JBR

Research Paper

Nigerian Population Research on Environment, Gene and Health (NIPREGH) – objectives and protocol

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Abstract

Sub-Saharan Africa is currently undergoing an epidemiological transition from a disease burden largely attribu–table to communicable diseases to that resulting from a combination of both communicable and chronic non-com–municable diseases. Data on chronic disease incidence, lifestyle, environmental and genetic risk factors are sparse in this region. This report aimed at providing relevant information in respect to risk factors that increase blood pressure and lead to development of intermediate cardiovascular phenotypes. We presented the rationale, objectives and key methodological features of the Nigerian Population Research on Environment, Gene and Health (NIPREGH) study. The challenges encountered in carrying out population study in this part of the world and the approaches at sur–mounting them were also presented. The preliminary data as at 20 November 2013 showed that out of the 205 indi–viduals invited starting from early April 2013, 160 (72 women) consented and were enrolled; giving a response rate of 78%. Participants′ age ranged from 18 to 80 years, with a mean (SD) of 39.8 (12.4) years and they were of 34 different ethnic groups spread over 24 states out of the 36 states that constitute Nigeria. The mean (SD) of office and home blood pressures were 113.0 (15.2) mm Hg systolic, 73.5 (12.5) mm Hg diastolic and 117.3 (15.0) mm Hg systolic, and 76.0 (9.6) mm Hg diastolic, respectively. Forty-three (26.8%) participants were hypertensive and 8 (5.0%) were diabetic. In addition to having the unique potential of recruiting a cohort that is a true representative of the entire Nigerian population, NIPREGH is feasible and the objectives realisable.

Keywords: Africa, black populations, blood pressure, hypertension, population science

INTRODUCTION

Cardiovascular diseases (CVDs) have become a major public health challenge in low and middle income countries[1–5]. It is currently estimated that 80% of global deaths due to CVDs occur in these countries with most deaths and disabilities occurring in people at the most productive stage of their life, thus

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resulting in huge negative economic impact on the society[6]. High blood pressure is the main driver of CVDs and is a major risk factor for stroke, ischaemic heart and kidney diseases[7,8]

A key element necessary for developing an effective prevention and control strategy for CVDs in Nigeria is availability of country specific risk factor burden. Previous studies[2] were restricted to smaller regions of the country, involved participants from one ethnic group and made use of non-standardised protocol that makes comparison across studies impossible. Additionally, studies targeted at understanding the genetic basis of distinct characteristics of hypertension and other CVDs among Black people are rare. We therefore mounted the Nigerian Population Research on Environment, Gene and Health (NIPREGH) study with the following objectives: (i) to determine the association of lifestyle and environmental factors with different blood pressure and other intermediate cardiovascular phenotypes; (ii) to determine the common polymorph–ism associated with different blood pressure and other intermediate cardiovascular phenotypes in Nigeria; (iii) to evaluate possible gene-environment interaction of some environmental factors and identified genotypes; (iv) to generate the genetic material needed to join the international consortium.

SUBJECTS AND METHOD

Study site

Participants were recruited from the Federal Housing Authority Estate, Lugbe, Federal Capital Territory Abuja. Abuja is a new city, carved out in 1976 within the central region of Nigeria to serve as the new capital city of the country. It is located between latitude 8.25° and 9.20° north and longitude 6.45° and 7.39° east. The topography is majorly of highlands between 600 to 1,000 meters above sea level. Its climate is typically tropical and year round temperatures oscillate between 25°C to 38°C.

The population of Abuja has grown steadily from about 170,000 in 1991 to a current estimate of 1.4 mil–lion. This population growth is occasioned by the offi–cial movement of the seat of government from Lagos to Abuja in 1995. Inhabitants of the city are from different ethnic groups within Nigeria who have migrated from their ancestral homes. The study site, Federal Housing Authority Estate, Lugbe has about 4,200 housing units inhabited by about 16,800 middle income earners.

