Summary of key research findings at SAPRIN nodes in the last year

20 June 2023

Preface

On 19 June 2023, the 3 SAPRIN directors co-presented to the SAMRC Unit Directors Forum in the Science underway slot. Kobus Herbst prepared a synopsis of recent published work from the nodes by theme, and this is represented in this document as a summary of key SAPRIN findings in the last year. There are two introduction slides which provide an overview of SAPRIN and its mission, and a purview of the Health and Demographic Surveillance System Methodology which is standardised into the core protocol. The themes are as follows:

1. Introduction

DSI has funded SAPRIN the core surveillance operations of SAPRIN as a national research infrastructure since 2017 and is committed to the long-term funding of SAPRIN. A national infrastructure is described by DSI as facilities, resources and services used by the scientific community across all institutions and disciplines for conducting cutting-edge research for the generation, exchange and preservation of knowledge. NRIs should be open access to users selected through peer-review with a requirement on users to share their research results in the public domain; provide access to research capacity building opportunities; and have as a mission and goal a clear national scientific priority.

SAPRIN is hosted by the MRC and governed by a steering committee chaired by the MRC President/Vice-president with membership from key stakeholders, including DSI, STATSSA, & HSRC, and nodal directors.

Each SAPRIN node has a complete population (all household members including children) of at least 100 000 under surveillance. I will explain how this works in a subsequent slide. There are three founding nodes, that existed prior to SAPRIN's inception:

1. Agincourt HDSS based in the Bushbuckridge local authority in Mpumalanga, in operation since 1991.
2. DIMAMO HDSS in the Polokwane local authority in Limpopo, in operation since 1996.
3. AHRI HDSS in the Mtubatuba local authority in KwaZulu-Natal, in operation since 2000.

We have started up three new urban nodes:

1. GRT-INSPIRED in Hillbrow, Atteridgeville and Melusi in Gauteng, who just completed their baseline census
2. C-SHARP in Bishop-Lavis and Nomzamo in the Cape Town Metro
3. USINGA in Umlazi, Ethekwini

The latter two will start baseline data collection later this year

I need to point out that, although, the SAPRIN and nodal leadership are scientists, with their own research portfolios, as a national research infra-structure SAPRIN is and must be accessible to all scientists in the country and their international collaborators.

SAPRIN Nodes (Research Population = 750,000)

- Established in 2017 as part of the South African Research Infrastructure Roadmap (SARIR) by the Dept of Science and Innovation (DSI).
- Hosted by the South African Medical Research Council.
- Mission: to enable impactful population -based research through supporting a network of standardised longitudinal, whole population health and demographic surveillance nodes in South Africa

2. Health and Demographic Surveillance System Methodology

A SAPRIN HDSS node follows a complete population (all households and their members) in a defined geographic area over time. In the nodes currently operating there are 340 000 individuals under observation, but we have encountered more than half a million and have amassed 5,6 million person years of observation.

Individuals enter this dynamic cohort through birth or in-migration and exit through death or out-migration. Actually, in just under half of out-migrations, we don't end follow-up because the individual retains membership of a locally resident household who can report on their status. The household surveillance is augmented by individual-level health questionnaires and the collection of dried blood-spot samples. All deaths are documented using verbal autopsies.

This longitudinal data allows the ongoing measurement of accurate population dynamics, including mortality, fertility and migration, which we share with STATSSA to deepen understanding of national census and sample surveys.

We do not just observe, but HDSS host a number of randomised controlled trials and intervention studies of priority concerns.

As you have seen from the presentation, HDSSs are the setting of detailed and accurate disease surveillance, including rapid response to emerging diseases.

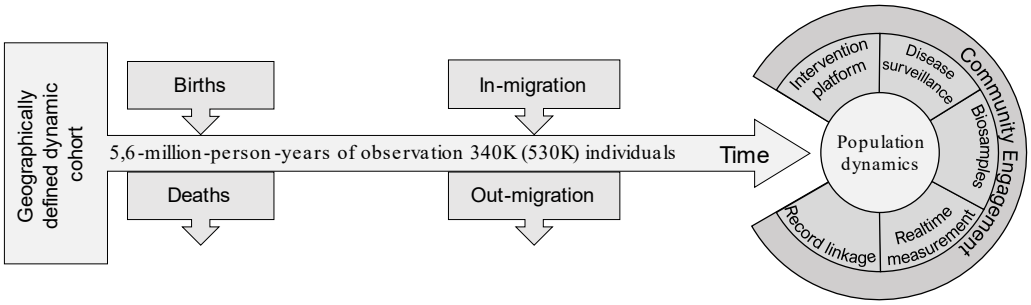
HDSSs also caters for basic research by collecting bio-samples for genetic and other biological studies to aid discovery of disease risks and treatment modalities.

With technological advances in real time measurement of environmental and biological parameters by sensors and wearables, SAPRIN is exploring the future of real-time surveillance.

The full power of the HDSS is realised by linking our detailed, geolocated population database with service delivery records, such as electronic medical records, social grants, educational outcomes enabling us to accurately measure need and assess universal health and social coverage. The is particularly important as we approach the implementation of National Health Insurance, as HDSS are the only viable means of continually assessing need at individual population level and verify whether access to care has taken place, thereby measuring universal health coverage and its determinants as a basis for precision public health.

Finally, the most important component of a HDSS is the surveillance community. They co-create the science with us through community advisory boards and community dialogues, benefit from our presence through job creation and access to interventions to improve their health and well-being. An example of such co-creation is the verbal autopsy result based participation action research done by the VAPAR team at Agincourt.

Common surveillance protocol



- 3 surveillance contacts per year
- 250K DBS samples from 100K individuals
- SAPRIN Data Repository https://saprindata.samrc.ac.za

1. Herbst, K., Juvekar, S., Jasseh, M., Berhane, Y., Chuc, N. T. K., Seeley, J., ... & Collinson, M. A. (2021). Health and demographic surveillance systems in low -and middle-income countries: history, state of the art and future prospects . Global health action, 14(sup1), 1974676.
2. Collinson, M. A., Mudzana, T., Mutevedzi, T., Kahn, K., Maimela, E., GÔnez -OlivÁ, F. X., ... & Herbst, K. (2022). Cohort Pro¸le: South African Population Research Infrastructure Network (SAPRIN). International Journal of Epidemiology, 51(4), e206 -e216.
3. van der Merwe, Maria, et al. "Collective reflections on the ¸rst cycle of a collaborative learning platform to strengthen ru ral primary healthcare in Mpumalanga, South Africa." Health Research Policy and Systems 19 (2021): 1 -13.

