah OS, Okpechi I, Chukwuonye II, Akinyemi OJ, Onwubere BJC, Falase AO, *et al.* Blood pressure, prevalence of hypertension and hypertension related complications in Nigerian Africans: A review. *World J Cardiol* 2012; **4**(12): 327–340.
30. Mvo Z, Dick J, Steyn K. Perceptions of overweight African women about acceptable body size of women and children. *Curationis* 1999; **22**(2): 27–31.

Strategic investments in non-communicable diseases (NCD) research in Africa: the GSK Africa NCD Open Lab

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Abstract

In March 2014, GSK announced a number of new strategic investments in Africa. One of these included investment of up to 25 million Pounds Sterling (£25 million) to create the world's first R&D Open Lab to increase understanding of non-communicable diseases (NCDs) in Africa. The vision is to create a new global R&D effort with GSK working in partnership with major funders, academic centres and governments to share expertise and resources to conduct high-quality research. The Africa NCD Open Lab will see GSK scientists collaborate with scientific research centres across Africa. An independent advisory board of leading scientists and clinicians will provide input to develop the strategy and selection of NCD research projects within a dynamic and networked open-innovation environment. It is hoped that these research projects will inform prevention and treatment strategies in the future and will enable researchers across academia and industry to discover and develop new medicines to address the specific needs of African patients.

Keywords: non-communicable diseases, Africa, open innovation, collaboration, training, capacity building

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In 2012, the World Health Assembly endorsed an important new health goal (the '25 by 25' goal) to reduce avoidable mortality from non-communicable diseases (NCDs) by 25% by 2025.[1] Furthermore, the 66th World Health Assembly, United Nations (UN) member states adopted a resolution on NCDs that reinforces commitments made in 2011's UN Declaration on NCDs and signals consensus on the three pillars of the global NCD architecture – action, accountability and coordination.[2] This alignment of the UN's World Health Assembly, the World Health Organisation, and other entities are recognised as positive steps for combating NCDs.

NCDs account for 63% of all deaths globally, with 80% of the global burden occurring in low- and middle-income countries.[3] While NCDs are currently the leading cause of death in all regions except Africa, current projections indicate that by 2020, the largest increases in NCD deaths will occur in Africa. Furthermore, by 2030, the number of deaths from NCDs in Africa is projected to exceed the combined deaths from communicable, nutritional, maternal and perinatal deaths as the most common causes of death, if current trends continue.[3]

Currently, NCDs are increasing in Africa. Mbanya and colleagues found that approximately 12 million people were living with diabetes in Africa in 2010; this is projected to increase to approximately 24 million by 2030.[4] Other contributors to the increase in diabetes may also include anti-retroviral treatment (ART) for HIV/AIDS. ART has been shown to increase the risk of cardiometabolic dysregulation; this dysregulation is associated with obesity and increased insulin resistance.[5] Therefore increase in incidences of NCDs will result from the aforementioned factors, including the increased lifespan of people living with infectious diseases.

GSK understands that there is much more to be done to appreciate and address the burden of NCDs, with a particular focus on Africa. As a science-led global healthcare company, GSK is committed to harnessing its scientific expertise, partnerships and global reach to develop and make products for people who need them, wherever they live. Research and development areas include HIV, vaccines, and diseases of the developing world. GSK has pioneered a number of innovative new models to help stimulate innovation: working in partnership with others, and opening up access to its expertise, facilities and intellectual property.[6]

For example, the Tres Cantos Open Lab Foundation was established by GSK in 2010 and offers a unique approach to discovering novel, safe, appropriate and affordable medicines for diseases of the developing world with industry, academia, non-governmental organisations and governments working together. The Tres Cantos Open Lab is the world's first open laboratory for diseases of the developing world and provides an opportunity for scientists from around the world to partner with GSK scientists, using GSK's facilities and expertise, to test their own ideas and design appropriate projects at the very early stages of drug discovery.[7]

Building on this and other initiatives, GSK's chief executive officer, Sir Andrew Witty, announced new strategic investments in sub-Saharan Africa at the 5th European Union–Africa Business Forum in Brussels in March 2014. These investments also included the Africa NCD Open Lab, which was designed to address pressing health needs and contribute to long-term business growth. Over the next five years, GSK will make targeted investments of up to £130 million in Africa, which will contribute to the development of home-grown capabilities and skills in Africa.[8] The long-term goal is to equip Africa to discover, develop and produce the medicines required for African patients.

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The projected increase in NCDs across developing countries offers an opportunity for GSK to participate alongside global players to help improve the collective understanding of the specific variations of disease in low-resource settings. Building on the success of GSK's Tres Cantos Open Lab, the company's vision is to create a new global R&D effort, the Africa NCD Open Lab, with GSK working in partnership with African researchers to conduct NCD-related research in Africa. The results of this research will be published in order to disseminate relevant insights to the wider community. To do this, GSK will fully engage with the scientific and clinical research communities in Africa to bring on-the-ground expertise and experience to address the problem.

GSK working in global collaboration

GSK recognises that by working in partnership with non-governmental organisations, governments, academic institutions and other companies, it can achieve more for patients than it can alone. It currently has research collaborations with more than 3 000 external organisations, including other companies, academic institutions and research charities.[9] For example, a five-year strategic partnership with Save the Children aims to help save one million children's lives.[10] The partnership will combine expertise, resources, and capabilities and bring much-needed medicines and vaccines to some of the world's poorest children, train thousands of healthcare workers, and develop medicines to address diseases in these paediatric populations. As part of the Save the Children partnership, GSK's Maternal and Neonatal R&D Unit is developing a gel form of a GSK antiseptic product used in mouthwash to help prevent sepsis in newborn babies.

Vision for Africa NCD Open Lab

Improving healthcare infrastructure and access to care is a key element of addressing NCDs in Africa. Before discovering and developing new medicines specifically for African patients, more needs to be done to understand the burden of these diseases. In addition, there are significant gaps in our knowledge about the diversity of the causes of NCDs in Africa, their presentation, and the responses to medicines (possibly driven by genetic variation, environmental influence or behavioural factors).

To address the knowledge gaps, the research will focus on better understanding the unique aspects (e.g. genotypic, phenotypic, cultural and environmental context) of NCDs in the African setting through translational research that will integrate basic laboratory-based, clinical and population-based research. New research is required to better understand how these diseases develop, how they present, and how patients can best be treated in the African context.

The Africa NCD Open Lab will be centred at GSK's R&D hub in Stevenage, UK, which together with the multiple partnerships, including with local African research institutes, will provide a world-class, dynamic and highly networked R&D environment that will deliver high-quality and impactful research outputs. This environment will provide a unique opportunity to strengthen African research capability and train a new generation of African scientific leaders in NCDs.

While the GSK component will be managed as an independent laboratory, it will have full access to wider GSK R&D expertise and infrastructure. The majority of the research will be conducted in Africa by African researchers, with GSK contributing resources and expertise. Examples of the kinds of support GSK could provide for African principal investigators in this collaborative framework include clinical study design, biostatistics, genetic analysis expertise, bio-informatics, epidemiology and therapeutic expertise in cardiovascular, metabolic and respiratory medicine, and oncology.

A key aim of the Open Lab will be to support a robust R&D training programme in collaboration with leading academic groups, linked with research centres in Africa to build local scientific capability. The training programme will be integrated with the activities of the laboratory; GSK will aim to ensure the active involvement of local scientists in the research projects so that sustainable and local expertise will be built. The Open Lab will also support the education and training of African scientific researchers through partnering African researchers with GSK/academic researchers. Furthermore, the Africa NCD Open Lab will build on existing GSK partnerships and establish capability, combining the strengths of a large research-based healthcare company with academic and field experts.

An independent scientific advisory board will be established and charged to provide input on the strategy of the collaborative R&D effort, support the identification of high-quality and impactful research projects for inclusion in the portfolio, and monitor delivery progress. The scientific advisory board will be chaired by a leading African scientist, will include recognised external experts in the field, and will have majority African representation. Specific research opportunities will be reviewed and approved by the board and teams assembled by GSK.

In November 2014, the first call for research proposals was launched. Up to £4 million will be made available to fund research proposals. It is anticipated that funded projects will generate new knowledge on the unique disease mechanisms, pathophysiology and aetiology of NCDs in African patients.

Ambition by 2025

By 2025, the aim is to initiate and deliver 25 high-impact research projects whose outputs will lead to better understanding of NCDs in Africa, and the improved use of medicines, contributing towards reaching the World Health Assembly goal to reduce avoidable mortality from NCDs by 25% by 2025. Moreover, the

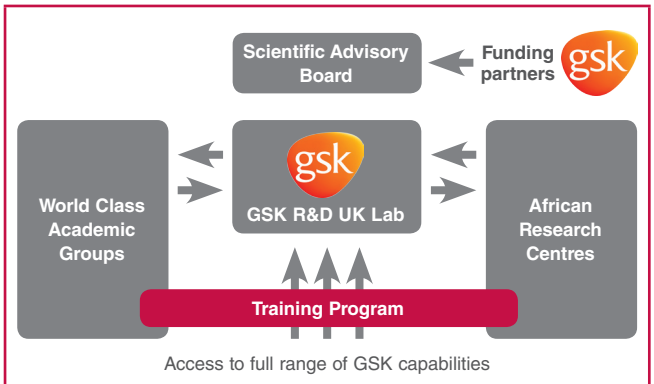

Fig. 1. Overview of the GSK Africa NCD Open Lab partnership model.

Open Lab will partner with and contribute towards developing NCD research capability at up to 10 African research centres. A detailed search and evaluation of the relevant academic and clinical laboratories will be conducted to identify optimal partners. These centres will be recognised as emerging world-class centres of excellence for R&D on NCDs in Africa, and will attract and retain the next generation of scientific talent in Africa.

For more information please visit www.gsk.com/africa-ncd-openlab.

References

1. 65th World Health Assembly closes with new global health measures. http://www.who.int/mediacentre/news/releases/2012/wha65_closes_20120526/en/index.html. Accessed 12 December 2014.
2. A major victory at the World Health Assembly for NCDs. http://ncdalliance.org/news/major-victory-world-health-assembly-ncds. Accessed 12 December 2014.
3. Alwan A. Global status report on noncommunicable diseases 2010. Geneva: World Health Organization, 2011. http://www.who.int/nmh/publications/ncd_report2010/en/. Accessed 12 December 2014.
4. Mbanya JC, Motala AA, Sobngwi E, Assah FK, Enoru ST. Diabetes in sub-Saharan Africa. *Lancet* 2010; **375**(9733): 2254–2266. DOI: 10.1016/S0140-6736(10)60550-8.
5. Dillon DG, Gurdasani D, Riha J, *et al.* Association of HIV and ART with cardiometabolic traits in sub-Saharan Africa: a systematic review and meta-analysis. *Int J Epidemiol* 2013; **42**(6): 1754–1771. DOI: 10.1093/ije/dyt198.
6. Witty A. New strategies for innovation in global health: a pharmaceutical industry perspective. *Health Affairs* 2011; **30**(1): 118–126. DOI: 10.1377/hlthaff.2010.0933.
7. Tres Cantos Open Lab Foundation. http://www.openlabfoundation.org. Accessed 12 December 2014.
8. GSK announces new strategic investments in Africa to increase access to medicines, build capacity and deliver sustainable growth. http://www.gsk.com/en-gb/media/press-releases/2014/gsk-announces-new-strategic investments-in-africa-to-increase-access-to-medicines-build-capacity-and-deliver-sustainable-growth/. Accessed 12 December 2014.
9. GSK Pharmaceuticals: our pharmaceuticals business develops and makes a broad range of medicines to treat both acute and chronic diseases. http://www.gsk.com/en-gb/about-us/what-we-do/pharmaceuticals/. Accessed 11 March 2015.
10. GSK and Save the Children form unique partnership to save the lives of one million children. http://www.gsk.com/en-gb/media/press-releases/2013/gsk-and-save-the-children-form-unique-partnership-to-save-the-lives-of-one-million-children/. Accessed 12 December 2014.

NHLBI perspectives on the growth of heart, lung, blood and sleep conditions in Africa: global and domestic insights, challenges and opportunities

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'Of all forms of inequity, injustice in healthcare is the most shocking and inhumane'

Dr Martin Luther King, Jr, March 25, 1966, 2nd National Convention of the Medical Committee for Human Rights

Keywords: health inequities, cardiovascular diseases, lung diseases, sickle cell disease, sleep disorders, biomedical research

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The mission of the National Heart, Lung, and Blood Institute (NHLBI) centres on global leadership in research, training and education aimed at promoting the prevention and treatment of heart, lung, blood and sleep (HLBS) disorders, and thereby enhance the pursuit of a healthy, long and fulfilling existence by all individuals.[1] The global horizon of this mission reflects an appreciation of the collective destiny shared by all humanity.

Martin Luther King envisioned a world that is increasingly inter-dependent, a world in which we are all part of a 'beloved community', where every life matters. In this vision of a 'beloved community' he also said that '…injustice anywhere is a threat to justice everywhere…'. If indeed health inequity is an injustice; then it is incumbent upon the global public health community to recognise the threat that health inequities pose to the entire human family all around the world.

The advent of globalisation and the attendant shrinkage of the degrees of human separation compel us to work collectively to address the critical challenges that stand in the way of ideal health everywhere. The NHLBI is committed to working with health researchers from sub-Saharan Africa (SSA) and across the globe to build this future together.[2]

In this research endeavour, the NHLBI's strategy for successful stewardship at national and global levels rests on several enduring principles, which include: valuing and supporting investigator-initiated fundamental discovery science; maintaining a balanced, cross-disciplinary research portfolio; supporting implementation science that empowers patients and enables partners to apply knowledge that improves the health of the nation; training and nurturing a diverse new generation of leaders in science; engaging key thought-leaders to collectively identify and pursue high-yield opportunities that will advance the field; valuing the health of all communities; and innovating an evidence-based elimination of health inequities in the United States and around the globe. The continued prioritisation of these enduring principles is supported by the observed trends in HLBS conditions and other chronic non-communicable diseases at the global and domestic fronts.

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Relevant trends

Several recent trends in the burden of heart, lung and blood diseases provide illustrative examples of why our collective effort in this endeavour is necessary. For example, in 2010 the global age-standardised disability-adjusted life years (DALYs) per 100 000 population associated with sickle cell disorders in SSA was 281.16 (CI: 196.70–368.44), substantially in excess of the estimated 77.86 (CI: 58.01–98.96) for other developing regions, and compared to 80.09 (CI: 60.00–102.40) globally.[3] Piel and colleagues project that the numbers of newborns with sickle cell anaemia (SCA) globally will increase from 305 800 (238 400–398 800) in 2010 to 404 200 (242 500–657 600) by the year 2050, and that Nigeria and the Democratic Republic of Congo will remain the countries most in need of policies for the management of SCA.[4]

Additionally, the report indicates that the implementation of large-scale universal screening can save the lives of up to 9 806 000 (6 745 800–14 232 700) newborns with SCA globally, 85% (81–88%) of whom will be born in SSA. Similarly, we can achieve significant reduction in mortality and prolong the lives of 5.3 million newborns with SCA if we implement basic health interventions such as prenatal diagnosis, penicillin prophylaxis and vaccination for children under five years of age.[4]

Obesity is a major public health problem with significant impact on global morbidity, mortality and economic development. In developed regions, the age-standardised deaths per 100 000 population associated with high body mass index (BMI) decreased from 77.42 (CI: 65.37–89.31) in 1990 to 68.23 (CI: 59.09–77.06) in 2010, however in SSA the rates increased from 21.01 (CI: 14.73–28.28) to 37.85 (CI: 29.80–46.70) during the same period.[5] Likewise, in developed regions, the age-standardised DALYs associated with high BMI decreased from 1978.99 (CI: 1660.99–2299.62) in 1990 to 1914.45 (CI: 1649.36–2190.76) in 2010. On the contrary, the rates in SSA increased from 623.03 (431.17–842.82) in 1990 to 1 141.23 (CI: 889.99–1 412.23) in 2010.[5]

Global trends reflecting challenges and opportunities in achieving HLBS health include those existing on the domestic front. The 2013 US National Healthcare Disparities report demonstrates that there is ample room for improvement. The risk-adjusted in-patient mortality rate for heart attack hospital admissions fell significantly between 2001 and 2010 for each racial/ethnic and area income group; however residents of the lowest area income quartile had higher in-patient mortality rates than residents of the highest area income group in five of the 10 years evaluated.[6]

In 2008, Hispanic men and women were less likely to receive blood pressure measurements compared with their white counterparts. Furthermore, although vaccination for pneumococcal pneumonia is a cost-effective strategy for reducing illness, death and disparities associated with pneumonia and influenza, blacks and Asians were less likely than whites, and Hispanics were less likely than non-Hispanics to receive immunization, among the elderly who reported ever receiving pneumococcal vaccination.

Similarly, among hospital patients, age 50 years and above with pneumonia who received influenza immunisation status assessment or provision, black, Hispanic, American Indians/Alaskan natives (AI/AN) and Asian patients were less likely than white patients to receive influenza immunisation status assessment or provision. Also, among long-term nursing home residents, black, AI/AN, multiple-race and Hispanic residents were less likely than white residents to receive both influenza and pneumococcal immunisation.

From 2003 to 2010, the percentage of people with current asthma who reported taking preventative asthma medicine daily or almost daily fell from 29.6 to 26.5%. In five of eight years, blacks compared with whites, and poor and low-income people compared with high-income people, were less likely to take daily preventative asthma medicine.

New and evolving insights

The above noted trends occur in an era where new insights are reshaping our understanding of the complexities of disease mechanisms, while prompting us to contemplate transformative ways to prevent and pre-empt the burden of HLBS conditions. In the wake of recent reports, the intimate and intricate interplay between social and biological systems in the pathobiology of HLBS conditions is increasingly appreciated.

In the context of obesity, a central risk factor in the domain of HLBS disorders, the report by Christakis and Fowler evokes the notion of the social contagion of disease.[7] They demonstrated that obesity appears to spread though social ties, and therefore network phenomena may be relevant to the biological and behavioural trait of obesity. Simply stated, a socio-ecological construct underpins trends in disease evolution, which implies that it matters where we live, learn, work and play, and that culture, religion, war, food desserts and unhealthy diets all play into the determinants of HLBS conditions. The philosophy of social contagion of disease has profound implications for disease intervention, because if we are to successfully tackle inequities in HLBS conditions, we have to embrace the understanding that we are dealing with a complex multi-level problem that warrants a systems science intervention approach.[8,9]

The mechanisms by which socio-behavioural and biological factors interact in the pathobiology of disease are now increasingly palpable and not just a figment inspired by epidemiological studies. Recent evidence suggests a relationship between long-term dietary patterns and gut microbial enterotypes,[10] that a link exists between intestinal microbial metabolism and cardiovascular risk,[11] and that the microbiota of the gut is a potentially novel target for atherosclerosis prevention and treatment.[12] In addition to the emerging evidence for the impact of diet on human health via modulation of the composition of gut microbiome, we are reminded that complex genetic interplay attend disease mechanisms, and therefore can inform our approaches for risk prediction, pharmacogenomics and new therapies, particularly in the context of genomic-based medicine strategies to reduce health inequities.[13,14]

Challenges and opportunities

The above insights should inspire the deployment of systems science in search of major proximal targets in the socio-ecological model that could lead to a transformative impact on HLBS conditions. Despite the challenge of austere budgets for biomedical research, we remain committed to making a transformative impact by maintaining a balanced portfolio to reflect the strategic goals of the NHLBI, which include promoting the understanding of human health and disease, translating basic research into preventative and therapeutic interventions, and developing a biomedical workforce with the requisite set of skills for advancing HLBS research. There also exists the challenge of maintaining a balance between achieving these goals and encouraging creativity. These challenges converge to significantly impact on our decisions and approaches for tackling health inequities at home or abroad to advance the unfinished business of maximising the public health impact.

In the focus on addressing health inequities, we often fail to recognise the extraordinary resilience and resourcefulness of people working to improve health in high-risk communities. As we work collectively to overcome the challenge of reducing global health inequities, we should recall the admonition of Theodore Roosevelt: 'Do what you can, with what you have, where you are'. This is an opportune moment in history to tap in to the resilience and resourcefulness of this 'beloved' global community in order to create a collective future in which population health systems serve to promote the health of the entire human family, and we bend the curves of health inequities at the domestic and global level.

The optimum approach for addressing this question is to catalyse systems science, which will entail the employment of community health knowledge networks; a diverse pool of cross-disciplinary investigators; and leveraging NHLBI study platforms such as health systems clinical or population-based cohorts to optimise the prediction, pre-emption and treatment of HBLS conditions using new tools and platforms. Herein, outstanding possibilities attend the confluence of advances in genomics research and technology, imaging, informatics, computational modelling, stem cell research, nanotechnology and bioengineering, and collaborative knowledge-intervention networks. These new tools and platforms provide impetus for us to consider transformative questions.

What if we could develop new paradigms for citizen-enabled community health and next-generation cardiovascular disease

prevention, i.e. networks and systems of learning communities that continually seek wellness and innovate to improve health? What if we were able to realise precision and personalised medicine to prevent and pre-empt the burden of cardiovascular, lung and blood diseases? What if we could eliminate stroke and cognitive impairment in persons living with SCD by providing access to the benefits of chronic blood transfusions,[15] or better still, what if we could find ways to up-regulate modifier genes or identify new vasculopathy targets that could completely transform the landscape of cerebrovascular outcomes in SCD patients?

While we seek novel approaches, including systems science, new tools and platforms and genomics, we would be remiss if we forgot implementation research, which is paramount for advancing adherence to best practices for health promotion: diets rich in fruits and vegetables, physical activity, tobacco avoidance or smoking cessation; and the prevention and treatment of cardinal risk factors such as high blood pressure, dyslipidaemia and diabetes, which are central to HLBS conditions. In this regard, can we imagine the hypothetical scenario wherein we optimally disseminate and implement evidence-based 'best buy' approaches, with the resultant improvement in the social wellbeing and productivity of many around the world?

Conclusion

The importance of disease prevention and treatment, as well as the social significance of science, call for collaborative partnerships in response to adverse trends in HLBS conditions and related disorders, both at the domestic and global fronts. It is gratifying to observe the evolution of such a collaborative network under the umbrella of the H3Africa initiative. The SSA region as well as the USA will benefit immensely from such partnership models in an effort to rise to the emerging challenges posed by the growth of HLBS diseases and risk factors.

More importantly, vertical integration of efforts across continents may prove to be very helpful and synergistic as we seek to discover new targets or transformative approaches for maximising population-level impact and consequently reduce health inequities. For instance, lessons learned from novel approaches for improving outcomes among SCD patients in SSA may be very helpful for SCD patients in the domestic USA. Therefore there are benefits that can come full circle when we address life's most persistent and urgent question, as eloquently posed by Dr Martin Luther King Jr: 'What are we doing for others?' This is the era to create a collective future, because the concept of collective destinies could not be more palpable than it is now.

References

1. The NHLBI Mission Statement. http://www.nhlbi.nih.gov/about/org/mission. Accessed December 26, 2014.
2. Mensah GA, Kiley J, Mockrin SC, Lauer M, Hoots WK, Patel YC, *et al*. National Heart, Lung, and Blood Institute Strategic Visioning: Setting an agenda together for the NHLBI of 2025. *Am J Public Health* 2015: e1–e4.
3. Sampson UK, Mensah GA, Foroufanzar MH, Roth G, Naghavi M, Ezzati M, *et al*. The burden of sickle cell disease: a comparison of global and sub-Saharan African estimates of disability adjusted life years. H3Africa Cardiovascular Workshop, Stellenbosch, South Africa, 2014.
4. Piel FB, Hay SI, Gupta S, Weatherall DJ, Williams TN. Global burden of sickle cell anaemia in children under five, 2010–2050: modelling based on demographics, excess mortality, and interventions. *PLoS Med* 2013; **10**: e1001484.
5. Sampson UK, Mensah GA, Foroufanzar MH, Roth G, Naghavi M, Ezzati M, *et al*. The burden of high body mass index from 1990 to 2010: a comparison of sub-Saharan Africa and developed regions. H3Africa Cardiovascular Workshop, Stellenbosch, South Africa, 2014.
6. National Healthcare Disparities Report (2013). U.S. Department of Health and Human Services, Agency for Healthcare Research and Quality. http://www.ahrq.gov/research/findings/nhqrdr/nhqr13/2013nhqr.pdf. December 26, 2014.
7. Christakis NA, Fowler JH. The spread of obesity in a large social network over 32 years. *N Engl J Med* 2007; **357**: 370–379.
8. Barabasi AL. Network medicine – from obesity to the "diseasome". *N Engl J Med* 2007; **357**: 404–407.
9. Miranda ML, Ferranti J, Strauss B, Neelon B, Califf RM. Geographic health information systems: a platform to support the 'triple aim'. *Health Affairs* 2013; **32**: 1608–1615.
10. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, *et al*. Linking long-term dietary patterns with gut microbial enterotypes. *Science* 2011; **334**: 105–108.
11. Tang WH, Wang Z, Levison BS, Koeth RA, Britt EB, Fu X, *et al*. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N Engl J Med* 2013; **368**: 1575–1584.
12. Wang D, Xia M, Yan X, Li D, Wang L, Xu Y, *et al*. Gut microbiota metabolism of anthocyanin promotes reverse cholesterol transport in mice via repressing miRNA-10b. *Circ Res* 2012; **111**: 967–981.
13. Thomson R, Genovese G, Canon C, Kovacsics D, Higgins MK, Carrington M, *et al*. Evolution of the primate trypanolytic factor APOL1. *Proc Natl Acad Sci USA* 2014; **111**: E2130–2139.
14. Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, *et al*. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science* 2010; **329**: 841–845.
15. Verduzco LA, Nathan DG. Sickle cell disease and stroke. *Blood* 2009; **114**: 5117–5125.

Review Articles

Rheumatic heart disease in Africa: is there a role for genetic studies?

Ana Olga Mocumbi

Abstract

Rheumatic heart disease (RHD) constitutes a leading cause of premature death and incapacity in Africa, where it is encountered in younger people, and shows a much faster and more malignant course than that seen in Europe or North America. While it is well established that RHD is a consequence of recurrent, untreated group A β-haemolytic streptococcal infections (GAS), the pathogenesis is incompletely understood, and the variation in natural history and phenotypes are not fully explained. In Africa patients are rarely diagnosed with acute rheumatic fever (ARF). They usually present in the late stages of RHD, with the severe and virulent forms occurring at early ages, therefore leading to high morbidity and mortality in young patients.

Evidence suggests that genetic factors may be involved in determining susceptibility to ARF as well as the severity and outcomes of RHD. However, the results of genetic studies have been inconsistent, and conflicting results have been found in series from Africa when compared to other parts of the globe. Genetic studies in the African context are therefore justified to understand the genomic and epigenetic drivers of heterogeneity in individual responses to GAS infections and progression to RHD. Platforms such as the global registry of RHD represent an opportunity for adequately powered genome-wide association studies. The discovery of all genetic susceptibility loci through whole-genome scanning may provide a clinically useful genetic risk-prediction tool that will potentially allow echocardiographic screening and secondary prophylaxis for moderate lesions to be directed to those at higher risk, therefore reducing the burden of the disease to the health system, the work health force and the communities of this resource-strained continent.

Keywords: rheumatic fever, rheumatic heart disease, genetic susceptibility

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Epidemiology of ARF and RHD

The global burden of disease caused by rheumatic fever (RF) and rheumatic heart disease (RHD) currently falls disproportionately on children living in the developing world and in marginalised communities where poverty is widespread. Acute rheumatic fever (ARF) follows in 0.4 to 3.0% of cases of group A β-haemolytic streptococcal pharyngitis (GAS) in children. It is thought that as many as 39% of patients with acute rheumatic fever may develop varying degrees of pancarditis with associated valve regurgitation and heart failure and in some cases death. RHD is the only long-term consequence of ARF, and the most serious.[1] Progression to chronic RHD is determined by several factors, among which, repeated episodes of rheumatic fever seem to be the most important.

The World Health Organisation (WHO) reported trends in the incidence and prevalence of ARF and RHD for each continent,[2] based on literature from 100 countries around the world between 1970 and 2009. These studies on ARF incidence and RHD prevalence used population-based screening, national health registries, prospective disease surveillance, surgical series, autopsy series, and retrospective reviews of hospital admissions or discharges for ARF or RHD. However, data from Africa are scarce and do not capture the entire timeframe. According to this study, the reported incidence of ARF is decreasing in all WHO regions, except for the Americas and the western Pacific, where it appears to be increasing. The prevalence of RHD is increasing in all regions except for Europe, where it appears to be decreasing.[2]

A systematic review and meta-analysis of population-based studies published between January 1993 and June 2014 recently reported on the prevalence of RHD among children and adolescents assessed in 37 populations, six of which were from Africa.[3] It revealed a prevalence of RHD detected by cardiac auscultation at 2.9 per 1 000 individuals and by echocardiography at 12.9 per 1 000 people, with substantial heterogeneity between individual reports for both screening modalities. Prevalence of clinically silent RHD in this study (21.1 per 1 000) was about seven to eight times higher than that of manifest disease (2.7 per 1 000). Prevalence progressively increased with advancing age, from 4.7 per 1 000 at age five years to 21.0 per 1 000 people at 16 years. There was no gender-related differences in prevalence; an association was found between social inequality expressed by the Gini coefficient and prevalence of RHD ($p = 0.0002$).[3]

The exact incidence and prevalence of RHD in Africa are unclear because of the recognised differences in epidemiology between countries, availability of diagnostic approaches, differences between rural and urban environment, age groups included in the study, and more importantly, lack of knowledge

about the outcome of the mild lesions found in community-based studies on asymptomatic children. In Western countries, marked reduction in RHD prevalence occurred with improvement in health systems (education of health professionals for quicker diagnosis and correct management with antibiotics) and socio-economic status (less overcrowding, education of the population).

RHD was the leading cause of death 100 years ago in people aged five to 20 years in the United States but, as in other developed countries, its incidence has declined.[4] This reduction is related to the adequate treatment of streptococcal pharyngitis with penicillin, as well as less overcrowding, better sanitation and improvement in general living conditions. The incidence of ARF has dropped dramatically since the 1960s; a few localised outbreaks of GAS occurred in civilian and military populations in the 1980s.[4] The reported increase in RHD prevalence[2] is likely to be related to increased survival due to advances in diagnosis, and medical and surgical treatments for RHD.

RHD remains the most common cardiovascular disease in people under 25 years and is the leading cause of valve disease in developing countries.[5,6] The African continent has the highest prevalence in the world,[2] and RHD represents the most common form of acquired cardiovascular disease in children and adolescents.[7] RHD affects between 15.6 and 19.6 million people worldwide and causes 233 000 to 492 000 deaths annually,[8] imposing a substantial burden on the families, health systems and communities in many low-income settings.