General design/recruitment

NIPREGH is a prospective cohort study that will recruit about 1,200 Nigerians, 18 years and above,

and residing within the Federal Housing Authority Estate Lugbe, Abuja. Prior to actual recruitment, a community mobilisation through the churches and mosques within the housing estate is carried out. Billboards containing messages explaining the place of health survey in informing health policies as well as the accruing benefits of the health survey to partici–pants are placed at a strategic position of a street to be visited 1 week before the street was visited by trained field workers. Individual homes within the streets are visited on Saturdays and Sundays when the majority of the residents are expected to be available at home.

Field workers visit each house (First home visit) within a street and inhabitants who are willing to par–ticipate will have their blood pressure measured after signing an informed consent. Thereafter, they are invited to the field centre which is located within 1 km radius of all houses in the estate for other exam–inations as detailed in **Table 1**. The visit to the field centre should take place within 2 weeks of first home visit. A second home visit takes place 1 week after the field centre visit. A follow up visit is expected to take place 3 years after the baseline examinations. NIPREGH adheres strictly with ethics of research involving human subjects as stipulated in the principles the Declaration of Helsinki[9] and has been granted ethical approval by the Health Research Ethics Committee of University of Abuja Teaching Hospital.

Data Collection Questionnaire

Standardised questionnaire which had been applied previously in different Caucasian[10,11] and Asian[12,13] populations was adapted for use in NIPREGH. Questions about alcohol and tobacco consumption include past and present consumption, and type/method of tobacco use as well as passive smoking. Standard

Table 1 **Examination at Office and during Home visits**

	First home visit	Office visit	Second home visit
History			
Socio-demographic	X		
Family	X		
Medical		X	
Lifestyle factors		X	
Examination			
Anthropometry	X	X	
Blood pressure	X	X	X
Arterial phenotype		X	
Blood biochemistry	X	X	
Malaria parasitology		X	

validated questionnaires are adapted to assess other life style factors, for example, International Physical activity Questionnaire[14,15], Sheldon Cohen Perceived Stress Scale (PSS)[16] and Berlin Sleep Questionnaire[17] for physical activity, psychosocial stress and sleep disor–dered breathing, respectively (**Table 2**).

Anthropometry

With the shoes off, light clothing on, and no cap or head gear, height and weight were measured with a standard stadiometer; to the nearest 0.2 cm and 0.1 kg, respectively. Heberden′s callipers are used to check skin fold thickness at the triceps, sub-scapular and right iliac region. The waist circumference is mea–sured with a non-expansible tape without clothing or light clothing, in between the lower coastal margin and the iliac crest with the arm relaxed by the side. The waist circumference should be done preferable after an overnight fast but in the event where this is not fea–sible, the time of the last meal must be documented.

Blood pressure measurement

The observer measures the blood pressure with a standard mercury sphygmomanometer according to the 2007 guidelines of European Society of Hypertension (ESH)/European Society of Cardiology (ESC)[18] after the subject has been seated for at least 10 minutes in a quiet room. The patient′s chair should provide comfor–table back support and cuff size is chosen based on arm circumference according to recommendation. The cuff must be deflated at approximately 2 mm Hg per second and systolic and phase V diastolic blood pressure recorded to the nearest 2 mm Hg. If phase V diastolic blood pressure cannot be measured, or if phase V dia–stolic blood pressure is lower than 30 mm Hg, phase IV diastolic blood pressure must be recorded. Five con–secutive blood pressure readings are obtained in the sit–ting position with a 30–60 second interval between

the readings. The results of all blood pressure readings must be immediately recorded on the study forms. Maintaining the same conditions as for the examination with the mercury sphygmomanometer, two blood pres–sure measurements are carried out by the observer with a validated[19] oscillometric device (Omron 705IT, OMRON Healthcare Europe BV, Nieuwegein, the Netherlands). Individual subjects are trained on the use of the Omron device and are subsequently guided to measure their blood pressure under the supervision of the observers immediately after the training. Subsequently, the participant takes the Omron device home to measure his/her blood pressure two times in the morning within one hour of waking up and two times in the evening just before going to bed for 6 days. A recording diary with provisions for entry of blood pressure values immediately after each reading is also handed over to the subject. A second home visit takes place by the end of the 6 days of self-monitoring of home blood pressure during which an observer takes the blood pressure of the participant home five times consecutively using the mercury sphygmomanometer.