3. Research on HIV

Violence and HIV risk

Using data from the HPTN 068 a phase 3 randomized controlled trial of cash transfers conditional on school attendance among adolescent girls and young women (AGYW) in Agincourt, Leddy showed that any emotional interpersonal violence (IPV) and verbal IPV were associated with increased odds of condomless sex, transactional sex and alcohol use. Threats were associated with transactional sex.

Leddy, Anna M., et al. "Emotional violence is associated with increased HIV risk behavior among South African adolescent girls and young women in the HPTN 068 Cohort." AIDS and Behavior (2021): 1-8.

Linkage to Care

SAPRIN nodes track attendances at clinics of the surveillance population, and in papers such as the one by Etoori from Agincourt, can provide insight into documented and undocumented transfers between clinics, improving the interpretation of routine service statistics.

Etoori, David, et al. "Investigating clinic transfers among HIV patients considered lost to follow-up to improve understanding of the HIV care cascade: Findings from a cohort study in rural north-eastern South Africa." PLOS Global Public Health 2.5 (2022): e0000296

Spatial risk

Combining the geolocation data in SAPRIN nodes where every household is geocoded with longitudinal HIV surveillance data allows studies that give us insight into small area transmission dynamics of HIV, that may lead to novel interventions. In this study by Cuadros found that the key-populations at risk located in a peri-urban area suffering a high HIV burden are also highly connected populations that might play a significant role in the diffusion of the virus across the entire transmission network

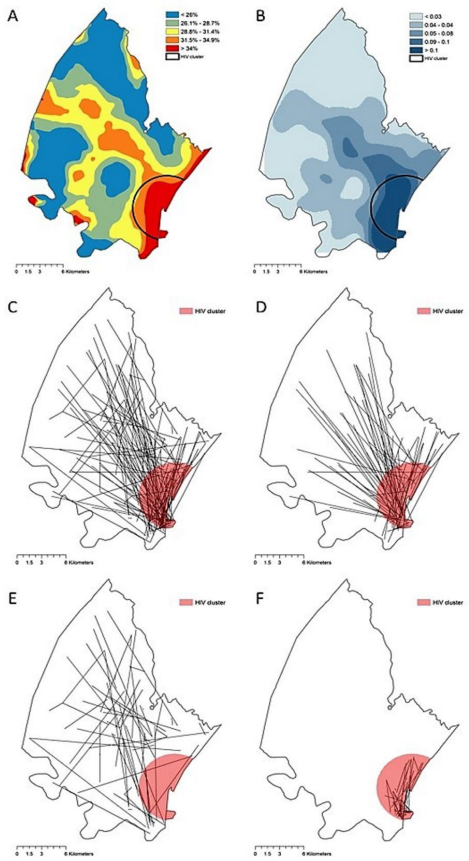


Fig 2.

A) Kernel interpolation of the HIV prevalence in the area of study.
B) Estimated HIV sero-conversion per pixel (300m x 300m).
C) All transmission links.
D) Transmission links in which at least one individual is located inside the HIV high-risk area.
E) Transmission links outside of the HIV high-risk area.
F) Transmission links within the HIV high-risk area.

Red circle encloses the geographical HIV high-risk area (HIV geographical cluster).

Cuadros, Diego F., et al. "The role of high-risk geographies in the perpetuation of the HIV epidemic in rural South Africa: a spatial molecular epidemiology study." PLOS Global Public Health 2.2 (2022): e0000105.

Policy evaluation

Determined, Resilient, Empowered, AIDS-free, Mentored and Safe (DREAMS) was a PEPFAR-funded multicomponent intervention that sought to address the underlying causes of vulnerability to HIV infection, including by empowering adolescent girls and young women (AGYW) from 2016-18. These broad-based interventions difficult to evaluate. This multi-site study that included a SAPRIN nodes showed increased social support for AGYW with some impact on self-sufficiency.