Screening with portable echocardiography has uncovered a large burden of latent RHD among asymptomatic children in endemic regions of Africa,[9,10] the significance of which remains unclear.[11] In marked contrast, there are almost no data on ARF, probably related to low access to healthcare, inadequate resources for diagnosis of throat and skin streptococcal infection, lack of awareness of the importance of correct treatment of bacterial pharyngitis, and overall, to the absence of national prevention and control programmes. These usually allow notification of the disease and the institution of long-term secondary prophylaxis to those at risk of developing RHD.

The reduction in the burden of ARF and RHD among the less than 20% of the world's population living in high-income countries has led to a decrease in research on rheumatic fever (RF) and RHD.[12] Despite being a major cause of premature death and disability, the pathogenesis is still incompletely understood, the natural history is not fully explained, phenotypes have been only partially described, and some aspects of management remain debatable.

Pathogenesis of ARF and RHD

Throat infection by GAS is the common trigger for RF/RHD. In resource-limited tropical settings however, where both impetigo and rheumatic disease are endemic, there is a growing body of opinion implicating impetigo in the pathogenesis of rheumatic fever and rheumatic heart disease.[13] Repeated GAS infection is necessary for the first episode of ARF to occur, and similarly, RHD usually develops due to cumulative damage to the heart valves secondary to recurrent episodes of ARF.[14]

Molecular mimicry explains the triggering of RF, but an intense and sustained inflammation is needed to cause sequelae.[15,16] Antigens in the cell wall and cell membrane of GAS are immunologically similar to molecules in human myosin, tropomyosin, actin, laminin and other common proteins. GAS carbohydrate epitope (N-acetyl glucosamine) and the α-helical coiled-coil streptococcal M protein structurally mimic cardiac myosin.[17] When GAS antigens reach the blood, they are recognised by B cells in the spleen; they may also enter the lymph and be recognised by B cells in local lymph nodes.

B cells specific for GAS antigens become activated and begin to proliferate and secrete antibodies, activate complement and promote the opsonisation and phagocytosis of the bacteria.[16,18] An autoimmune response is triggered in susceptible children, in whom antibodies against streptococcal antigens (mainly the M protein) cross-react with heart tissue proteins such as cardiac myosin (in the myocardium) and laminin (on valve endothelium and basement membrane).[17] At the same time, antigens taken up at the site of infection by antigen-presenting cells become activated and migrate to local lymph nodes where they present the antigens to T cells. Activated T cells begin to proliferate and additionally stimulate B cells to produce antibodies against the GAS antigens. It is believed that both T cell and antibody cross-reactions occur between GAS and host proteins.[19]

In rheumatic carditis, attachment of anti-GAS antibodies to the myocardium and valve endothelium leads to the release of inflammatory cytokines that up-regulate vascular cell adhesion molecule-1 (VCAM-1) on the valve surface endothelium; this up-regulation of VCAM-1 promotes lymphocyte adhesion to the endothelium and subsequent infiltration of lymphocytes into the valve. Both inflammatory (transforming necrosis factor-alpha: TNF-α, and interferon-gama: IFN-γ) and regulatory (interleukin: IL-4) cytokines are produced, increasing local inflammatory reactions in both the myocardium and the valves. Granulomatous lesions containing lymphocytes and macrophages are formed, the so-called Aschoff nodules, which are identifiable and regarded as pathognomonic for rheumatic carditis.[20]

The initial attack with ARF increases vulnerability to reactivation of the disease, with subsequent pharyngeal infection.[21] Exposure of the valve surface to inflammation ensures further binding of cross-reactive antibodies to the valve, leading to endocarditis, which is on the basis of rheumatic heart valve disease (RHVD),[16] and the lack of production of regulatory cytokines may contribute to permanent valve damage.[18.] Chronic RHVD can result from a single episode of ARF, but usually follows repeated episodes of ARF, with cumulative valve damage occurring due to fibrotic healing of acute inflammatory lesions and turbulent flow induced by ongoing valve damage.[22] The major morphological changes of the valves include commissural fusion, shortening and fusion of the chordae tendinae, and leaflet thickening.[23]

Gaps in knowledge and management

Although the diagnosis of GAS pharyngitis may be suspected on clinical examination, several procedures are involved in its confirmation, because clinical presentation performance as a diagnostic test is low. Laboratory test availability is important, especially culture, virulence test, antibiotic sensitivity, C-reactive protein and erythrosedimentation rate.[24] Because these examinations are expensive and time consuming, rapid antigen testing is a more attractive solution for Africa.[25] Therefore the diagnosis of ARF relies on a high index of suspicion from

health workers, a high level of awareness of the community, and laboratory criteria of recent infection or previous ARF.

Some symptoms and signs included on the Jones criteria are unspecific and may be present in various febrile conditions affecting children in Africa. Moreover, the time gap between GAS infection and the occurrence of ARF is variable, and therefore many patients do not recall having had pharyngitis. Therefore ARF is usually underdiagnosed in developing countries.[26] Additionally, many patients are not correctly treated, secondary prophylaxis is not instituted and progression to RHD occurs, explaining the high incidence of newly diagnosed RHD in adults.[27]

Subclinical disease is commonly found in Africa when echocardiographic screening is used.[9-11] The advent of portable battery-powered ultrasound machines has allowed access to the communities and recognition of the need for an update of the WHO criteria for echocardiographic diagnosis of subclinical RHD. It has been suggested that in endemic areas the diagnosis can be based on the presence of pathological valve regurgitation without considering the morphological features of the valves.[28]

African scientists were also part of the World Heart Federation panel of experts that created a set of screening criteria using morphological and Doppler features, aimed at standardising the diagnosis across different areas of the world.[29] Therefore, although echocardiographic diagnosis of RHD is not yet readily available in some parts of Africa, its use has allowed better characterisation of cardiac abnormalities, definition of the natural history of the disease and assessment of the current practice in managing these patients on the continent. The Global Registry of RHD[30] confirmed the extremely virulent forms of chronic RHVD in Africa.

RHD in Africa is encountered in young people, showing a much faster and malignant progression of cardiac involvement than that seen in Europe or North America.[31] Severe disease and rapid progression to complications such as mitral stenosis, heart failure and atrial fibrillation occur at younger ages.[30-32] It is believed that this pattern results from environmental factors such as higher occurrence of skin and pharyngeal streptococcal infections in these settings, recurrent GAS infections early in life, inadequate treatment of GAS infections, and inappropriate secondary prophylaxis after the first episode of RF, but the role of host specificity in determining the malignant course of the disease in Africa cannot be excluded.

Benzathine penicillin G (BPG), the gold standard for secondary prophylaxis of RF/RHD, is usually administered every three or four weeks. Occurrence of ARF in patients on adequate secondary prophylaxis with BPG has been attributed to the low quality of the product, inadequate storage, inappropriate technique for injection, and incorrect dosage for the patient's weight.[33]

Knowing that HLA-DRA variants were found to predict penicillin allergy in genome-wide fine-mapping genotyping, one may speculate on the need to explore whether genetic polymorphisms determine differences in pharmacokinetics and/or pharmacodynamics of penicillin in African individuals. This is of particular relevance considering that the correct management of GAS pharyngitis and secondary prophylaxis of RF with penicillin prevent the occurrence of RHD. Currently, there are no data to support a higher occurrence of penicillin allergy in Africa than is seen in other parts of the globe. However, of importance for the implementation of control programmes in Africa, it has been suggested that analysis of gene variants of HLA-DRA and the HLA-DRA|HLA-DRB5 inter-region, which may be significant predictors of allergy to penicillin, should occur in African populations.[34]

The role of genetic studies

ARF and RHD are caused by a combination of immune, environmental and genetic factors. While the role of GAS and social conditions that determine progression to RHD is well understood,[35,36] there is a major gap in knowledge of the mechanisms of host susceptibility to the disease.[28] Familial aggregation, similarity of disease patterns between siblings, concordance of disease in identical twins, and HLA correlation studies are evidence for a genetic influence on RF susceptibility.[37] A systematic review and meta-analysis of 435 twin pairs from six independent studies concluded that ARF has high heritability, estimated at 60% across all the studies; the pooled proband-wise concordance risk for ARF was 44% in monozygotic twins and 12% in dizygotic twins.[38]

Only 0.4 to 3.0% of patients with untreated GAS pharyngitis develop ARF, but higher attack rates occur when a stronger host immune response occurs, approaching 50% in patients with a prior episode of ARF. In patients with the first episode of ARF, the rate of progression to RHD will differ, probably being related not only to environmental factors such as the high recurrence of GAS and different virulence of the circulating GAS, but also to a particular immune response geared by genetic susceptibility.[37] Similarly, the genetic background directing the immune response towards a predominantly Th1 or Th2 pattern may contribute to explain variations in RF clinical phenotype by modulating the intense and sustained inflammation that is needed to cause sequelae such as RHD.[17,37]

Inherited susceptibility to ARF was initially studied around the major histocompatibility class II human leucocyte antigens (HLA). Several genes associated with RHD have been described, most of them involved with immune responses.[39] Given the current state of the literature, it is hard to make generalisations

Table 1. RHD genetic susceptibility; HLA class II alleles found in studies in patients from different regions of the globe (adapted from Guillerme *et al*.[39] and updated).

Continent	*Country, reference*	*HLA class II alleles*
Africa	South Africa	DR1, DR6
	Uganda	DR1, DR11
	Egypt	DRB1*0701, DQA1*0201, DRB1*13, QA1*0501/0301
Americas	United States of America	DR2 (Africans); DR4, DR6, DR9 (Caucasians)
	Mexico	DRB1*1602, DQB1*0301, DQA1*0501
	Martinique	DR1
	South Brazil	DR7, DR53
	India	DR3
	Kashmir	DR4
	Japan	DQB1*05031, DQA1*0104
	South China	DQA1*0101
	Saudi Arabia	DR4
Asia	Turkey	DR3, DR7, DR11
Europe	Latvia	DRB1*0701, DQB1*0302, DQB1*0401-2

Table 2. Genes found in ARF/RHD studies. The country and number of participants are indicated.

Author, year	*Country*	*Sample size*	*Genes*
Gupta *et al.* 2014[41-43]	India	400 RHD patients 300 controls	PTPN22 polymorphisms JAK/STAT polymorphisms
		300 RHD patients 200 controls	ACE I/D polymorphisms
Aksoy *et al.* 2011[49]	Turkey	120 RHD 160 controls	PTPN22 R620W gene polymorphism
Mahomed *et al.* 2010[44]	Saudi Arabia	80 RHD patients 50 controls	TNF-α polymorphisms
Kamal *et al.* 2010[47]	Egypt	73 RHD patients 55 controls	TGF-β1 polymorphisms

about a single 'rheumatic' HLA allele, and there are likely multiple HLA alleles that, in combination, increase an individual's susceptibility to ARF and RHD.[2]

HLA-D8/17 and HLA-DR7 types are the most represented in the literature, but many other HLA alleles have been identified in single studies of patients with ARF and RHD (Table 1), a variability that could be caused by genetic differences in the populations studied or differences in local streptococcal strains. A study in Uganda comparing the frequency of HLA class II DR alleles between RHD cases and healthy controls found HLA-DR1 to be more common in normal controls while HLA-DR11 was more common among RHD cases.[1] Candidate HLA gene studies that have been performed to date had small sample sizes and found inconsistent and conflicting results.[36,40] High-resolution HLA analysis and genome-wide association studies have therefore been recommended.

Single-nucleotide polymorphisms in a number of genes were found in patients with RHD compared to controls, namely protein tyrosine phosphatase non-receptor 22 (PTPN22),[41] signal transducers and activators of transcription (STAT),[42] angiotensin converting enzyme (ACE I/D),[43] TNF-α,[44,45] transforming growth factor (TGF-β1),[46,47] and TLR5[48] (Table 2). Studies in North Indians with RHD suggest that the (PTPN22) haplotype, which encodes an important negative regulator of T-cell activation, modulates the risk of developing RHD.[41] In a Turkish population, however, it was demonstrated that the PTPN22 R620W polymorphism was not associated with RHD,[49] showing that genetic differences exist among populations from different regions of the world, therefore making it relevant to implement similar studies in Africa.

Overall, the current knowledge of genetic susceptibility for RHD comes from small studies (Table 2). Moreover, because subclinical disease is frequent in Africa and RHD is diagnosed in the late stages, it is related to high morbidity rates, premature mortality and excessive social and economic costs. The finding of genetic biomarkers could direct the scarce resources available on the continent to those persons at higher risk, thus reducing the workload of health professionals, avoiding the high burden related to this condition, and improving outcomes.

The Global Registry of RHD[30] represents a platform for such genetic studies on RHD in Africa. These studies will improve our understanding of genomic and epigenetic drivers of heterogeneity in the response of different individuals to GAS infections, and explore the determinants and drivers of the variability in natural history, clinical phenotype, prognosis, and the role of genetic differences in determining allergy and drug resistance to penicillin in sub-Saharan Africa. The discovery of genetic susceptibility loci through whole-genome scanning may be clinically useful by introducing genetic risk-prediction tools for ARF and RHD.

Key messages

- ARF, the precursor of RHD, is usually underdiagnosed
- RHD is highly prevalent in Africa, where it affects much younger people
- ARF and RHD are caused by a combination of immune, environmental and genetic factors
- The magnitude of the genetic effect remains unclear but high heritability has been shown
- Africa has the most virulent and rapidly progressive forms of ARF and RHD
- Genetic studies may help to explore determinants of variability in the natural history and phenotype.

Conclusion

Research to determine the role of genetic factors in determining susceptibility to ARF and RHD in African populations is needed. These genetic studies in the African context may contribute to a greater understanding of the genomic and epigenetic drivers of heterogeneity in individual responses to GAS infections and progression to RHD. Discovery of genetic susceptibility loci through whole-genome scanning may provide a clinically useful genetic risk-prediction tool that will potentially allow echocardiographic screening and secondary prophylaxis to be directed to those at higher risk, thus reducing the burden of the disease on the health system, the work health force and the communities of this resource-strained continent.

References

1. Okello E, Beaton A, Mondo CK, Kruszka P, Kiwanuka N, Odoi-Adome R, *et al.* Rheumatic heart disease in Uganda: the association between MHC class II HLA DR alleles and disease: a case control study. *BMC Cardiovasc Disord* 2014; **14**: 28. doi: 10.1186/1471-2261-14-28
2. Seckeler MD, Hoke TR. The worldwide epidemiology of acute rheumatic fever and rheumatic heart disease. *Clin Epidemiol* 2011; **3**: 67–84. doi: 10.2147/CLEP.S12977.
3. Rothenbühler M, O'Sullivan CJ, Stortecky S, Stefanini GG, Spitzer E, Estill J, *et al.* Active surveillance for rheumatic heart disease in endemic regions: a systematic review and meta-analysis of prevalence among children and adolescents. *Lancet Glob Health* 2014; **2**(12): e717–726. doi: 10.1016/S2214-109X(14)70310-9.
4. Shulman ST, Stollermwan R, Beall B, Dale JB, Tanz RR. Temporal changes in streptococcal M protein types and the near-disappearance of acute rheumatic fever in the United States. *Clin Infect Dis* 2006; **42**: 441–447.
5. Remenyi B, Carapetis J, Wyber R, Taubert K, Mayosi BM; World Heart Federation. Position statement of the World Heart Federation on the prevention and control of rheumatic heart disease. *Nat Rev Cardiol* 2013; **10**(5): 284–292. doi: 10.1038/nrcardio.2013.34.
6. Maganti K, Rigolin VH, Sarano ME, Bonow RO. Valvular heart disease: diagnosis and management. *Mayo Clinic Proc* 2010; **85**(5): 483–500. doi: 10.4065/mcp.2009.0706.
7. WHO Regional Committee for Africa. Cardiovascular diseases in

the African region: current situation and perspectives – report of the regional director 2005. http://www.afro.who.int/rc55/documents/afr_rc55_12_cardiovascular.pdf
8. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. *Lancet Infect Dis* 2005; **5**: 685–694
9. Marijon E, Ou P, Celermajer DS, Ferreira B, Mocumbi AO, Jani D, *et al*. Prevalence of rheumatic heart disease detected by echocardiographic screening. *N Engl J Med* 2007; **357**: 470–476.
10. Rossi E, Felici AR, Banteyrga L. Subclinical rheumatic heart disease in an Eritrean high-school population, detected by echocardiography. *J Heart Valve Dis* 2014; **23**(2): 235–239.
11. Beaton A, Okello E, Aliku T, Lubega S, Lwabi P, Mondo C, *et al*. Latent rheumatic heart disease: outcomes 2 years after echocardiographic detection. *Pediatr Cardiol* 2014; **35**(7): 1259–1267. doi: 10.1007/s00246-014-0925-3.
12. Carapetis J. Rheumatic heart disease in developing countries. *N Engl J Med* 2007; **357**(5): 439–441.
13. Parks T, Smeesters PR, Steer AC. Streptococcal skin infection and rheumatic heart disease. *Curr Opin Infect Dis* 2012; **25**(2): 145–153. doi: 10.1097/QCO.0b013e3283511d27.
14. Viswanathan V. Acute rheumatic fever. *Indian J Rheumatol* 2012; 7(1): 36–43.
15. Delunardo F, Scalzi V, Capozzi A, Camerini S, Misasi R, Pierdominici M, *et al*. Streptococcal-vimentin cross-reactive antibodies induce microvascular cardiac endothelial proinflammatory phenotype in rheumatic heart disease. *Clin Exp Immunol* 2013; **173**(3): 419–429. doi: 10.1111/cei.12135.
16. Guilherme L, Kalil J. Rheumatic fever and rheumatic heart disease: cellular mechanisms leading autoimmune reactivity and disease. *J Clin Immunol* 2010; **30**: 17–23.
17. Guilherme L, Kalil J. Rheumatic heart disease: molecules involved in valve tissue inflammation leading to the autoimmune process and anti-S. pyogenes vaccine. *Front Immunol* 2013; **4**: 352. doi: 10.3389/fimmu.2013.00352.
18. Guilherme L, Kalil J. Rheumatic fever – from innate to acquire immune response. *Ann NY Acad Sci* 2007; **1107**: 426-433
19. Cunningham MW. Molecular mimicry, autoimmunity and infection in the pathogenesis of rheumatic fever. *Int Congr Ser* 2006; **1289**: 14–19.
20. Love GL, Restrepo C. Aschoff bodies of rheumatic carditis are granulomatous lesions of histiocytic origin. *Mod Pathol* 1988; **1**(4): 256–261.
21. Kumar V, Abbas AK, Fausto N, Aster JC. *Robbins and Cotran Pathologic Basis of Disease.* 8th edn. Philadelphia: Elsevier Inc, 2010.
22. McPhee SJ, Papadakis MA. *2011 Current Medical Diagnosis & Treatment.* 50th edn. United States: McGraw-Hill, 2011.
23. Marijon E, Mirabel M, Celermajer DS, Jouven X. Rheumatic heart disease. *Lancet* 2012; **379**: 953–964.
24. Júnior AR, Oliveira CD, Fontes MJ, Lasmar LM, Camargos EP. Diagnosis of streptococcal pharyngotonsillitis in children and adolescents: clinical picture limitations. *Rev Paul Pediatr* 2014; **32**(4): 285–291. doi: 10.1016/j.rpped.2014.04.001. Portuguese.
25. Leung AK, Newman R, Kumar A, Davies HD. Rapid antigen detection testing in diagnosing group A β-hemolytic streptococcal pharyngitis. *Expert Rev Mol Diagn* 2006; **6**(5): 761–766.
26. Parks T, Kado J, Colquhoun S, Carapetis J, Steer A. Underdiagnosis of acute rheumatic fever in primary care settings in a developing country. *Trop Med Int Health* 2009; **14**: 1407–1413. doi: 10.1111/j.1365-3156.2009.02385.x
27. Sliwa K, Carrington M, Mayosi BM, Zigiriadis E, Mvungi R, Stewart S. Incidence and characteristics of newly diagnosed rheumatic heart disease in urban African adults: insights from the heart of Soweto study. *Eur Heart J* 2010; **31**(6): 719–727. doi: 10.1093/eurheartj/ehp530. Epub 2009 Dec 7.
28. Marijon E, Mirabel M, Celermajer DS, Jouven X. Rheumatic heart disease. *Lancet* 2012; **379**: 953–964.
29. Reményi B, Wilson N, Steer A, Ferreira B, Kado J, Kumar K, *et al*. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease – an evidence-based guideline. *Nat Rev Cardiol* 2012; **9**(5): 297–309.
30. Zühlke L, Engel ME, Karthikeyan G, Rangarajan S, Mackie P, Cupido B, *et al*. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). *Eur Heart J* 2014. pii: ehu449.
31. Essop MR, Nkomo VT. Rheumatic and Non-rheumatic valvular heart disease: epidemiology, management and prevention in Africa. *Circulation* 2005; **112**: 3584–3591.
32. Tadele H, Mekonnen W, Tefera E. Rheumatic mitral stenosis in children: more accelerated course in sub-Saharan patients. *BMC Cardiovasc Dis* 2013; **13**: 95. doi:10.1186/1471-2261-13-95.
33. Currie BJ. Are the currently recommended doses of benzathine penicillin G adequate for secondary prophylaxis of rheumatic fever? *Pediatrics* 1996; **97**(6 Pt 2): 989–991.
34. Guéant JL, Romano A, Cornejo-Garcia JA, Oussalah A, Chery C, Blanca-López N, *et al*. HLA-DRA variants predict penicillin allergy in genome-wide fine-mapping genotyping. *J Allergy Clin Immunol* 2014. pii: S0091-6749(14)01051-3. doi: 10.1016/j.jaci.2014.07.047
35. Cunningham MW. Streptococcus and rheumatic fever. *Curr Opin Rheumatol* 2012; **24**: 408–416.
36. Gourley M, Miller FW. Mechanisms of disease: environmental factors in the pathogenesis of rheumatic disease. *Nat Clin Pract Rheum* 2007; **3**: 172–180.
37. Azevedo PM, Pereira RR, Guilherme L. Understanding rheumatic fever. *Rheumatol Int* 2012; **32**(5): 1113–1120. doi: 10.1007/s00296-011-2152-z.
38. Engel ME, Stander R, Vogel J, Adeyemo AA, Mayosi BM. Genetic susceptibility to acute rheumatic fever: a systematic review and meta-analysis of twin studies. *PLoS One* 2011; **6**(9): e25326. doi: 10.1371/journal.pone.0025326. Epub 2011 Sep 30.
39. Guilherme L, Köhler K F, Postol E, Kalil J. Genes, autoimmunity and pathogenesis of rheumatic heart disease. *Ann Pediatr Card* 2011; **4**: 13–21.
40. Bryant PA, Robins-Browne R, Carapetis JR, Curtis N. Some of the people, some of the time: Susceptibility to acute rheumatic fever. *Circulation* 2009; **119**: 742–753.
41. Gupta U, Mir SS, Chauhan T, Garg N, Agarwal SK, Pande S, *et al*. Influence of protein tyrosine phosphatase gene (PTPN22) polymorphisms on rheumatic heart disease susceptibility in North Indian population. *Tissue Antigens* 2014; **84**(5): 492–496.
42. Gupta U, Mir SS, Srivastava A, Garg N, Agarwal SK, Pande S, Mittal B. Signal transducers and activators of transcription (STATs) gene polymorphisms related with susceptibility to rheumatic heart disease in north Indian population. *Immunol Lett* 2014; **161**(1): 100–105.
43. Gupta U, Mishra A, Rathore SS, Agarwal SK, Pande S, Garg N, Mittal B. Association of angiotensin I-converting enzyme gene insertion/deletion polymorphism with rheumatic heart disease in Indian population and meta-analysis. *Mol Cell Biochem* 2013; **382**(1–2): 75–82.
44. Mohamed AA, Rashed LA, Shaker SM, Ammar RI. Association of tumor necrosis factor-alpha polymorphisms with susceptibility and clinical outcomes of rheumatic heart disease. *Saudi Med J* 2010; **31**(6): 644–649.
45. Rehman S, Akhtar N, Ahmad W, Ayub Q, Mehdi SQ, Mohyuddin A.

Human leukocyte antigen (HLA) class II association with rheumatic heart disease in Pakistan. *J Heart Valve Dis* 2007; **16**(3): 300–304.
46. Chou HT, Chen CH, Tsai CH, Tsai FJ. Association between transforming growth factor-beta 1 gene C-509T and T869C polymorphisms and rheumatic heart disease. *Am Heart J* 2004; **148**(1): 181–186.
47. Kamal H, Hussein G, Hassoba H, Mosaad N, Gad A, Ismail M. Transforming growth factor-beta1 gene C-509T and T869C polymorphisms as possible risk factors in rheumatic heart disease in Egypt. *Acta Cardiol* 2010; **65**(2): 177–183.
48. Zhu L, Zou LJ, Hua R, Li B. Association of single-nucleotide polymorphisms in toll-like receptor 5 gene with rheumatic heart disease in Chinese Han population. *Int J Cardiol* 2010; **145**(1): 129–130. doi: 10.1016/j.ijcard.2009.06.046. Epub 2009 Jul 17.
49. Aksoy R, Duman T, Keskin O, Düzgün N. No association of PTPN22 R620W gene polymorphism with rheumatic heart disease and systemic lupus erythematosus. *Mol Biol Rep* 2011; **38**(8): 5393–5396.

The burden of stroke in Africa: a glance at the present and a glimpse into the future

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Abstract

Objective: Information on the current burden of stroke in Africa is limited. The aim of this review was to comprehensively examine the current and projected burden of stroke in Africa.
Methods: We systematically reviewed the available literature (PubMed and AJOL) from January 1960 and June 2014 on stroke in Africa. Percentage change in age-adjusted stroke incidence, mortality and disability-adjusted life years (DALYs) for African countries between 1990 and 2010 were calculated from the Global Burden of Diseases (GBD) model-derived figures.
Results: Community-based studies revealed an age-standardised annual stroke incidence rate of up to 316 per 100 000 population, and age-standardised prevalence rates of up to 981 per 100 000. Model-based estimates showed significant mean increases in age-standardised stroke incidence. The peculiar factors responsible for the substantial disparities in incidence velocity, ischaemic stroke proportion, mean age and case fatality compared to high-income countries remain unknown.
Conclusions: While the available study data and evidence are limited, the burden of stroke in Africa appears to be increasing.

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African countries are undergoing an epidemiological transition driven by socio-demographic and lifestyle changes.[1] The burden of non-communicable diseases (NCD), including cardiovascular risk factors is increasing.[1-3] Consequently, the incidence of stroke, a cardinal complication of cardiovascular risk factors, appears to be rising in Africa and other low- and middle-income country (LMIC) settings.[3] Therefore, 86% of all stroke deaths around the world is contributed by LMIC in Africa and other continents.[4] By contrast, the incidence of stroke appears to be declining in high-income countries.[4,5]

Ironically, there is insufficient information on the current epidemiology of stroke in African countries and other LMICs, where this knowledge is needed most. This is due to and contributes to deficient manpower and other resources to combat the epidemic.[6] Accurate, up-to-date information on stroke burden is necessary for the development and evaluation of effective and efficient preventative acute care and rehabilitation programmes for stroke patients.

In an attempt to fill this gap, in 2013 and 2014, the Global Burden of Diseases (GBD) collaborators published data on the burden of stroke and stroke subtype based on multi-state models implemented in the software program DisMod III. These models were used to estimate the incidence, prevalence and disability-adjusted life years (DALYs) of ischaemic and haemorrhagic stroke in various countries across the globe but without specific focus on Africa.[2,7]

However, one meta-analysis[8] focused solely on the prevalence and incidence of stroke in Africa, albeit with pooled data of uneven quality. In addition, there are some publications derived from primarily hospital-based data on the burden of stroke in Africa. Nevertheless, no recent publication has examined the burden of stroke in Africa, longitudinally and in its entirety,[9] while identifying gaps in data and proposing appropriate interventions. This complete longitudinal picture is

urgently needed for the design of appropriate interventions and the formulation of policy objectives within the framework of T4 (system and policy level) and T5 (global) translational science.[10]

The objectives of this systematic review were to examine the current burden and recent epidemiological trends of stroke in Africa using available resources (existing epidemiological data and models) while identifying knowledge gaps; and estimating the future burden and proposing a responsive and holistic action plan to control the epidemic. This comprehensive analysis will include data on incidence, mortality, case fatality, prevalence, DALYs, quality of life, vascular cognitive impairment, and cost of care.

Methods

A systematic review of the literature was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11] PubMed database was searched for 'Africa' combined with each of the following keywords: 'stroke', 'cerebrovascular accident', 'intracerebral hemorrhage' and 'subarachnoid hemorrhage'. Further search was conducted using combinations of the keywords and sub-Saharan African countries such as 'stroke Nigeria'. Other words were also used in association with the keywords, country names and Africa. These were 'epidemiology', 'prevalence', 'incidence' and 'mortality'. Background references and citations were identified and screened to obtain more articles. Articles were included in the quantitative synthesis if they had an abstract in English, were published between January 1960 and October 2014, and described the epidemiological burden or determinants of stroke in Africa whether it was original or not.

The search yielded a total of 1 274 articles (Fig. 1). All the articles were initially screened by one reviewer. We excluded 404 articles that were indexed in both PubMed and AJOL, did not have abstracts or full text in English, or were not based on human studies. Two reviewers read the remaining 870 articles in full to assess their eligibility for the quantitative synthesis. Fig. 1 shows the details of the review selection process. In addition, data were extracted from Global Burden of Diseases (GBD) model-derived figures.

Statistical analysis was performed to calculate percentage change in age-adjusted stroke incidence, mortality and DALYs for African countries between 1990 and 2010.

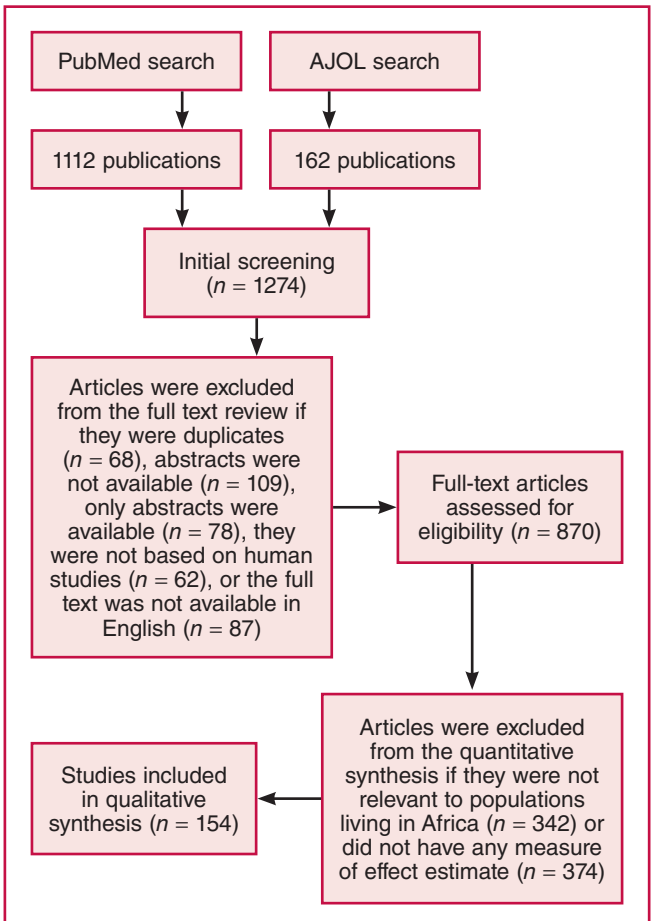

Fig. 1. Review selection process. AJOL: African Journals online.

