



# Data Resource Profile

# Data resource profile: Cardiovascular H3Africa Innovation Resource (CHAIR)

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#### **Data resource basics**

Low- and middle-income countries (LMIC) constitute the majority of the world's population and bear more than 80% of the global burden of cardiovascular disease (CVD).<sup>1,2</sup> The recent increases in CVD globally are also reflected in LMIC, where the prevalence of overall deaths from CVD was 28% in 2001<sup>3</sup> and premature CVD mortality was 37% in 2015.<sup>4</sup> The paucity of data regarding the drivers of the CVD epidemic and contextualized solutions is, in part, because less than 10% of the global research resources and facilities for implementation are found in LMIC.<sup>5,6</sup> Therefore LMIC are particularly disadvantaged in dealing with the CVD burden with targeted interventions. at the individual and community levels. due to the lack of data availability.

A key development poised to improve the understanding and control of CVD in LMICs in Africa is the Human Heredity and Health in Africa (H3Africa) Consortium, of which the H3Africa Cardiovascular Disease Working Group (CVDWG) is a core component. <sup>6,7</sup> The CVDWG includes six of the H3Africa projects spread across 13 African countries (Figure 1). The six projects include: the African Collaborative Center for Microbiome and

Genomics Research (ACCME), which also collects data on CVD; the Genomic and Environmental Risk Factors for Cardiometabolic Disease in Africans (AWI-Gen); the burden, spectrum and aetiology of type 2 diabetes mellitus in sub-Saharan Africa (DM group); the H3Africa Kidney Disease Research Network (Kidney group); the Genetics of Rheumatic Heart Disease Network (RHDGen); and the Stroke Investigative Research and Educational Network (SIREN).

The CVDWG is focused on developing genomic research and training infrastructure that will enable Africa to benefit from the genomic revolution. Specifically, the CVDWG is building the Cardiovascular H3Africa Innovation Resource (CHAIR), which aims to include >55 000 participants, with 30 044 participants in the first phase, as the largest cohort of continental Africans for studies on genomic and environmental contributions to CVD in Africa. CHAIR comprises phenotype data relevant to the cardiovascular disease spectrum, including sociodemographic, anthropometric, clinical, biochemical (blood and urine biomarkers) and genomic data as well as stored biological samples for future research.

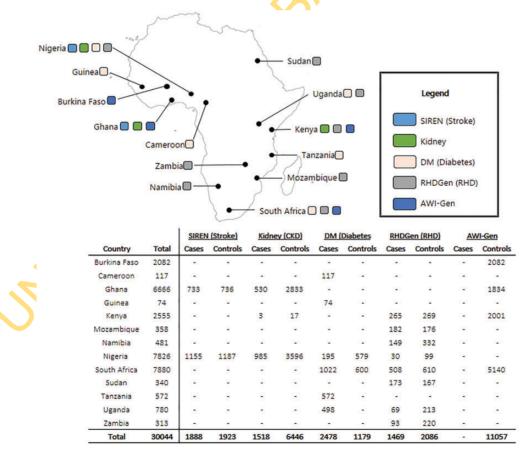


Figure 1. Map of Africa showing location or study sites of the participants from the six H3Africa studies, based on recruitment as at 30 September 2016.