Quality control for office and home blood pressure monitoring

The following measures are to improve the quality of blood pressure measurement. First, the last digit of the blood pressure value must be even i.e., 0, 2, 4, 6, or 8 (and not 3, 5, 7, or 9). Digit preferences of the observers are monitored at 3-monthly intervals through–out the NIPREGH project. Second, every 3 months, the observers must pass a test requiring them to read blood pressures from a video tape featuring a falling mercury column with Korotkoff sounds (Blood pressure mea–surements, British Medical Association, London, England) and the readings must comply within 5 mm Hg of those of experienced physicians.[20,21]

Table 2 Interview structure and components

| Questionnaire	Variable(s)
Socio-demographic characteristics	Age, gender, ethnicity, state of origin (of father), Educational and occupational history, marital history.
Family history	History of hypertension in first degree relatives
Medical history	Self-rated health, past history of hypertension, diabetes, kidney disease and frequency of malaria attacks
Medication use	Prescription and non-prescription drugs, use of antimalarial
Alcohol	Present and past consumption and type and of alcohol consumed. Reason for stopping
Tobacco	Past and current smoking. Type tobacco and method of consumption, second hand smoking
Physical activity[14;15]	Leisure, occupation and sport-related place activity
Sleep disordered breathing[17]	Presence and severity of snoring, daytime somnelence
Psychosocial factors[16]	Perception of stress in daily activities, ability to cope with situations perceived as stressful
Reproductive health	Menarche, Previous pregnancies, use of contraceptives, hormonal therapy, previous history of hypertension or diabetes in pregnancy, premenstrual syndrome[39]
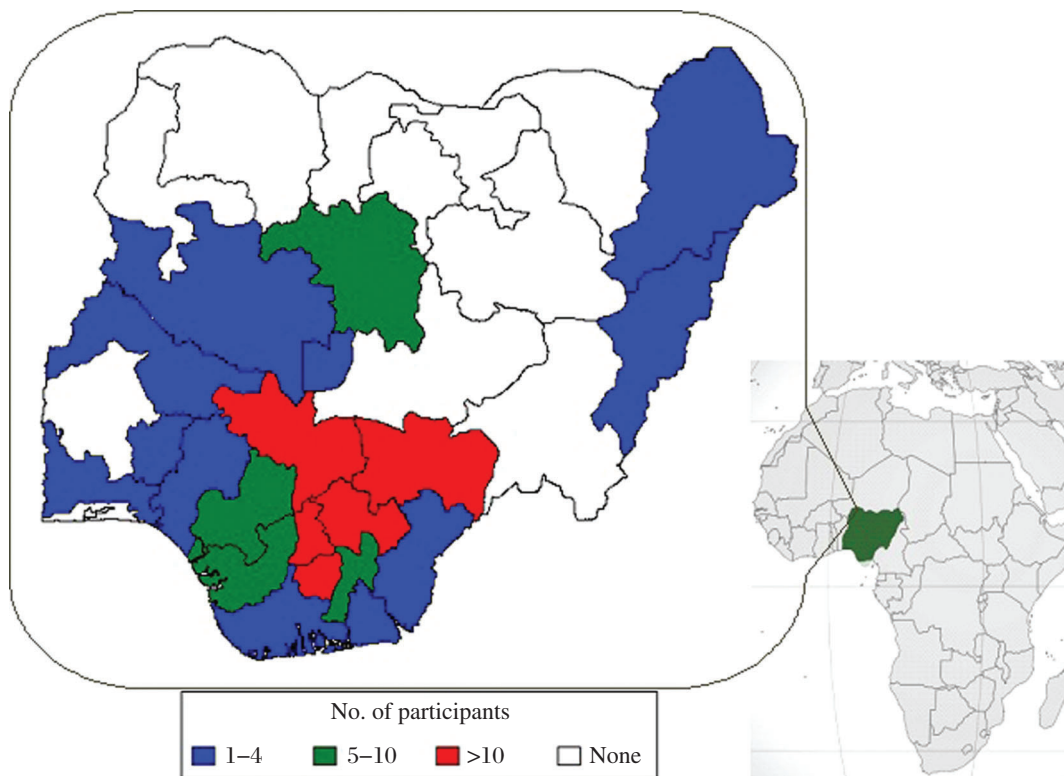
Fig. 1 **Map of Nigeria showing the state of origin of recruited participants across Nigeria.** Inset is the location of Nigeria within the continent of Africa