Results and Discussion

Incidence

Studies of stroke in Africa are mostly hospital-based case series. Hospital-based data cannot provide prevalence or incidence estimates (Tables 1, 2) because the population at risk (i.e. the denominator) is not known. Moreover, they are also affected by referral bias. Patients who die quickly from stroke or those with mild stroke may not be captured.[12] Nevertheless, case series provide information about the relative frequency of stroke in comparison to other diseases requiring hospitalisation.

Stroke is the leading cause of medical coma in Nigeria.[13] It is also the leading cause of admissions from hypertension-related complications, accounting for 40% of hypertensive complications in the University of Port Harcourt Teaching

Table 1. Studies reporting crude incidence of stroke in Africa

			Crude incidence per 100 000 per year			
Year	*Country/location/setting*	*Author*	*Overall*	*Male*	*Female*	*Age*
	Hospital-based					
1984	Libya, Benghazi, urban	Ashok[28]	63	69	58	15+
1985	South Africa: Atteridgeville and Mamelodi, suburban areas of Pretoria, urban	Rosman[29]	101	108	93	20+
1991	Zimbabwe, Harare, urban	Matenga[18]	31	30	32	All
1993	Libya, Benghazi, urban	El Zunni[30]	48	52	42	15+
2006	Mozambique, Maputo, urban	Damasceno[19]	149	174	128	15+
	Population/community-based					
1975	Nigeria, Ibadan, urban	Osuntokun[20]	26	25	13	All
1993	Egypt, Sohag, mixed*	Kandil[31]	180	100	85	All
1993	Egypt, Sohag, urban	Kandil[31]	150	90	53	All
1993	Egypt, Sohag, rural	Kandil[31]	210	97	119	All
2006	Tanzania, Hai, rural	Walker[32]	95	107	77	All
2006	Tanzania, Dares Salaam, urban	Walker[32]	108	115	100	All
2007	Nigeria, Lagos, urban	Danesi[24]	25	28	21	All
2007	Egypt, Al-Kharga, mixed*	Farghaly[22]	250	270	230	All
2007	Egypt, Al-Kharga, rural	Farghaly[22]	230	250	220	All
2007	Egypt, Al-Kharga, urban	Farghaly[22]	260	280	240	All
2012	Egypt,Al Quseir, urban	El Tallawy[21]	181	212	150	20+

*Combined rates including both rural and urban communities.

Hospital, Nigeria.[14] In several studies from the West African sub-region, it emerged as the leading cause of adult neurological admissions, constituting up to 65% of such admissions.[15]

Furthermore, a steady increase in stroke admissions has been observed in some institutions that have monitored their stroke admissions over time. In Tanzania, stroke admissions increased from 23 per 100 000 in 1935 to 86 per 100 000 in 1962.[16] In Ghana, the number of stroke patients admitted per year increased from about 50 in 1960 to 622 in 1993, and the percentage of total adult medical admissions due to stroke increased from less than 2% in 1960 to about 12% in 1993.[16]

Stroke admissions to hospital are clearly rising in Africa. Although this could be due to increased patronage of orthodox medicine, increasing stroke incidence in an ageing population in the throes of epidemiological transition is a more plausible explanation.[12]

Using hospital data, five studies estimated stroke crude incidence rates ranging from 31/100 000 per year in Harare, Zimbabwe in 1991[8,17,18] to 149/100 000 per year in Maputo, Mozambique in 2006[8,17,19] (Table 1). In a meta-analysis by Adeloye, the pooled estimate of 77.39/100 000 per year (95% CI = 51.31–103.48) from hospital-based studies[8] was lower than from community-based studies. This may suggest that the available hospital-based African studies underestimated stroke incidence as a result of exclusion of fatal or mild cases who do not present in these hospitals.

Stroke incidence, estimated on the basis of representative community samples with rigorous case ascertainment and accurate diagnosis over a minimum period of three years, provides far more information about stroke burden than hospital-based studies. Nevertheless, such studies require considerable resources and rigorous methods.[16]

There are several community-based incidence studies from sub-Saharan Africa (Table 1). From the (1973–75) stroke registry in Ibadan, Nigeria, the crude annual incidence of first-ever stroke was 26 per 100 000. However, this is likely an underestimate, because of difficulties with case ascertainment resulting from the very large population, small study staff, and non-inclusion of those who patronised traditional healers.[20]

In Tanzania, stroke incidence was recorded in two demographic surveillance sites: Hai (rural) and Dar-es-Salaam (urban) from 2003–2006. Patients with stroke were identified by the use of a system of community-based investigators and liaison with local hospital and medical centre staff. Patients who died from stroke before recruitment were identified via verbal autopsy, which might have included non-incident strokes.[16] Overall crude annual stroke incidence rates were 94.5 per 100 000 in Hai and 107.9 per 100 000 in Dar-es-Salaam (Table 1). When age-standardised to the WHO world population, annual stroke incidence rates were 108.6 per 100 000 in Hai and 315.9 per 100 000 in Dar-es-Salaam.[16]

Age-standardised stroke incidence rates in Hai were similar to those reported in developed countries. However, age-standardised incidence rates in Dar-es-Salaam were higher than those published from developed countries. This could be because of differences in the prevalence of risk factors, which emphasises the importance of health screening at a community level.[16]

A recent door-to-door survey of every household in Al Quseir (urban), Egypt[8,17,21] from 2009 to 2012 reported a crude annual incidence of 181 per 100 000 population but the age-standardised incidence was not calculated (Table 1). Furthermore, Farghaly *et al.* performed a door-to-door screening in Al Kharga district, Egypt,[8,17,22] from 2005 to 2009 and reported a crude annual incidence of 250 per 100 000 population (Table 1). Although the age-standardised incidence was likely to be higher than that in Tanzania (Dar-es-Salaam), which is the global highest,[23] it was not reported.

Generally, population-based crude incidence rates were higher than hospital-based rates, ranging from 26.0/100 000 person years in Ibadan, Nigeria in 1979,[8,17,20,24] to 250/100 000 person years in Al-Kharga, Egypt in 2007[8,17,22] (Table 1). The random-effects meta-analysis of crude population-based incidence rates was 112.94/100 000 person years (95% CI = 90.7–135.0).[8] However, this meta-analysis included incidence studies with incomplete case ascertainment,[24] conducted over one year rather than the recommended three-year period.[8,12,16,17] The studies reporting low rates, therefore, could have been marked by underestimation of the stroke burden in Africa, and the pooled estimate[8] reported might therefore be much lower than the true rates.

Crude rates provide valuable information that reflects the public health burden of stroke, given the age distribution for the country (i.e. if a specific country has a large number of strokes because it has a relatively large elderly population, they must nevertheless care for this larger number of people), whereas adjusted rates allow a more comparable basis between the risk of stroke across the life course of residents of the country and for comparison between countries.[23] Crude rates underestimate the impact of stroke on a country, particularly when strokes are occurring at younger ages, as occurs in Africa.

Nevertheless, the annual crude incidence rate in Egypt was higher than reports by Béjot *et al.* in France (113.5 per 100 000), Corso *et al.* in Italy (223 per 100 000), Vega *et al.* in Spain (113.5 per 100 000),[22] and Pandian *et al.* in India (119 to 145/100 000).[25,26]

Table 2. Population/community-based studies reporting prevalence of stroke survivors in Africa

			Crude prevalence per 100 000			
Year	*Country/location/setting*	*Author*	*Overall*	*Male*	*Female*	*Age*
1982	Nigeria, Igbo-Ora, rural	Osuntokun[37]	58	–	–	All
1985	Tunisia Kelibia, mixed*	Atia-Romdhane[41]	42	–	–	All
1988	Ethiopia, central Ethiopia, rural	Tekle Haimanot[34]	15	–	–	20–85
1993	Egypt, Sohag, mixed*	Kandil[31]	508	520	490	All
1993	Egypt, Sohag, urban	Kandil[31]	410	460	470	All
1993	Egypt, Sohag, rural	Kandil[31]	540	510	570	All
1994	Tanzania, Hai, rural	Walker[42]	127	155	103	15+
2002	South Africa: Agincourt Health and Population Unit, Limpopo province, rural	Connor[43]	243	188	296	15+
2006	Nigeria, Lagos, urban	Danesi[38]	114	151	69	All
2009	Benin, Cotonou, urban	Cossi[44]	460	610	360	15+
2009	Egypt, Al-Kharga, mixed*	Farghaly[22]	560	610	510	All
2009	Egypt, Al-Kharga, urban	Farghaly[22]	580	620	530	All
2009	Egypt, Al-Kharga, rural	Farghaly[22]	520	580	458	All
2010	Tanzania, Hai district, rural	Dewhurst[39]	2300	2971	1752	70+
2010	Egypt, Assuit, urban	Khedr[35]	963	1174	736	All
2013	Egypt, Qena, mixed*	Khedr[40]	922	1103	726	All

*Combined rates including both rural and urban communities.

The age-standardised incidence of stroke in Tanzania was similar to the rates in China where the age-standardised incidence of first-ever stroke per 100 000 person years increased rapidly from 124.5 in 1992–1998 to 190.0 in 1999–2005, and to 318.2 in 2006–2012.[27]

Unfortunately, no rigorously conducted stroke-incidence study has been performed twice in the same location to provide secular trend data on the incidence 'velocity' (trend) of stroke in Africa. Using the GBD data (Fig. 2), increase in age-standardised ischaemic stroke incidence from 1990 to 2010 ranged between 5.2% (South Africa) and 27.8% (DRC, Table 3).

Overall, in Africa, there was significant ($p < 0.001$) mean increase in age-standardised ischaemic stroke incidence of 14.8% (± 4.1%) between 1990 and 2010. Similarly (Fig. 2), increase in age-standardised haemorrhagic stroke incidence from 1990 to 2010 ranged between 13.0% (the Gambia) and 45.7% (Burundi, Table 3). Overall, in Africa, there was significant ($p < 0.001$) mean increase in age-standardised haemorrhagic stroke incidence of 28.7% (± 11.1%) between 1990 and 2010. Therefore, the incidence of stroke in Africa is not only among the highest in the world, the incidence velocity is also very high.

Urbanisation and other socio-demographic and lifestyle changes in Africa, as in other parts of the developing world, are increasing rapidly, and the results from this study suggest that, in the absence of effective preventive measures, this is likely to lead to further substantial increases in stroke incidence.

Prevalence

A retrospective chart review of clinically and CT-diagnosed stroke patients evaluated between January 2000 and March 2005 in Tikur Anbessa tertiary referral and teaching hospital (Addis Ababa, Ethiopia) showed that stroke accounted for 5% of all head CT indications done in Ethiopia.[33] A prevalence rate could not be calculated in the absence of the number in the referral base.

Community-based studies constitute the best way to determine the true prevalence of stroke, although they are very rare in Africa due to lack of manpower and research funds. Estimating the prevalence of stroke survivors in the community is complicated by the difficulty in making a retrospective and yet accurate diagnosis of stroke and stroke type months or years after the event.[16] Estimations are also biased by under-representation of fatal cases.[16] Therefore, prevalence, which depends on incidence and case fatality, is better estimated from incidence studies of first-ever stroke and survival. However in sub-Saharan Africa, incidence studies are very rare and difficult to conduct.[16]

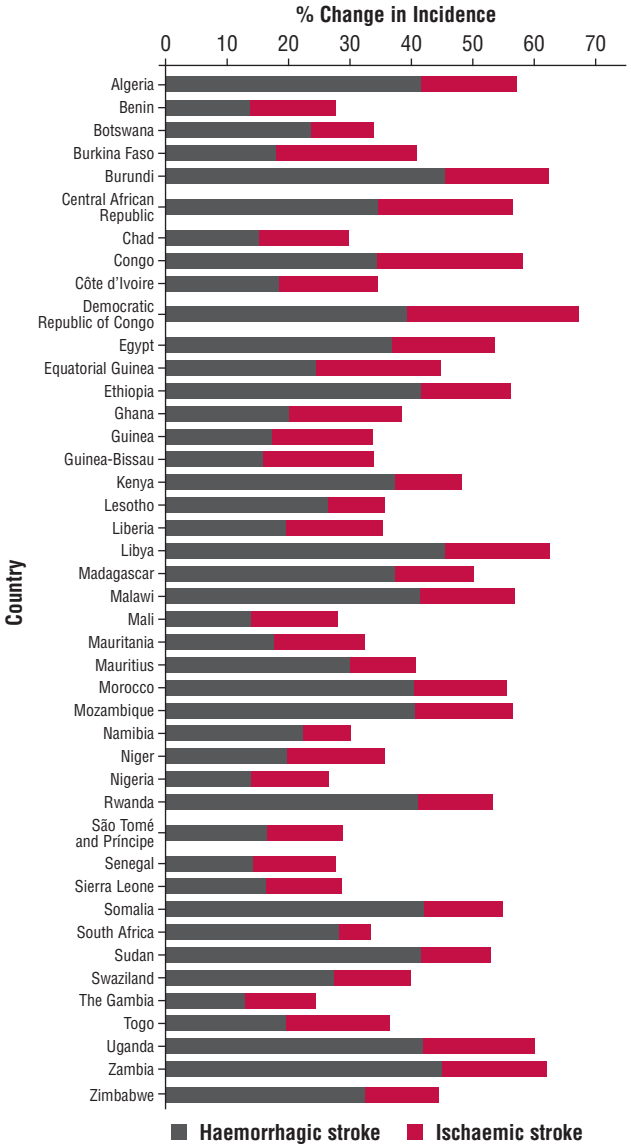

Fig. 2. Model-derived percentage changes in ischaemic and haemorrhagic stroke incidence in African countries between 1990 and 2020.

Table 3. Estimates of average percentage change over 1990 to 2010 in age-adjusted incidence, mortality and DALYs of stroke in Africa

Rates per 100 000 person years	*1990 (mean, SD)*	*2010 (mean, SD)*	*Min. change* (%)*	*Country with min. change*	*Max. change* (%)*	*Country with max. change*	*Mean/ median change** (%)*	*SD*	p-*value*
Age-standardised incidence ischaemic	129.4, 15.1	148.4, 16.3	5.18	South Africa	27.8	Democratic Republic of Congo	+14.8	4.05	< 0.001
Age-standardised incidence haemorrhagic	58.9, 11.0	75.2,12.9	13.0	The Gambia	45.7	Burundi	+28.7	11.1	< 0.001
Age-standardised mortality ischaemic	53.3, 15.2	48.1, 12.5	–45.5	Mauritius	95.0	Burkina Faso	–7.5**		0.001
Age-standardised mortality haemorrhagic	69.2, 20.1	58.8, 16.9	–52.2	Equatorial Guinea	67.9	Burkina Faso	–12.7**		< 0.001
DALYs lost ischaemic	853.8, 231.7	756.1, 192.7	–53.1	Mauritius	79.0	Burkina Faso	–10.3**		< 0.001
DALYs lost haemorrhagic	1574.7, 451.1	1287.1, 383.9	–57.4	Equatorial Guinea	51.6	Zimbabwe	–18.9**		< 0.01

*Countries with the minimum and maximum changes in rates are depicted. **Median percentage change.

There were many population-/community-based studies reporting crude prevalence of stroke survivors with prevalence rates ranging from 15/100 000 population in Ethiopia in 1988,[8,17,34] to 963/100 000 population in Egypt in 2010 (Table 2).[8,17,34,35] The low prevalence rate recorded in Ethiopia in 1988, included in the meta-analysis, may have been due to the high fatality rates from stroke, which have generally been reported in many parts of Africa.[8,17,34,36] It may also reflect low stroke incidence in rural Ethiopia at that period, or simply that patients with mild strokes who had recovered were not detected. Moreover, the Ethiopian study was a broad door-to-door survey of neurological disorders in the community, which could imply that active case recognition of specific stroke cases may be less rigorous.[8]

In 1982, in Igbo Ora, Nigeria, stroke had an estimated crude prevalence of 58 per 100 000 (Table 2). However, the denominator population was far too small to establish stroke prevalence accurately.[37] In 2005 to 2006, another study conducted in Lagos, Nigeria yielded a crude prevalence rate of stroke of 114/100 000 persons.[38] This may suggest at least a doubling of the stroke prevalence in Nigeria. As reported by several other studies, males were more affected (males:female = 1.51) and age was a strong risk factor with prevalence of nearly 5% for those in the ninth decade of life.[38]

Stroke-prevalence studies in demographic surveillance sites that provide an accurate denominator have arguably provided the most accurate measures of stroke burden in recent years, despite their limitations.[16] The largest study of the prevalence of disabling hemiplegic stroke in sub-Saharan Africa was done in 1994 in the rural Hai district of Tanzania (Table 2).[16] It provided an age-standardised (Segi world population) prevalence of disabling stroke of 154 per 100 000 in men and 114 per 100 000 in women over 15 years of age.

In 2001, a stroke-prevalence study in Agincourt, rural South Africa, with diagnosis of stroke based on the WHO definition of stroke, provided an age-standardised (Segi world population) stroke prevalence of 290 per 100 000 people over the age of 15 years (male: 281 per 100 000, females 315 per 100 000).[16]

The rural Tanzanian (1994) and Agincourt studies (2001) both have the advantage of accurate denominators and careful assessment of people who screened positive for stroke. However, the higher prevalence of stroke in Agincourt may be because Agincourt is further along the epidemiological transition, or due to the fact that the Tanzanian study included only disabling hemiplegic stroke.[16] A repeat rural Tanzanian study[8,17,39] showed an increase in prevalence per 100 000 population from 127 among people aged 15 years and above in 1994 to 2 300 in 2010 among people aged 70 years and above (Table 2).[8,16,17,39] Similarly, as shown in Table 2, comparison between studies performed in Egypt in 1993 and 2009 showed an increase in prevalence per 100 000 population from 508 to 560 (mixed) and 410 to 580 (urban).

Supporting this increase, two recent studies in Egypt produced crude prevalence rates of 922[40] and 963 per 100 000 population (Table 2), with an age-adjusted local prevalence rate of 699.2/100 000 and an age-adjusted prevalence relative to the standard world population of 980.9/100 000.[35] There was a significantly higher prevalence of ischaemic (895/100 000) than haemorrhagic (68/100 000) stroke. Stroke prevalence was the same in rural and urban areas but significantly higher in illiterate (2 413/100 000) than literate participants (3 57/100 000).[35]

Overall in Africa, the observed population-based prevalence rates of stroke survivors were generally high and rising, with a pooled crude prevalence rate of 387.9/100 000 population (which may be an under-estimate due to the inclusion of the Ethiopian study among the 11 studies used for the estimate[8]) and a range of up to 963 per 100 000 all population.[8,17,22] This prevalence lies within the range of that recorded in other LMICs (500–1 000 per 100 000) and is in agreement with that found in India (550 per 100 000), but higher than that recorded in Saudi Arabia (180 per 100 000) and Italy (140 per 100 000).[22] The high prevalence of stroke in the study population may reflect the increased exposure to risk factors for stroke due to ongoing epidemiological and demographic transitions.

Mortality

Cause-of-death data from Africa are usually not from standard vital registration, but are predominantly gathered from verbal autopsy studies, police reports, sibling histories, and burial and mortuary reports. With the exception of a few higher-quality studies, most data on CVD in Africa are from small community surveys and hospital-based registries.[3,23]

Hospital-based data show that NCDs are the leading cause of death in Africa. In a rural hospital in Nigeria, NCDs constituted 63% of deaths, with stroke being the leading NCD cause.[45,46] Similarly, hypertension-related NCD deaths led by stroke constituted the leading cause of death in a Tanzanian hospital from 2009 to 2011.[47]

Based on verbal autopsies from burial surveillance of 58 010 deaths in Addis Ababa from 2006 to 2009, about 11% of the deaths were attributed to stroke. The mortality rate increased with age (15–34 years: 1%; 35–54 years: 7%; 55–74 years: 16%; > 74 years: 18%) but there were no differences by gender.[48]

The Agincourt community-based study in South Africa found that stroke caused 6% of all deaths between 1992 and 1995.[16] Stroke was the most common cause of death in the age group 55–74 years, and the second most common cause of death in the age group 35–54 years and the > 75 years group.[16] The crude stroke mortality rate was 127 per 100 000 over age 35 years.[16] In a verbal autopsy study in Tanzania, stroke caused 5.5% of adult deaths in three regions [Dar-es-Salaam (urban), Hai (prosperous rural) and Morogoro (impoverished rural)].[16]

Age-specific stroke mortality rates in Agincourt and the three regions of Tanzania mentioned above may be as high as in England and Wales, and perhaps higher in younger age groups, but larger studies based on accurate vital registration data are clearly needed.[16] Such data will produce evidence of any change in stroke mortality rate particularly as lifestyle, cardiovascular risk burden, population age structure, relative stroke incidence and case fatality rates change in Africa.

The GBD dealt with the problem of absent or low-quality epidemiological data from sub-Saharan Africa by incorporating covariates (CVD risk factors, national income, differences in measurement method) and 'borrowing strength' from nearby regions and years of observation in CODEm and DisMod-MR models; and using standard assumptions about the relationship between disease-specific incidence, prevalence, case fatality, and mortality in DisMod-MR models.[3] The ensemble approach combined different model results developed with different combinations of covariates and statistical approaches.[2,7,49]

Using these models, the leading CVD cause of death and disability in 2010 in sub-Saharan Africa was stroke.[3] Furthermore, Krishnamurthi[50] reported higher age-adjusted stroke mortality rates for haemorrhagic stroke in sub-Saharan Africa than in North America and Europe.

Overall, the GBD generated an age-standardised stroke mortality rate of between 52.0 and 136.7 per 100 000 people for 2010.[2,49] Indeed there was as much as a 10-fold difference between the lowest stroke mortality rates, seen primarily in developed nations, and the highest mortality rates, seen primarily in numerous countries across central and western Africa and other LMIC.[5]

In addition to comparing the mortality rates at a given time point, it is also important to examine the trend to forecast future disease burden. In the Seychelles, mortality rates (per 100 000, age-standardised to WHO standard population) decreased from 250/140 (male/female) to 141/86 for stroke, corresponding to 44/39% over 22 years. However, overall stroke mortality rates remained high, emphasising the need to strengthen neurological disease prevention and control.[2,49]

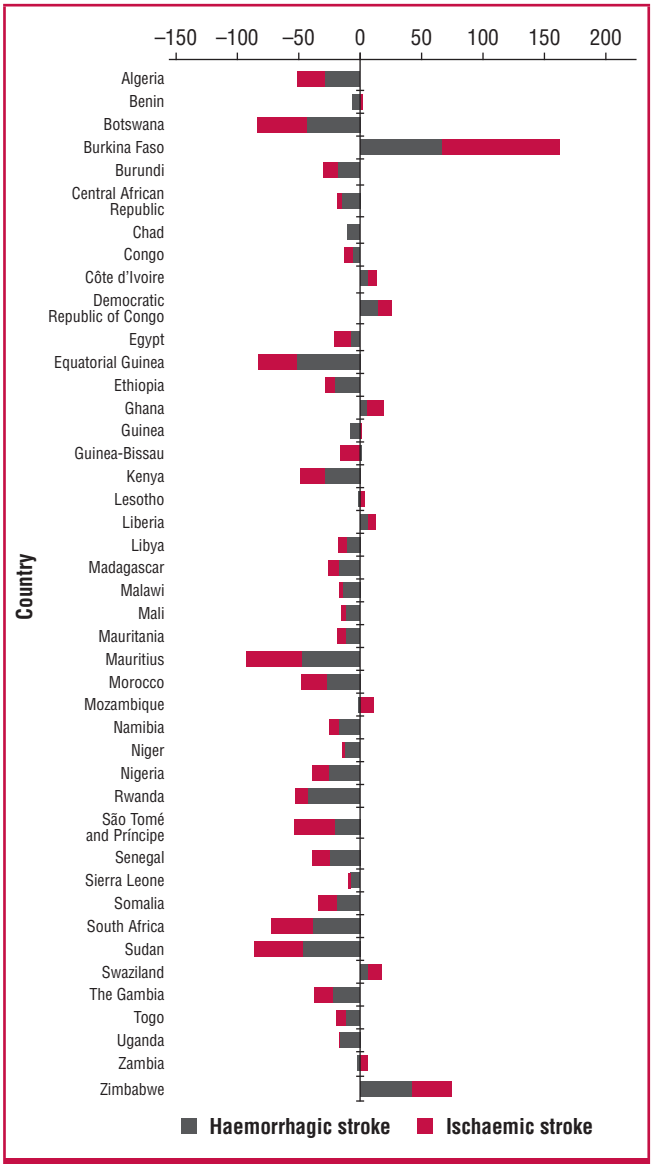

Fig. 3. Model-derived percentage changes in ischaemic and haemorrhagic stroke mortality rates in African countries between 1990 and 2020.

Using the GBD data (Table 3, Fig. 3), percentage change in age-standardised ischaemic stroke mortality rates from 1990 to 2010 ranged between –45.5% (Mauritius) and 95.0% (Burkina Faso). Overall, in Africa, there was a statistically significant ($p = 0.001$) median change in age-standardised ischaemic stroke mortality rates of –7.5% between 1990 and 2010. Similarly, (Table 3, Fig. 5), change in age-standardised haemorrhagic stroke mortality rates for the same period ranged between –52.2% (Equatorial Guinea) and 67.9% (Burkina Faso). Overall, in Africa, there was significant ($p < 0.001$) median change in age-standardised haemorrhagic stroke mortality rates of –12.7% between 1990 and 2010.

In the GBD, although age-standardised mortality rates decreased between 1990 and 2010 in Africa, crude mortality rates increased in sub-Saharan Africa, south Asia, and central and Latin America, but decreased in high-income North America, western and central Europe, North Africa and the Middle East, Australasia, and high-income Asia Pacific.[2,49] These changes are in keeping with the expected increase in crude mortality rate due to the increasing crude incidence.[23]

Africa is at an earlier stage of health transition with a higher ratio of stroke death to coronary death.[51,52] As a population undergoes health transition, the pattern of vascular disease is thought to change from one dominated by stroke, with a high proportion caused by cerebral haemorrhage, to a pattern dominated by atherosclerotic stroke, coronary heart disease and peripheral vascular disease.[16,53] This scenario is expected to occur in Africa, as suggested by a study exploring the relationship of vascular risk factors to stroke type among Africans, in which we found age above 61 years and previous transient ischaemic attack to be associated with ischaemic stroke, while uncontrolled hypertension predicted haemorrhagic stroke.[54]

With increasing proportion of the population over 61 years and improving control of blood pressure, the proportion of ischaemic stroke is expected to rise in African countries.[54] Therefore, relevant components of the stroke-intervention quadrangle (described below) should be tailored toward this need to mitigate the burden.[54]

Case fatality

Hospital-based studies have demonstrated a one-month case fatality rate of between 27 and 46% in Africans.[16,32,55] In the hospital-based INTERSTROKE study, the one-month case fatality rate for stroke was 22% in the African region compared to 4% in high-income countries.[56] Reports of post-stroke deaths in sub-Saharan Africa are, however, unreliable due to factors such as limited death certification and lack of coverage of primary healthcare services.[55] Post-stroke case fatality rates should ideally be calculated using community-based studies because of the heterogeneity of stroke type and severity, and the likelihood that many patients are not admitted to hospital.[16]

In the Ibadan community-based stroke registry (1975), case fatality rate at three weeks was 35% for all strokes and highest for cerebral haemorrhage (61%) and subarachnoid hemorrhage (62%). However, this case fatality rate may not be very reliable because stroke types had most probably been diagnosed unreliably without CT scanning.[20,57]

In the Tanzanian community-based incident stroke study (2003), case fatality rate was 28.7% at 28 days and 84.3% at three years. The 28-day case fatality rate was at the lower end of rates reported for other LMIC, even when including those identified by verbal autopsy, while the three-year case fatality rates were notably higher than seen in most developed-world studies. Recent studies from the developed world suggest three-year case fatality rates of 43 to 54% and five-year case fatality rates of 53 to 60%.[32]

In a South African study (published in 2012), 25.5% of patients died within three months of discharge and 38% within the 12-month follow-up period.[58] This high fatality rate may be due to the severe scarcity and prohibitive costs of facilities and human resources for investigations, acute care and rehabilitation of stroke patients in Africa.[6] The region has the lowest neurologist-to-population and doctor-to-population ratio in the world,[6] with an average of one neurologist to one million people in comparison to one to 100 000 in high-income countries.[6]

With high proportion of the population living below the poverty line, the few available facilities for investigation and care of stroke patients are not accessible to most of the population who have to pay out of their pockets.[6,59] For instance, there is probably only one multidisciplinary holistic neuro-rehabilitation centre in East, West and Central Africa.[60, 61]

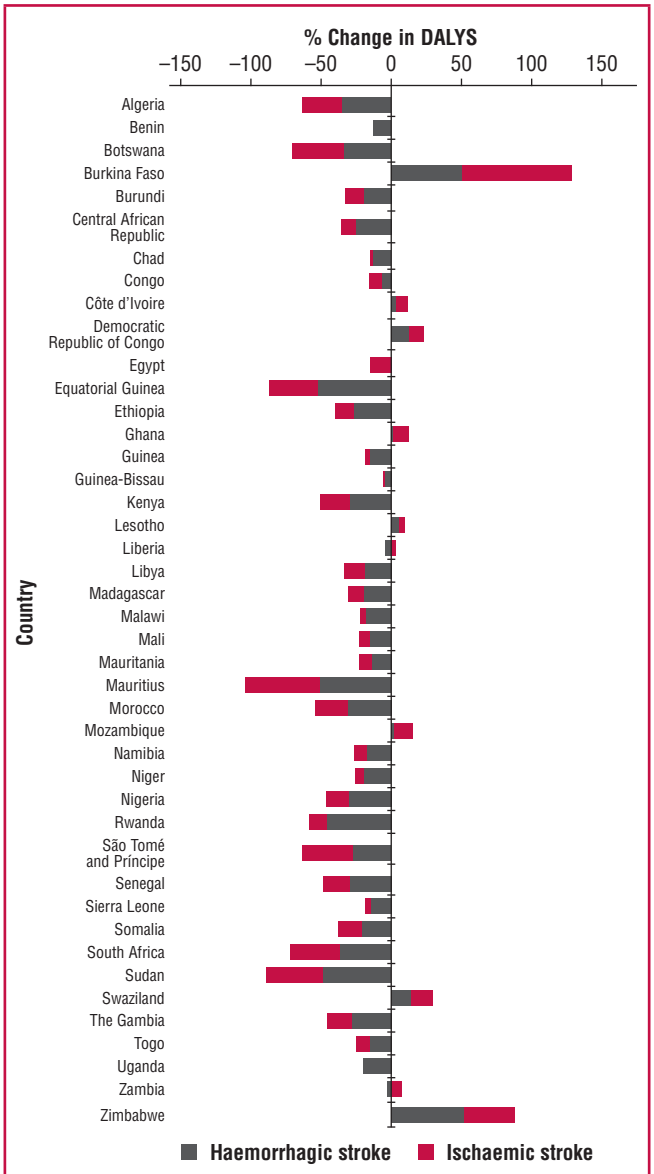

Fig. 4. Model-derived percentage changes in ischaemic and haemorrhagic stroke disability-adjusted life years (DALYs) in African countries between 1990 and 2020.