Table 1. Participating H3Africa Consortium Projects that constitute CHAIR

Project (PI reference)	Descriptive title	Study design	Countries involved in recruitment	Current sample size (target sample size)/sources
ACCME (Adebomowo) <sup>8</sup>	African Collaborative Center for Microbiome and Genomics Research	Prospective cohort study	Nigeria	Population-based sample of 11 700 female partici- pants (targeted)
AWI-Gen (Ramsay and Sankoh) <sup>9</sup>	Genomic and Environmental Risk Factors for Cardiometabolic Disease in Africans	Cross-sectional: population-based cohort of adults	Burkina Faso Ghana Kenya South Africa	Community-based (randomized by household and unrelated individuals) 11 057 (targeted: ~12 000) participants
DM Group (Motala) <sup>10</sup>	Burden, spectrum and aeti- ology of type 2 diabetes in sub-Saharan Africa	Cros-sectional: clinical and population-based cohort	Cameroon Guinea Malawi Nigeria South Africa Tanzania Uganda	Health facility-based recruitment of cases and community(population)-based recruitment of controls 3657 (targeted: ~6000 DM cases and ~6000 DM-free controls)
Kidney Group (Adu and Ojo) <sup>11</sup>	H3Africa Kidney Disease Research Network	Prospective and population-based cohort	Ghana Ethiopia Kenya Nigeria	Cases: outpatient clinics and patient admissions Controls: outpatient clinics 7964 (targeted: ~4000 kidney disease cases and ~4000 kidney disease- free controls)
RHDGen (Mayosi) <sup>12</sup>	Genetics of rheumatic heart disease (RHDGen) Network	Case-control cohort and family trios	Kenya Mozambique Namibia Nigeria South Africa Sudan Uganda Zambia	Hospital-based recruitment of cases and community-based controls with no valvular heart disease 3555 (targeted: ~2700 RHD cases, ~2700 RHD-free controls and ~200 family trios)
SIREN (Owolabi and Ovbiagele) <sup>13,14</sup>	Stroke Investigative Research and Educational Network	Prospective and pop- ulation-based cohort	Ghana Nigeria	Hospital-based cases, community and hospital-based controls 3811 (~3000 stroke cases and ~3000 stroke-free controls)

PI, Principal investigator (www.h3a.org).

## **Data collected**

# Datasets and population coverage

CHAIR is the combined resource of six independent research projects (Table 1; Supplementary Table 1, available as Supplementary data at *IJE* online). In this first phase, combined data from 30 044 participants of both genders and across age groups, from 15 African countries, have been combined using a careful harmonization process to ensure data equivalency. It is anticipated that the CHAIR resource will have data on close to 100 CVD-related phenotypes and genomic data for >55 000 participants. At the current wave of data collection, data completeness is

>90% for most important CVD risk factors and almost 100% for stored samples (Table 2).

Participants include cases (selected by disease status) and controls (specific disease-free controls and cross-sectional population-based controls) and are resident in Burkina Faso, Cameroon, Ghana, Guinea, Kenya, Mozambique, Namibia, Nigeria, South Africa, Sudan, Tanzania, Uganda or Zambia (Figure 1). Recruitment strategies and CVD phenotypes that were measured are similar but not identical across the projects. Most projects have also published their research protocols. 8,15–19 Each study had its own inclusion and exclusion criteria, and

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M/F, male/female.

 Table 2. Key variables being collected across different projects in CHAIR

	ACCME		AWI-Gen		DM Group		Kidney group	d	RHDGen		SIREN	
	n = 11700	% Complete	$n = 11 \ 0.57$	% Complete	n = 3657	% Complete	n = 7964	% Complete	n = 3555	% Complete	n = 3811	% Complete
Age distribution	>18 years	100.0	40–60 years	100.0	$\geq$ 25 / $\geq$ 18 years	100.0	0–74 years	100.0	Paediatrics and adult	100.0	>18-100 years	100.0
Sex	Female only	100.0	M/F	100.0	M/F	100.0	M/F	100.0	M/F	100.0	M/F	100.0
Weight (199)	>	0 00	>	1000	>	1000	>	1000	>	2 00	>	07.0
weight (kg)	< >	0 00	< >	100.0	< >	100.0	< >	0.001	< >	6.87	< >	6.76
Waist circumference (cm)	< >	8 66	< ×	100.0	< ×	100.0	< ×	7.66	<	<b>+</b> : CC	< >	94.6
Hip circumference (cm)	< ×	6.66	×	100.0	< ×	100.0	4				< ×	95.5
General health:	:				;						<b>!</b>	
Smoking/tobacco	×	8.66	×	100.0	×	100.0	×	100.0			×	98.3
Alcohol	×	8.66	×	6.66	×	100.0	×	6.66			×	6.86
Cancer history	×	8.66	×	6.66	×	100.0	×	8.66			×	98.5
Diet	×	2.66	×	8.66	×	100.0					×	95.4
Exercise	×	8.66	×	100.0	×	100.0					×	98.3
Cardiovascular health:				•								
Blood pressure	×	6.66	×	100.0	×	100.0	×	100.0	×	8.98	×	9.96
Atrial fibrillation (ECG)					\ )		×	100.0	×	12.1	×	98.3
Stroke and stroke-free status	×	8.66	×	6.66	×	100.0	×	100.0			×	100.0
Myocardial infarction	×	8.66		77.0	×	100.0					×	9.86
Blood collection for biomarkers												
Lipid profile			×	100.0	×	100.0					×	0.66
Fasting plasma Glucose			×	100.0	×	100.0					×	9.09
HbA1c			×		×	100.0					×	41.7
Insulin			×	100.0	×	100.0						
Infection history												
TB infection			×	6.66	×	100.0	×	6.66			×	9.86
HIV status	×	100.0	×	6.66	×	100.0	×	6.66			×	9.86
Malaria			×	6.66	×	100.0	×	100.0			×	98.4
Urine collection			×		×	100.0						
Albumin (microalbumin)			×	8.66	×	100.0	×	100.0				
Total protein			×	6.66			×	6.66				
Creatinine			×	6.66	×	100.0	×	100.0	く		×	80.0
Samples to be stored												
DNA	×	6.66	×	6.66	×	100.0			×	0.66	×	6.66
Buffy coat	×	6.66	×	6.66					×	70.0	×	6.66
Plasma	×	6.66	×	6.66	×	100.0			×	82.0	×	6.66
Serum	×	6.66	×	6.66	×	100.0			×	6.62	×	6.66
Urine	×	7.66	×	8.66	×	100.0				1	×	