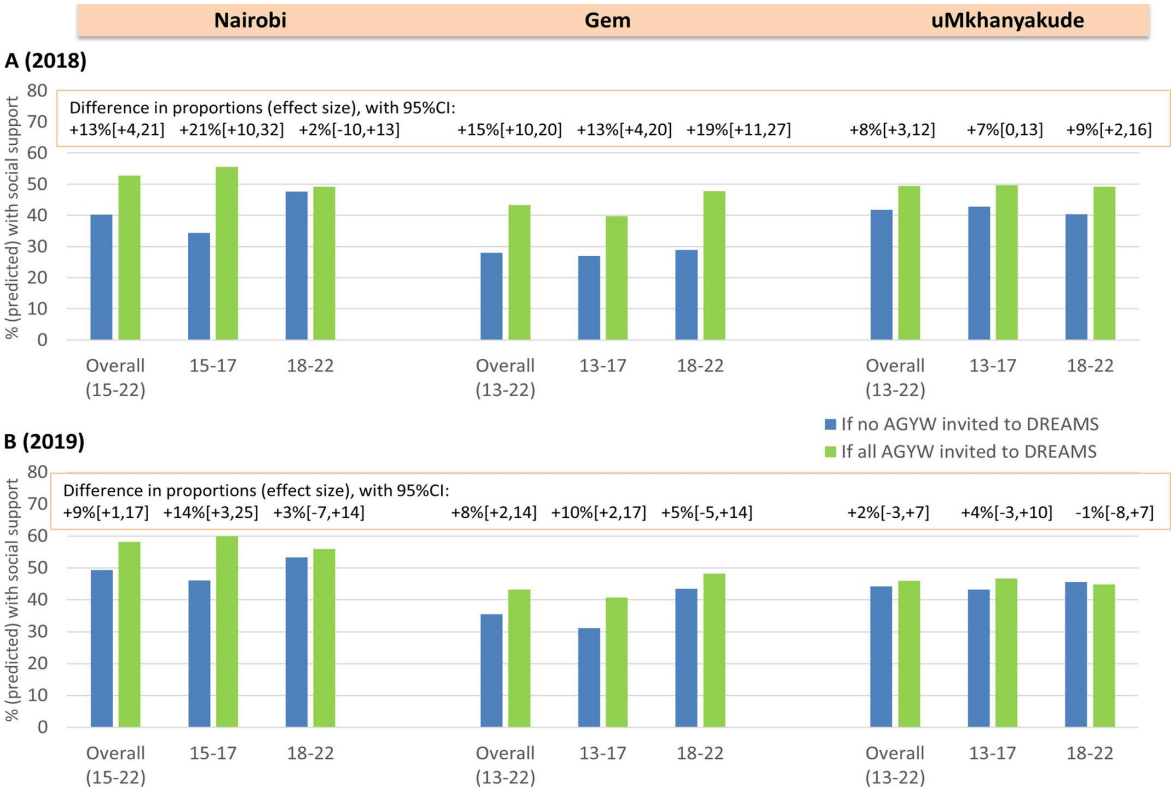


Figure 1 Predicted proportions who have social support in 2018 (A) and in 2019 (B) if no AGYW versus all AGYW were invited to DREAMS, overall and by age group at enrolment in three settings. AGYW, adolescent girls and young women; DREAMS, Determined, Resilient, Empowered, AIDS-free, Mentored and Safe.

Gourlay, Annabelle, et al. "Impact of the DREAMS Partnership on social support and general self-efficacy among adolescent girls and young women: causal analysis of population-based cohorts in Kenya and South Africa." *BMJ Global Health* 7.3 (2022): e006965.

4. Research on Non-communicable diseases and HIV

HIV & Hypertension – mortality risk

Houle showed that HIV and elevated blood pressure are acting as separate, non-interacting epidemics affecting high proportions of the older adult populations.

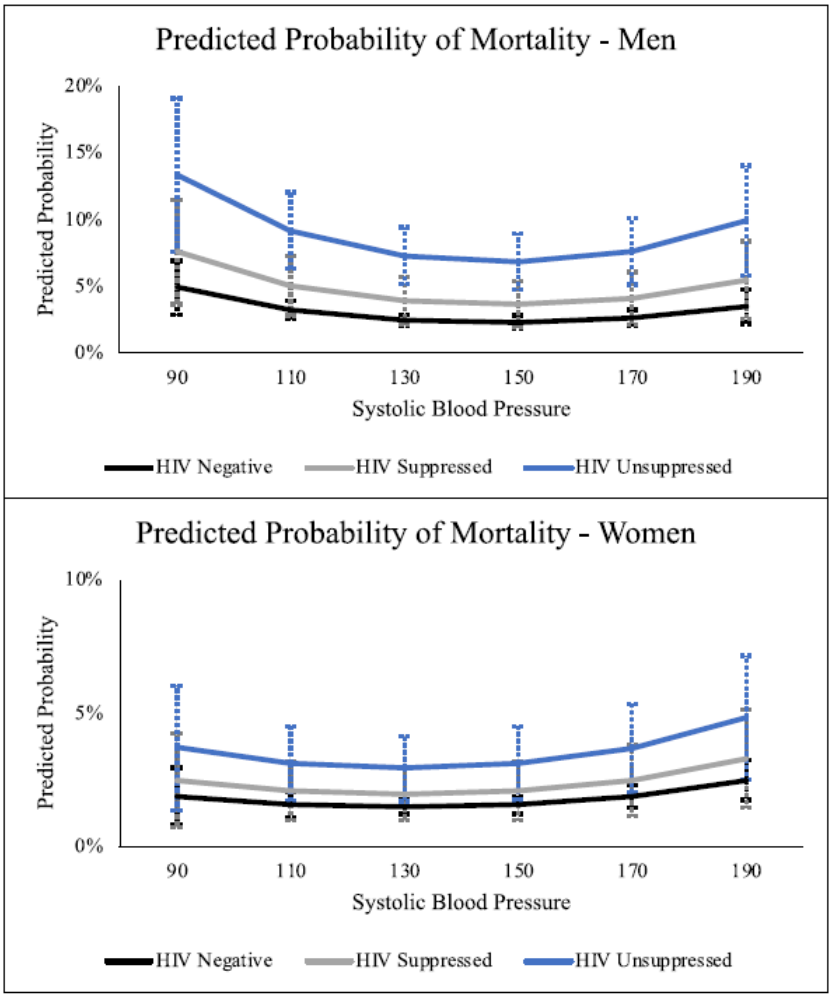
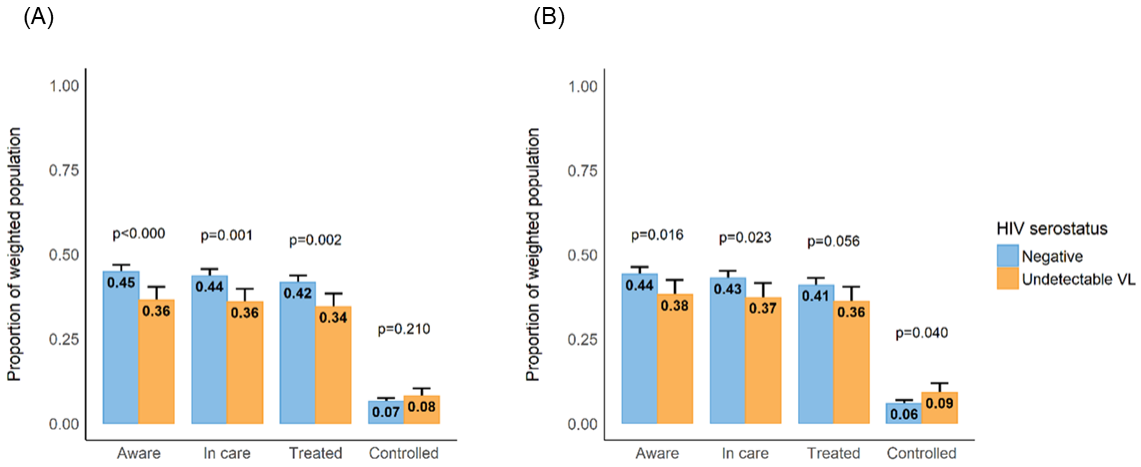