Disability-adjusted life years

Direct studies of DALYs due to stroke are very rare in Africa. The burden of disease due to stroke in South Africa (2008) was 564 000 DALYs.[62] Of this, 17% was contributed by years lost to disability (YLD) (14–20% in sensitivity analysis).[62] The estimated DALYs lost due to stroke was 1 230 per 100 000 in Angola, Africa, compared to 200 per 100 000 in Switzerland, Europe in 2002.[53,63]

Using the GBD data (Table 3, Fig. 4), percentage change in age-standardised ischaemic stroke DALYs from 1990 to 2010 ranged between –53.1 (Mauritius) and 79.0 (Burkina Faso). Overall, in Africa, there was significant ($p < 0.001$) median change in age-standardised ischaemic stroke DALYs of –10.31 between 1990 and 2010. Similarly (Table 3, Fig. 7), change in age-standardised haemorrhagic stroke DALY for the same period ranged between –53.8 (Equatorial Guinea) and 51.6 (Zimbabwe).

Overall, in Africa, there was a statistically significant ($p < 0.001$) median change in age-standardised haemorrhagic stroke DALYs of –18.9 between 1990 and 2010. However, stroke remained the leading cause of cardiovascular DALYs in sub-Saharan Africa, increasing from 5 930 040 (39.5%) in 1990 to 7 824 920 (52.0%) of CVD DALYs in 2010.[3]

Stroke type and risk factors

The proportion of haemorrhagic stroke in Africa ranges from 29 to 57%, in comparison with 16 to 20% in North America.[53] In the INTERSTROKE study, haemorrhagic stroke was 34% in Africa and 9% in high-income countries.[56] This suggests a higher burden of uncontrolled hypertension in Africa, because the proportion of haemorrhagic stroke in a population seems to correlate with the prevalence and severity of uncontrolled hypertension.[16,32,53-55]

Up to 98% of stroke patients in Africa have hypertension.[32,53,55] Ischaemic stroke is more associated with diabetes mellitus, cardiac disease, age above 61 years and previous transient ischaemic attacks.[54] The population-attributable ratio of stroke due to hypertension in South Africa in 2000 was 50%,[64] and 60% in North Africa.[65]

Hypertension

Hypertension, once rare in West Africa, is emerging as a serious endemic threat. It has been referred to as a silent killer, as it often has no early detectable symptoms despite being a major cause of serious health conditions, including heart disease, stroke and renal disease.[66] Of the 10 predominant modifiable risk factors accounting for 90% of the risk of stroke, hypertension is the strongest.[56]

Prevalence rates for hypertension vary across and within regions in Africa. An analysis of all national data in Zimbabwe in the 1990s found that between 1990 and 1997, the national

crude prevalence of hypertension increased from one to 4%. According to Adedoyin *et al.*, up to 36.6% of adult Nigerians were hypertensive in 2008.[67]

The impact of migration from rural to urban areas was demonstrated in a longitudinal study in Kenya, in which moving from a rural to an urban setting produced significant increases in blood pressure within a short time. Growing migration from rural to urban areas also portends a worsening prevalence of hypertension as migrants adopt lifestyle changes in physical activity, dietary habits and stress levels. Regardless of gender or type of community, advancing age is associated with an increased prevalence of hypertension, and this implies a greater burden of hypertension (and indeed stroke)[68] as population aging occurs in Africa.[67-69]

Several surveys have demonstrated a very low prevalence of hypertension awareness and control (BP < 140/90 mmHg) in Africa. In Tanzania, slightly less than 20% of hypertensive subjects were aware of their diagnosis, approximately 10% of them were treated, and < 1% were controlled.[70] A survey in Ghana showed that 34% were aware of their condition, of whom 18% were treated and only 4% were controlled. However, in the United States, 69% of hypertensive subjects were aware of their diagnosis, 58% of them were treated, and 31% were controlled.[70] The low prevalence of awareness, treatment, and control of hypertension poses a serious challenge for stroke prevention in Africa.[70] This scenario also applies to several other NCDs such as diabetes mellitus and dyslipidaemia, which are on the increase in Africa.[66]

Type 2 diabetes mellitus

According to International Diabetes Federation (IDF), the current estimated prevalence rate of type 2 diabetes in Africa is about 2.8%. Countries such as Malawi and Ethiopia have rates under 2%, whereas Ghana, Sudan and South Africa have prevalence rates over 3%.[66] Currently, there are 10.4 million individuals with diabetes in sub-Saharan Africa, representing 4.2% of the global population with diabetes. By 2025, it is estimated that this figure will have increased by 80% to reach 18.7 million in this region, with a higher prevalence in the urban areas.[66] Studies indicate that an aging population, coupled with rapid urbanisation, is expected to lead to the increasing prevalence of diabetes in Africa.[66]

Dyslipidaemia

Dyslipidaemia has emerged as an important risk factor in Africa. For example, Norman and colleagues found that high cholesterol levels (≥ 3.8 mmol/l) accounted for 59% of ischaemic heart disease and 29% of ischaemic stroke burden in adults aged 30 years and over.[66] The prevalence of dyslipidaemia, especially cholesterol has been shown to vary across regions in Africa.

In a study of healthy workers in Nigeria, 5% of the study population had hypercholesterolaemia, 23% elevated total serum cholesterol levels, 51% elevated low-density lipoprotein (LDL) cholesterol levels and 60% low high-density lipoprotein (HDL) cholesterol levels, with females recording better overall lipid profiles.[66] Population-based studies in Tanzania and Gambia also showed elevated total serum cholesterol levels of > 5.2 mmol/l in up to 25% of people aged > 35 years. Elevated cholesterol levels appear to be more prevalent in urban areas and among the higher socio-economic classes. [66]

Other factors

The epidemic of stroke, hypertension, diabetes and dyslipidaemia in Africa is driven by multiple factors working collectively. Obesity and lifestyle factors such as poor diet, sedentary lifestyle and smoking contribute to the increasing rates of stroke in Africa.

In a meta-analysis among West African populations, the prevalence of obesity was 10.0%. A study in Benin found that abdominal obesity was positively associated with increased probability of the metabolic syndrome. Obesity was a predominant risk factor for women compared to men, but smoking was mostly a risk factor for men.[66] Additionally, structural and system-level issues such as lack of infrastructure for healthcare, urbanisation, poverty and lack of government programmes also drive this epidemic and hamper proper prevention, surveillance and treatment efforts.[66]

Carotid atherosclerosis measured by increased carotid intima–media thickness (CIMT) and carotid diameter have been associated with stroke among Africans.[54,71-73] Furthermore white matter hyperintensities may be a risk factor for stroke in Africans.[74]

Elevated homocysteine levels (associated with cardiovascular endothelial injury)[75,76] and the metabolic syndrome (implying concomitant hypertension, obesity, dyslipidaemia, and/or hyperglycaemia)[77] have also been documented as risk factors for stroke in Africans.

Unique aspects of stroke survivors in Africa

In Nigerian Africans, stroke impairs all facets of health-related quality of life (HRQOL), particularly domains in the physical sphere (physical, cognitive, psycho-emotional and eco-social domains). The severity of impairment correlates with stroke severity.[78-80] Many of these disabling strokes occur in young people. Stroke occurs at a younger mean age of 57 years in Africa compared to 66.0 years in high-income countries (HICs); in those ≤ 45 years: 24% in Africa, 8% in HICs).[53,56]

Overall, stroke tended to occur in a younger population in Africans compared to high-income countries.[53,56] This may be due to genetic factors, a high proportion of undiagnosed and uncontrolled hypertension, the shorter life expectancy in African countries and a higher proportion of younger people.[53,81]

Stroke is a leading cause of late-onset seizure disorder among Africans.[82] It accounts for 22.5% of seizures after the age of 25 years.[82] In a Nigerian study, the most common seizure type was simple partial, while the most common electro-encephalographic finding was the presence of focal epileptiform discharges, followed by focal slowing.[82] At the three-month follow up, 52% of the patients had good seizure control.[82] In other studies, 48.3% of Nigerian stroke patients had vascular cognitive impairment,[83] while major depression was found among 30% of African stroke patients.[84] Despite these deleterious consequences of stroke, there is poor community awareness of its risk factors and warning signs in Ghana,[84,85] and poor awareness of its risk factors and features among hospital workers in Nigeria.[83]

Cost of care

The economic burden of stroke is considerable. The cost of stroke for the year 2002 was estimated to be as high as $49.4

billion in the United States, while costs after hospital discharge were estimated to amount to 2.9 billion Euros in France.[16,70,86,87] Clearly, even a fraction of such amounts can cause enormous economic damage to low-income countries.[70]

There are very few studies on the cost of stroke care in Africa. A study in Togo estimated direct cost per person of 936 Euros in only 17 days, about 170 times more than the average annual heath spend of a Togolese.[88] Subsidising and improving post-stroke care may help to reduce stroke case fatality rates and morbidity in Africa.[89]

The gaps

Although age-standardised rates of stroke mortality have decreased worldwide in the past two decades, the absolute number of people who have a stroke every year, stroke survivors, related deaths, and the overall global burden of stroke (DALYs lost) are great and increasing. Further studies are needed to improve understanding of stroke determinants and burden worldwide, and to establish causes of disparities, and changes in trends in stroke burden between countries of different income levels.[2]

In Africa, despite the enormous and growing burden, numerous gaps have been identified in the required data and interventions to tame the scourge. For most of the direct observational studies and models, a time lag of about three to six years was observed between data collection, analyses and publication. There is incomplete understanding of the pattern and determinants of stroke occurrence, type, subtype, outcome, complications and burden. Furthermore, the incidence, prevalence, relative risk, and population-attributable risks (PAR) of genomic and environmental risk factors for stroke among Africans are not known. Assessment of hypertension and its risk factors is needed.[90] Accurate population demographic information essential for determining rates is also needed.

Moreover, causes of disparities and changes in trends of stroke burden in LMIC/HIC, whites/Africans, as well as the genomic architecture of stroke among Africans are unknown. The peculiar genomic, gene–environment and environmental risk, and protective factors for stroke occurrence, pattern, type, subtype, outcome and current incidence velocity among people of African ancestry is unclear. There is also a need for indicators and determinants of blood pressure levels and dietary intake.

Shaping the future

Projections based on the current trends, incidence velocity, risk-factor prevalence, population-attributable risks, and relative risk for risk factors concluded that by 2030, stroke will be the second leading cause of death globally, the first leading cause of death in middle-income countries and the third in low-income countries. [91]

The stroke quadrangle is hereby proposed as a holistic synergy of four pillars aimed at reversing the rising burden. This approach is consistent with the successful high-impact interventions implemented in the United States over the past five decades,[68] as well as the global stroke burden-reduction objectives from the World Stroke Association (http://www.world-stroke.org/) and the World Hypertension League (http://www.worldhypertensionleague.org/), which has resulted in a decline in stroke burden in high-income countries.[2] It is expected that if resources are applied efficiently in a similar manner in LMICs, the burden of stroke will be reduced. These resources include:

- synergistic epidemiological surveillance and research networks exploring and monitoring trends in the burden, pattern and determinants (gene, environment, gene–gene, gene–environment, transcriptomics, etc) such as the Stroke Investigative Research and Educational Network (SIREN) project
- primordial, primary and secondary prevention programmes at individual, family, systems and community levels, e.g. the Tailored Hospital-based Risk reduction to Impede Vascular Events after Stroke (THRIVES) project,[10,92,93] improvement of stroke literacy and early recognition
- acute stroke care facilities with rapid evacuation services
- stroke rehabilitation and recovery services.

Conclusions

In contrast to the declining stroke rates in several developed countries, the incidence of stroke in Africa, especially haemorrhagic stroke, has risen substantially over the last 20 years. This rise can only be expected to continue unabated unless widespread coordinated efforts based on plausible paradigms that incorporate established and accumulating scientific evidence are promptly instituted.

The results of this assessment suggest intervention models such as 'the stroke quadrangle' implemented through the SIREN project may be an effective effort to catalyse risk reduction in this global high-risk population. SIREN is poised to identify the unique risk factors (genetic and environmental) associated with stroke occurrence, type, subtype, pattern and outcome in black Africans (in Africa and the USA). SIREN is designed to substantially enhance our understanding of factors that could be addressed to improve stroke outcomes, and possibly other vascular disease entities such as coronary artery disease and chronic kidney disease in people of African ancestry.

Over 3 000 case–control African pairs will be compared to 1 000 African-Americans and 12 000 white Americans in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. The study aims to discover/explore potentially modifiable genetic pathways to stroke risk that may be common to people of African ancestry.

Key messages

- Accurate epidemiological data on stroke in Africa is scanty.
- However, age-adjusted standardised annual stroke incidence rates may be up to 316 per 100 000, and age-adjusted standardised prevalence rates may be up to 981 per 100 000.
- From the Global Burden of Disease model-based estimates, stroke incidence appears to be increasing in Africa.
- Rigorous comprehensive and prospective epidemiological surveillance is urgently needed to assess and monitor the actual burden and determinants as well as the epidemiological trend of stroke in Africa.
- Appropriate intervention paradigms such as the stroke quadrangle are urgently required.

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References

1. Owolabi MO, Mensah GA, Kimmel PL, Adu D, Ramsay M, Waddy SP, *et al*. Understanding the rise in cardiovascular diseases in Africa: harmonising H3Africa genomic epidemiological teams and tools. *Cardiovasc J Afr* 2014; **25**(3): 134–136.
2. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, *et al*. Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet* 2014; **383**(9913): 245–254.
3. Moran A, Forouzanfar M, Sampson U, Chugh S, Feigin V, Mensah G. The epidemiology of cardiovascular diseases in sub-Saharan Africa: the Global Burden of Diseases, Injuries and Risk Factors 2010 Study. *Prog Cardiovasc Dis* 2013; **56**(3): 234–239.
4. Feigin VL. Stroke epidemiology in the developing world. *Lancet* 2005; **365**(9478): 2160–2161.
5. Norrving B, Kissela B. The global burden of stroke and need for a continuum of care. *Neurology* 2013; **80**(3 Suppl 2): S5–12.
6. Owolabi MO, Bower JH, Ogunniyi A. Mapping Africa's way into prominence in the field of neurology. *Arch Neurol* 2007; **64**(12): 1696–1700.
7. Krishnamurthi RV, Feigin VL, Forouzanfar MH, Mensah GA, Connor M, Bennett DA, *et al*. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet Glob Health* 2013; **1**(5): e259–e281.
8. Adeloye D. An estimate of the incidence and prevalence of stroke in Africa: a systematic review and meta-analysis. *PLoS One* 2014; **9**(6): e100724.
9. O'Neill D. Global burden of stroke: an underestimate. *Lancet* 2014; **383**(9924): 1205.
10. Owolabi MO, Ovbiagele B. Global clinical neuroscience: Journey of a thousand miles begins with a single step. *J Neurol Sci* 2014; **344**(1–2): 223.
11. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; **4**(1): 1.
12. Owolabi MO. Taming the burgeoning stroke epidemic in Africa: stroke quadrangle to the rescue. *West Indian Med J* 2011; **60**(4): 412–421.
13. Obiako OR, Oparah SK, Ogunniyi A. Prognosis and outcome of acute stroke in the University College Hospital Ibadan, Nigeria. *Niger J Clin Pract* 2011; **14**(3): 359–362.
14. Onwuchekwa AC, Chinenye S. Clinical profile of hypertension at a University Teaching Hospital in Nigeria. *Vasc Health Risk Manag* 2010; **6**: 511–516.
15. Ekenze OS, Onwuekwe IO, Ezeala Adikaibe BA. Profile of neurological admissions at the University of Nigeria Teaching Hospital Enugu. *Niger J Med* 2010; **19**(4): 419–422.
16. Connor MD, Thorogood M, Modi G, Warlow CP. The burden of stroke in sub-Saharan Africa. *Am J Prev Med* 2007; **33**(2): 172–173.
17. Adeloye D, Basquill C. Estimating the prevalence and awareness rates of hypertension in Africa: a systematic analysis. *PLoS One* 2014; **9**(8): e104300.
18. Matenga J. Stroke incidence rates among black residents of Harare – a prospective community-based study. *S Afr Med J* 1997; **87**(5): 606–609.
19. Damasceno A, Gomes J, Azevedo A, Carrilho C, Lobo V, Lopes H, *et al*. An epidemiological study of stroke hospitalizations in Maputo, Mozambique: a high burden of disease in a resource-poor country. *Stroke* 2010; **41**(11): 2463–2469.
20. Osuntokun BO, Bademosi O, Akinkugbe OO, Oyediran AB, Carlisle R. Incidence of stroke in an African City: results from the Stroke Registry at Ibadan, Nigeria, 1973–1975. *Stroke* 1979; **10**(2): 205–207.
21. El-Tallawy HN, Farghaly WM, Rageh TA, Shehata GA, Badry R. Door-to-door survey of major neurological disorders (project) in Al Quseir City, Red Sea Governorate, Egypt. *Neuropsychiatr Dis Treat* 2013; **9**: 767–771.
22. Farghaly WM, El-Tallawy HN, Shehata GA, Rageh TA, bdel-Hakeem NM, Elhamed MA, *et al.*. Epidemiology of nonfatal stroke and transient ischemic attack in Al-Kharga District, New Valley, Egypt. *Neuropsychiatr Dis Treat* 2013; **9**: 1785–1790.
23. Thrift AG, Cadilhac DA, Thayabaranathan T, Howard G, Howard VJ, Rothwell PM, *et al*. Global stroke statistics. *Int J Stroke* 2014; **9**(1): 6–18.
24. Danesi MA, Okubadejo NU, Ojini FI, Ojo OO. Incidence and 30-day case fatality rate of first-ever stroke in urban Nigeria: the prospective community based Epidemiology of Stroke in Lagos (EPISIL) phase II results. *J Neurol Sci* 2013; **331**(1–2): 43–47.
25. Pandian JD, Sudhan P. Stroke epidemiology and stroke care services in India. *J Stroke* 2013; **15**(3): 128–134.
26. Prasad K, Vibha D, Meenakshi. Cerebrovascular disease in South Asia – Part I: A burning problem. *JRSM Cardiovasc Dis* 2012; **1**(7).
27. Wang J, An Z, Li B, Yang L, Tu J, Gu H, *et al*. Increasing stroke incidence and prevalence of risk factors in a low-income Chinese population. *Neurology* 2015; **84**(4): 374–381.
28. Ashok PP, Radhakrishnan K, Sridharan R, el-Mangoush MA. Incidence and pattern of cerebrovascular diseases in Benghazi, Libya. *J Neurol Neurosurg Psychiat* 1986; **49**(5): 519–523.
29. Rosman KD. The epidemiology of stroke in an urban black population. *Stroke* 1986; **17**(4): 667–669.
30. El ZS, Ahmed M, Prakash PS, Hassan KM. Stroke: Incidence and pattern in Benghazi, Libya. *Ann Saudi Med* 1995; **15**(4): 367–369.
31. Kandil MR, El-Tallawy HN, Farawez HM, Khalifa G, Ahmed MA. Epidemiology of Cerebrovascular Stroke and TIA in Upper Egypt (Sohag) -Relative Frequency of Stroke in Assiut University Hospital. *Egypt J NeurolPsychiat Neurosurg* 2006; **43**: 593–602.
32. Walker R, Whiting D, Unwin N, Mugusi F, Swai M. Stroke incidence in rural and urban Tanzania: a prospective, community-based study. *Lancet Neurol* 2010; **9**: 786–792.
33. Asefa G, Meseret S. CT and clinical correlation of stroke diagnosis, pattern and clinical outcome among stroke patients visting Tikur Anbessa Hospital. *Ethiop Med J* 2010; **48**(2): 117–122.
34. Tekle-Haimanot R, Abebe M, Gebre-Mariam A, Forsgren L, Heijbel J, Holmgren G, *et al*. Community-based study of neurological disorders in rural central Ethiopia. *Neuroepidemiology* 1990; **9**(5): 263–277.
35. Khedr EM, Elfetoh NA, Al AG, Ahmed MA, Ali AM, Hamdy A, *et al*. Epidemiological study and risk factors of stroke in Assiut Governorate, Egypt: community-based study. *Neuroepidemiology* 2013; **40**(4): 288–294.
36. Bonita R, Truelsen T. Stroke in sub-Saharan Africa: a neglected chronic disease. *Lancet Neurol* 2003; **2**(10): 592.
37. Osuntokun BO, Adeuja AO, Schoenberg BS, Bademosi O, Nottidge VA, Olumide AO, *et al*. Neurological disorders in Nigerian Africans: a community-based study. *Acta Neurol Scand* 1987; **75**(1): 13–21.
38. Danesi M, Okubadejo N, Ojini F. Prevalence of stroke in an urban, mixed-income community in Lagos, Nigeria. *Neuroepidemiology* 2007; **28**(4): 216–223.
39. Dewhurst F, Dewhurst MJ, Gray WK, Aris E, Orega G, Howlett W, *et al*. The prevalence of neurological disorders in older people in Tanzania. *Acta Neurol Scand* 2013; **127**(3): 198–207.

40. Khedr EM, Fawi G, Abdela M, Mohammed TA, Ahmed MA, El-Fetoh NA, *et al*. Prevalence of ischemic and hemorrhagic strokes in Qena Governorate, Egypt: Community-based Study. *J Stroke Cerebrovasc Dis* 2014; **23**(7): 1843–1848.
41. Attia Romdhane N, Hamida MB, Mrabet A, Lamaout A, Samoud S. Prevalence study of neurologic disorders in Kelibia (Tunisia). *Neuroepidemiology* 1993; **12**(5): 285–299.
42. Walker R. Hypertension and stroke in sub-saharan Africa. *Trans R Soc Trop Med Hyg* 1994; **88**(6): 609–611.
43. Connor MD, Thorogood M, Casserly B, Dobson C, Warlow CP. Prevalence of stroke survivors in rural South Africa: results from the Southern Africa Stroke Prevention Initiative (SASPI) Agincourt field site. *Stroke* 2004; **35**(3):627–632.
44. Cossi MJ, Gobron C, Preux PM, Niama D, Chabriat H, Houinato D. Stroke: prevalence and disability in Cotonou, Benin. *Cerebrovasc Dis* 2012; **33**(2): 166–172.
45. Olarinde OJ, Olatunji OY. Pattern of deaths in medical wards of a rurally situated tertiary health institution, Ido-Ekiti, Nigeria. *Niger J Clin Pract* 2014; **17**(2): 237–240.
46. Sanya EO, Abiodun AA, Kolo P, Olanrewaju TO, Adekeye K. Profile and causes of mortality among elderly patients seen in a tertiary care hospital in Nigeria. *Ann Afr Med* 2011; **10**(4): 278–283.
47. Peck RN, Green E, Mtabaji J, Majinge C, Smart LR, Downs JA, *et al*. Hypertension-related diseases as a common cause of hospital mortality in Tanzania: a 3-year prospective study. *J Hypertens* 2013; **31**(9): 1806–1811.
48. Misganaw A, Mariam DH, Araya T. The double mortality burden among adults in Addis Ababa, Ethiopia, 2006–2009. *Prev Chronic Dis* 2012; **9**: E84.
49. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA. Global burden of stroke: an underestimate - Authors' reply. *Lancet* 2014; **383**(9924): 1205–1206.
50. Krishnamurthi R, Moran A, Forouzanfar M. The global burden of hemorrhagic stroke: a summary of findings from the GBD 2010 study. *Glob Heart* 2014; **9**: 101–106.
51. Kim AS, Johnston SC. Global variation in the relative burden of stroke and ischemic heart disease. *Circulation* 2011; **124**(3): 314–323.
52. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation* 2001; **104**(22): 2746–2753.
53. Owolabi MO, Ugoya S, Platz T. Racial disparity in stroke risk factors: the Berlin-Ibadan experience; a retrospective study. *Acta Neurol Scand* 2009; **119**(2): 81–87.
54. Owolabi MO, Agunloye AM. Which risk factors are more associated with ischemic rather than hemorrhagic stroke in black Africans? *Clin Neurol Neurosurg* 2013; **115**(10): 2069–2074.
55. Walker RW, Jusabani A, Aris E, Gray WK, Whiting D, Kabadi G, *et al*. Post-stroke case fatality within an incident population in rural Tanzania. *J Neurol Neurosurg Psychiat* 2011; **82**(9): 1001–1005.
56. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, *et al*. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 2010; **376**(9735): 112–123.
57. Osuntokun BO. Stroke in the Africans. *Afr J Med Med Sci* 1977; **6**(2): 39–53.
58. Mudzi W, Stewart A, Musenge E. Case fatality of patients with stroke over a 12-month period post stroke. *S Afr Med J* 2012; **102**(9): 765–767.
59. Mills A. Health care systems in low- and middle-income countries. *N Engl J Med* 2014; **370**(6): 552–557.
60. First Center for Neurorehabilitation in East, West, and Central Africa. *Internet* 2015;Available at: URL: http://www.blossom.org.ng/. AccessedFebruary 3, 2015.
61. WFNR. World Federation for Neurorehabilitation (WFNR). *Internet* 2015; Available at: URL: www.wfnr.co.uk. AccessedMarch 3, 2015.
62. Bertram MY, Katzenellenbogen J, Vos T, Bradshaw D, Hofman KJ. The disability adjusted life years due to stroke in South Africa in 2008. *Int J Stroke* 2013; **8**(Suppl A100): 76–80.
63. Johnston SC, Mendis S, Mathers CD. Global variation in stroke burden and mortality: estimates from monitoring, surveillance, and modelling. *Lancet Neurol* 2009; **8**(4): 345–354.
64. Norman R, Gaziano T, Laubscher R, Steyn K, Bradshaw D. Estimating the burden of disease attributable to high blood pressure in South Africa in 2000. *S Afr Med J* 2007; **97**(8 Pt 2): 692–698.
65. Tran J, Mirzaei M. The population attributable fraction of stroke associated with high blood pressure in the Middle East and North Africa. *J Neurol Sci* 2011; **308**(1–2): 135–138.
66. BeLue R, Okoror TA, Iwelunmor J, Taylor KD, Degboe AN, Agyemang C, *et al*. An overview of cardiovascular risk factor burden in sub-Saharan African countries: a socio-cultural perspective. *Glob Health* 2009; **5**: 10.
67. Adedoyin RA, Mbada CE, Balogun MO, Martins T, Adebayo RA, Akintomide A, *et al*. Prevalence and pattern of hypertension in a semiurban community in Nigeria. *Eur J Cardiovasc Prev Rehabil* 2008; **15**(6): 683–687.
68. Lackland DT, Roccella EJ, Deutsch AF, Fornage M, George MG, Howard G, *et al*. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. *Stroke* 2014; **45**(1): 315–353.
69. Ogedegbe G. Barriers to optimal hypertension control. *J Clin Hypertens (Greenwich)* 2008; **10**(8): 644–646.
70. Lemogoum D, Degaute JP, Bovet P. Stroke prevention, treatment, and rehabilitation in sub-saharan Africa. *Am J Prev Med* 2005; **29**(5 Suppl 1): 95–101.
71. Agunloye AM, Owolabi MO. Exploring carotid sonographic parameters associated with stroke risk among hypertensive stroke patients compared to hypertensive controls. *J Ultrasound Med* 2014; **33**(6): 975–983.
72. Owolabi MO, Agunloye AM. Risk factors for stroke among patients with hypertension: A case-control study. *J Neurol Sci* 2013; **325**(1–2): 51–56.
73. Owolabi MO, Agunloye AM, Ogunniyi A. The relationship of flow velocities to vessel diameters differs between extracranial carotid and vertebral arteries of stroke patients. *J Clin Ultrasound* 2014; **42**: 16–23.
74. Ogbole GI, Owolabi MO, Yusuf BP. White matter changes on magnetic resonance imaging: a risk factor for stroke in an African population? *J Stroke Cerebrovasc Dis* 2013; **22**(7): e227–e233.
75. Akpalu A, Nyame P. Plasma homocysteine as a risk factor for strokes in ghanaian adults. *Ghana Med J* 2009; **43**(4): 157–163.
76. Ganguly P, Alam SF. Role of homocysteine in the development of cardiovascular disease. *Nutr J* 2015; **14**: 6.
77. Akpalu J, Akpalu A, Ofei F. The metabolic syndrome among patients with cardiovascular disease in Accra, Ghana. *Ghana Med J* 2011; **45**(4): 161–166.
78. Owolabi MO, Platz T. Proposing the Stroke Levity Scale: a valid, reliable, simple, and time-saving measure of stroke severity. *Eur J Neurol* 2008; **15**(6): 627–633.
79. Owolabi MO. Impact of stroke on health-related quality of life in diverse cultures: the Berlin-Ibadan multicenter international study. *Health Qual Life Outcomes* 2011; **9**: 81.
80. Owolabi MO. Consistent determinants of post-stroke health-related

quality of life across diverse cultures: Berlin-Ibadan study. *Acta Neurol Scand* 2013; **128**(5): 311–320.
81. Abegunde DO, Shengelia B, Luyten A, Cameron A, Celletti F, Nishtar S, *et al*. Can non-physician health-care workers assess and manage cardiovascular risk in primary care? *Bull World Health Organ* 2007; **85**(6): 432–440.
82. Owolabi LF, Akinyemi RO, Owolabi MO, Sani MU, Ogunniyi A. Profile of stroke-related late onset epilepsy among Nigerians. *J Med Trop* 2013; **15**(1): 29–32.
83. Akinyemi RO, Ogah OS, Ogundipe RF, Oyesola OA, Oyadoke AA, Ogunlana MO, *et al*. Knowledge and perception of stroke amongst hospital workers in an African community. *Eur J Neurol* 2009; **16**(9): 998–1003.
84. Ojagbemi A, Owolabi M, Atalabi M, Baiyewu O. Stroke lesions and post-stroke depression among survivors in Ibadan, Nigeria. *Afr J Med Med Sci* 2013; **42**(3): 245–251.
85. Donkor ES, Owolabi MO, Bampoh P, Aspelund T, Gudnason V. Community awareness of stroke in Accra, Ghana. *BMC Public Health* 2014; **14**: 196.
86. Feigin VL, McNaughton H, Dyall L. Burden of stroke in Maori and Pacific peoples of New Zealand. *Int J Stroke* 2007; **2**(3): 208–210.
87. World Health Organization. WHO STEPS Stroke Manual: The WHO STEPwise approach to stroke surveillance. 2006.
88. Guinhouya KM, Tall A, Kombate D, Kumako V, Apetse K, Belo M, *et al*. [Cost of stroke in Lome (Togo)]. *Sante* 2010 August 4 [Epub ahead of print].
89. Ortegon M, Lim S, Chisholm D, Mendis S. Cost effectiveness of strategies to combat cardiovascular disease, diabetes, and tobacco use in sub-Saharan Africa and South East Asia: mathematical modelling study. *Br Med J* 2012; 344: e607.
90. Lackland DT. An international working party on assessing hypertension control in populations: a proposal. *J Hum Hypertens* 1996; **10**(Suppl 1): S29–S31.
91. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006; **3**(11): e442.
92. Owolabi MO, Akinyemi RO, Gebregziabher M, Olaniyan O, Salako BL, Arulogun O, *et al*. Randomized controlled trial of a multipronged intervention to improve blood pressure control among stroke survivors in Nigeria. *Int J Stroke* 2014; **9**(8): 1109–1116.
93. Owolabi MO, Akinyemi RO, Hurst S, Arulogun O, Olaniyan O, Gebregziabher M, Salako BL, Ovbiagele B. Tailored Hospital-based Risk Reduction to Impede Vascular Events After Stroke (THRIVES) study: qualitative phase protocol. *Crit Pathw Cardiol* 2014; **13**(1): 29–35.