most studies started recruitment in 2012 and completed recruitment in 2017. Most studies are planning longitudinal follow-up of participants. Study instruments used by the participant studies were administered by well-trained fieldworkers and research professionals, using validated approaches to harmonize data.

## Survey frequency

One of the two cross-sectional studies is a populationbased study (both have plans for longitudinal follow-up in the next wave of data collection), and four studies are population-based longitudinal cohorts or case-control disease-based studies. Studies with longitudinal data collections within the first phase of H3Africa (mid-2012 to mid-2017) are shown in Supplementary Table 2, available as Supplementary data at IJE online; and one is planning follow-up in a second phase. For instance, the Kidney group used a case-control study design and plan annual follow-up visits of the cases over a period of 5 years, to assess kidney disease progression and other clinical events.<sup>18</sup> The SIREN study followed up patients with stroke at 1, 3, 6, 9 and 12 months after discharge from hospital.8 The ACCME group conducted a prospective cohort study where demographic and clinical data were collected at baseline and then during follow-up visits every 6 months for 2 years. 9,15 The AWI-Gen study is a cross-sectional population-based study of older adults which will be developed into a longitudinal cohort with follow-up after approximately 5 years from the first recruitment, to assess progression of, or transition to, cardiometabolic disease states. 16 The DM group is a cross-sectional study comprising two arms: a 'clinic/case-series' arm which includes participants with known diabetes attending a health facility; and in parallel, from the same geographical area, are drawn participants for the 'population survey' arm. 17 RHDGen is a case-control study with cases with rheumatic disease recruited in a hospital-based setting and community-based controls, which can be contacted for further data collection. 19 The CHAIR studies have obtained broad consent from most participants for the reuse of data and samples, and participants either been consented to be approached for future studies or will be reconsented when approached again for longitudinal data collection.

#### Measures

Each participating study in CHAIR has independent but related robust case report forms (CRFs) for phenotype and laboratory data collection. Study CRFs consist of validated measures for capturing data on several phenotypes. For example, the Questionnaire for Verifying Stroke-Free Status

(QVSFS)<sup>8</sup> is used for determining stroke-free status with baseline blood pressure measured according to the American Heart Association Council on High Blood Pressure Research.<sup>9</sup> Standing height, body weight, waist circumferences and obesity are measured in accordance with the recommendations of the World Health Organization (WHO) Multinational Monitoring of Trends in Cardiovascular Disease (MONICA) project.<sup>10</sup>