Intermediate cardiovascular phenotype assess–ment

A paperless Cardiax device (http://www.rdsm.eu/cardiax.html) interfaced with a computer is used to obtain a standard 12-lead ECGs. Using the Cardiax software, version 3.50.2 (RDSM, Hasselt, Belgium), the ECG recordings are printed both electronically and as a hard copy. Voltages and duration of ECG waves are derived from 16-sec ECGs, while 5-min recordings are analyzed for the spectral variability of heart rate in the frequency domain.

Both carotid-femoral pulse wave velocity and pulse wave analysis are derived by means of radial tonome–try using the SphygmoCor device. After the partici–pants had rested in the supine position for 10 to 15 minutes, an 8-second record of the radial waveform at the dominant arm is obtained by applanation tono–metry using a high-fidelity SPC-301micromanometer (Millar Instrument, Inc., Houston, TX, USA) interfaced with a laptop computer running SphygmoCor software, version 7.1 (AtCor Medical Pty. Ltd., WestRyde, New South Wales, Australia). Recordings depicting more than 5% variability in the systolic or diastolic consecu–tive waveforms or the amplitude of the pulse wave sig–nal less than 80 mV are discarded. The pulse wave is calibrated using the systolic and diastolic blood pres–

sures recorded immediately before the procedure with the oscillometric OMRON 705IT recorders.

Biochemical examination

For haematological and biochemical examination, samples are collected using appropriate recipients and handled according to standard laboratory methods. Immediate assessment of blood glucose and total cho–lesterol is done with an Accutrend Plus® device (Roche Diagnostics GmbH, Germany). Four aliquots (two each of plasma and serum) are separated and stored immediately at -20°C. Stored samples are shipped to the biobank of Studies Coordinating Centre Leuven, Belgium and stored at -80°C for future analysis

DNA extraction and genotyping

Blood for DNA extraction and genotyping is drawn in EDTA and stored at -20C. DNA extraction will be done at Central Laboratory in Milan. NucleoSpin BloodL Columns (Macherey Nagel) will be used for DNA purification. The average DNA yield is 20–30 μg per mL of human blood. Genotyping will be performed starting from 200 ng DNA following the Illumina Infinium II protocol that allows interrogation up to hundreds of thousands polymorphic loci per sample. Very briefly, DNA is isothermally amplified,

and then the amplified DNA is enzymatically frag–
mented, precipitated and re-suspended. Re-suspended
samples are hybridized to the array where DNA
anneals to locus specific probes covalently linked to
the array surface. After hybridization, a base extension
step followed by fluorescence staining allows confer–
ing allele specificity to each locus. Fluorescence sig–
nals are detected by the Illumina iScan reader and
analysed with the Illumina GenomeStudio Software
that converts fluorescence to allele and genotype calls.