Stroke genomics in people of African ancestry: charting new paths

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Abstract

One in six people worldwide will experience a stroke in his/her lifetime. While people in Africa carry a disproportionately higher burden of poor stroke outcomes, compared to the rest of the world, the exact contribution of genomic factors to this disparity is unknown. Despite noteworthy research into stroke genomics, studies exploring the genetic contribution to stroke among populations of African ancestry in the United States are few. Furthermore, genomics data in populations living in Africa are lacking. The wide genomic variation of African populations offers a unique opportunity to identify genomic variants with causal relationships to stroke across different ethnic groups. The Stroke Investigative Research and Educational Network (SIREN), a component of the Human Health and Heredity in Africa (H3Africa) Consortium, aims to explore genomic and environmental risk factors for stroke in populations of African ancestry in West Africa and the United States. In this article, we review the literature on the genomics of stroke with particular emphasis on populations of African origin.

Keywords: stroke, cerebrovascular risk factors, genomics, genetics, Nigeria, Ghana, Africa, African ancestry

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Stroke is the clinical culmination of several complex processes and interacting pathways that involve various genetic and environmental factors.[1] However, the exact nature and level of the contribution of genetic factors to stroke and its different subtypes have not been clearly established. Presumably, genetic contributions to stroke may result from common variants with small effect sizes, rare variants with large effect sizes, or a combination of both.[2-4] Nevertheless, studies exploring the genetic underpinnings of the peculiarities of stroke in populations of African ancestry in the United States are few,[3,5-7] while there are hardly any data on populations living in Africa.

The diverse genomic variation of African populations[8-10] offers a unique opportunity to identify novel genes and molecular pathways of stroke that may lead to new and better prevention and treatment options for stroke in people of African ancestry and other global populations. Understanding the interplay of genetic and environmental risk factors for stroke is critical to the prediction of its occurrence, severity and outcome as well as the formulation of successful tailored treatment and prevention programmes. In addition, the biology of stroke subtypes will be better deciphered.

In this review article, we provide an overview of the changing global and in particular, African epidemiology of stroke, the known peculiarities of stroke in Africa, extant literature on the genomics of stroke and cerebrovascular risk factors, with particular attention to people of African ancestry, as well as opportunities for charting new paths through the Human, Health and Heredity in Africa (H3Africa) initiative.[11,12]

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Changing global and African epidemiology of stroke

Stroke has attracted global attention, as one in six people will develop stroke in their lifetime.[13,14] Stroke is a significant medical and public health problem, with loss of productivity and burden on families, caregivers and society.[13-15] The lifetime risk of stroke is one in five women and one in six men.[13] Stroke is the most common cause of acquired disability and the second most common cause of death worldwide. The World Health Organisation (WHO) estimates for 2001 indicated that death from stroke and disability-adjusted life years (DALYs) due to stroke was at least seven times higher in low- and middle-income countries (LMIC) than in high-income countries (HIC).[16] Recent incidence estimates[17,18] indicate that whereas stroke incidence declined 12% in HIC, it increased by 12% in LMIC over the last decade.

Africa, in epidemiological transition,[19,20] is currently faced with an exploding but neglected burden of non-communicable diseases (NCDs), including hypertension, diabetes mellitus and dyslipidaemia, which often culminate in stroke. The recent United Nations high-level meeting on the global burden of NCDs highlighted their disproportionately high burden and stressed the urgent need to tackle them, particularly in developing countries.

The burgeoning incidence of stroke in Africa is attributable to rising cardiovascular risk profile, which is in turn driven by epidemiological transition, an aging population, rapid urbanisation and accompanying lifestyle changes. Africa, with a current population of over one billion, has a stroke prevalence rate of up to 963/100 000 population,[21] an incidence rate of up to 315/100 000 population and a three-year mortality rate as high as 84%. About 3.2 million Africans develop incident stroke every year.[15] Recent data from Nigeria, Tanzania and Sudan showed that stroke was the leading cause of elderly medical admissions,[22] while up to 78% of neurological hospital admissions were due to stroke.[23] The impact of this on mental capacity, quality of life and economic productivity portends great danger for the emerging economies of Africa.[24-26]

Peculiarities of stroke in people of African ancestry

Enhanced predisposition, different pattern of subtypes, worse severity and often poorer outcome of stroke in people of African descent is quite well established. According to data from the INTERSTROKE study, ischaemic stroke accounts for 66% while haemorrhagic stroke accounts for 34% in Africa, compared to 91 and 9%, respectively for ischaemic and haemorrhagic stroke in HIC. Ischaemic stroke subtypes diagnosed in African populations were small vessel (27%), cardio-embolism (25%), large vessel (14%), others (20%) and undetermined (14%).[27]

Among sub-Saharan Africans, stroke affects a relatively younger age group and productive workforce than in developed economies.[27,28] Data from the USA suggest that African Americans have a higher predisposition, worse severity and often poorer outcomes compared to Caucasian Americans.[29,30] In a recent report from the multi-ethnic South London Stroke Registry study, black stroke survivors had worse cognitive outcome compared to other racial groups.[31] Although, this may be due to socio-economic differences, disparities in healthcare-seeking practices and differential access to healthcare services, the influence of underlying differences in genetic factors cannot be underestimated.[32,33]

Genomics and health disparities

Genetics and genomics research offer insight into disparities in the risk profile, phenotypes and outcome of diseases among different populations as a result of accumulated small differences in common alleles or rare variants, interactions among multiple genetic loci and interactions between genes and environmental factors, which may include cultural practices and health-seeking behaviour.[34,35] The potential of treatment approaches tailored to individual, unique genomic profiles represents a distinct potential impact of genomics on improving health disparities. Also, the globalisation of complex chronic diseases further suggests that all populations are susceptible, and that variation in rates may also be explained as a result of differential exposure to environmental causes, including lifestyles, cultural practices and health-seeking behaviours.[36]

African human genomic variation

African populations present the highest genomic diversity, the lowest levels and most divergent patterns of linkage disequilibrium, as well as smaller haplotype block sizes across human populations.[8,37] Although the human species is believed to have originated from Africa about 200 000 years ago, studies of genomic variation in Africa suggest that the present pattern of variation within and between populations is a product of several factors. These include demographic history, population structure, diversities of geographical location, language classification and different patterns of subsistence, dietary differences, multiple migrations with accompanying high levels of genetic admixture and survival related to exposure to infectious diseases.[38,39]

For example, Tishkoff and colleagues[8] identified 14 ancestral population clusters in Africa with four predominant clusters that broadly represent populations from major African geographical regions and the four dominant African language families. These are Niger-Kordofanian (spoken primarily by agriculturalist populations located in large contiguous regions of sub-Saharan Africa from West Africa to eastern and southern Africa), Nilo-Saharan (spoken predominantly by pastoralist populations in central and eastern Africa), Afro-Asiatic (spoken predominantly by agro-pastoralists and pastoralist populations in northern and eastern Africa), and Khoisan (a language family that contains click consonants, spoken by hunter–gatherer San populations in southern Africa as well as the Hadza and Sandawe hunter–gatherers in Tanzania). The remaining 10 are mainly restricted to specific geographic regions, languages, or in some cases, individual populations.

More recently, Shriner and colleagues[9] analysed ancestry data from 12 global and regional diversity projects with genome-wide genotype data for 3 528 unrelated individuals from 163 samples from around the world. They identified 19 ancestral components with 94.4% of individuals showing mixed ancestry. Furthermore, they validated the earlier findings of Tishkoff and colleagues and identified an additional ancestral component in Africa, the Omotic-speaking peoples of Ethiopia.

Our knowledge of African human genomic variation is growing. This was previously limited by the small number of African populations involved in landmark projects such as the International HapMap project[40] and the more recent 1 000 Genomes project.[41] In these projects, participation was limited

to largely Niger-Kordofanian-speaking Yoruba and Esan from Nigeria, Mende from Sierra Leone, Bantu-speaking Luhya from Kenya, and Nilo-Saharan-speaking Maasai from Kenya. A large proportion of African human genomic variation therefore remained unexplored.

However, recent data from the African Genome Variation project (AGVP) have provided evidence and more detailed characterisation of African genomic diversity.[10] The AGVP utilised dense genotypes from 1 481 individuals and whole-genome sequences from 320 individuals across sub-Saharan Africa. Novel evidence of complex, regionally distinct widespread hunter–gatherer and Eurasian admixture across sub-Saharan Africa was apparent and substantial hunter–gatherer and Eurasian ancestry admixture of up to 23 and 50%, respectively, were found in many African populations with detailed chronology of the timing of the admixture. For instance, whereas the Eurasian admixture among the Yoruba occurred 7 500–10 500 years ago, it was more recent among the Fula tribe of Gambia, occurring only about 320–780 years ago.

These admixtures provide evidence for back-to-Africa migration, the existence of hunter–gatherer populations in West Africa and a pattern of gene flow consistent with the Bantu expansion. The AGVP also found new loci related to susceptibility, pathogenesis, severity and outcome of several diseases, including malaria, Lassa fever, trypanosomiasis, trachoma and hypertension. For instance, they identified highly differentiated variants within genes involved in osmoregulation (*ATP1A1* and *AQP2*), deregulation of *AQP2* expression, and loss-of-function mutations in *ATP1A1* have been associated with essential and secondary hypertension, respectively.[42,43] The study also established an efficient genotype array design capturing common genetic variation in Africa, which would be useful for future African genomic studies.[11,12]

African American genomic variation

African Americans have mixed ancestry originating from Africa and other continents, especially Europe. Studies have shown the average amount of African ancestry in African Americans to be about 80% (predominantly of western and central African origin),[8,44,45] although there is substantial variation in the level of African ancestry in individual African Americans, as the proportion of African ancestry in a given individual can range from one to 99%.[39]

Genomic variation and related phenotype data on variable traits contribute novel information useful for identifying population-specific variants that play a role in gene function, phenotypic adaptation and susceptibility to complex diseases, such as stroke in Africans and populations of African descent. The APOE ε4 allele, a well-studied example that contributes to a small extent to individual and population risks of traits such as stroke, heart disease and dementia, is found in virtually all populations, albeit at varying rates. The frequency of homo- or heterogeneous APO ε4 alleles varies across populations but confers different attributable risks of Alzheimer's disease; the risk being higher among the Japanese but much lower among people of African ancestry with higher allele frequencies. This suggests possible intervening roles for epigenetic interactions from certain modifier genes or some other environmental factors.[34]

Genomics of stroke and cerebrovascular risk factors

Stroke is a complex polygenic, heterogeneous and multifactorial disorder involving many complex mechanisms, intermediate phenotypes and the interplay of genetic and non-genetic factors. Evidence from twin studies, family history studies, animal models and heritability studies of vascular risk factors and intermediate phenotypes suggests a likely significant contribution of genetic factors to the neurobiology and phenomenology of stroke.[1,4,46]

Family history and heritability

Among individuals with a positive family history of stroke, there is an increased risk of stroke, which may be due to expression of genetic susceptibility, a shared environment or both.[47] In the Family Heart study, personal and familial histories of stroke were assessed in 3 168 individuals (probands) who were at least 45 years old and 29 325 of their first-degree relatives. The odds of stroke were 2.00 (1.13–3.54) for a positive paternal and 1.41 (0.80–2.50) for a positive maternal history of stroke after adjusting for age, gender, ethnicity and presence of vascular risk factors, and the pattern was similar between African Americans and European Americans.[48]

In a systematic review of the heritability of stroke in 53 independent studies (three twin studies, 33 case–control studies and 17 cohort studies), it was found that monozygotic twins were more likely to be concordant than dizygotic twins (OR, 1.65; 95% CI, 1.2–2.3; $p = 0.003$) while a positive family history was a risk factor for stroke in both case–control (OR, 1.76; 95% CI, 1.7–1.9; $p < 0.00001$) and cohort (OR, 1.30; 95% CI, 1.2–1.5; $p < 0.00001$) studies. Besides, positive family history was more associated with small-vessel and large-vessel strokes.[49]

Cerebrovascular risk factors

Genomic factors may contribute to the neurobiology of stroke through their influence on established risk factors, such as hypertension, diabetes, dyslipidaemia, obesity and cigarette smoking or through their influence on intermediate phenotypes, such as white matter hyperintensities (WMH) and carotid intima–media thickness (CIMT). For instance, research evidence has shown racial and ethnic disparities in cardiovascular and cerebrovascular diseases, with Americans of African ancestry showing a higher prevalence of hypertension and earlier onset, and faster and more severe end-organ damage, including stroke.[50] Apart from non-inherited factors such as lifestyles, health-related practices, socio-economic profile and differential access to healthcare, genetic factors contributed significantly to this disparity.[32]

A recent genome-wide association study (GWAS) of hypertension and blood pressure in African Americans using the pathway-focused approach established the genome-wide significant association of the genetic variants *PMS1, SLC24A4, YWHA7, IPO7* and *CACANA1H* with systolic blood pressure levels, with significant replication of some single-nucleotide polymorphisms (SNPs) in a sample of West Africans.[51] Using a similar approach, a more recent study has found association between multiple variants in several genes in the adrenergic alpha-1 receptor (ADRA1) pathway and hypertension in Yoruba Nigerians.[52] A meta-analysis of genome-wide linkage scans for blood pressure variation in Nigerians and African Americans

reported association in two loci: 2p14 –p13.1 and 7p21.3 –p15.3, the second locus being attributed to the Nigerian sample and suggesting a unique locus for blood pressure variation in people of African ancestry.[53]

In the GenHAT study evaluating the pharmacogenetic effects of candidate gene complexes on stroke, significant genetic difference was found between hypertension drug treatment groups in patients who had experienced stroke, especially among African Americans and non-Hispanic whites.[54] Given the fact that hypertension is the most dominant risk factor for stroke among people of African ancestry in Africa,[15,24,27,28] and the diaspora,[30,50] it would be worthwhile exploring the possible contribution of these hypertension-related genotypes in people of African ancestry.

A Nigerian study assessed glucose and insulin responses to an oral glucose load among offspring of parents with type 2 diabetes mellitus (T2DM) and found higher levels of fasting plasma glucose, fasting plasma insulin, and two-hour post-glucose load plasma insulin, indicating a higher risk for developing diabetes.[55] A Cameroonian case–control pedigree study showed increased prevalence of diabetes and impaired glucose tolerance in the offspring of parents with T2DM.[56]

The Africa America Diabetes Mellitus (AADM) study has utilised genome-wide linkage and association studies to provide insight into the genomics of T2DM in Niger-Kordofanian African populations of Nigeria and Ghana. Multiple linkage analysis provided evidence of regions of chromosome 12, 19 and 20 (the strongest being 20q13.3).[57] The loci found to influence C-peptide plasma levels (10q23, 4p15) were found to harbour multiple T2DM candidate genes [phosphatase and tensin homolog (PTEN), protein phosphatase 1, regulatory subunit 3C (PPP1R3C), insulin degrading enzyme (IDE), and peroxisome proliferator activated receptor gamma, coactivator 1 alpha (PPARGC1)].[58] Collaborative GWAS and other studies have identified further susceptibility (CDKAL1, CAPN10, TCF7L2 variants and PPARG variants) and protective loci (TCF2, AGRP -38C/T).[57]

Chronic kidney disease (CKD) is an identified risk factor for cerebral vascular disease.[59] Multiple common SNPs in the gene that encodes non-muscle myosin heavy-chain type II isoform A (MYH9) have been associated with an increase in the risk of focal segmental glomerulosclerosis and end-stage renal disease,[60] while more recently the apolipoprotein L1 (*APOL1*) gene has been identified as a risk locus for CKD in African Americans, and replications confirmed in Nigerian Yoruba CKD patients.[61,62]

In Africa, *APOL1* confers resistance to infection from *Trypanosoma brucei brucei*, one of the trypanosomes that cause African sleeping sickness and it is believed that its evolutionary history lies in its positive selection due to its protection against sleeping sickness.[63] Interestingly, an inverse relationship between high-density lipoprotein cholesterol (HDL-C) and kidney function in African ancestry populations has also been described in individuals with the nephropathy risk *APOL1* gene.[64] Higher HDL-C was associated with worse kidney function in those with the risk genotype, while no association was observed among those without the genotype. Therefore, the increasing incidence of cardiovascular disorders (CVDs) in Africa along with the evidence of genetic variants that increase susceptibility to CVDs signals the need for large-scale genomic epidemiology studies in Africa in search of other putative protective and susceptibility loci.[12]

Population-attributable risks of genetic variants differ depending on whether they are monogenic, common variants or rare variants of multiple genes of polygenic disorders.[2,3] More important, however, is the functional significance of the variants in the biological pathways where their gene products contribute to the biology of the disease and may possibly be of therapeutic or preventative importance.[65] This is the major thrust of our proposed study of genetic variants relevant to stroke in people of African ancestry. African representation in the 1 000 Genomes study is limited,[41] while the H3Africa projects[11] offer robust opportunities for detailed exploration of genomic data relevant to African and global populations.

Intermediate phenotypes: WMH and CIMT

Both twin and family studies have shown that magnetic resonance imaging of white matter hyperintensities has shown a heritability (proportion of variation explained by genetic factors) of up to 70%.[66] CIMT measured by ultrasound and believed to represent the early stages of atherosclerosis and related to large-artery stroke has been estimated to have a heritability of between 30 and 70%.[67]

Monogenic stroke disorders

Monogenic disorders may cause stroke as part of multi-systemic manifestations or solely as a clinical phenotype limited to the central nervous system. They are important for individual patients but may not account for much population-attributable risk.[46]

Sickle cell disease (SCD) is of particular importance in people of African ancestry. It is caused by a point mutation at codon 6 of the beta-globin gene, leading to a glutamic acid to valine (Glu→Val) substitution in the beta-globin chain of human adult haemoglobin, and producing sickle haemoglobin (HbS). Inherited autosomal recessively, either two copies of HbS or one copy of HbS plus another beta-globin variant (such as HbC) are required for disease expression. HbS carriers are protected from malaria infection, and this selective pressure is believed to have led to the high frequency of HbS (up to 40%) in individuals of African ancestry, especially in areas of high malaria endemicity.[68,69]

The spread of SCD to the Americas is inextricably linked to slavery and the large-scale forced translocation of populations from West Africa.[70] Large- or small-vessel cerebral 'vasculopathy' characterised by proximal intracranial arterial stenoses, often leading to a moyamoya pattern, commonly complicates SCD and may manifest as abnormal transcranial Doppler velocity (> 200 cm/s) or frank stroke, particularly in younger patients with sickle cell anaemia, while complicated (hemiplegic) migraine was previously reported in Nigerian adults with sickle cell trait (HbAS).[71] By middle age, up to 25% of SCD patients develop overt stroke.[72]

Certain genetic polymorphisms may be associated with stroke in SCD as modifier genes. For instance whereas α-thalassaemia genes may be protective, mutations in the glucose-6-phosphate dehydrogenase (G6PD) genes and certain SNPs, including *ANXA2*, *rs11853426*, *TEK rs489347*, and *TGFBR3 rs284875* variants, have been associated with increased stroke risk.[73] A recent whole-exome sequencing (WES) study identified two

modifier mutations *GOLGB1* (*Y1212C*) and *ENPP1* (*K173Q*) associated with protection from stroke in a cohort of children with sickle cell anaemia.[74]

However, the interactions between SCD, its associated modifier genes, and environmental factors to produce an intermediate phenotype (TCD velocity > 200 cm/s) and stroke have not been examined in people of indigenous sub-Saharan Africa. Knowledge of these interactions and the metabolic pathways involved may unmask targets for preventative and therapeutic interventions in the sub-population of people living with SCD.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is associated with mutations in the *NOTCH3* gene and presents with migraine headache, followed by depression and ischaemic stroke in the deep gray structures and subcortical white matter, cognitive decline, and dementia.[75,76] A model of small-vessel disease, the first case of CADASIL in populations of African ancestry, was recently reported in a 73-year-old African American with a 15-base-pair heterozygous duplication of the exon 7 of the *NOTCH 3* gene.[77] Other related monogenic small-vessel cerebrovascular disorders include cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), retinal vasculopathy with cerebral leukodystrophy (RVCL), and Fabry disease.[78]

Genetic linkage studies

Genetic linkage studies have contributed to our understanding of the heritability of stroke and especially chromosomal regions and sub-regions involved, even though most studies have focused more on the ischaemic phenotype. Table 1 shows findings from a few linkage studies in stroke,[79-82] including genome-wide linkage studies. Much of these findings are further confirmed by more specific candidate gene analysis and the more rigorous approaches of association studies. A relative strength of linkage studies is the feasibility of working with a few hundred subjects using the case–control approach.

Stroke candidate genes

Identification of the phosphodiesterase 4D (*PDE4D*) and 5-lipoxygenase activating protein (*ALOX5AP*) genes through linkage analysis by the Icelandic Decode group was a significant landmark in the history of stroke genomics.[1,2,4] The rs918592 SNP variant of *PDE4D* was found to be significantly associated with stroke in current smokers in an African American cohort,[7] while mutations in the *NOS3* have also been significantly associated with large-artery stroke in African Americans.[6] Other variants significantly associated with ischaemic stroke in African Americans include the *IL6R* polymorphisms and the kappa-casein gene *CSN3* found on chromosome 4, the latter through exome sequencing.[3,5]

The genetics of intracerebral haemorrhage (ICH) has also been explored through a range of candidate gene and GWAS approaches. Genes involved in the renin–angiotensin–aldosterone system, coagulation pathway, lipid metabolism, homocysteine metabolism and inflammation are among the most explored.[83] The *APOE* ε2 and *APOE* ε4 genes have been associated with lobal ICH in Caucasian, Asian and African American populations with a high prevalence of cerebral amyloid angiopathy (CAA).[84,85]

The association of *APOE* ε4 genes with deep ICH is rather inconsistent.[85] It is widely accepted that CAA is a frequent cause of ICH and the presence of an APOE ε4 allele substantially increases the risk of CAA.[86] Whether the risk of CAA or ICH is different in Africans is uncertain but it has long been known that the frequency of the APOE ε4 alleles, irrespective of tribal origin, is highly represented in the general African population.[87]

Deep ICH is also more aetiologically related to hypertensive chronic small-vessel disease and is likely to be more relevant in African populations where hypertension is the dominant stroke risk factor. Other genes with significant polymorphisms related to ICH include the methylenetetrahydrofolatereductase (*MTHFR*), interleukin-6, tumour necrosis factor-α, angiotensin converting enzyme (ACE), factor VII, factor XIII, platelet activating factor and β-tubulin, although most are described in populations of non-African ancestry.[83]

Stroke GWAS and WES studies

The candidate genes approach has proved disappointing in identifying genes contributing to the risk of multifactorial or polygenic stroke. This is a situation shared with other complex diseases.[88] Recently, the GWAS approach has revolutionised the field of stroke genetics. GWAS enables markers spanning the whole genome to be genotyped in a single experiment. Using a case–control methodology and rigorous statistical methods to account for the multiple comparisons made, associations between completely unexpected chromosomal loci and disease can be identified.[88,89]

Table 1. Genetic linkage studies in stroke

First author (year)	*Study type*	*Phenotype*	*Sample*	*Salient findings*
Craig *et al.* (1998)[74]	Linkage analysis	Cerebral cavernous malformation	20 non-Hispanic Caucasian families	CCM – 1(7q) (found in Hispanic Americans), CCM2 (7p13-15) and CCM3 at 3q25.2-27 all found in non-Hispanic Caucasian families.
Nilsson-Ardnor *et al.* (2007)[76]	Genome-wide linkage analysis	All strokes; ischaemic stroke	56 Swedish families with familial stroke	LOD scores > 1.2 at 9 1ocations: 1p34, 5q13, 7q35, 9q22, 9q34, 13q32, 14q32, 18p11, and moderate linkage on chromosomes 5q, 9q, 13q, and 18p.
			Additional 53 families with familial strokes	Analysis of 53 additional families, further confirmed linkage on chromosomes 5q, 13q, and 18p.
Janunger *et al.* (2009)[75]	Genome-wide linkage analysis	All strokes	7 nuclear Swedish families with a common ancestor and connected over 8 generations	A maximum allele-sharing LOD score of 4.81 on chromosome 9q31-q33 was detected. Haplotype analysis identified a region for intracerebral haemorrhage.
Wang *et al.* (2014)[77]	Linkage and association analysis	Ischaemic stroke	227 Chinese families with ischaemic stroke	SNP rs1800798 in the IL-8 gene is signficantly linked to ischaemic stroke ($p = 0.002$) and small arterial occlusion (small-vessel disease) ($p = 0.022$).

GWAS has been employed to identify genetic loci for many other cardiovascular diseases such as coronary heart disease, diabetes and hypertension, and is just being applied to stroke. The pitfalls of previous studies of genomic contributions to stroke include poor phenotyping, underpowered studies, confounders, winner's curse, and non-validation in independent populations.[88,90] For example, the Siblings With Ischemic Stroke study (SWISS) did not demonstrate any significant genome-wide association.[91] However, certain novel genetic variants have been identified as risk factors in stroke populations, with some being replicated in other populations.

The International Stroke Genetics Consortium and the Wellcome Trust Case–Control Consortium published the largest GWAS for ischaemic stroke carried out to date. This study successfully demonstrated the importance of very large multicentre study samples, identified a new associated genetic variant and replicated findings of previous stroke GWAS. The findings also demonstrated the value of clear phenotyping and the fact that different stroke phenotypes may differ in their genetic architectures. Table 2 summarises the findings of salient recent GWAS studies in stroke, including a single study by Cole *et al*. in 2012, which utilised exome sequencing.[3,92-103]

Genetic studies of stroke in Africa

To date, only a few stroke genetic studies (Table 3) have been reported from North Africa and remarkably, none from sub-Saharan Africa where the burden of stroke is disproportionately heavy and the phenomics of stroke appears relatively different. Saidi and colleagues working consistently with a growing Tunisian stroke cohort have reported significant association between ischaemic stroke and polymorphisms in several genes, including plasminogen activator inhibitor, *APOE* ε4, human plasminogen activator, human platelet antigen, angiotensin converting enzyme *Del*/*Del* genotype, angiotensinogen, endothelial nitric oxide synthase and aldosterone synthase.[104-111]

A single study from Egypt noted that the presence of the *ACE* D allele significantly predisposed to stroke in children with sickle cell anaemia.[112] It is, however, significant to note that the people of North Africa have a different ancestral origin (predominantly Arabian and Berber) from sub-Saharan African populations.[9] Therefore, significant differences may be anticipated in the genomic profile of stroke and subtypes in sub-Saharan Africans.

Problems and perspectives

Apart from the lack of community-based ideal stroke epidemiological data sets and the challenge of accurate phenotypic characterisation of cases in sub-Saharan Africa, there are other inherent problems of genomic research ranging from the negative impact of cultural and religious beliefs, issues of autonomy of decision making and voluntary participation, as well as poor understanding of the health impact of genomics.[113-115] In a qualitative study assessing knowledge and attitude towards personal genomics testing for complex diseases among Nigerians, even though respondents felt the outcome of genomic testing might aid healthful lifestyle modifications, attitude was influenced by religion and culture, especially aspects that might directly contradict beliefs and practices or lead to actions contradicting religious beliefs.[115]

All these aspects introduce critical ethical issues into the framework of genomics research in Africa, which need to be addressed in order to achieve success and popularise the prospects of personalised genomic medicine. In addition, there are also the challenges of adequate infrastructure for genomic studies and analysis of genomic data, a paucity of appropriately trained scientists and physicians who have the capacity to design, implement and interpret such studies and lead translational applications, and insufficient bio-informaticians with analysis expertise and research managers. Unstable power supply and political instability are other bottlenecks.