Fig. 2 Predicted probability of mortality by sex, HIV status and systolic blood pressure, Agincourt, South Africa, 2010-2018

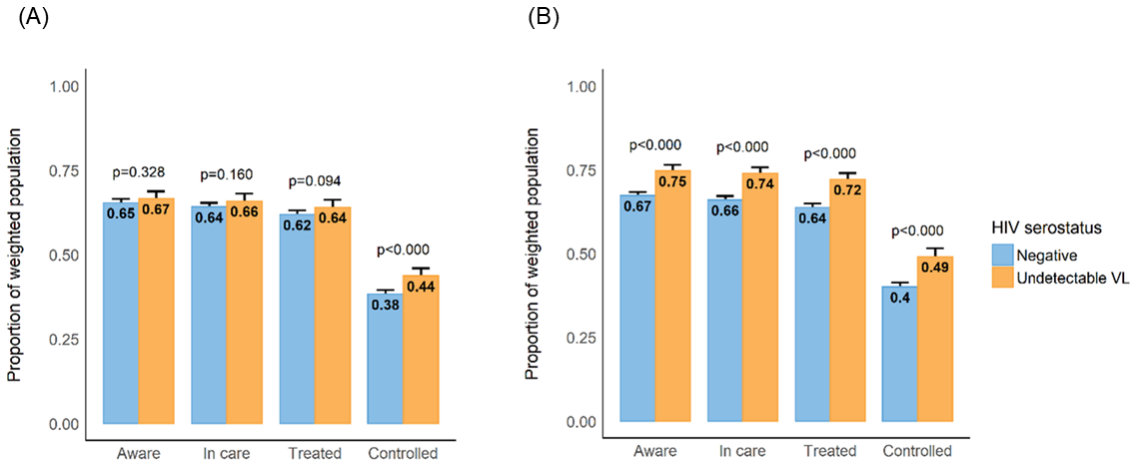
Houle, Brian, et al. "Twin epidemics: the effects of HIV and systolic blood pressure on mortality risk in rural South Africa, 2010-2019." BMC Public Health 22.1 (2022): 387.

Linkage to HIV care and hypertension and diabetes control

Magodoro found little evidence suggesting that engagement in HIV care is associated with substantial improvement in hypertension or diabetes care. Marginally higher awareness and enagemenet in care amongst individuals in HIV care compared to HIV negatives, whereas for diabetes the opposite was found.



The cascade of **diabetes care** among HIV negative versus HIV positive/successful ART adults in uMkhanyakude, KwaZulu-Natal, South Africa, according to HIV/ART status. **A.** Minimally adjusted diabetes care cascade. **B.** Fully adjusted diabetes care cascade.



The cascade of hypertension care among HIV negative versus HIV positive/successful ART adults in uMkhanyakude, KwaZulu-Natal, South Africa. A. Minimally adjusted hypertension care cascade. B. Fully adjusted hypertension care cascade.

Magodoro, Itai M., et al. "Linkage to HIV care and hypertension and diabetes control in rural South Africa: Results from the population-based Vukuzazi Study." PLOS Global Public Health 2.11 (2022): e0001221.

Tuberculosis and dysglycemia

Treated TB disease was not associated with dysglycemia in an HIV-endemic, rural South African population. However, Castle found a significant interaction between prior TB and HIV status among men, suggesting distinct pathophysiological mechanisms between the two infections that may impact glucose metabolism.

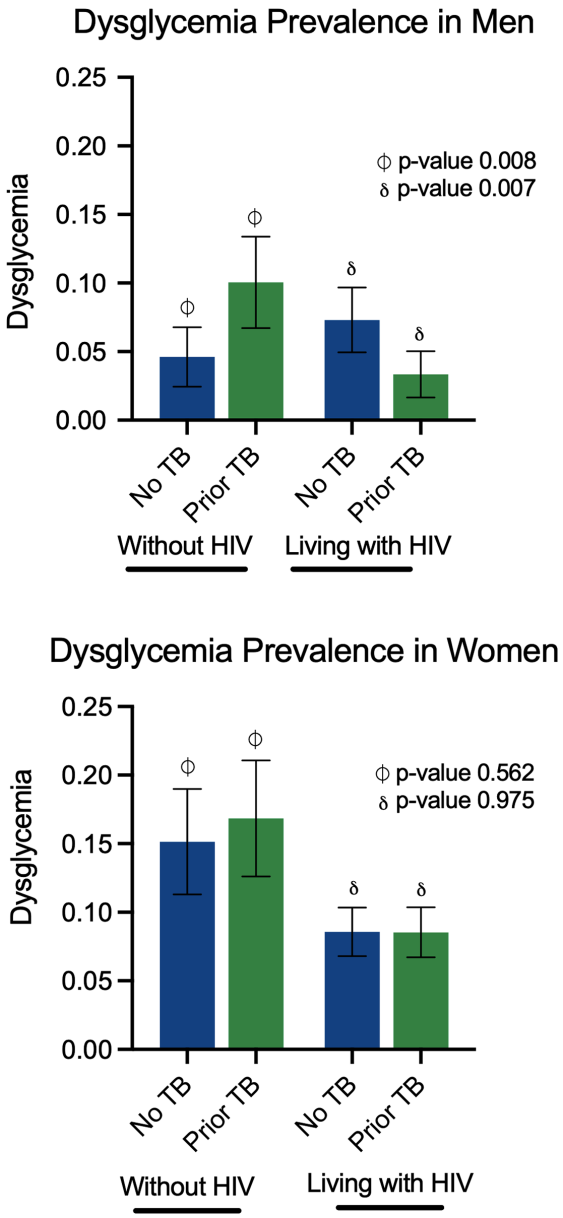


Fig 1. Prior TB and HIV interactions stratified by sex.

Among **men** without HIV (top), dysglycemia prevalence is higher in those with prior history of TB disease compared to men without prior TB. The inverse relationship was found in men living with HIV, where dysglycemia prevalence was lower in those with prior TB.

Women (bottom) did not have an association between HIV status, prior TB, and dysglycemia prevalence.

Castle, Alison C., et al. "Association between prior tuberculosis disease and dysglycemia within an HIV-endemic, rural South African population." Plos one 18.3 (2023): e0282371.