Notification of and referral for study findings

Study participants and their physicians if requested
by the participants will be notified via a report form
that contains anthropometric records, ECG findings,
blood glucose and cholesterol values. Subjects who
are found to have unfavourable lifestyle factors receive
education on ways of reducing risk associated with
CVDs by physician members of the NIPREGH team.
Any medical condition discovered that should be trea–
ted on an urgent basis will be communicated via phone
to the participant and/ or their physician.

Data management/statistics

Trained technicians code the questionnaire and all
data are keyed in twice using a password protected
computer into a SAS dataset and the paper form stored
as backup in a fireproof cabinet. Data generated by the
computer interfaced instruments are exported and
backed up in an external storage device and are trans–
ferred periodically to Studies Coordinating Centre
Leuven via E mail. Duplicate data sets are compared
with the PROC COMPARE procedure in SAS to
detect input errors. Data coders and SAS programmes
check the internal consistencies of questionnaire
replies. Data derived from Cardiax ECG are exported
in both XML and PDF format while that from the
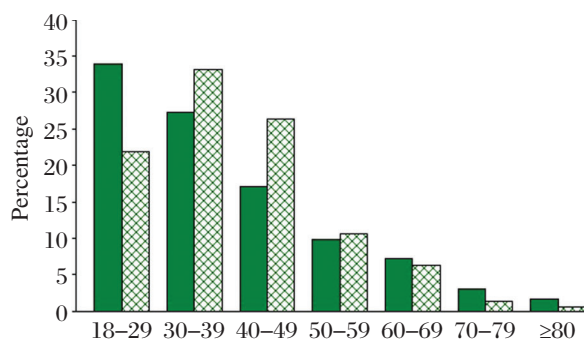SphygmoCor device in Excel format and then stored

Fig. 2 **Age distribution of recruited participants (hatched bars) in comparison with the country age distribution (solid bars) as reported in the 2006 census figures.**

for subsequent offline analysis. Laboratory specimens
are identified with a code that is made up of the unique
identification number, type of specimen and date of
collection. Aliquot of both plasma and the serum sam–
ples are periodically shipped to Studies Coordinating
Centre Leuven, Belgium for storage in the biobank.

RESULTS

The state of origin of the 160 participants, 58% of
whom are women; spanned across 24 out of 36 states
of Nigeria (**Fig. 1**) The age distribution as shown in
Fig. 2 typifies the age structure of Nigeria with age
ranging from 18 to 80 years and mean (SD), 39.8
(12.4) years. 66 (41.3%) participants consume signifi–
cant alcohol while 4 (2.5%, all men) smoked cigarette.
43 (26.8%) and 8 (5.0%) were hypertensive and diabetic
respectively. Women were significantly more obese
($P < 0.01$) than men, mean (SD) BMI; 27.9 (5.3) vs.
25.7 (4.2) kg/m^2. Other aspects of the baseline charac–
teristics are shown in **Table 3**. The office blood pres–
sure averaged 113 mmHg systolic and 73.5 mmHg
diastolic, while the corresponding self-measured home
values were 117.3 mmHg, and 76.0 mmHg, respec–
tively (**Table 4**).