Opportunities through H3 Africa: SIREN charting new paths

Although African populations harbour the greatest human genomic diversity, the potential of this for understanding human evolutionary biology and disparities in health and disease are

Table 2. Recent GWAS and WES studies in stroke

First author	*Study type*	*Phenotype*	*Sample size*	*Sample ancestry*	*Associated regions*
Hata *et al.* (2011)[85]	GWAS	Ischaemic stroke	1 112 cases, 1 112 controls	Japanese	14q22 (PRKCH), 11q12 (AGTRL1)
Matarin *et al.* (2009)[89]	GWAS	Ischaemic stroke	249 cases, 268 controls	White	None
Gretasrdottri and Gudjartsson *et al.* (2008, 2009)[87,88]	GWAS	Ischaemic stroke	1 661 cases, 10 815 controls	Icelandic	4q25 (PITX2), 16q22.3 (ZFHX3)
Bilguvar *et al.* (2008)[89]	GWAS	Intracranial aneurysms	2 100 cases, 8 000 controls	Finish, Dutch, Japanese	2q33 (PLCL1), 8q12 (SOX17), 9p21.3 (CDKN2A, CDK N2B, ANRIL)
Ikram *et al.* (2009)[90]	GWAS	Ischaemic stroke	Cohort of 19 602, 1 164 events	Caucasian	12p13.33 (NINJ2)
Yamada *et al.* (2009)[91]	GWAS	Ischaemic stroke	992 cases, 5 349 controls	Japanese	22q13 (CELSR1)
Zhang *et al.* (2012)[92]	GWAS	Ischaemic and haemorrhagic stroke	1 657 cases, 1 664 controls	Chinese	9p21.3 (ANRIL)
Matsushita *et al.* (2010)[93]	GWAS	Atherothrombotic stroke	2 775 cases, 2 839 controls	Japanese	ARHGEF 10
ISGC and WTCCC (2012)[94]	GWAS	Large-vessel stroke	3 548 cases, 5 972 controls	European	7p21.1 (HDAC9); replicated previous finding for cardio-embolic stroke near PITX2 and ZFHX3
Holliday *et al.* (2012)[95]	GWAS	Large-vessel stroke	1 162 cases, 1 244 controls	Australian	6p21.1
Cole *et al.* (2012)[3]	WES	Lacunar stroke	889 cases, 927 controls (10 for exome sequencing)	African American European American	4q21.1 (CSN3) **identified by exome sequencing following previous GWAS
Zhou *et al.* (2014)[96]	GWAS	Lacunar strokes systemic vasculopathy	9 subjects (exome sequencing)	European American, European	*ADA*2 gene

Table 3. Genetic studies of stroke in Africa

First author (year)	*Study type*	*Stroke phenotype*	*Sample*	*Salient findings*
Saidi *et al.* (2007)[97]	Genotyping	Ischaemic stroke	135 cases, 118 controls (Tunisian)	Altered plasminogen activator inhibitor 1 (PAI-1) and tissue-type plasminogen activator (tPA) levels: Significant ↑ in PAI-1 and marked ↓ in tPA levels correlated with 4G/5G, but not with -844G/A, PAI-1 variants 4G/4G carriers had reduced risk of stroke compared with other genotypes
Saidi *et al.* (2007)[98]	Genotyping	Ischaemic stroke	216 cases, 282 controls (Tunisian)	ApoE ε3 lower (0.546 vs 0.736; $p < 0.001$) in stroke vs control ApoE ε4 higher (0.370 vs 0.181; $p < 0.001$) in stroke vs control Prevalence of Apo ε4-containing phenotypes higher in: • ischaemic versus haemorrhagic ($p < 0.001$) • small-vessel versus large-vessel stroke cases ($p < 0.001$) • increased need for statin drugs ($p = 0.040$).
Mourad *et al.* (2008)[105]	Genotyping	Sickle cell anaemia	20 SCA cases, 10 controls (Egyptian)	Presence or ACE D allele significantly predisposed to stroke in children with sickle cell anaemia (SCA).
Saidi *et al.* (2008)[99]	Genotyping	Ischaemic stroke	216 stroke patients, 318 controls (Tunisian)	Human platelet alloantigen (HPA) – 1 a/b ($p < 0.001$) and HPA-5 a/b ($p < 0.001$) alleles were associated with stroke-susceptible genotypes: 1a/b-2a/a-3a/b-4a/a-5a/b protective genotypes: 1a/a-2a/a-3a/a-4a/a-5a/a; 1a/a-2a/a-3a/b-4a/a-5a/a; 1a/b -2a/a-3a/a-4a/a-5a/a; 1a/b-2a/a-3a/b-4a/a-5a/a)
Saidi *et al.* (2008)[100]	Genotyping	Ischaemic stroke	329 cases, 444 controls	Lower human platelet alloantigen, HPA-1a ($p < 0.001$) and higher HPA-1b ($p < 0.001$) allele frequencies were seen in cases than control subjects. Homozygosity for HPA-1b ($p < 0.001$) alleles was more prevalent in stroke cases than in controls.
Saidi *et al.* (2009)[101]	Genotyping	Ischaemic stroke	228 cases, 323 controls	Frequency of APOE ε3 allele and Apo E3/E3 genotype lower ($p < 0.001$) in stroke vs controls Frequency of Apo ε4 allele and genotypes (E3/E4 and E4/E4) elevated ($p < 0.001$) in stroke vs controls Higher proportion of Apo ε4-carrying + ACE Del/Del positive cases seen in young (< 50 years) patients ($p = 0.012$) and associated with large-vessel stroke ($p = 0.035$).
Saidi *et al.* (2009)[102]	Genotyping	Ischaemic stroke	329 cases, 444 controls	Angiotensinogen AGT 174T/235M/-6A, AGT 174T/235T/-6G. AGT 174T/235T/-6A and AGT 174M/235T/-6A haplotypes were significantly associated with an increased risk of stroke.
Saidi *et al.* (2010)[103]			329 IS patients, 444 controls	Endothelial nitric oxide synthase (eNOS) gene polymorphisms (298Asp allele and 298Asp/4b/-786T and 298Asp/4b/-786C haplotypes, and in addition identified 298Asp/4a/-786T haplotypes) were significantly associated with ischaemic stroke.

not yet fully explored. The H3Africa Consortium, with funding support from the National Institutes of Health (NIH) and the Wellcome Trust, is currently executing 24 different disease-based projects involving 50 000 to 75 000 participants across the African continent.[11] This initiative will deeply enhance our understanding of human genomic variation while unravelling the genomic bases of several communicable and non-communicable diseases on the continent, while facilitating genomic infrastructural development and capacity building.

The H3Africa Consortium is revolutionising genomic research in Africa and closing the huge genomics gap between Africa and the developed world. The initiative will reduce health disparities and enhance understanding of health issues for the benefit of Africans and the human race through the discovery of new genes and disease pathways with therapeutic and preventative potentials.

The Stroke Investigative Research and Education Network (SIREN) project is one of the H3Africa-funded projects. The SIREN investigators propose to explore genomic factors in stroke in 6 000 native West Africans (3 000 case–control pairs) in comparison with 1 000 African Americans (80% of whom are of West African ancestral origin) and 12 000 Americans of European ancestry in the REGARDS study (comparison among three tracks).[116,117] The wide genomic variation of African populations offers a unique opportunity to identify novel genomic variants with causal relationships to stroke across different ethnic groups.

The SIREN project has three main streams: phenomics (including community engagement), genomics, and bio-informatics (Fig. 1). An ethnically diverse sample increases the scope and generalisability of findings, because pan-ethnic

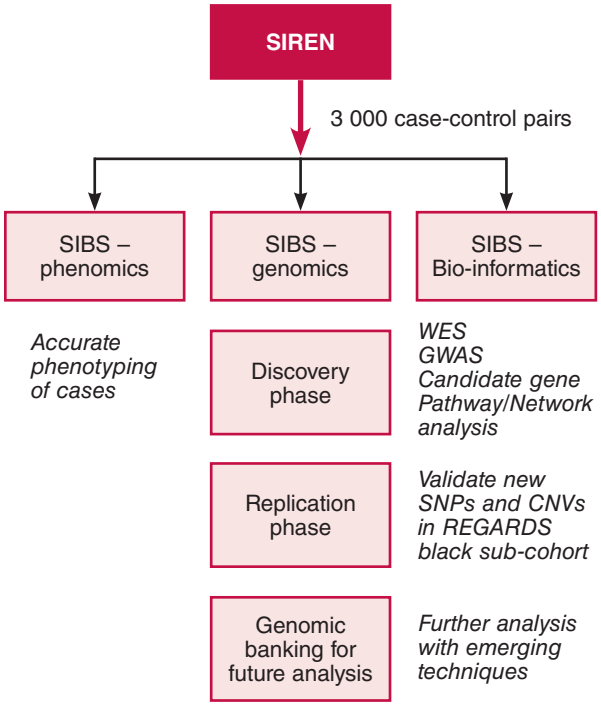

Fig 1. SIREN component projects.

Table 4. Unique features of SIREN meeting the standard criteria for stroke genomics studies

Criteria for Stroke Genomics Studies[81]	*How met in SIREN – SIBS Genomics*
Venice ' A' rating for sample size	large sample size > 3000 case – control pairs
Phenomic characterization	Rigorous phenotypic assessment in patients and in controls Detailed investigations (min of CT) and accurate classification using OCSP, TOAST, ASCO, CCS. Data verification and Quality control System
Control for confounders	Measurement and documentation of conventional vascular risk factors to be controlled for in the analysis
External validation	External Validation in REGARDS cohort (12,500)
Others	Low genotyping error rate (Hardy-Weinberg Equilibrium will be stated in cases and controls) Genomic controls, and other methods to account for population stratification, low P value (corrected for multiple testing)

replicability of association between a candidate SNP and trait outcome provides support for a causal relationship. However, the high levels of genomic diversity among Africans pose a potential challenge of false-positive associations due to population stratification, while heterogeneity of haplotype structure may reduce statistical power to detect true-positive signals by GWAS.

To combat these challenges, the SIREN project has been designed in compliance with the recommendations of Dichgans *et al*.[88] with due attention to adequate sample size, rigorous and accurate phenomic characterisation of cases, control for confounders, and planned validation of findings in an independent African American stroke population participating in the REGARDS study[29,116,117] (Table 4). In addition, the SIREN project will utilise GWAS approaches using customised chips including unique African variants,[10] whole-genome and whole-exome sequencing (WGS/WES) and other emergent high-throughput approaches for future analyses. Furthermore, 'pathway-based analysis' of genomic data[52] will chart new paths in our understanding of the molecular trajectories of stroke and unravel new options of stroke diagnostics and therapeutics in the emerging milieu of personalised medicine

Conclusion

Understanding the interaction between genetic and environmental conditions that predispose to stroke and impede favourable post-stroke outcomes is crucial for the formulation of targeted treatment strategies aimed at the successful prevention of and recovery from stroke. Unravelling the genomic underpinnings of stroke in populations of African ancestry will greatly improve our broad understanding of the molecular pathways of stroke and likely add substantially to ongoing efforts to mitigate the devastating global consequences of stroke.

The negative impact of cultural and religious beliefs, issues of autonomy of decision making and voluntary participation, as well as poor understanding of the health impact of genomics are potential challenges to translating genomic advances into real-world clinical applications in Africa. These suggest that caution should be exercised with regard to the expectations from stroke genomics research in Africa, while rigorous detection, evaluation, treatment and control of high blood pressure cannot be over-emphasised as a pragmatic strategy to curtail stroke in Africa.

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References

1. Lanktree MB, Dichgans M, Hegele RA, Advances in genomic analysis of stroke: what have we learned and where are we headed? *Stroke* 2010; **41**(4): 825–832.
2. Bevan S, Markus HS. Genetics of common polygenic ischaemic stroke: current understanding and future challenges. *Stroke Res Treat* 2011; **2011**: 179061.
3. Cole JW, Stine OC, Liu X, Pratap A, Cheng Y, Tallon LJ, *et al*. Rare variants in ischemic stroke: an exome pilot study. *PLoS One* 2012; **7**(4): e35591.
4. Markus HS. Stroke genetics. *Hum Mol Genet* 2011; **20**(R2): R124–131.
5. Cole JW, Brown DW, Giles WH, Stine OC, O'Connell JR, Mitchell BD, *et al*. Ischemic stroke risk, smoking, and the genetics of inflammation in a biracial population: the stroke prevention in young women study. *Thromb J* 2008; **6**: 11.
6. Grewal RP, Dutra AV, Liao YC, Juo SH, Papamitsakis NI. The intron 4c allele of the NOS3 gene is associated with ischemic stroke in African Americans. *BMC Med Genet* 2007; **8**: 76.
7. Song Q, Cole JW, O'Connell JR, Stine OC, Gallagher M, Giles WH, *et al*. Phosphodiesterase 4D polymorphisms and the risk of cerebral infarction in a biracial population: the Stroke Prevention in Young Women Study. *Hum Mol Genet* 2006; **15**(16): 2468–2478.
8. Tishkoff SA, Reed FA, Friedlaender FR, Ehret C, Ranciaro A, Froment A, *et al*. The genetic structure and history of Africans and African Americans. *Science* 2009; **324**(5930): 1035–1044.
9. Shriner D, Tekola-Ayele F, Adeyemo A, Rotimi CN. Genome-wide genotype and sequence-based reconstruction of the 140,000 year history of modern human ancestry. *Sci Rep* 2014; **4**: 6055.
10. Gurdasani D, Arstensen T, Tekola-Ayele F, Pagani L, Tachmazidou I, Hatzikotoulas K, *et al*. The African Genome Variation Project shapes medical genetics in Africa. *Nature* 2015; **517**(7534): 327–332.
11. H3Africa Consortium. Research capacity. Enabling the genomic revolution in Africa. *Science* 2014; **344**(6190): 1346–138.
12. Owolabi MO, Mensah GA, Kimmel PL, Adu D, Ramsay M, Waddy SP, *et al*. Understanding the rise in cardiovascular diseases in Africa: harmonising H3Africa genomic epidemiological teams and tools. *Cardiovasc J Afr* 2014; **25**(3): 134–136.
13. Seshadri S, Wolf PA. Lifetime risk of stroke and dementia: current concepts, and estimates from the Framingham Study. *Lancet Neurol* 2007; **6**(12): 1106–1114.
14. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol* 2009; **8**(4): 355–69.
15. Owolabi MO. Taming the burgeoning stroke epidemic in Africa: stroke quadrangle to the rescue. *West Indian Med J* 2011; **60**(4): 412–421.
16. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006; **367**(9524): 1747–1757.
17. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah G A, Connor M, Bennett DA, *et al*. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet* 2014; **383**(9913): 245–254.
18. Moran A, Forouzanfar M, Sampson U, Chugh S, Feigin V, Mensah G. The epidemiology of cardiovascular diseases in sub-Saharan Africa: the

Global Burden of Diseases, Injuries and Risk Factors 2010 Study. *Prog Cardiovasc Dis* 2013; **56**(3): 234–239.
19. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation* 2001; **104**(22): 2746–2753.
20. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: Part II: variations in cardiovascular disease by specific ethnic groups and geographic regions and prevention strategies. *Circulation* 2001; **104**(23): 2855–2864.
21. Khedr EM, *et al*. Epidemiological study and risk factors of stroke in Assiut Governorate, Egypt: community-based study. *Neuroepidemiology* 2013; **40**(4): 288–294.
22. Akinyemi RO, Izzeldin IM, Dotchin C, Gray WK, Adeniji O, Seidi OA, *et al*. Contribution of noncommunicable diseases to medical admissions of elderly adults in Africa: a prospective, cross-sectional study in Nigeria, Sudan, and Tanzania. *J Am Geriatr Soc* 2014; **62**(8): 1460–1466.
23. Owolabi LF, Shehu MY, Shehu MN, Fadare J. Pattern of neurological admissions in the tropics: Experience at Kano, Northwestern Nigeria. *Ann Indian Acad Neurol* 2010; **13**(3): 167–170.
24. Akinyemi RO, Allan L, Owolabi MO, Akinyemi JO, Ogbole G, Ajani A et al. Profile and determinants of vascular cognitive impairment in African stroke survivors: The CogFAST Nigeria Study. *J Neurol Sci* 2014; **346**(1–2): 241–249.
25. Akinyemi RO, Mukaetova-Ladinska EB, Attems J, Ihara M, Kalaria RN. Vascular risk factors and neurodegeneration in ageing related dementias: Alzheimer's disease and vascular dementia. *Curr Alzheimer Res* 2013; **10**(6): 642–53.
26. Owolabi MO. Impact of stroke on health-related quality of life in diverse cultures: the Berlin–Ibadan multicenter international study. *Health Qual Life Outcomes* 2011; **9**: 81.
27. O'Donnell MJ. Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, *et al*. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 2010; **376**(9735): 112–123.
28. Adeloye D, Basquill C. Estimating the prevalence and awareness rates of hypertension in Africa: a systematic analysis. *PLoS One* 2014; **9**(8): e104300.
29. Howard VJ, Kleindorfer DO, Judd SE, McClure LA, Safford MM, Rhodes JD, *et al*. Disparities in stroke incidence contributing to disparities in stroke mortality. *Ann Neurol* 2011; **69**(4): 619–627.
30. Gutierrez J, Williams OA. A decade of racial and ethnic stroke disparities in the United States. *Neurology* 2014; **82**(12): 1080–1082.
31. Douiri A, Rudd AG, Wolfe CD. Prevalence of poststroke cognitive impairment: South London Stroke Register 1995–2010. *Stroke* 2013; **44**(1): 138–145.
32. Rotimi CN, Jorde LB. Ancestry and disease in the age of genomic medicine. *N Engl J Med* 2010; **363**(16): 1551–1558.
33. Saab KR, Kendrick J, Yracheta JM, Lanaspa MA, Pollard M, Johnson RJ. New insights on the risk for cardiovascular disease in African Americans: The role of added sugars. *J Am Soc Nephrol* 2015; **26**(2): 247–257.
34. Burchard EG, Ziv E, Coyle N, Gomez SL,Tang H, Karter AJ, *et al*. The importance of race and ethnic background in biomedical research and clinical practice. *N Engl J Med* 2003; **348**(12): 1170–1175.
35. Collins FS. *W*hat we do and don't know about 'race', 'ethnicity', genetics and health at the dawn of the genome era. *Nat Genet* 2004; **36**(Suppl 11): S13–15.
36. Cooper RS, Kaufman JS, Ward R, Race and genomics. *N Engl J Med* 2003; **348**(12): 1166–1170.
37. Adeyemo AA, Chen G, Chen Y, Rotimi C. Genetic structure in four West African population groups. *BMC Genet* 2005. **6**: 38.
38. Ramsay M, Tiemessen CT, Choudhury A, Soodyall H. Africa: the next frontier for human disease gene discovery? *Hum Mol Genet* 2011; **20**(R2): R214–220.
39. Gomez F, Hirbo J, Tishkoff SA. Genetic variation and adaptation in Africa: implications for human evolution and disease. *Cold Spring Harb Perspect Biol* 2014; **6**(7): a008524.
40. International HapMap Consortium. A second generation human haplotype map of over 3.1 million SNPs. *Nature* 2007; **449**(7164): 851–861.
41. Genomes Project Consortium. An integrated map of genetic variation from 1,092 human genomes. *Nature* 2012; **491**(7422): 56–65.
42. Graffe CC, Bech JN, Lauridsen TG, Vase H, Pedersen EB. Abnormal increase in urinary aquaporin-2 excretion in response to hypertonic saline in essential hypertension. *BMC Nephrol* 2012; **13**: 15.
43. Beuschlein F, Boulkroun S, Osswald A, Wieland T, Nielsen HN, Lichtenauer UD, *et al*. Somatic mutations in ATP1A1 and ATP2B3 lead to aldosterone-producing adenomas and secondary hypertension. *Nat Genet* 2013; **45**(4): 440–4, 444e1–2.
44. Bryc K, Auton A, Nelson MR, Oksenberg JR, Hauser SL, Williams S, *et al*. Genome-wide patterns of population structure and admixture in West Africans and African Americans. *Proc Natl Acad Sci USA* 2010; **107**(2): 786–791.
45. Bryc K, Durand EY, Macpherson JM, Reich D, Mountain JL. The Genetic Ancestry of African Americans, Latinos, and European Americans across the United States. *Am J Hum Genet* 2015; **96**(1): 37–53.
46. Dichgans M. Genetics of ischaemic stroke. *Lancet Neurol* 2007; **6**(2): 149–161.
47. Morrison AC, Fornage M, Liao D, Boerwinkle E. Parental history of stroke predicts subclinical but not clinical stroke: the Atherosclerosis Risk in Communities Study. *Stroke* 2000; **31**(9): 2098–2102.
48. Liao D, Myers R, Hunt S, Shahar E, Paton C, Burke G, *et al*. Familial history of stroke and stroke risk. The Family Heart Study. *Stroke* 1997; **28**(10): 1908–1912.
49. Flossmann E, Schulz UG, Rothwell PM. Systematic review of methods and results of studies of the genetic epidemiology of ischemic stroke. *Stroke* 2004; **35**(1): 212–227.
50. Minor DS, Wofford MR, Jones DW. Racial and ethnic differences in hypertension. *Curr Atheroscler Rep* 2008; **10**(2): 121–127.
51. Adeyemo A, Gerry N, Chen G, Herbert A, Doumatey A, Huang H, *et al.* A genome-wide association study of hypertension and blood pressure in African Americans. *PLoS Genet* 2009; **5**(7): e1000564.
52. Reder NP, Tayo BO, Salako B, Ogunniyi A, Adeyemo A, Rotimi C, *et al.* Adrenergic alpha-1 pathway is associated with hypertension among Nigerians in a pathway-focused analysis. *PLoS One* 2012; **7**(5): e37145.
53. Rice T, Cooper RS, Wu X, Bouchard C, Rankinen T, Rao DC, *et al.* Meta-analysis of genome-wide scans for blood pressure in African American and Nigerian samples. The National Heart, Lung, and Blood Institute GeneLink Project. *Am J Hypertens* 2006; **19**(3): 270–274.
54. Sorensen IF, Vazquez AI, Irvin MR, Sorensen P, Davis BR, Ford CE, *et al.* Pharmacogenetic effects of 'candidate gene complexes' on stroke in the GenHAT study. *Pharmacogenet Genomics* 2014; **24**(11): 556–563.
55. Adeleye JO, Abbiyesuku FM. Glucose and insulin responses in offspring of Nigerian Type 2 diabetics. *Afr J Med Med Sci* 2002; **31**(3): 253–257.
56. Mbanya JC, Pani LN, Mbanya DN, Sobngwi E, Ngogang J, *et al.* Reduced insulin secretion in offspring of African type 2 diabetic parents. *Diabetes Care* 2000; **23**(12): 1761–1765.
57. Tekola-Ayele F, Adeyemo AA, Rotimi CN. Genetic epidemiology of type 2 diabetes and cardiovascular diseases in Africa. *Prog Cardiovasc*

Dis 2013; **56**(3): 251–260.
58. Chen G, Adeyemo A, Zhou J, Chen Y, Huang H, Doumatey A, *et al.* Genome-wide search for susceptibility genes to type 2 diabetes in West Africans: potential role of C-peptide. *Diabetes Res Clin Pract* 2007; **78**(3): e1–6.
59. Ovbiagele B. Impairment in glomerular filtration rate or glomerular filtration barrier and occurrence of stroke. *Arch Neurol* 2008; **65**(7): 934–938.
60. Kopp JB, Smith MW, Nelson GW, Johnson RC, Freedman BI, Bowden DW, *et al*. *MYH9* is a major-effect risk gene for focal segmental glomerulosclerosis. *Nat Genet* 2008; **40**(10): 1175–1184.
61. Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, *et al.* Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science* 2010; **329**(5993): 841–845.
62. Tayo BO, Kramer H, Salako BL, Gottesman O, McKenzie CA, Ogunniyi A, *et al.* Genetic variation in APOL1 and MYH9 genes is associated with chronic kidney disease among Nigerians. *Int Urol Nephrol* 2013; **45**(2): 485–494.
63. Tzur S, Rosset S, Shemer R, Yudkovsky G, Selig S, Tarekegn A, *et al.* Missense mutations in the *APOL1* gene are highly associated with end-stage kidney disease risk previously attributed to the *MYH9* gene. *Hum Genet* 2010; **128**(3): 345–350.
64. Bentley AR, Doumatey AP, Chen G, Huang H, Zhou J, Shriner D, *et al.* Variation in APOL1 Contributes to Ancestry-Level Differences in HDLc-Kidney Function Association. *Int J Nephrol* 2012; **2012**: 748984.
65. Van der Sijde MR, Ng A, Fu J. Systems genetics: From GWAS to disease pathways. *Biochim Biophys Acta* 2014; **1842**(10): 1903–1909.
66. Atwood LD, Wolf PA, Heard-Costa NL, Massaro JM, Beiser A, D'Agostino RB, *et al.* Genetic variation in white matter hyperintensity volume in the Framingham Study. *Stroke* 2004; **35**(7): 1609–1613.
67. Moskau S, Golla A, Grothe C, Boes M, Pohl C, Klockgether T. Heritability of carotid artery atherosclerotic lesions: an ultrasound study in 154 families. *Stroke* 2005; **36**(1): 5–8. Epub 2004 Nov 29.
68. Tsaras G, Owusu-Ansah A, Boateng FO, Amoateng-Adjepong Y. Complications associated with sickle cell trait: a brief narrative review. *Am J Med* 2009; **122**(6): 507–512.
69. Piel FB, atil AP, Howes RE, Nyangiri OA, Gething PW, Williams TN, *et al.* Global distribution of the sickle cell gene and geographical confirmation of the malaria hypothesis. *Nat Commun* 2010; **1**: 104.
70. Lemos Cardoso G, Farias Guerreiro J. African gene flow to north Brazil as revealed by HBB*S gene haplotype analysis. *Am J Hum Biol* 006; **18**(1): 93–98.
71. Osuntokun BO, Osuntokun O. *C*omplicated migraine and haemoglobin AS in Nigerians. *Br Med J* 1972; **2**(5814): 621–622.
72. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, *et al*. Cerebrovascular accidents in sickle cell disease: rates and risk factors. *Blood* 1998; **91**(1): 288–294.
73. Flanagan JM, Frohlich DM, Howard TA, Schultz WH, Driscoll C, Nagasubramanian R, *et al.* Genetic predictors for stroke in children with sickle cell anemia. *Blood* 2011; **117**(24): 6681–6684.
74. Flanagan JM, heehan V, Linder H, Howard TA, Wang YD, Hoppe CC, *et al*. Genetic mapping and exome sequencing identify 2 mutations associated with stroke protection in pediatric patients with sickle cell anemia. *Blood* 2013; **121**(16): 3237–3245.
75. Ruchoux MM, Maurage CA. CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *J Neuropathol Exp Neurol* 1997; **56**(9): 947–964.
76. Yamamoto Y, Craggs L, Baumann M, Kalimo H, Kalaria RN. Review: molecular genetics and pathology of hereditary small vessel diseases of the brain. *Neuropathol Appl Neurobiol* 2011; **37**(1): 94–113.
77. Lee SJ, Meng H, Elmadhoun O, Blaivas M, Wang MM. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy affecting an African American man: identification of a novel 15-base pair NOTCH3 duplication. *Arch Neurol* 2011; **68**(12): 1584–1586.
78. Meschia JF, Worrall BB, Rich SS. Genetic susceptibility to ischemic stroke. *Nat Rev Neurol* 2011; **7**(7): 369–378.
79. Craig HD, Gunel M, Cepeda O, Johnson EW, Ptacek L, Steinberg GK, *et al*. Multilocus linkage identifies two new loci for a Mendelian form of stroke, cerebral cavernous malformation, at *7p15-13* and *3q25.2-27*. *Hum Mol Genet* 1998;. **7**(12): 1851–1858.
80. Janunger T, Nilsson-Ardnor S, Wiklund PG, Lindgren P, Escher SA, Lackovic K, *et al.* A novel stroke locus identified in a northern Sweden pedigree: linkage to chromosome 9q31-33. *Neurology* 2009; **73**(21): 1767–1773.
81. Nilsson-Ardnor S, Janunger T, Wiklund PG, Lackovic K, Nilsson AK, Lindgren P, *et al*. Genome-wide linkage scan of common stroke in families from northern Sweden. *Stroke* 2007; **38**(1): 34–40.
82. Wang XY, Wang JW, Tang X, Li N, Chen DF, Wu YQ, *et al.* Linkage and association between interleukin-6 gene polymorphisms and ischemic stroke: a family-based study in the northern Chinese Han population. *Genet Test Mol Biomarkers* 2014; **18**(11): 761–766.
83. Liu B, Zhang L, Yang Q. Genetics of intracerebral hemorrhage: Insights from candidate gene approaches. *Neurol India* 2012; **60**(1): 3–8.
84. Biffi A, Anderson CD, Jagiella JM, Schmidt H, Kissela B, Hansen BM, *et al.* APOE genotype and extent of bleeding and outcome in lobar intracerebral haemorrhage: a genetic association study. *Lancet Neurol* 2011; **10**(8): 702–709.
85. Brouwers HB, Biffi A, Ayres AM, Schwab K, Cortellini L, Romero JM, *et al*. Apolipoprotein E genotype predicts hematoma expansion in lobar intracerebral hemorrhage. *Stroke* 2012; **43**(6): 1490–1495.
86. Premkumar DR, Cohen DL, Hedera P, Friedland RP, Kalaria RN. Apolipoprotein E-epsilon4 alleles in cerebral amyloid angiopathy and cerebrovascular pathology associated with Alzheimer's disease. *Am J Pathol* 1996; **148**(6): 2083–2095.
87. Kalaria RN, Ogeng'o JA, Patel NB, Sayi JG, Kitinya JN, Chande HM, *et al.* Evaluation of risk factors for Alzheimer's disease in elderly east Africans. *Brain Res Bull* 1997; **44**(5): 573–577.
88. Dichgans M, Markus HS. Genetic association studies in stroke: methodological issues and proposed standard criteria. *Stroke* 2005; **36**(9): 2027–2031. Epub 2005 Jul 28.
89. Meschia JF. Stroke genome-wide association studies: the large numbers imperative. *Stroke* 2010; **41**(4): 579–580.
90. Markus HS, Alberts MJ. Update on genetics of stroke and cerebrovascular disease 2005. *Stroke* 2006; **37**(2): 288–290. Epub 2006 Jan 12.
91. Meschia JF, Nalls M, Matarin M, Brott TG, Brown RD Jr, Hardy J, *et al*. Siblings with ischemic stroke study: results of a genome-wide scan for stroke loci. *Stroke* 2011; **42**(10): 2726–2732.
92. Hata J, Kubo M, Kiyohara Y. [Genome-wide association study for ischemic stroke based on the Hisayama study]. *Nihon Eiseigaku Zasshi* 2011; **66**(1): 47–52.
93. Matarin M, Brown WM, Dena H, Britton A, De Vrieze FW, Brott TG, *et al.* Candidate gene polymorphisms for ischemic stroke. *Stroke* 2009; **40**(11): 3436–3442.
94. Gretarsdottir S, Thorleifsson G, Manolescu A, Styrkarsdottir U, Helgadottir A, Gschwendtner A, *et al.* Risk variants for atrial fibrillation on chromosome 4q25 associate with ischemic stroke. *Ann Neurol* 2008; **64**(4): 402–409.
95. Gudbjartsson DF, Holm H, Gretarsdottir S, Thorleifsson G, Walters GB, Thorgeirsson G, *et al.* A sequence variant in ZFHX3 on 16q22

associates with atrial fibrillation and ischemic stroke. *Nat Genet* 2009; **41**(8): 876–878.