A total of 67 phenotypes including: sociodemographic details (age, sex, country of residence, ethnicity, marital status, educational attainment and occupational status); socioeconomic status; medical history (infection with HIV, TB or malaria; history of hypertension, diabetes, stroke, myocardial infarction, cancer and other infectious and non-infectious diseases and traits); lifestyle data (tobacco and alcohol exposure); family health history; and biomarkers of CVD relevance in blood and urine; are included in the CHAIR dataset (Table 2; and Supplementary Table 3, available as Supplementary data at IJE online). The questionnaires used for collecting data on these phenotypes are based on existing validated questionnaires and differ, in some cases, between participating studies. Where possible, when comparable measures were used, data have been harmonized across datasets. For instance, hypertension data were harmonized and defined as sustained systolic BP > 140 mmHg or diastolic BP > 90 mmHg, history of hypertension, or taking antihypertensive medications. Diabetes mellitus was harmonized and defined as history of diabetes mellitus, use of medications for diabetes mellitus, fasting glucose levels >126 mg/dL (or >200 mg/dL if failing to fast) and/or HBA1c >6.5%. Obesity was based on body mass index (kg/m<sup>2</sup>) calculated and classified as underweight (<18.5), normal (18.5-24.9), overweight (25-29.9) or obese (30+) or based on waist-to-hip ratio tertiles.

All studies collect blood and/or other tissues or body fluids (e.g. urine) for DNA extraction and biomarker analysis. Several aliquots of each DNA sample from all participants are stored in an H3Africa Biorepository in Nigeria, Uganda or South Africa. Genome-wide variation data will be available for all studies. Four studies have used the H3Africa SNP genotyping array (~2.3 M SNP Illumina Array enriched for common variation across African populations). RHDGen has used the Illumina Omni 2.5 M array, and the DM group will use a different array. African-based imputation panels are available to harmonize the disparate genomic data types.

#### Data resource use

Although each project has its own research objectives, the shared resource will be able to tackle cross-cutting research questions and test hypotheses which the individual projects are underpowered to explore. For instance, we have collected and harmonized data on potential risk factors, including age, setting (urban or rural), weight, height, waist and hip circumference across the entire CHAIR cohort. In addition, we have stored biological samples including urine, serum, plasma and DNA from the majority of the participants. We have also developed an inclusive model for data harmonization which makes it possible to investigate multiple hypotheses, to address a wide spectrum of CVD risk factors in disease causation or influence. Therefore, CHAIR provides the opportunity to examine genomic associations with cardiovascular phenotypes across various African regions and urban/rural settings. This enhances the potential for discovery, validation and generalizability. CHAIR offers a pan-African perspective with unique opportunities for collaboration, including sharing of data on controls, provision of validation cohorts, meta-analyses, capacity-building for genomic research and development of infrastructure for CVD epidemiological, genomic, biobanking and bioinformatics research.

The findings from the CHAIR research promise to inform the development of cost-effective diagnostic, preventive and therapeutic interventions at individual, health care system and population levels. 12,13,20 Such interventions could be implemented through robust advocacy efforts involving all stakeholders working within and across African countries and regions. This would enhance the emergence of a healthy and economically vibrant continent.

Baseline characteristics for 30 044 participants of CHAIR with available data as of 30 September 2016 are presented in Table 3. Overall, 57.0% were women. The proportion with hypertension (defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or confirmed diagnosis of hypertension by a health care worker or current use of antihypertensive medication) was 48.8% among men and 47.4% among women. Based on the 2017 guidelines for hypertension diagnosis (i.e. systolic blood pressure ≥120 mm Hg or diastolic blood pressure >80 mm Hg in addition to confirmed diagnosis of hypertension by a health care worker or current use of antihypertensive medication, the proportion with hypertension was 74.8% among men and 69.6% among women, and the proportion with obesity [body mass index (BMI)  $>30 \text{ kg/m}^2$  was 10.8% among men and 32.8% among women (Table 3). The proportion with hypertension and obesity varied among projects, influenced by individual participant selection. For instance, the proportion with hypertension was highest in the SIREN study on stroke, and

Table 3. Preliminary baseline characteristics for 30 044 CHAIR participants from five studies as at 30 September 2016