5. Research on Covid-19

Covid-19 Epidemiology

These to two papers in high impact journals shows the potential of an established population cohort to accommodate detailed epidemiological studies to provide accurate estimates of key epidemiological parameters.

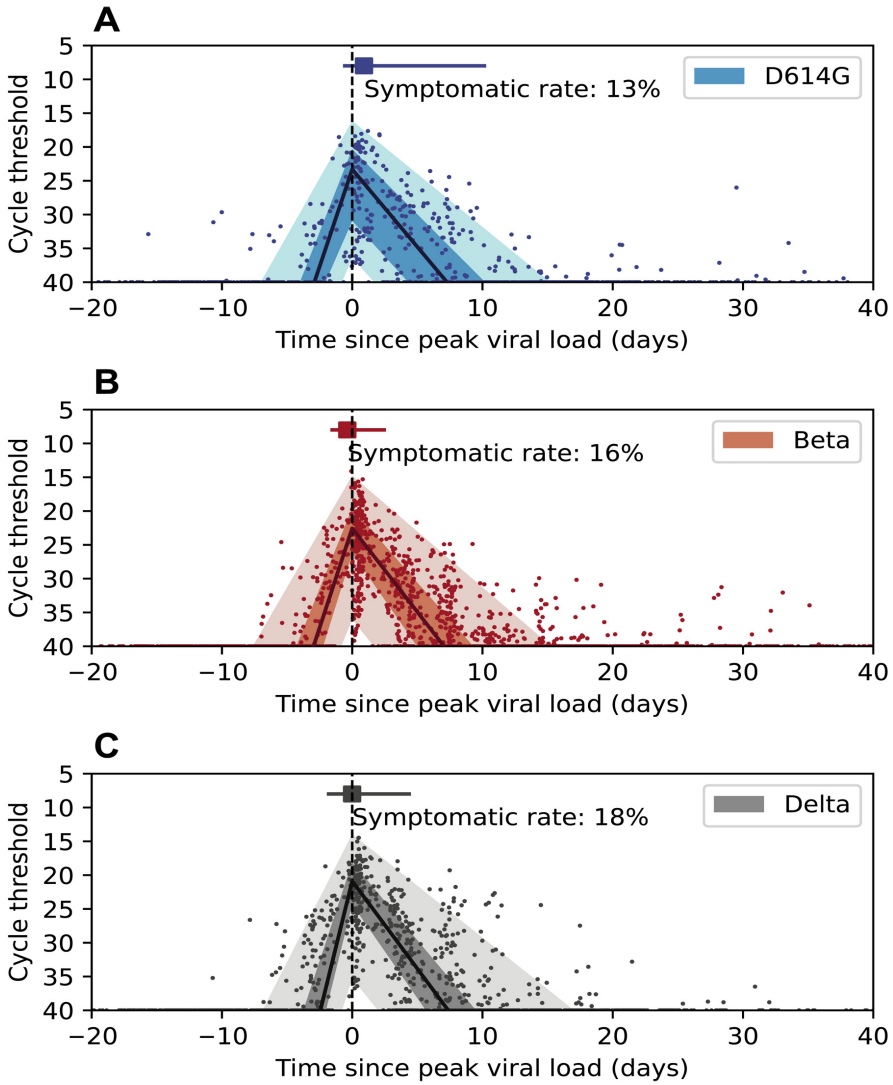


Fig. 2. SARS-CoV-2 shedding patterns by D614G, Beta, and Delta variants.

(A to C) Characterization of the RNA shedding kinetics for D614G (A), Beta (B), and Delta (C) infections. The solid dots are longitudinal Ct values observation for each infection episode, aligned based on the estimated timing of trough Ct. The solid line is the population median of all individual fits, the dark shade is the interquartile range, and the light shade is the 95% confidence interval (CI). Vertical dashed vertical line indicates the timing of peak viral load. The square marker and the horizontal line indicate the median time and interquartile range of symptom onset for symptomatic infections.

Cohen, Cheryl, et al. "SARS-CoV-2 incidence, transmission, and reinfection in a rural and an urban setting: results of the PHIRST-C cohort study, South Africa, 2020–21." The Lancet Infectious Diseases 22.6 (2022): 821-834.