96. Bilguvar K, Yasuno K, Niemelä M, Ruigrok YM, von Und Zu Fraunberg M, van Duijn CM, *et al*. Susceptibility loci for intracranial aneurysm in European and Japanese populations. *Nat Genet* 2008; **40**(12): 1472–1477.
97. Ikram MA, Seshadri S, Bis JC, Fornage M, DeStefano AL, Aulchenko YS, *et al*. Genome-wide association studies of stroke. *N Engl J Med* 2009; **360**(17): 1718–1728.
98. Yamada Y, Fuku N, Tanaka M, Aoyagi Y, Sawabe M, Metoki N, *et al.* Identification of CELSR1 as a susceptibility gene for ischemic stroke in Japanese individuals by a genome-wide association study. *Atherosclerosis* 2009; **207**(1): 144–149.
99. Zhang W, Chen Y, Liu P, Chen J, Song L, Tang Y, *et al*. Variants on chromosome 9p21.3 correlated with ANRIL expression contribute to stroke risk and recurrence in a large prospective stroke population. *Stroke* 2012; **43**(1): 14–21.
100. Matsushita T, Ashikawa K, Yonemoto K, Hirakawa Y, Hata J, Amitani H, *et al.* Functional SNP of ARHGEF10 confers risk of atherothrombotic stroke. *Hum Mol Genet 2*010; **19**(6): 1137–1146.
101. International Stroke Genetics Consortium (ISGC); Wellcome Trust Case–Control Consortium 2 (WTCCC2), Bellenguez C, Bevan S, Gschwendtner A, Spencer CC, *et al*. Genome-wide association study identifies a variant in HDAC9 associated with large vessel ischemic stroke. *Nat Genet* 2012; **44**(3): 328–333.
102. Holliday EG, Maguire JM, Evans TJ, Koblar SA, Jannes J, Sturm JW, *et al*. Common variants at 6p21.1 are associated with large artery atherosclerotic stroke. *Nat Genet* 2012; **44**(10): 1147–1151.
103. Zhang Y, Tong Y, Zhang Y, Ding H, Zhang H, Geng Y, *et al*. Two novel susceptibility SNPs for ischemic stroke using exome sequencing in Chinese Han population. *Mol Neurobiol* 2014; **49**(2): 852–862.
104. Saidi S, Slamia LB, Mahjoub T, Ammou SB, Almawi WY. Association of PAI-1 4G/5G and -844G/A gene polymorphism and changes in PAI-1/tPA levels in stroke: a case-control study. *J Stroke Cerebrovasc Dis* 2007; **16**(4): 153–9.
105. Saidi S, Slamia LB, Ammou SB, Mahjoub T, Almawi WY. Association of apolipoprotein E gene polymorphism with ischemic stroke involving large-vessel disease and its relation to serum lipid levels. *J Stroke Cerebrovasc Dis* 2007; **16**(4): 160–166.
106. Saidi S, Mahjoub T, Slamia LB, Ammou SB, Al-Subaie AM, Almawi WY. Association of human platelet alloantigen 1 through 5 polymorphisms with ischemic stroke. *Cerebrovasc Dis* 2008; **25**(1-2): 81–86.
107. Saidi S, Mahjoub T, Slamia LB, Ammou SB, Al-Subaie AM, Almawi WY. *P*olymorphisms of the human platelet alloantigens HPA-1, HPA-2, HPA-3, and HPA-4 in ischemic stroke. *Am J Hematol* 2008; **83**(7): 570–573.
108. Saidi S, Zammiti W, Slamia LB, Ammou SB, Almawi WY, Mahjoub T. Interaction of angiotensin-converting enzyme and apolipoprotein E gene polymorphisms in ischemic stroke involving large-vessel disease. *J Thromb Thrombol* **27**(1): 68–74. Epub 2007 Nov 21.
109. Saidi S, Mallat SG, Almawi WY, Mahjoub T. Association between renin–angiotensin–aldosterone system genotypes and haplotypes and risk of ischemic stroke of atherosclerotic etiology. *Acta Neurol Scand* 2009. **119**(6): 356–363.
110. Saidi S, Mallat SG, Almawi WY, Mahjoub T. Endothelial nitric oxide synthase Glu298Asp, 4b/a, and *-786T>C* gene polymorphisms and the risk of ischemic stroke. *Acta Neurol Scand* 2010; **121**(2): 114–119.
111. Saidi S, Mahjoub T, Almawi WY. Aldosterone synthase gene (*CYP11B2*) promoter polymorphism as a risk factor for ischaemic stroke in Tunisian Arabs. *J Renin Angiotensin Aldosterone Syst* **11**(3): 180–186.
112. Mourad H, Fadel W, El Batch M, Rowisha M. Heamostatic and genetic predisposing factors for stroke in children with sickle cell anemia. *Egypt J Immunol* 2008; **15**(1): 25–37.
113. Marshall PA, Adebamowo CA, Adeyemo AA, Ogundiran TO, Strenski T, Zhou J, *et al.* Voluntary participation and comprehension of informed consent in a genetic epidemiological study of breast cancer in Nigeria. *BMC Med Ethics* 2014; **15**: 38.
114. Olaitan PB, Odesina V, Odesina V, Ademola S, Fadiora SO, Oluwatosin OM, Reichenberger EJ. Recruitment of Yoruba families from Nigeria for genetic research: experience from a multisite keloid study. *BMC Med Ethics* 2014; **15**: 65.
115. Fagbemiro L, Adebamowo C. Knowledge and attitudes to personal genomics testing for complex diseases among Nigerians. *BMC Med Ethics* 2014; **15**: 34.
116. Howard G, Wagenknecht LE, Kernan WN, Cushman M, Thacker EL, Judd SE, *et al.* Racial differences in the association of insulin resistance with stroke risk: the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *Stroke* 2014; **45**(8): 2257–2262.
117. Howard VJ, Cushman M, Pulley L, Gomez CR, Go RC, Prineas RJ, *et al*. The reasons for geographic and racial differences in stroke study: objectives and design. *Neuroepidemiology* 2005; **25**(3): 135–143.

Sickle cell disease and H3Africa: enhancing genomic research on cardiovascular diseases in African patients

Ambroise Wonkam, Julie Makani, Solomon Ofori-Aquah, Obiageli E Nnodu, Marsha Treadwell, Charmaine Royal, Kwaku Ohene-Frempong, as members of the H3Africa Consortium

Abstract

Background: Sickle cell disease (SCD) has a high prevalence in sub-Saharan Africa. There are several cardiovascular phenotypes in SCD that contribute to its morbidity and mortality.
Discussion: SCD is characterised by marked clinical variability, with genetic factors playing key modulating roles. Studies in Tanzania and Cameroon have reported that single-nucleotide polymorphisms in *BCL11A* and *HBS1L-MYB* loci and co-inheritance of alpha-thalassaemia impact on foetal haemoglobin levels and clinical severity. The prevalence of overt stroke among SCD patients in Cameroon (6.7%) and Nigeria (8.7%) suggests a higher burden than in high-income countries. There is also some evidence of high burden of kidney disease and pulmonary hypertension in SCD; however, the burden and genetics of these cardiovascular conditions have seldom been investigated in Africa.
Conclusions: Several H3Africa projects are focused on cardiovascular diseases and present major opportunities to build genome-based research on existing SCD platforms in Africa to transform the health outcomes of patients.

Keywords: sickle cell disease, stroke, kidney diseases, pulmonary hypertension, genetics, Africa

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Sickle cell disease (SCD) is a genetic disorder of public health significance with high prevalence, high mortality rate and limited interventions. An estimated 305 800 births are affected annually worldwide by homozygous SCD (SCD-SS), nearly two-thirds of this incidence occurs in Africa.[1] This estimate does not include SCD-SC, which is more prevalent than SCD-SS in some West African countries.

Although the first clinical description of SCD occurred over 100 years ago and this condition was described in 1949 as the first molecular disease, to date only one drug, hydroxyurea, is available for its specific treatment.[2] Furthermore, despite the evidence from high-income countries that new-born screening (NBS) and comprehensive care are associated with a 70% reduction in early childhood deaths,[3] and can have a significant impact on reducing morbidity,[4,5] few African countries have programmes dedicated to NBS, follow-up care, family and patient education and counselling, and prevention and treatment of disease complications. As a consequence, in sub-Saharan Africa, mortality rates are high before the age of five years and estimates suggest that without intervention, up to 90% of affected infants may die in childhood.[6,7]

The role of genomic research to improve health of SCD patients: preliminary data from Cameroon and Tanzania

Genomics of foetal haemoglobin-promoting loci

Advancement in genomic research offers an unprecedented opportunity to address the health challenges of SCD in an integrated manner. As a Mendelian disorder caused by a single gene mutation on the β-globin gene ($\beta^{Glu6Val}$) on chromosome 11, there is considerable phenotypic diversity in SCD, due largely to the influence of genetic and environmental factors.[8-10]

Although there are several key phenotypes (anaemia, stroke, infections), foetal haemoglobin (HbF) has emerged as a central disease modifier; importantly, the expression of this modifier is amenable to therapeutic manipulation.[11,12] Genetic variants at three principal loci, *BCL11A*, *HBS1L-MYB* and the *HBB* cluster account for 10–20% of HbF variation among SCD patients in the USA, Brazil and the UK.[8,9]

Initial studies in Tanzania[13] and recently in Cameroon[14,15] have shown that single-nucleotide polymorphisms (SNPs) in the *BCL11A* loci are prevalent in both Tanzanian and Cameroonian patients [minor allele frequency (MAF) of rs4671393 = 0.30], with significant association of these SNPs with HbF (Table 1). These studies have also shown that rs9399137, which acts as a tagging SNP for the *HMIP-2* sub-locus in European

populations,[10] occurred at a low frequency in both Cameroonian[14] and Tanzanian patients.[13] Nevertheless, in the *HMIP-2* sub-locus, there was a much higher MAF of rs9389269 in Cameroonian (0.18)[14] compared to the Tanzanian SCD patients (0.03).[13] This observation could indicate a high degree of variation in the MAF of this SNP among SCD patients in African population groups.[16]

Furthermore, studies in Cameroon and Tanzania lacked power to replicate the association of a sub-locus (rs7482144) in *HBG2* (Table 1), which explained 2.2% of the variation in HbF levels in African American patients.[8] This is likely to be due to the absence of Senegal and Indian–Arab beta-globin locus haplotypes that contain the rs7482144 in most Cameroonian patients.[17]

Similarly, a strong signal adjacent to the *HBB* cluster recently detected in African-American patients at rs5006884 in *OR51B5/6*[18] was not found to have significant association in either Tanzanian[14] or Cameroonian SCD patients.[13] These findings suggest that studies of multiple SCD populations in Africa are warranted to improve our understanding of the impact of human diversity on HbF expression in SCD.[19]

The co-inheritance of alpha-thalassaemia and SCD

The co-inheritance of α-thalassaemia is associated with a milder phenotype in patients with HbSS and Sβ^0 thalassaemia, e.g. higher haemoglobin level and lower stroke rate.[20] However, the effect of α-thalassaemia is not all positive; pain and aseptic necrosis may be higher.[21]

In Cameroon, the co-inheritance of α-thalassaemia and SCD was associated with late onset of clinical manifestations and potentially increased survival in Cameroonian patients; this could explain the much higher allele frequency of 3.7kb α-globin gene deletion among SCD patients than in controls.[22,23] In Tanzania, the co-inheritance of α-thalassaemia and SCD was associated with a lower stroke risk.[24]

These preliminary data indicate an urgent need to replicate and expand genetic studies in many other African SCD populations, including studies focused on loci that are linked to stroke[25] and other cardiovascular conditions, to fully measure the opportunities of their implementation to improve the care of patients with SCD.

Addressing the burden of cardiovascular diseases in SCD in Africa

Cardiovascular phenotypes in SCD include complications involving the heart (e.g. heart failure), brain (e.g. stroke), lung (e.g. pulmonary hypertension) and kidney (e.g. proteinuria). Cerebrovascular disease is perhaps the most devastating complication for children with SCD, including overt stroke, transient ischaemic attacks, silent infarcts and neurocognitive dysfunction. Longitudinal cohort data from the USA have shown that between five and 10% of patients with SCD will experience a clinically overt stroke during childhood.[26] The prevalence of overt stroke in SCD in Africa may be higher than that reported in high-income countries.

Overt stroke is a clinical diagnosis and should be easily detected in any cohort of closely monitored SCD patients. Brain computerised tomography (CT) and magnetic resonance imaging (MRI) are used to rule out haemorrhage or localise the tissue/vascular pathological basis for the stroke event. Clinical examination and CT scans identified a stroke prevalence of 6.7% in Cameroon.[27,28] A study of children with SCD in Nigeria found a stroke prevalence of 8.7%.[29]

The prevalence of silent cerebral infarcts (SCI) and cerebral vasculopathies has been shown to be even greater than overt stroke risk: SCI occurs in 27% of this population before their sixth, and 37% by their 14th birthdays.[30] SCI is diagnosed by MRI, but has not been studied in Africa because of the limited availability of MRI equipment. In fact SCI is not really silent, as falling school performance and other signs of neurocognitive dysfunction and change in personality/behaviour may all raise suspicion for increased risk of overt stroke, and suspicion of stroke with absence of motor or speech defect. SCI could be better called covert cerebral infarction.

The lack of longitudinally monitored SCD cohorts in Africa weakens incidence and prevalence estimates. Indeed, the cognitive

Table 1. Foetal haemoglobin association results for SNPs at the *BCL11A*, *HBS1L-MYB* and beta-globin loci in the Cameroonian and Tanzanian sickle cell anaemia cohort

Locus	*Genomic variations*			*HbSS Cameroon* (n = *596*)[14]			*HbSS Tanzania* (n = *1 124*)[13]		
	SNP	*Position on the chromosome**	*Allele change*	*MAF*	*Effect size*	p-*value*	*MAF*	*Effect size*	p-*value*
Chromosome 2									
BCL11A	rs11886868	60720246	T>C	0.31	0.167	0.0129	0.26	–0.406	3.00E-30
BCL11A	rs4671393	60720951	G>A	0.3	0.201	0.0062	0.3	–0.412	3.90E-28
Chromosome 6									
HBS1L-MYB	rs28384513	135376209	A>C	0.2	–0.3002	0.0002	0.21	–0.146	1.90E-04
HBS1L-MYB	rs9376090	135411228	T>C	0	NA	NA	0.01	0.471	1.60E-02
HBS1L-MYB	rs9399137	135419018	T>C	0.04	0.412	0.0086	0.01	0.668	8.30E-06
HBS1L-MYB	rs9389269	135427159	T>C	0.18	0.09561	0.2468	0.03	0.4	1.40E-05
HBS1L-MYB	rs9402686	135427817	G>A	0.03	0.1447	0.4437	0.06	0.342	1.60E-04
HBS1L-MYB	rs9494142	135431640	T>C	0.11	0.3391	0.0023	0.13	0.085	6.00E-02
Chromosome 11									
HBG2	rs7482144	5276169	G>A	0	–0.05843	0.9076	0.01	0.562	1.60E-04
OR51B5/6	rs5006884	5373251	C>T	0.08	0.04163	0.7385	0.05	0.164	2.40E-02

NA, not applicable; monomorphic T for the entire sample; MAF, minor allele frequency; SNP, single-nucleotide polymorphisms.
*Chromosome, position on NCBI Build 36.1.

performance of Cameroonian SCD children was evaluated using a neuropsychological test battery assessing four domains of cognitive functioning (executive function, attention, memory and sensory-motor skills). A high prevalence of cognitive deficits was found, increasing with age, and with a specific impairment of executive functions and attention.[31] Up to 37.5% of the 96 SCD patients aged six to 24 years (M = 13.5, SD = 4.9) had mild-to-severe cognitive deficits, which tended to increase with age.

Structural equation models showed a significant association between (1) severe anaemia and lower executive functioning, (2) low foetal haemoglobin levels and lower executive functioning and attention, (3) history of cerebrovascular accidents and lower performances on executive functioning, sensory-motor and memory tasks, (4) pathological electroencephalogram and lower attention span, and (5) abnormal transcranial Doppler and lower memory function.[31]

The feasibility of using transcranial Doppler (TCD) ultrasonography in Africa to determine risk of stroke in children with SCD has been demonstrated in studies in Tanzania,[24] Cameroon,[31] Nigeria[32] and Kenya.[33] However, because of limited resources and inefficient transfusion services, TCD is seldom established as part of routine healthcare followed by transfusion therapy to prevent overt stroke in those found to have abnormal blood flow velocity.[33]

Pulmonary arterial hypertension (PAH) is common, with a prevalence of 30% in SCD patients, and all-cause mortality rates of 40% at 40 months after diagnosis in the USA.[34] Studies in Nigeria indicate PAH could represent a significant complication of SCD on the African continent.[35]

N-terminal (NT) pro-brain natriuretic peptide (proBNP) ≥ 160 ng/l has a 78% positive predictive value for pulmonary hypertension. NT-proBNP elevation is common and is associated with markers of anaemia, inflammation and iron status and with severe functional impairment among sickle cell anaemia patients in Nigeria.[36]

The prevalence of elevated tricuspid regurgitant velocity (TRV) measured by echocardiogram, which predicts risk for pulmonary hypertension and death in adult sickle cell anaemia, was similar among SCD patients in Tanzania and those from the USA.[37] In addition, there is accumulating clinical evidence to suspect a high prevalence of kidney disease among African SCD patients in France,[38] Nigeria,[39,40] Ghana[41] and the Congo.[42] The data revealed and emphasised the need to draft a specific research agenda to include Africa in future comprehensive studies on the epidemiology and genetics of end-organ complications of SCD.

Addressing the genomics of cardiovascular diseases in SCD in Africa

Despite the evidence of a high burden of cardiovascular events in SCD patients, the magnitude of this problem in Africa has not been defined. The clinical variability and environmental factors influencing these events have not been clearly and systematically studied, despite the availability of some encouraging data on the genetics of these cardiovascular phenotypes of SCD among African populations from the diaspora (Table 2). Previous studies of sibling pairs have demonstrated a genetic component to the development of cerebrovascular disease in SCD stroke.[43] In addition, a child with SCD had an increased risk for stroke if they had siblings who had experienced an overt stroke.[44]

A few genetic modifiers have confirmed the association with stroke, such as α-thalassaemia trait being protective against stroke[20] (Table 1), but these do not explain the entire genetic contribution to stroke risk. In addition, several retrospective studies, mostly among African Americans, have identified specific SNPs associated with stroke in patients with SCD, using candidate gene approaches, but failed to be replicated using independent validation cohorts.[45]

Recent data that used genetic mapping and exome sequencing revealed that one mutation in *GOLGB1* (Y1212C) and another mutation in *ENPP1* (K173Q) were confirmed as having significant associations with a decreased risk for stroke among African Americans with SCD[25] (Table 1). These studies need to be validated and extended in SCD patients in Africa.

Like stroke, renal failure occurs in 5–18% of SCD patients and is associated with early mortality.[46] At-risk SCD patients cannot be identified prior to the appearance of proteinuria. The myosin, heavy-chain 9, non-muscle (*MYH9*) and apolipoprotein L1 (*APOL1*) genes have been associated with risk for focal segmental glomerulosclerosis and end-stage renal disease in African Americans.[47]

Seven SNPs in *MYH9* and one in *APOL1* were significantly associated with proteinuria among African American SCD patients. In addition, glomerular filtration rate was negatively correlated with proteinuria ($p < 0.0001$), and was significantly predicted by an interaction between *MYH9* and *APOL1*[48] (Table 2). Further studies with independent data sets from sub-Saharan Africa are now needed to confirm this association, to identify more of the genes involved, and the interaction with various African environments, in order to address preventative measures of SCD nephropathy.

Moreover, an increased tricuspid regurgitation jet velocity (TRV > 2.5 m/s) and pulmonary hypertension defined by right heart catheterisation both independently conferred increased mortality in SCD.[34] A preliminary genetic association study comparing patients with an elevated ($n = 49$) versus normal ($n = 63$) TRV revealed significant association with five SNPs within *GALNT13* ($p < 0.005$), and a quantitative trait locus upstream of the adenosine-A2B receptor gene (*ADORA2B*)[49] (Table 2).

Limited genetic studies associated with these critical cardiovascular phenotypes in SCD (stroke, pulmonary hypertension, kidney disease) have not been reported in SCD patients who reside in Africa. This indicates an urgent need to perform these studies, which could inform the global SCD communities in a unique way, on the value of gene and environmental interactions in the pathogenesis and hopefully the care of SCD.

Table 2. Selected genes associated with cardiovascular phenotypes among African American SCD patients

Cardiovascular phenotypes in SCD	*Associated genes*	*References*
Stroke	*HBA* (3.7 alpha-globin gene deletion)	Hsu *et al. J Pediatr Hematol Oncol* 2003; **25**(8): 622–628
	GOLGB1 (Y1212C)	Flanagan *et al. Blood* 2013; **121**(16): 3237–3245
	ENPP1 (K173Q)	
Kidney disease (proteinuria)	*MYH9*	Ashley-Koch *et al. Br J Haematol* 2011; **155**(3): 386–394
	APOL1	
Pulmonary hypertension	*GALNT13*	Desai *et al. Am J Respir Crit Care Med* 2012; **186**(4): 359–368
	ADORA2B	

Integrating outcomes of genetics research into new-born screening and interventions to reduce childhood mortality and survival in SCD

Major benefits in the health and survival of children with SCD have been attained through the implementation of a few simple, evidence-based interventions. The most striking achievements have resulted from early diagnosis of SCD through new-born screening and the subsequent enrolment of these patients into comprehensive care programmes. These programmes provide interventions that include prophylaxis against pneumococcal infection using penicillin, and early detection and treatment of acute clinical events such as anaemia, septicaemia, stroke and acute chest syndrome. These interventions have been introduced in a limited manner in Africa, despite the fact that they have been shown to be highly effective in developed countries.

Hydroxyurea, an important therapeutic intervention for SCD in high-income settings, is beginning to be used more frequently in several African countries.[50-53] There is no doubt that hydroxyurea will have a large public health impact in Africa.[54] However there are questions regarding the effectiveness of hydroxyurea in some individuals possessing characteristics associated with poor response to treatment. This includes SCD populations with low levels of haemolysis,[55] low HbF level and Central African Republic (CAR) haplotype,[56] as well as children under five years of age with SCD, even though some data indicate that efficacy is just as good or better in younger children.[57] These questions should not delay the use of hydroxyurea in Africa, but it is strongly recommended that research trials should be conducted to monitor and evaluate effectiveness in this setting.

The second challenge regarding use of hydroxyurea in SCD in Africa is access due to limited supply and high cost. It has also been suggested that patients and families may resist adherence with this treatment. In Cameroon, only 3.4% of SCD patients had access to hydroxyurea.[58] Sociological data on the barriers associated with prescription of and adherence with hydroxyurea is needed in order to plan effective strategies to address these issues in Africa.

Despite the limited access to hydroxyurea and other care and therapies, about 3% of the 700 studied Cameroonian patients with SCD lived longer than 40 years.[14] Specific survivor SCD populations in sub-Saharan Africa can offer new research opportunities to uncover possible variation that could improve the life of SCD patients. With more and more genomic data available, it is anticipated that new-born screening could also allow early identification of genetic factors (e.g. HbF-promoting SNPs or stroke-associated SNPs) to potentially assess each individual patient's risks and plan appropriate anticipatory guidance.

Perspectives: H3Africa and opportunity for genomic research of cardiovascular diseases in SCD

Currently, H3Africa extends across African countries, comprising 23 grants. It is anticipated that, together, H3Africa projects will analyse samples from 50 000 to 75 000 participants. Specifically, three projects have the objective to study stroke, kidney disease and other cardiovascular diseases (rheumatic heart disease) in various African countries where SCD is also prevalent[59] (e.g. Cameroon, Tanzania, Nigeria, Ghana, Mali, Uganda). These projects offer the opportunity to extend the existing network of researchers in Cameroon, Ghana, Nigeria, South Africa and Tanzania, which have been assembled to conduct multicentre, Africa-based studies on the genetics and genomics of SCD.

To strengthen the case for genomic studies in Africa, several genetic variations have been discovered through molecular studies on the African continent.[60] There is enough evidence, including whole-genome data from African populations, that emphasises the high levels of genomic variation and the heterogeneity of African populations.[61,62]

Some of the tremendous genetic variation in Africa is responsible for problems in clinical management of SCD, such as red blood cell transfusion, red blood cell Rh D polymorphism and allo-immunisation,[63] and response to medications (cytochrome P450 polymorphisms and codeine/other opioids for pain therapy).[64] Polymorphisms in ribonucleotide reductase, the target enzyme for hydroxyurea, may have variable effects on SCD patient response and deserves further investigation in Africa.

One SCD project currently funded under the H3Africa umbrella is focused on research in Cameroon, Ghana and Tanzania (FOA: RM12-005, 1 U01 HG007459-01). The project aims to: (1) explore perspectives and attitudes regarding genomic research and its implementation and implications in Africa, and (2) assess perceptions about public health interventions to increase awareness, early detection and prevention of SCD-related complications. Beyond this project, the investigators are building on biological materials, preliminary clinical and genomics data from Cameroon, Tanzania, Nigeria and Ghana, and extending the experience to other African countries, with the goal to improve infrastructure for research and training. The ultimate goal is to conduct research to understand the relationship between genes, the environment and disease, in order to translate genome-based knowledge into health benefits for SCD patients and their families in Africa.

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Key messages

- SCD is characterised by marked clinical variability, with genetic factors playing key modulating roles. Studies in Tanzania and Cameroon have reported that SNPs in the *BCL11A* loci and *HBS1L-MYB* region (*HMIP*), and co-inheritance of alpha-thalassaemia impact on HbF level and clinical severity.
- There are several cardiovascular phenotypes in SCD, such as stroke, heart failure, pulmonary hypertension and renal disease that contribute to its morbidity and mortality.
- The prevalence of overt stroke among SCD patients in Cameroon (6.7%) and Nigeria (8.7%) suggests a higher burden than in high-income countries.
- The genetics of stroke, kidney disease and pulmonary hypertension have seldom been investigated in SCD in Africa.
- Several H3Africa projects are focused on cardiovascular phenotypes, which creates a major opportunity to build on existing SCD work in Africa, a genome-based research on key cardiovascular phenotypes to transform the health benefits of SCD patients.

References

1. Piel FB, Patil AP, Howes RE, *et al*. Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. *Lancet* 2013; **381**(9861): 142–151.
2. Platt OS, Orkin SH, Dover G, *et al.* Hydroxyurea enhances fetal hemoglobin production in sickle cell anemia. *J Clin Invest* 1984; **74**(2): 652–656.
3. Yanni E, Grosse SD, Yang Q, Olney RS. Trends in pediatric sickle cell disease-related mortality in the United States, 1983-2002. *J Pediatr* 2009; **154**(4): 541–545.
4. Rahimy MC, Gangbo A, Ahouignan G, *et al*. Effect of a comprehensive clinical care program on disease course in severely ill children with sickle cell anemia in a sub-Saharan African setting. *Blood* 2003; **102**(3): 834–838.
5. Vichinsky EP. Comprehensive care in sickle cell disease: its impact on morbidity and mortality. *Semin Hematol* 1991; **28**(3): 220–226.
6. Piel FB, Hay SI, Gupta S, Weatherall DJ, Williams TN. Global burden of sickle cell anaemia in children under five, 2010–2050: modelling based on demographics, excess mortality, and interventions. *PLoS Med* 2013; **10**(7): e1001484.
7. Makani J, Cox SE, Soka D, *et al*. Mortality in sickle cell anemia in Africa: a prospective cohort study in Tanzania. *PLoS One* 2011; **6**(2): e14699.
8. Lettre G, Sankaran VG, Bezerra MA, *et al*. DNA polymorphisms at the *BCL11A*, *HBS1L-MYB*, and beta-globin loci associate with fetal hemoglobin levels and pain crises in sickle cell disease. *Proc Natl Acad Sci USA* 2008; **105**(33): 11869–11874.
9. Thein SL, Menzel S. Discovering the genetics underlying foetal haemoglobin production in adults. *Br J Haematol* 2009; **145**(4): 455–467.
10. Bae HT, Baldwin CT, Sebastiani P, *et al*. Meta-analysis of 2040 sickle cell anemia patients: *BCL11A* and *HBS1L-MYB* are the major modifiers of HbF in African Americans. *Blood* 2012; **120**(9): 1961–1962.
11. Xu J, Peng C, Sankaran VG, *et al*. Correction of sickle cell disease in adult mice by interference with fetal hemoglobin silencing. *Science* 2011; **334**(6058): 993–996.
12. Bauer DE, Kamran SC, Lessard S, *et al.* An erythroid enhancer of *BCL11A* subject to genetic variation determines fetal hemoglobin level. Science 2013; **342**(6155): 253–257.
13. Makani J, Menzel S, Nkya S, *et al*. Genetics of fetal hemoglobin in Tanzanian and British patients with sickle cell anemia. *Blood* 2011; **117**(4): 1390–1392.
14. Wonkam A, Ngo Bitoungui VJ, Vorster AA, *et al*. Association of variants at *BCL11A* and *HBS1L-MYB* with hemoglobin F and hospitalization rates among sickle cell patients in Cameroon. *PLoS One* 2014; **9**(3): e92506.
15. Bitoungui VJ, Ngogang J, Wonkam A. Polymorphism at *BCL11A* compared to *HBS1L-MYB* loci explains less of the variance in HbF in patients with sickle cell disease in Cameroon. *Blood Cells Mol Dis* 2014 Nov 25. pii: S1079-9796(14)00143-0.
16. Menzel S, Rooks H, Zelenika D, *et al*. Global Genetic Architecture of an Erythroid Quantitative Trait Locus, *HMIP-2*. *Ann Hum Genet* 2014 Jul 29. doi: 10.1111/ahg.12077.
17. Ngo Bitoungui VJ, Pule GD, Hanchard N, Ngogang J, Wonkam A. Beta-globin gene haplotypes among Cameroonians and review of the global distribution: is there a case for a single sickle mutation origin in Africa? *OMICS J Integrat Biol* 2015; **19**(3): DOI: 10.1089/omi.2014.0134.
18. Solovieff N, Milton JN, Hartley SW, *et al*. Fetal hemoglobin in sickle cell anemia: genome-wide association studies suggest a regulatory region in the 5′ olfactory receptor gene cluster. *Blood* 2010; **115**(9): 1815–1822.
19. Mtatiro SN, Singh T, Rooks H, *et al*. Genome wide association study of fetal hemoglobin in sickle cell anemia in Tanzania. *PLoS One* 2014; **9**(11): e111464.
20. Hsu LL, Miller ST, Wright E, *et al*. Stroke Prevention Trial (STOP) and the Cooperative Study of Sickle Cell Disease (CSSCD). Alpha thalassemia is associated with decreased risk of abnormal transcranial Doppler ultrasonography in children with sickle cell anemia. J *Pediatr Hematol Oncol* 2003; **25**(8): 622–628.
21. Embury SH, Dozy AM, Miller J, *et al.* Concurrent sickle-cell anemia and alpha-thalassemia: effect on severity of anemia. *N Engl J Med* 1982; **306**(5): 270–274.
22. Wonkam A, Rumaney MB, Ngo Bitoungui VJ, *et al*. Coinheritance of sickle cell anemia and α-thalassemia delays disease onset and could improve survival in Cameroonian's patients (Sub-Saharan Africa). *Am J Hematol* 2014; **89**(6): 664–665.
23. Rumaney MB, Ngo Bitoungui VJ, Vorster AA, *et al*. The co-inheritance of alpha-thalassemia and sickle cell anemia is associated with better hematological indices and lower consultations rate in Cameroonian patients and could improve their survival. *PLoS One* 2014; **9**(6): e100516.
24. Cox SE, Makani J, Soka D, *et al*. Haptoglobin, alpha-thalassaemia and glucose-6-phosphate dehydrogenase polymorphisms and risk of abnormal transcranial Doppler among patients with sickle cell anaemia in Tanzania. *Br J Haematol* 2014; **165**(5): 699–706.
25. Flanagan JM, Sheehan V, Linder H, *et al*. Genetic mapping and exome sequencing identify 2 mutations associated with stroke protection in pediatric patients with sickle cell anemia. *Blood* 2013; **121**(16): 3237–3245.
26. Ohene-Frempong K, Weiner SJ, Sleeper LA, *et al*. Cerebrovascular accidents in sickle cell disease: rates and risk factors. *Blood* 1998; **91**(1): 288–294.
27. Njamnshi AK, Mbong EN, Wonkam A, *et al*. The epidemiology of stroke in sickle cell patients in Yaounde, Cameroon. *J Neurol Sci* 2006; **250**(1–2): 79–84.
28. Njamnshi AK, Wonkam A, Djientcheu Vde P, *et al*. Stroke may appear to be rare in Saudi Arabian and Nigerian children with sickle cell disease, but not in Cameroonian sickle cell patients. *Br J Haematol* 2006; **133**(2): 210.
29. Aliyu ZY, Gordeuk V, Sachdev V, *et al*. Prevalence and risk factors for pulmonary artery systolic hypertension among sickle cell disease patients in Nigeria. *Am J Hematol* 2008; **83**(6): 485–490.
30. DeBaun MR, Armstrong FD, McKinstry RC, *et al*. Silent cerebral infarcts: a review on a prevalent and progressive cause of neurologic injury in sickle cell anemia. *Blood* 2012; **119**(20): 4587–4596.
31. Ruffieux N, Njamnshi AK, Wonkam A, *et al*. Association between biological markers of sickle cell disease and cognitive functioning amongst Cameroonian children. *Child Neuropsychol* 2013; **19**(2): 143–160.
32. Lagunju I, Sodeinde O, Telfer P. Prevalence of transcranial Doppler abnormalities in Nigerian children with sickle cell disease. *Am J Hematol* 2012; **87**(5): 544–547.
33. Makani J, Kirkham FJ, Komba A, *et al*. Risk factors for high cerebral blood flow velocity and death in Kenyan children with sickle cell anaemia: role of haemoglobin oxygen saturation and febrile illness. *Br J Haematol* 2009; **145**(4): 529–532.
34. Gladwin MT, Sachdev V, Jison ML, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. *N Engl J Med* 2004; **350**: 886–895.
35. Aliyu ZY, Kato GJ, Taylor J 6th, *et al*. Sickle cell disease and pulmonary hypertension in Africa: a global perspective and review of epidemiology,