Studies (number of participants)	Sex (%)	n	Age in years (SD)	Proportion with obesity <sup>a</sup>	Proportion with hypertension (definition 1: $\geq$ 140/90 mmHg) <sup>a</sup>	Proportion with hypertension (definition 2: $\geq$ 120/80 mmHg) <sup>a</sup>
AWI-Gen (11 057)	Male (45.2)	4999	50.61±6.96	7.8	34.4	64.3
	Female (54.8)	6058	50.83±6.95	31.2	37.9	60.7
Subtotal		11 057	50.73±6.95	20.6	36.3	62.3
DM (3657)	Male (32.8)	1199	49.01±16.69	18.5	55.2	77.1
	Female (67.2)	2458	50.71±14.46	51.8	64.8	80.5
Subtotal		3657	$50.16 \pm 15.24$	40.9	61.7	79.4
Kidney (7964)	Male (42.7)	3398	47.40±14.69	11.7	60.8	82.7
	Female (57.3)	4566	46.40±13.70	26.9	52.2	73.5
Subtotal		7964	$46.83 \pm 14.14$	20.4	55.9	77.5
RHDGen (3555)	Male (34.2)	1217	$34.00 \pm 12.81$	8.0	21.6	67.1
	Female (65.8)	2338	$38.78 \pm 13.78$	27.9	21.4	58.1
Subtotal		3555	37.14±13.64	21.1	21.5	61.1
SIREN (3811)	Male (55.3)	2108	$57.43 \pm 12.89$	14.4	75.7	90.1
	Female (44.7)	1703	$58.62 \pm 14.10$	32.5	78.6	90.7
Subtotal		3811	57.96±13.45	22.4	77.9	90.4
Combined CHAIR (30 044)	Male(43.0)	12 921	49.17±13.35	10.8	48.8	74.8
	Female(57.0)	17 123	$48.76 \pm 13.02$	32.8	47.4	69.6
Grand total		30 044	$48.94 \pm 13.17$	23.4	48.0	71.8

Percentages of completed data for the baseline characteristics were: 100.0% for sex; 100.0% for age; 97.0% for height; 97.1% for weight; 98.8% for systolic blood pressure; 98.8% for diastolic blood pressure.

SD, standard deviation.

<sup>&</sup>lt;sup>a</sup>These rates may have been affected by the design and disease focus of the individual study.

similarly the proportion with obesity was highest in the type 2 diabetes study (Table 3).

The CVDWG has published position papers<sup>6,7</sup> describing the current knowledge of CVD in Africa and also articulating the opportunities and challenges for future CVD research in Africa. 6,7,21-30 To ensure accurate exclusion of stroke mimics, a pictographic version of the Questionnaire for Verifying Stroke-Free Status with superior diagnostic properties including 98% certainty for determining strokefree status, which was validated in three languages commonly spoken in West Africa (including Ghana), was developed.31 Such free but robust instruments for stroke diagnosis, a leading cause of CVD in Africa, could be deployed in the follow-up of study participants across the CHAIR consortium. Some cardiovascular disease-specific findings from some of the collaborating studies<sup>32</sup> suggest the need for a unique cardiovascular risk calculator for Africans. In a recent report, one of the studies (SIREN)<sup>14,33</sup> identified leading risk factors for stroke in the continent, that is: hypertension, dyslipidaemia, regular meat consumption, elevated waist-to-hip ratio, diabetes, low green leafy vegetable consumption, stress, salt added at the table, cardiac disease, physical inactivity and tobacco use. These factors will be investigated further using the CHAIR resource. 14,33

The AWI-Gen study found significant sex differences in the prevalence of hypertension in four of their six study centres and regional differences in prevalence, awareness and control of hypertension.<sup>34</sup> This suggests the need for the implementation of regionally appropriate and contextdriven targeted interventions for hypertension in Africa. In a cohort of sexually active HIV-negative adult women with no previous history of cervical abnormalities, cervical cancer or total abdominal hysterectomy, the ACCME study found a 21% prevalence of persistent human papilloma virus (HPV) infection. 15 There was also a reported history of physician-diagnosed hypertension (15%), diabetes (2%), hypercholesterolaemia (4%) or heart disease (0.3%). These results provide important data for studies of associations between these characteristics and HPVassociated cancers including cervical cancer. 15 The RHDGen project, in a 5-year follow-up study of latent Rheumatic heart diseases (RHD) among school pupils and using the World Heart Federation (WHF) echocardiographic criteria, found that latent RHD resolves to normal in nearly half of school pupils. 19 It is therefore a necessity to repeat echocardiography in cases of latent RHD before considering an intervention.

A comprehensive list of publications from the CVDWG is available on the H3Africa website: [http://h3africa.org/links/publications].