Table 3 **Baseline clinical characteristics**

Characteristic	Women	Men	All
Number of subjects (%)	72(45)	88(160)	160(100)
Smokers	0(0.0)	4(4.5)	4(2.5)
Drinking alcohol	21(29.2)	45(51.1)†	66(41.3)
Diabetes mellitus	5(6.9)	3(3.4)	8(5.0)
Hypertension	21(29.2)	22(25.0)	43(26.8)
Masked hypertension	3(4.2)	6(6.8)	9(5.6)
White-coat hypertension	7(9.7)	6(6.8)	13(8.1)
Mean characteristic(SD)			
Age, y	39.3(13.4)	40.3(11.6)	39.8(12.4)
Weight, kg	74.9(15.9)	79.6(14.4)	77.5(15.3)
Height, m	163.7(5.7)	175.8(6.2)‡	170.4(8.5)
Body mass index, kg/m2	27.9(5.3)	25.7(4.2)†	26.7(4.8)
Waist circumference, cm	95.5(12.2)	92.9(17.0)	94.0(15.0)
Hip circumference, cm	108.5(10.9)	102.6(11.4)†	105.3(11.5)
Waist-to-hip ratio	0.87(0.06)	0.9(0.1)	0.89(0.09)
Skin fold thickness, mm	17.5(9.0)	15.1(7.8)	16.2(8.4)
Arm circumference, cm	33.5(5.7)	32.5(4.1)	32.9(4.8)
Casual blood glucose, mmol/l	6.2(1.7)	5.8(0.8)	6.0(1.4)
Heart rate, beats per minute	75.9(10.5)	71.9(9.8)*	73.7(10.3)

Comparison between women and men, *$P < 0.05$, †$P < 0.01$, ‡$P <$
0.001. Hypertension: either on antihypertensive treatment or office
blood pressure ≥ 140/90mmHg; Diabetes mellitus: either on treatment
or casual blood glucose (measured irrespective of last meal greater than
11.1 mmol/L).

Table 4 **Baseline haemodynamic characteristics of office and home examination**

Characteristic	Women	Men	All
	N=72	N=88	N=160
Office blood pressure			
Systolic, mm Hg	110.9(16.7)	114.7(13.6)	113.0(15.2)
Diastolic, mm Hg	71.4(12.7)	75.2(12.2)	73.5(12.5)
Home blood pressure			
Morning and evening			
Systolic, mm Hg	110.8(15.2)	122.3(13.0)*	117.3(15.0)
Diastolic, mm Hg	74.5(10.3)	77.2(8.8)	76.0(9.6)
Morning			
Systolic, mm Hg	111.9(15.5)	122.4(13.0)*	117.8(15.5)
Diastolic, mm Hg	75.6(10.1)	78.1(9.4)	77.0(9.7)
Evening			
Systolic, mm Hg	109.7(15.4)	121.6(12.3)*	116.5(14.9)
Diastolic, mm Hg	73.2(11.4)	76.5(9.0)	75.1(10.2)

Comparison between women and men, $*P < 0.0001$

DISCUSSION

To our knowledge, NIPREGH is the first prospective population based study on CVD that recruits participants from diverse ethnic groups in Nigeria. NIPREGH has the potential to generate important insights into the burden of risk factors and their contribution to subclinical and clinical cardiovascular disease in Nigeria, a middle income country currently undergoing rapid epidemiolo-gical and demographic transition. This information will inform future health policies.

Some of the strengths of NIPREGH deserve to be discussed. The location of the study in Abuja offers the best opportunity to study the diverse ethnic groups in Nigeria. Abuja, founded in 1976 as the new Federal Capital Territory of Nigeria is located at the centre of the country. Nigerians of different ethnic background migrate from their ancestral homes to Abuja in search of rapidly growing employment opportunities. The population dynamics of Abuja shows that much more immigration than emigration is the case and this offers additional opportunity of retention of participants during follow up. Furthermore, Inhabitants of Federal Housing Authority Estate, the direct location of the study are mainly educated workers in government offices with few of them owning private business. The choice of such cohort allows, in addition to aforementioned advantages, the administration of relatively complex questionnaire which might not be readily understood by participants of lower educational status.

By enrolment age starting at 18 years, NIPREGH is poised to investigate the early processes leading to subclinical and subsequent overt CVDs among black people. Several longitudinal and observational studies that compared Blacks and Whites in the Western countries have reported that CVDs start earlier among Blacks and run a more aggressive course[1,22,23]. The reason for this difference has remained an unanswered research question. The information that will be derived from NIPREGH has the potential to address some of these questions.