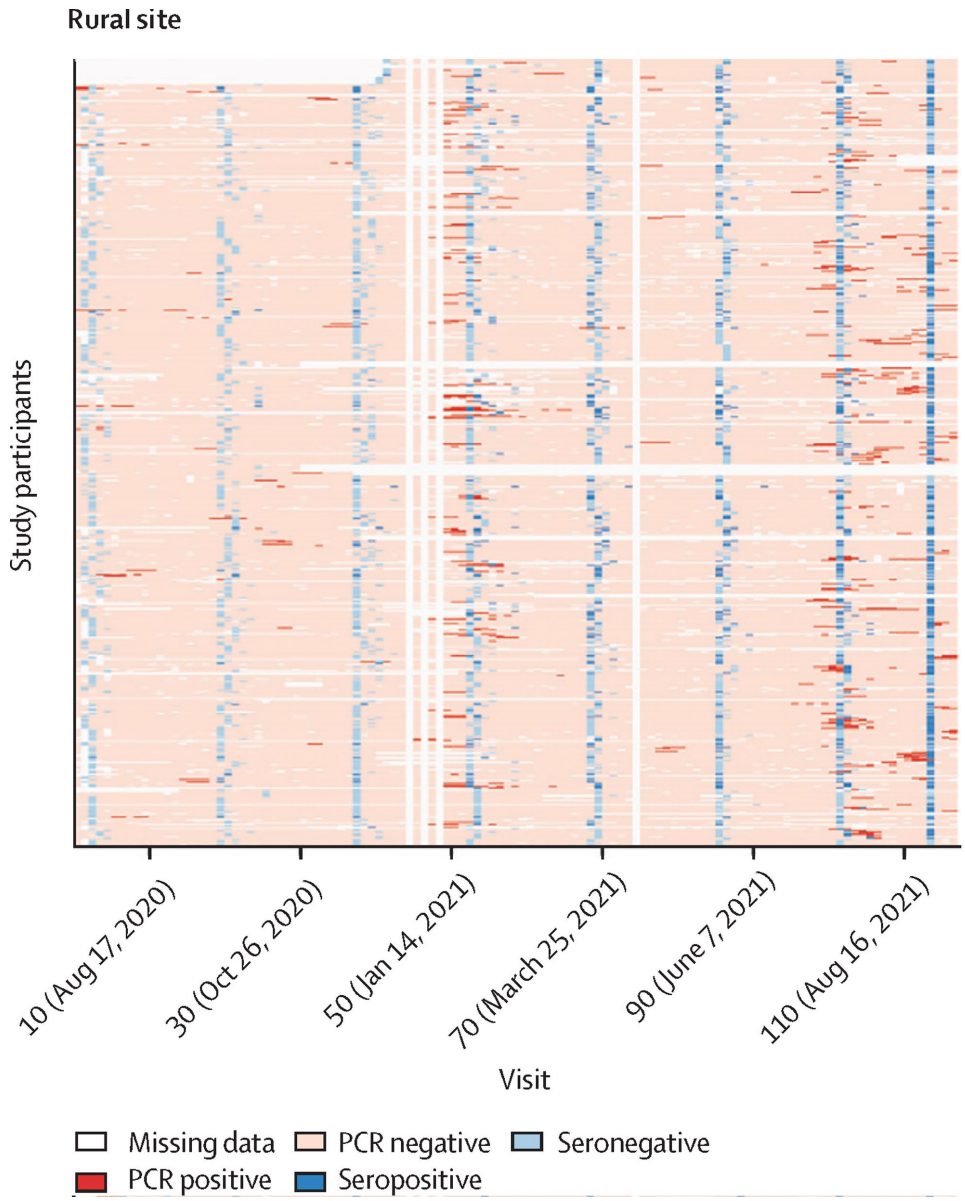


Figure 2. Results of serology and real-time RT-PCR among 1200 individuals (rural site, n=643)

Columns are individual follow-up visits and rows are individual participants. Individuals within the same household are numbered consecutively (appear below one another). Data were missing if no sample was tested. Cells at the time of serology blood draws are coloured according to the results of serology.

Sun, Kaiyuan, et al. "SARS-CoV-2 transmission, persistence of immunity, and estimates of Omicron's impact in South African population cohorts." Science Translational Medicine 14.659 (2022): eabo7081.

Covid-19 Vaccine hesitancy

This paper and other papers forthcoming from SAPRIN sites study Covid vaccine hesitancy and starting to pose the question whether the observed hesitancy has public health impact on the broader vaccine landscape, particularly childhood vaccinations.

Kahn, Kathleen, et al. "COVID-19 vaccine hesitancy in rural South Africa: Deepening understanding to increase uptake and access." Journal of Global Health 12 (2022).

Impact

These three papers explored the impact of the Covid-19 pandemic on residents and internal migrants, the sexual and reproductive health needs of school-going young people and from the perspectives of the community and health care workers.

Ginsburg, Carren, et al. "The impact of COVID-19 on a cohort of origin residents and internal migrants from South Africa's rural northeast." SSM-population health 17 (2022): 101049.

Chimbindi, Natsayi, et al. "The sexual and reproductive health needs of school-going young people in the context of COVID-19 in rural KwaZulu-Natal, South Africa." African Journal of AIDS Research 21.2 (2022): 162-170.

Lalla-Edward, Samanta T., et al. "Essential health services delivery in South Africa during COVID-19: Community and healthcare worker perspectives." Frontiers in Public Health 10 (2022).

6. Health of the Elderly

These three papers explored the impact of the Covid-19 pandemic on residents and internal migrants, the sexual and reproductive health needs of school-going young people and from the perspectives of the community and health care workers.

Table 2 Linear regression models predicting baseline cognitive function score, HAALSI, Agincourt subdistrict, Mpumalanga, South Africa, 2014–19, N=3771

		Change in baseline cognitive score per one-rung increase on the SSP ladder	
Model	**Adjustments**	**β**	**95% CI**
1	Age, age^2, sex, country of birth	0.300	0.244 to 0.356
2	Model 1+ socioeconomic and social factors*	0.210	0.156 to 0.264
3	Model 2+ health-related factors†	0.198	0.144 to 0.253

All models incorporate IPWs for mortality and attrition.
*Adjusted for model 1 covariates, plus socioeconomic and social factors (father's main job during childhood, education, literacy, marital status, employment status, household asset quintile).
†Adjusted for model 1 and 2 covariates, plus health-related factors (self-rated health today compared with 1 year ago, alcohol intake frequency, number of depressive symptoms, diabetes, hypertension).
HAALSI, Health and Ageing in Africa: A Longitudinal Study of an INDEPTH Community in South Africa; IPW, inverse probability weights; SSP, subjective social position.

Herl, Carlos Riumallo, et al. "Pension exposure and health: Evidence from a longitudinal study in South Africa." The Journal of the Economics of Ageing 23 (2022): 100411.

Socioeconomic resources and cognitive health

They found that household material resources may support cognitive health during aging. Greater improvements in resources over time were associated with better cognition. Results were driven by resources for cooking, transportation, and communication.

Table 3

Multivariable-adjusted associations between total household resources from 2001 to 2013 and cognitive function in 2014/2015, Agincourt sub-district, Mpumalanga, South Africa, n = 4580.

Quintile of total household resources	Cognitive function z-score (SD units)	
	Coef.	95% CI
Mean total household resources, 2001–2013		
1 (lowest)	Ref	–
2	0.058	(-0.012, 0.128)
3	0.162	(0.092, 0.231)
4	0.191	(0.120, 0.263)
5 (highest)	0.237	(0.163, 0.312)
p-value for linear trend		<0.0001
Volatility in total household resources, 2001–2013		
1 (lowest)	Ref	–
2	−0.025	(-0.094, 0.044)
3	−0.043	(-0.110, 0.024)
4	−0.091	(-0.163, −0.020)
5 (highest)	−0.021	(-0.098, 0.057)
p-value for linear trend		0.193
Change over time in total household resources, 2001–2013		
1 (lowest)	Ref	–
2	−0.016	(-0.085, 0.054)
3	−0.023	(-0.097, 0.052)
4	0.059	(-0.016, 0.134)
5 (highest)	0.122	(0.040, 0.205)
p-value for linear trend		0.001

Kobayashi, Lindsay C., et al. "Long-term household material socioeconomic resources and cognitive health in a population-based cohort of older adults in rural northeast South Africa, 2001–2015." SSM-Population Health 20 (2022): 101263.