pathophysiology, and management. *Am J Hematol* 2008; **83**(1): 63–70.
36. Aliyu ZY, Suleiman A, Attah E, *et al*. NT-proBNP as a marker of cardiopulmonary status in sickle cell anaemia in Africa. *Br J Haematol* 2010; **150**(1): 102–107.
37. Cox SE, Soka D, Kirkham FJ, *et al*. Tricuspid regurgitant jet velocity and hospitalization in Tanzanian children with sickle cell anemia. *Haematologica* 2014; **99**(1): e1–4.
38. Arlet JB, Ribeil JA, Chatellier G, *et al*. Determination of the best method to estimate glomerular filtration rate from serum creatinine in adult patients with sickle cell disease: a prospective observational cohort study. *BMC Nephrol* 2012; **13**: 83.
39. Iwalokun BA, Iwalokun SO, Hodonu SO, Aina OA, Agomo PU. Evaluation of microalbuminuria in relation to asymptomatic bacteruria in Nigerian patients with sickle cell anemia. *Saudi J Kidney Dis Transpl* 2012; **23**(6): 1320–1330.
40. Adedoyin OT, Adesiyun OO, Adegboye OA, Bello OA, Fatoye OP. Sickle cell nephropathy in children seen in an African hospital – case report. *Niger Postgrad Med J* 2012; **19**(2): 119–122.
41. Osei-Yeboah CT, Rodrigues O. Renal status of children with sickle cell disease in Accra, Ghana. *Ghana Med J* 2011; **45**(4): 155–160.
42. Pakasa NM, Sumaïli EK. [Pathological peculiarities of chronic kidney disease in patient from sub-Saharan Africa. Review of data from the Democratic Republic of the Congo]. *Ann Pathol* 2012; **32**(1): 40–52.
43. Driscoll MC, Hurlet A, Styles L, *et al*. Stroke risk in siblings with sickle cell anemia. *Blood* 2003; **101**(6): 2401–2404.
44. Kwiatkowski JL, Hunter JV, Smith-Whitley K, Katz ML, Shults J, Ohene-Frempong K. Transcranial Doppler ultrasonography in siblings with sickle cell disease. *Br J Haematol* 2003; **121**(6): 932–937.
45. Flanagan JM, Frohlich DM, Howard TA, *et al*. Genetic predictors for stroke in children with sickle cell anemia. *Blood* 2011; **117**(24): 6681–6684.
46. Platt OS, Brambilla DJ, Rosse WF, *et al*. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med* 1994; **330**(23): 1639–1644.
47. Genovese G, Friedman DJ, Ross MD, *et al*. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science* 2010; **329**(5993): 841–845.
48. Ashley-Koch AE, Okocha EC, Garrett ME, *et al*. *MYH9* and *APOL1* are both associated with sickle cell disease nephropathy. *Br J Haematol* 2011; **155**(3): 386–394.
49. Desai AA, Zhou T, Ahmad H, *et al*. A novel molecular signature for elevated tricuspid regurgitation velocity in sickle cell disease. *Am J Respir Crit Care Med* 2012; **186**(4): 359–368.
50. Elira Dokekias A, Okandze Elenga JP, Ndinga J, Sanogo I, Sangare A. [Evaluation of clinical response by hydroxyurea in 132 patients with major sickle cell anemia]. *Tunis Med* 2005; **83**(1): 32–7.
51. Mellouli F, Bejaoui M. [The use of hydroxyurea in severe forms of sickle cell disease: study of 47 Tunisian paediatric cases]. *Arch Pediatr* 2008; **15**(1): 24–28.
52. Wonkam A, Ponde C, Nicholson N, Fieggen K, Ramessar R, Davidson A. The burden of sickle cell disease in Cape Town. *S Afr Med J* 2012; **102**(9): 752–754.
53. Makubi A, Soka D, Makani J. Moyamoya disease, a rare cause of recurrent strokes in an african sickle cell child: does hydroxyurea have a role in this context? *Int J Child Health Nutr* 2012; **1**: 82–85.
54. Ware RE. Hydroxycarbamide: clinical aspects. *Comptes Rendus Biol* 2013; **336**(3): 177–182.
55. Olabode JO, Shokunbi WA. Types of crises in sickle cell disease patients presenting at the haematology day care unit (HDCU), University College Hospital (UCH), Ibadan. *West Afr J Med* 2006; **25**(4): 284–288.
56. Steinberg MH, Lu ZH, Barton FB, Terrin ML, Charache S, Dover GJ. Fetal hemoglobin in sickle cell anemia: determinants of response to hydroxyurea. Multicenter Study of Hydroxyurea. *Blood* 1997; **89**(3): 1078–1088.
57. Wang WC, Ware RE, Miller ST, *et al*. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). *Lancet* 2011; **377**(9778): 1663–1672.
58. Wonkam A, Mba CZ, Mbanya D, *et al*. Psychosocial burden of sickle cell disease on parents with an affected child in Cameroon. *J Genet Couns* 2014; **23**(2): 192–201.
59. H3Africa Consortium. Research capacity. Enabling the genomic revolution in Africa. *Science* 2014; **344**(6190): 1346–1348.
60. Peprah E, Xu H, Tekola-Ayele F, Royal CD. Genome-wide association studies in Africans and African Americans: Expanding the framework of the genomics of human traits and disease. *Public Health Genom* 2015; **18**(1): 40–51.
61. Lambert CA, Tishkoff SA. Genetic structure in African populations: implications for human demographic history. *Cold Spring Harb Symp Quant Biol* 2009; **74**: 395–402.
62. Gurdasani D, Carstensen T, Tekola-Ayele F, *et al*. The African Genome Variation Project shapes medical genetics in Africa. *Nature* 2015; **517**(7534): 327–332.
63. Kappler-Gratias S, Auxerre C, Dubeaux I, *et al*. Systematic RH genotyping and variant identification in French donors of African origin. *Blood Transfus* 2014; **12**(Suppl 1): s264–272.
64. Dandara C, Swart M, Mpeta B, Wonkam A, Masimirembwa C. Cytochrome P450 pharmacogenetics in African populations: implications for public health. *Expert Opin Drug Metab Toxicol* 2014; **10**(6): 769–785.

Endothelial dysfunction: a unifying hypothesis for the burden of cardiovascular diseases in sub-Saharan Africa

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Abstract

It is well established that the leading causes of death and disability worldwide are cardiovascular diseases (CVD), chief among which is ischaemic heart disease. However, it is also recognised that ischaemic heart disease frequently coexists with other vascular conditions, such as cerebrovascular, renovascular and peripheral vascular disease, thus raising the notion of a common underlying pathobiology, albeit with differing manifestations, dictated by the implicated vascular bed.

The understanding that common metabolic and behavioural risk factors as well as social determinants and drivers are convergent in the development of CVD evokes the idea that the dysfunction of a common bio-molecular platform is central to the occurrence of these diseases. The state of endothelial activation, otherwise known as endothelial dysfunction, occurs when reactive oxygen signalling predominates due to an uncoupled state of endothelial nitric oxide synthase (eNOS). This can be a physiological response to stimulation of the innate immune system or a pathophysiological response triggered by cardiovascular disease risk factors.

The conventional wisdom is that the endothelium plays an important role in the initiation, progression and development of CVD and other non-communicable diseases. Consequently, the endothelium has remarkable relevance in clinical and public health practice as well as in health education, health promotion, and disease- and risk-factor prevention strategies. It also presents a plausible unifying hypothesis for the burden of CVD seen globally and in sub-Saharan Africa. Importantly, the heterogeneity in individual responses to metabolic, behavioural, and social drivers of CVD may stem from a complex interplay of these drivers with genomic, epigenetic and environmental factors that underpin eNOS uncoupling. Therefore, further biomedical research into the underlying genetic and other mechanisms of eNOS uncoupling may enlighten and shape strategies for addressing the burden of CVD in sub-Saharan Africa and other regions of the world.

Keywords: endothelium, risk factors, cardiovascular disease, public health, outcomes

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The understanding that hypertension, dyslipidaemia and tobacco use are powerful risk factors for the genesis of cardiovascular disease (CVD) has led to heavy investments in basic, clinical and population science research targeted at the prevention, treatment and control of CVD risk factors. Cumulative evidence from these research investments have informed clinical practice guidelines for the management of CVD, and largely account for the observed 60 to 80% decline in mortality from stroke and coronary artery disease in most developed nations in the past 50 years.[1] In the United States, we have witnessed a 68% decrease in age-adjusted death rates from heart disease (from 56 to 18 per 10 000 population) and a 79% decrease in stroke death rates (from 18 to four per 10 000 population) between 1958 and 2010.[2]

A more recent notion based on convergent lines of experimental and pathological evidence is that inflammation may be the unifying factor in the pathobiology of atherothrombosis and its complications, as well as most vascular diseases.[3] Herein, the aggregate of clinical trial evidence led to the coronation of statins as the undisputed heavy-weight champions of pharmacological strategies for modulating inflammation, over and beyond cholesterol levels, for primary and secondary prevention of CVD events.[4] The risk factor and inflammation hypotheses were pivotal in helping us understand the decline in CVD mortality rates in industrialised nations. However, despite the remarkable progress in reducing CVD mortality rates, recent evidence indicates that ischaemic heart disease and stroke remain leading causes of mortality in the United States and worldwide.[5]

Further significant reduction in CVD mortality rates may require new transformative paradigms that can have broad impact. In this context, there are clues that point to the endothelium as the expansive entity that links various vascular-related diseases. Most CVD is caused by atherosclerosis initiated by the loss of functional integrity of the endothelium, which can affect various vascular beds, resulting in disease conditions such as coronary heart disease, peripheral arterial disease and cerebrovascular disease.

Furthermore, the fact that common social determinants, and behavioral and metabolic risk factors attend these diseases and other major non-communicable diseases (NCDs) suggests the presence of a common broad unifying entity that has wide spatial distribution. In this light, we consider the endothelium as the unifying feature/element for the burden of CVD in sub-Saharan Africa (SSA), because its functional integrity, which comprises the genotypic, phenotypic and environmental context of its existence, can predispose individuals or populations to CVD. In this regard, we discuss the public health relevance of the endothelium and the challenges and opportunities regarding the quest for transformative paradigms for reducing CVD burden.[6,7]

The endothelium

Robert F Furchgott, Louis J Ignarro and Ferid Murad catalysed the wave of research that improved our understanding of endothelial function, which led to the joint award of the 1998 Nobel Prize in Physiology or Medicine 'for their discoveries concerning nitric oxide as a signaling molecule in the cardiovascular system'. We now recognise that the healthy endothelium is in a quiescent state where nitric oxide (NO) produced by the endothelial isoform of nitric oxide synthase (eNOS) in its membrane-bound configuration is released, to silence cellular processes, by targeting cysteine groups in regulator molecules such as NFκB and the mitochondria.[8]

On the other hand, endothelial dysfunction is an activated state where the regulatory proteins such as NFκB and phosphatases are targeted by reactive oxygen species (ROS) produced from oxidases and eNOS uncoupling. Endothelial activation can occur physiologically in response to immune system perturbation, as well as pathophysiologically secondary to cardiovascular risk factors. Persistent ROS signalling precipitates a loss of vascular integrity characterised by detachment of endothelial cells and dependence on circulating progenitor cells for repair due to limited capacity of contiguous endothelial cells.[8]

The relationship between risk-factor profile, endothelial dysfunction and circulating endothelial progenitor cells has been evaluated using flow-mediated dilatation (FMD) of the brachial artery. In their report, Hill and colleagues demonstrated that the presence of high levels of endothelial progenitor cells preserves endothelial function despite significant risk-factor burden.[9] Similarly, the relationships between FMD and coronary disease risk factors in asymptomatic adults,[10] diet and exercise in overweight teenagers,[11] and glucose and other metabolic syndrome components have been reported.[12]

Beyond the association with cardiovascular risk factors, other measures of endothelial function have been associated with cardiovascular disease outcomes. Greater event-free survival has been associated with intracoronary acetylcholine-induced vasodilatation in coronary angiography patients,[13] increased brachial artery reactivity indexed by FMD in vascular surgery patients,[14] and increased baseline levels of endothelial progenitor cells in CAD patients.[15] Furthermore, there is evidence to indicate early risk-factor exposure and endothelial dysfunction impact on the development of atherosclerosis and subsequent cardiovascular outcomes.[16,17]

The promotion of endothelial health and reversal of endothelial dysfunction have been associated with increased physical activity, consumption of diets rich in fruit and vegetables, and avoidance of tobacco use or exposure to tobacco smoke.[18-24] Consequently, the endothelium has remarkable relevance in clinical and public health practise as well as in health education, health promotion and prevention strategies, and therefore has implications for the epidemiological transition unfolding in developing world regions such as sub-Saharan Africa. In addition, it suggests that additional research into endothelial function, activation and dysfunction could provide novel proximal targets for clinical, public health and public policy interventions, in an effort to achieve maximum impact on population health.

Public health relevance

The structure of the endothelium constitutes a remarkable feature, given its complexity, vast spatial distribution, and heterogeneity in different vascular beds. Combined with its role in the control of vasomotor tone, inflammation, homeostasis, endocrine and paracrine regulation, and cell growth, trafficking and survival,[25] the endothelium has remarkable implications for CVD and other NCDs such as cancer, diabetes and chronic lung disease. Therefore, it is not surprising that endothelial biomedicine is recognised as a transdisciplinary field.

Population research evidence indicates that social determinants and drivers such as globalisation, urbanisation, ageing, income, education and housing are all linked with stress levels associated with CVD and other diseases, and connected with behavioral risk factors – unhealthy diet, tobacco use, physical inactivity and harmful use of alcohol, which are associated with metabolic risk factors such as high blood pressure, obesity, diabetes and raised blood lipid levels that ultimately lead to the manifestations of various diseases.

In a recent study of cardiovascular risk and events in 17 low-, middle- and high-income countries, it was noted that compared to high-income country populations, the risk factors for CVD were lower in low-income country populations, but disease outcomes were substantially worse, which potentially suggests both poor delivery of effective clinical care and higher stress levels in low-income country populations.[26]

The endothelium provides a construct for understanding how these networks of social, behavioural and metabolic factors converge to cause a network of diseases. The socio-behavioral and biological drivers lead to pathophysiological activation of the endothelium, resulting in a favourable bio-molecular milieu, for example inflammation and atherosclerosis, for disease in various vascular beds and organ systems due to the expansive spatial distribution of the endothelium (Fig. 1).

Therefore the endothelium provides a target for cross-cutting disease strategies given the broad implications of its dysfunction. Since moderate levels of physical activity on most days of the week, diets rich in fruit and vegetables and low in saturated and trans fats, and tobacco avoidance have been shown to improve endothelial health and reverse endothelial dysfunction, the adherence to public health strategies for improving physical activity and nutrition are essential for health promotion and the prevention of CVD, which aligns with clinical guideline-recommended interventions for the treatment and control of the common risk factors associated with CVD.

However, we need to move beyond current approaches by deliberately seeking transformative ways to achieve further substantial decline in CVD morbidity and mortality rates. Here, it is important to build on the wealth of scientific information on the endothelium, which has not been tapped by public health practitioners and researchers for translation into policies, programmes and research initiatives for advancing cardiovascular health promotion and the prevention of CVD.

Challenges and opportunities

Although the endothelium establishes dialogue with every tissue cell in the body, is affected by many disease processes and risk factors, and contributes to the initiation and progression of chronic diseases, it remains underappreciated until it is dysfunctional. Furthermore, although measures to improve or preserve endothelial health are relatively inexpensive, they are often less supported than more expensive disease-intervention strategies.

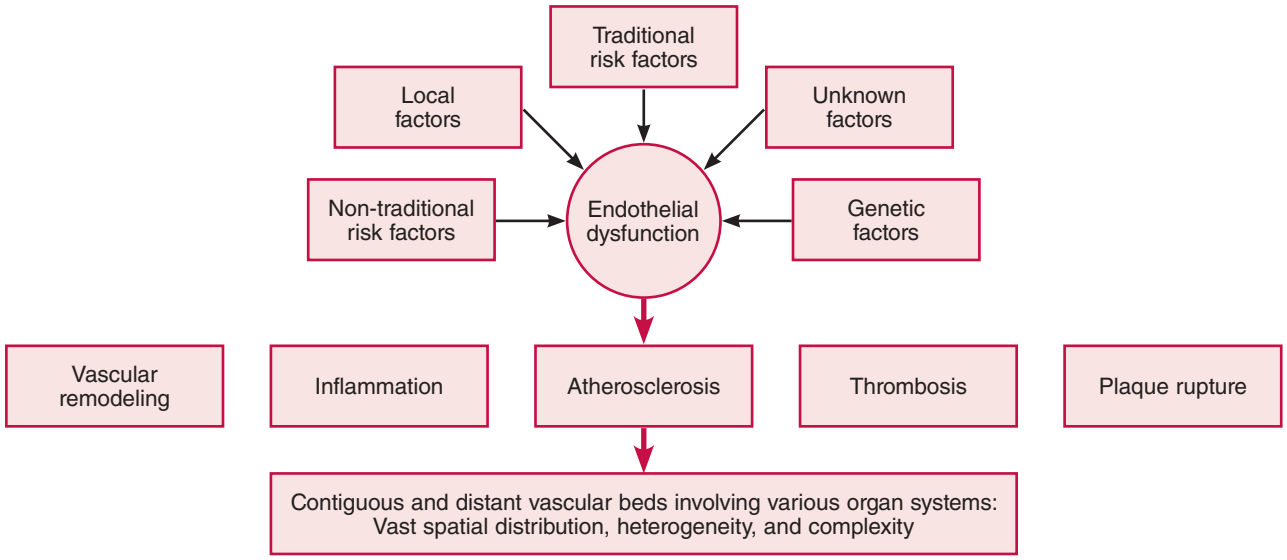

Fig. 1. The endothelium at the Center of Vascular Disease.

This overall lack of prioritisation highlights the need for improved awareness, understanding and focus, particularly if we are to unlock the potential that exists for discovering endothelial targets that could significantly impact on CVD mortality rates. On this point, it is interesting that there is heterogeneity in response to metabolic, behavioural and social drivers for CVD. What if we could understand why some individuals succumb to CVD risk factors while others don't? Why do we observe precocious CVD development in some subgroups exposed to the same drivers as the rest of a population? Why are there pockets of positive or negative deviance[27,28] in CVD prevalence and outcomes within populations exposed to the same socio-ecological and bio-behavioural risk factors and drivers?

Unlocking the mysteries behind these puzzling differential responses may rest on targeted efforts to understand the complicated interplay between known disease drivers and the genomic and epigenetic mechanisms that underpin pathways of eNOS uncoupling. Such enlightenment could shape strategies for addressing the burden of CVD in sub-Saharan Africa and other regions of the world.

The above notion is paramount, given the prospect of finding a robust proximal target(s) that can transform our approach to CVD prevention and treatment, and therefore should prompt us to reconsider the current status quo regarding our scientific investments. Insight from the Emerging Risk factor Collaboration study indicates that we have to screen 400 to 500 people to prevent one CVD event over a period of 10 years.[29] Such modest clinical benefits despite significant financial investments foster the increasing drum beat from camps that question the likelihood of meaningful clinical benefit from identifying and measuring biomarkers.

As a matter of fact, due to the vagaries of causality, some schools of thought now argue for fewer risk factors instead of more. Furthermore, although the search for independent risk factors in medical research has become necessary for the formulation of risk-stratification schemes, causality cannot be definitively ascertained, even in controlled clinical trials.[30]

In this context, we are beginning to learn that Mendelian randomisation studies can assess whether risk-factor associations are truly causal, or due to confounding or reverse causation. An illustrative NHLBI (National Heart, Lung, and Blood Institute) example of this is the large-scale Mendelian randomisation study of high-density lipoprotein (HDL) and the risk of myocardial infarction (MI), where the investigators found that low-density lipoprotein (LDL) is likely to be causally related to MI, whereas HDL is probably only a correlate.[31] This may explain why LDL-lowering drugs (e.g. statins) reduce risk, whereas every large trial of HDL-increasing drugs has failed, including the NHLBI-funded AIM-HIGH trial.[32]

Tools such as Mendelian randomisation could help us make better strategic decisions about drug development, risk stratification and prediction when deployed via large-scale cohort studies to identify candidate undiscovered biological pathways (e.g. endothelial dysfunction) and insights into distinguishing causality versus correlation. However, the application of such tools to decipher robust genetic lynchpins of endothelial dysfunction will require interdisciplinary collaboration and demand for paradigms that can transform CVD prevention and treatment efforts.[33] In this context, the H3Africa programme constitutes a platform to engender collaboration and employ synergy in intellectual enterprise to address novel research questions that will inform strategies for CVD diagnosis, treatment and prevention in sub-Saharan Africa.

Conclusions

Over the past half century, CVD mortality has declined appreciably in developed countries, largely secondary to the risk-factor paradigm that implicated hypertension, cholesterol and smoking in the genesis of CVD. This risk-factor model led to targeted research, prevention and treatment efforts to combat these culprits. More recently, the modulation of inflammation has presented a unifying framework for achieving further substantive decline in CVD mortality rates.

In SSA, the age-adjusted mortality from CVD has not declined, and the regional burden of CVD is rising, albeit modestly, largely due to population growth, aging and the epidemiological transition. To address this challenge in SSA and the persistent impact of CVD and other NCDs in developed nations, we need revolutionary ideas or targets. It is in this regard that we recognise the endothelium, which plays a remarkable role in health and disease. Its relevance to CVD warrants increased awareness and appreciation in public health and practice. It is now understood that socio-ecological and bio-behavioural drivers converge to affect various types of CVD and NCD via endothelial dysfunction. Furthermore, the varied response to these risk-factor exposures suggests a more complicated relationship with the underlying mechanisms for endothelial dysfunction.

Targeted efforts to understand the genomic and epigenetic mechanisms underpinning eNOS uncoupling may help explain the differential response to disease drivers and perhaps provide robust targets for CVD prevention and treatment. This concept requires the type of resources and framework for collaboration offered by the H3Africa platform. In the interim however, widespread dissemination, adoption and implementation of proven interventions for the prevention and control of CVD risk factors that are also affordable and acceptable in the SSA context are strongly encouraged.

The views expressed in this article are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute, National Institutes of Health, or the US Department of Health and Human Services.

References

1. Capewell S and O'Flaherty M. What explains declining coronary mortality? Lessons and warnings. *Heart* 2008; **94**: 1105–1108.
2. Marsh B. Declining lethality. *The New York Times*. January 4, 2014.
3. Libby P and Ridker PM. Inflammation and atherothrombosis from population biology and bench research to clinical practice. *J Am Coll Cardiol* 2006; **48**: A33–46.
4. Jahangir E, Fazio S, Sampson UK. Incident diabetes and statins: the blemish of an undisputed heavy weight champion? *Br J Clin Pharmacol* 2013; **75**: 955–958.
5. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; **385**(9963): 117–171.
6. Mensah GA, Catravas JD, Engelgau MM, Hooper WC, Madeddu P, Ryan US, *et al*. Vascular endothelium summary statement VI: Research directions for the 21st century. *Vasc Pharmacol* 2007; **46**: 330–332.
7. Mensah GA. Healthy endothelium: the scientific basis for cardiovascular health promotion and chronic disease prevention. *Vasc Pharmacol* 2007; **46**: 310–314.
8. Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. *Circulation* 2007; **115**: 1285–1295.
9. Hill JM, Zalos G, Halcox JP, Schenke WH, Waclawiw MA, Quyyumi AA, *et al*. Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. *N Engl J Med* 2003; **348**: 593–600.
10. Celermajer DS, Sorensen KE, Bull C, Robinson J, Deanfield JE. Endothelium-dependent dilation in the systemic arteries of asymptomatic subjects relates to coronary risk factors and their interaction. *J Am Coll Cardiol* 1994; **24**: 1468–1474.
11. Woo KS, Chook P, Yu CW, Sung RY, Qiao M, Leung SS, *et al*. Effects of diet and exercise on obesity-related vascular dysfunction in children. *Circulation* 2004; **109**: 1981–1986.
12. Thomas GN, Chook P, Qiao M, Huang XS, Leong HC, Celermajer DS, *et al*. Deleterious impact of "high normal" glucose levels and other metabolic syndrome components on arterial endothelial function and intima-media thickness in apparently healthy Chinese subjects: the CATHAY study. *Arterioscler Thromb Vasc Biol* 2004; **24**: 739–743.
13. Halcox JP, Schenke WH, Zalos G, Mincemoyer R, Prasad A, Waclawiw MA, *et al*. Prognostic value of coronary vascular endothelial dysfunction. *Circulation* 2002; **106**: 653–658.
14. Gokce N, Keaney JF, Jr., Hunter LM, Watkins MT, Nedeljkovic ZS, Menzoian JO, *et al*. Predictive value of noninvasively determined endothelial dysfunction for long-term cardiovascular events in patients with peripheral vascular disease. *J Am Coll Cardiol* 2003; **41**: 1769–1775.
15. Werner N, Nickenig G. Clinical and therapeutical implications of EPC biology in atherosclerosis. *J Cell Mol Med* 2006; **10**: 318–332.
16. Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PW, *et al*. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation* 2006; **113**: 791–798.
17. Juonala M, Viikari JS, Laitinen T, Marniemi J, Helenius H, Ronnemaa T, *et al*. Interrelations between brachial endothelial function and carotid intima-media thickness in young adults: the cardiovascular risk in young Finns study. *Circulation* 2004; **110**: 2918–2923.
18. Brown AA, Hu FB. Dietary modulation of endothelial function: implications for cardiovascular disease. *Am J Clin Nutr* 2001; **73**: 673–686.
19. Franco OH, Bonneux L, de Laet C, Peeters A, Steyerberg EW, Mackenbach JP. The Polymeal: a more natural, safer, and probably tastier (than the Polypill) strategy to reduce cardiovascular disease by more than 75%. *Br Med J* 2004; **329**: 1447–1450.
20. Franzoni F, Ghiadoni L, Galetta F, Plantinga Y, Lubrano V, Huang Y, *et al*. Physical activity, plasma antioxidant capacity, and endothelium-dependent vasodilation in young and older men. *Am J Hypertens* 2005; **18**: 510–516.
21. Fuchsjager-Mayrl G, Pleiner J, Wiesinger GF, Sieder AE, Quittan M, Nuhr MJ, *et al*. Exercise training improves vascular endothelial function in patients with type 1 diabetes. *Diabetes Care* 2002; **25**: 1795–1801.
22. Hamdy O, Ledbury S, Mullooly C, Jarema C, Porter S, Ovalle K, *et al*. Lifestyle modification improves endothelial function in obese subjects with the insulin resistance syndrome. *Diabetes Care* 2003; **26**: 2119–2125.
23. Hennig B, Toborek M, McClain CJ. High-energy diets, fatty acids and endothelial cell function: implications for atherosclerosis. *J Am Coll Nutr* 2001; **20**: 97–105.
24. Wildman RP, Schott LL, Brockwell S, Kuller LH, Sutton-Tyrrell K. A dietary and exercise intervention slows menopause-associated progression of subclinical atherosclerosis as measured by intima–media thickness of the carotid arteries. *J Am Coll Cardiol* 2004; **44**: 579–585.
25. Hwa C, Sebastian A, Aird WC. Endothelial biomedicine: its status as an interdisciplinary field, its progress as a basic science, and its translational bench-to-bedside gap. *Endothelium: J Endothelial Cell Res* 2005; **12**: 139–151.
26. Yusuf S, Rangarajan S, Teo K, Islam S, Li W, Liu L, *et al.,* and investigators P. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. *N Engl J Med* 2014; **371**: 818–827.
27. Krumholz HM, Curry LA, Bradley EH. Survival after acute myocardial infarction (SAMI) study: the design and implementation of a positive deviance study. *Am Heart J* 2011; **162**: 981–987 e9.

28. Bradley EH, Curry LA, Ramanadhan S, Rowe L, Nembhard IM, Krumholz HM. Research in action: using positive deviance to improve quality of health care. *Implement Sci* 2009; **4**: 25.
29. Emerging Risk Factors C, Kaptoge S, Di Angelantonio E, Pennells L, Wood AM, White IR, Gao P, *et al*. C-reactive protein, fibrinogen, and cardiovascular disease prediction. *N Engl J Med* 2012; **367**: 1310–1320.
30. Brotman DJ, Walker E, Lauer MS, O'Brien RG. In search of fewer independent risk factors. *Arch Intern Med* 2005; **165**: 138–145.
31. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, *et al*. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet* 2012; **380**: 572–580.
32. Investigators A-H, Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, *et al*. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011; **365**: 2255–2267.
33. Chatsuriyawong S, Gozal D, Kheirandish-Gozal L, Bhattacharjee R, Khalyfa AA, Wang Y, *et al*. Genetic variance in nitric oxide synthase and endothelin genes among children with and without endothelial dysfunction. *J Translational Med* 2013; **11**: 227.

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