## Strengths and weaknesses

The main strength of the CHAIR cohort is its large anticipated final sample size of over 55 000 African participants, which is powered to validate and examine many genetic risk factors for quantitative traits including BMI and lipid levels, where genetic markers have low or moderate effects.

With a sample size of at least 50 000, the study will have >95% power to detect associations with quantitative traits with an effect size (beta value) of 0.2 for single nucleotide polymorphisms (SNPs) with a minor allele frequency (MAF) of 0.05, and >90% power to detect a beta value of 0.1 for SNPs with MAF 0.20. In case-control studies with 6000 cases and 6000 controls, there will be >95% power to detect an odds ratio (OR) of 1.2 (MAF 0.05) and >90% to detect an OR of 1.1 (MAF 0.20). Other strengths include the harmonized high-quality phenotype data and the availability of genome-wide genotyping data on all participants and access to DNA samples.

All studies also have community engagement, training and capacity building components and have produced freely available protocols, guidelines, training materials and analysis tools that can be used in similar studies and are adapted to the African context. Also, although electronic medical records are scarce and diseases and vital registries are incomplete in Africa in general, some of the hospital-based studies could do passive follow-up from hospital records and the AWI-Gen study, which is nested in HDSS, can refer to verbal autopsies in the cases of deaths.

A limitation of CHAIR is the lack of standardization of data collection tools across all six studies. The harmonization process, however, has ensured that data are compared in a meaningful way for the cardinal CVD risk factors. Furthermore, most studies will also have genomic data and, for those not using the H3Africa Illumina SNP array, genetic analyses will use imputation strategies to develop a common dataset to analyse pooled phenotypic data using advanced meta-analytical techniques. 35,36

#### **Data resource access**

This CHAIR resource is available to researchers (members and non-members of the H3Africa Consortium) worldwide according to the H3Africa guidelines and policies [https://www.h3africa.org/consortium/documents]. Data will be submitted to the European Genome-phenome Archive (EGA) and will have a publication embargo of 12 months, or following the first publication, whichever is the soonest. The harmonized phenotype data of CHAIR will also be stored in a dedicated REDCap database<sup>37</sup> and will be linked through unique identifiers to genomic data. Genotype and phenotype data will be available at

H3ABioNet and the European Genome-phenome Archive (EGA).<sup>38</sup> DNA samples will be accessed from the H3Africa biorepositories.<sup>39</sup> A managed access model has been implemented for data and samples, and they will be available after approval by the H3Africa Data and Biospecimen Access Committee (DBAC). Imputation panels will be available to ensure that a rich joint genomic dataset can be developed for meta-analyses. Please contact the H3Africa Coordinating Centre for more information [h3africa@mail.nih.gov].

#### Profile in a nutshell

- CHAIR is the largest harmonized resource of cardiovascular diseases in Africans with genomic, environmental and phenotypic data from participants across the entire cardiovascular cascade. CHAIR is the first and only such initiative in Africa with the potential for addressing cross-cutting research questions with substantial power and validity.
- With an initial target of >30 000 (male and female) participants, the resource comprises data on adults from 15 African countries, recruited by six H3Africamember studies including the ACCME, AWI-Gen, DM group, Kidney group, RHDGen and SIREN at baseline enrolment, and with a subset having longitudinal follow-up data.
- Follow-up within CHAIR has been study-specific as follows: ACCME (every 6 months for 2 years), Kidney group (annually), SIREN (every 3 months for 1 year). Studies like AWI-Gen and DM group have planned for follow-up in the next wave of data collection. RHDGen is a cross-sectional study with no planned follow-up.
- Associated biological samples are available for future studies on genetic and epigenetic determinants of cardiovascular health, diseases and morbidity among individuals of African ancestry.
- CHAIR can be accessed through the H3Africa Coordinating Centre

## **Supplementary Data**

Supplementary data are available at IJE online.

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## **Author Contributions**

All authors contributed to study concept, design and data acquisition. O.M.A. and F.M. are CHAIR statisticians who contributed to data harmonization and analysis. M.O.O., M.R., O.M.A. and F.M. contributed to interpretation of results and drafting of the manuscript. All authors contributed to critical revision of the manuscript and approval of the final draft.

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