Subjective social position and cognitive function

Subjective Social Position was positively associated with baseline cognitive score (adjusted β=0.198 points per ladder rung increase) and follow-up cognitive score (adjusted β=0.078 points per ladder rung increase).

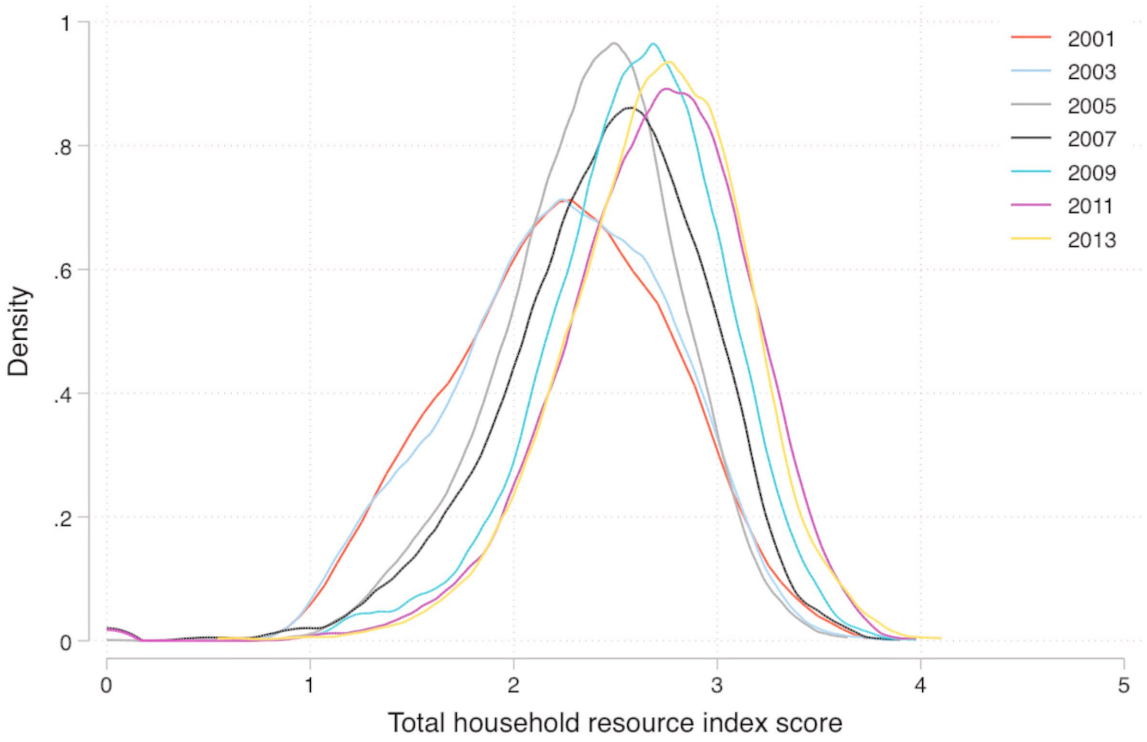


Fig. 1. Kernel density plot of total household resource score (possible range: 0-5) from 2001 through 2013, Agincourt sub-district, Mpumalanga, South Africa, n=4,580.

Pension exposure and health

The results show that pension exposure is associated with better health as measured by a set of health indices. Disentangling these effects, they find that pension exposure is most likely to improve health through the delayed onset of physical disabilities in the elderly population.

Association Between Old Age Grant Exposure and Three Composite Health Indices.

	(1)	(2)	(3)
	Health status index	Functionality index	PVW Health status index
Panel A			
Log[Exposure to pensions + 1]	0.058*	0.086***	0.062***
	(0.023)	(0.023)	(0.018)
Panel B			
Pension exposure: 1–5 years	0.114**	0.109***	0.087**
	(0.035)	(0.031)	(0.028)
Pension exposure: 6–10 years	0.147**	0.137**	0.098**
	(0.045)	(0.044)	(0.035)
Pension exposure: More than 10	0.123	0.182*	0.070
	(0.068)	(0.071)	(0.053)
Observations	9,192	9,192	9,192

Estimates from OLS regressions controlling for gender specific quadratic age functions, marital status, birthplace and education controls. Individual clustered standard errors in parenthesis. All three indices- *health status, functionality, and PVW health status*- were constructed such that higher values imply better health.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

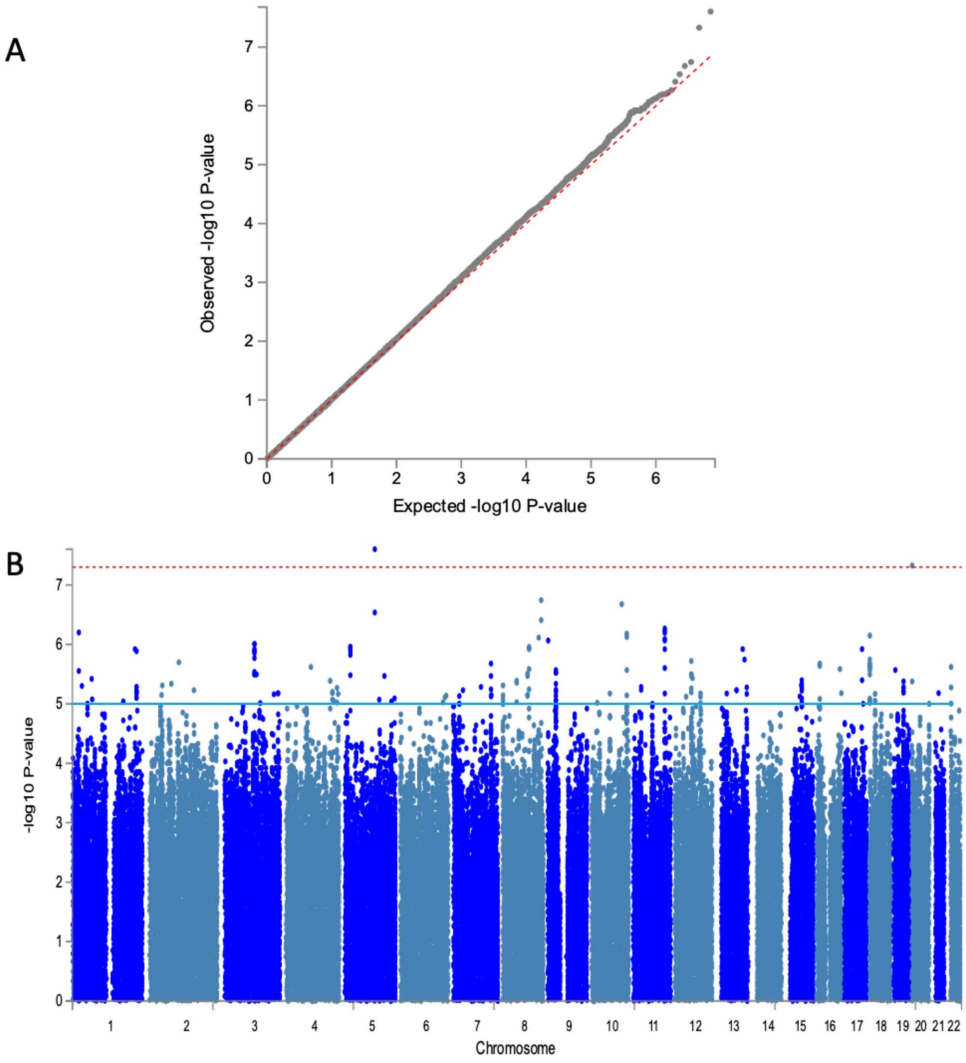
Kobayashi, Lindsay C., et al. "Subjective social position and cognitive function in a longitudinal cohort of older, rural South African adults, 2014–2019." J Epidemiol Community Health 76.4 (2022): 385-390.