The extensive nature of the measurements in NIPREGH is intended to contribute to the basic psy-chosocial and pathophysiological pathways of causation and progression of CVDs. Assessment of sleep disor-ders, psychosocial stress and self-home measured blood pressure is novel in this regard. Hitherto, data generated among blacks living in Europe and America is extrapo-lated to African blacks. Such extrapolation does not give account for differences in natural selection in previous generation[24], ethnic admixture[25] and living environ-ment and lifestyle[26]. Furthermore, interpretation of these findings is usually complicated by confounding variables including differential access to healthcare[27] and unequal racial representation[28] in many large scale clinical and population studies. These shortcomings are obviated in NIPREGH as the study population is made up of Blacks born and living in Africa. The self-mea-sured home blood pressure data will be useful for setting diagnostic thresholds as no report of home blood pres-sure measurement in sub-Saharan Africa is available in the literature up until now.

The result of the pilot phase of NIPREGH has demonstrated clearly that the protocol can be implemen-ted and the objectives achieved. At the moment, we have had a response rate of 78%, recruited participants of 34 different ethnic groups and from 24 out of the 36 states that constitute Nigeria (*Fig. 1*). The age distribution of the participants mirrors closely that reported in 2006 national census figures (*Fig. 2*)[29]. The data generated so far are of good quality. A recent check of blood pres-sure phenotype (the main phenotype of interest) shows that zero digit preference among observers was 27.1%. This compares favourably well with the 24% reported in the well standardised European Project of Gene in Hypertension (EPOGH) project[21]. The prevalence of hypertension and diabetes (*Tables 1* and *2*) in the pilot sample was 26.8 and 5.0% respectively. This falls within the range of the prevalence rates of between 22.3 to 35.4% for hypertension[30–33]; and 2.8 to 5.1%[33,34] for diabetes reported in previous community studies across different regions of Nigeria

Setting up a population based epidemiological study as NIPREGH in a resource poor setting as ours has been fraught with challenges. Lack of funding, poor research infrastructure, religious and cultural beliefs

and unsteady power supply are some of the challenges we have continued to grapple with. Some innovative ideas employed during the planning, design and the implementation of the pilot phase have helped immen–sely to surmount many of these challenges. The princi–pal investigator has been receiving training at the Studies Coordinating Centre, University of Leuven since 2010. This linkage has not only provided the needed skills for epidemiological research, it has also offered invaluable network opportunities within a wider international research consortium involving investiga–tors in Asia, Europe and South America. The success of NIPREGH so far owes largely to the support pro–vided through these collaborative efforts. The facilities available within the local environment have also been maximally utilised. Medical students of College of Health Sciences, University of Abuja as well as grad–uate youths undergoing the mandatory one year National Youth Service Corps Programme are engaged as volunteers for community mobilisation. We also benefit from the expertise of research institutions within Abuja metropolis in terms of sourcing for local con–sumables necessary for laboratory work. Continuous dialogue with religious and community leaders has helped a great deal with community mobilisation. Furthermore, home visits by observers, engaging parti–cipants in measurement of their own blood pressure at home, and health education for subjects identified to have some modifiable cardiovascular risks all serve as incentives in line with the principle of beneficence as stipulated in the Belmont Report[35]. These strategies have further increased trust and acceptability of the project among the community residents. Our group successfully concluded the first multinational anti–hypertensive drug trial in sub-Saharan Africa-Newer vs Older Anti-hypertensive Agents in African Hypertensive patients (NOAAH)[36–38]. This randomised clinical trial was carried out in 7 centres (2 of which were in Nigeria) located within sub-Saharan Africa. The experience gained in NOAAH trial has also been very useful in conducting NIPREGH. In conclusion, NIPREGH is a response to the epidemic of CVDs in sub-Saharan Africa. The challenges inherent in con–ducting such a population study in a low resource set–ting are huge but surmounting them through a creative epidemiological design reveals the enormous potentials therein for advancing human knowledge.

Acknowledgments

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