7. Population Genetics

These three papers incorporate results from the AWIGEN study in Agincourt and DIMAMO by Michele Ramsay.

Apolipoprotien L1 High-Risk Genotypes

APOL1 G1 and G2 alleles and high-risk genotype frequencies differed between and within West and South Africa and were almost absent from East Africa. APOL1 risk variants were associated with albuminuria but not eGFR ,60 ml/min per 1.73 m2.



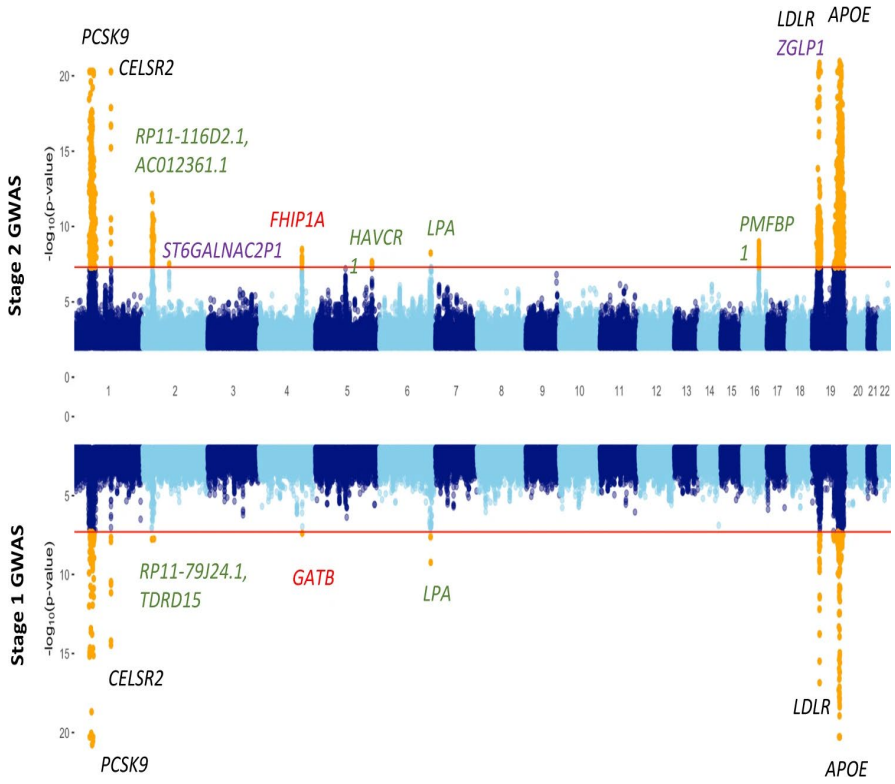
A QQ-plot for the combined dataset GIF = 0.997.

B Manhattan plot showing the −log10-transformed two-tailed P-value of each SNP from the GWAS for Mean-Max cIMT on the Y-axis and base-pair positions along the chromosomes on the X-axis. Adjustment was made for age, sex and 8 PCs. The red line indicates Bonferroni-corrected genome-wide significance (p < 5E-08); the blue line indicates the threshold for suggestive association (p < 1E-05).

Brandenburg, Jean-Tristan, et al. "Apolipoprotein L1 High-Risk Genotypes and Albuminuria in Sub-Saharan African Populations." Clinical Journal of the American Society of Nephrology 17.6 (2022): 798-808.

Lipid Traits

Polygenic risk score analysis shows increased predictive accuracy for LDL-C levels with the narrowing of genetic distance between the discovery dataset and our cohort. Novel discovery is enhanced with the inclusion of African data.



Miami plot showing summary data for

Stage 1 GWAS (AWI-Gen, downward facing, N = 10,603) and

Stage 2 GWAS (meta-analysis of AWI-Gen and four African cohorts, upward facing, N = 23,718).

The red horizontal lines show the genome-wide significance threshold (5 × 10−8) and SNPs with P-values below this threshold are shown in orange.

The loci corresponding to the region showing novel association in Stage 1 and Stage 2 GWAS are indicated in **red**.

Other possible novel loci that reached genome-wide significance only in the Stage 2 analysis are shown in **purple**.

Choudhury, Ananyo, et al. "Meta-analysis of sub-Saharan African studies provides insights into genetic architecture of lipid traits." nature communications 13.1 (2022): 2578.

Carotid intima-media thickness link to atherosclerosis

The study found significant enrichment for genes involved in oestrogen response from female-specific signals. The genes identified show biological relevance to atherosclerosis and/or CVDs, sex-differences and transferability of signals from non-African studies.

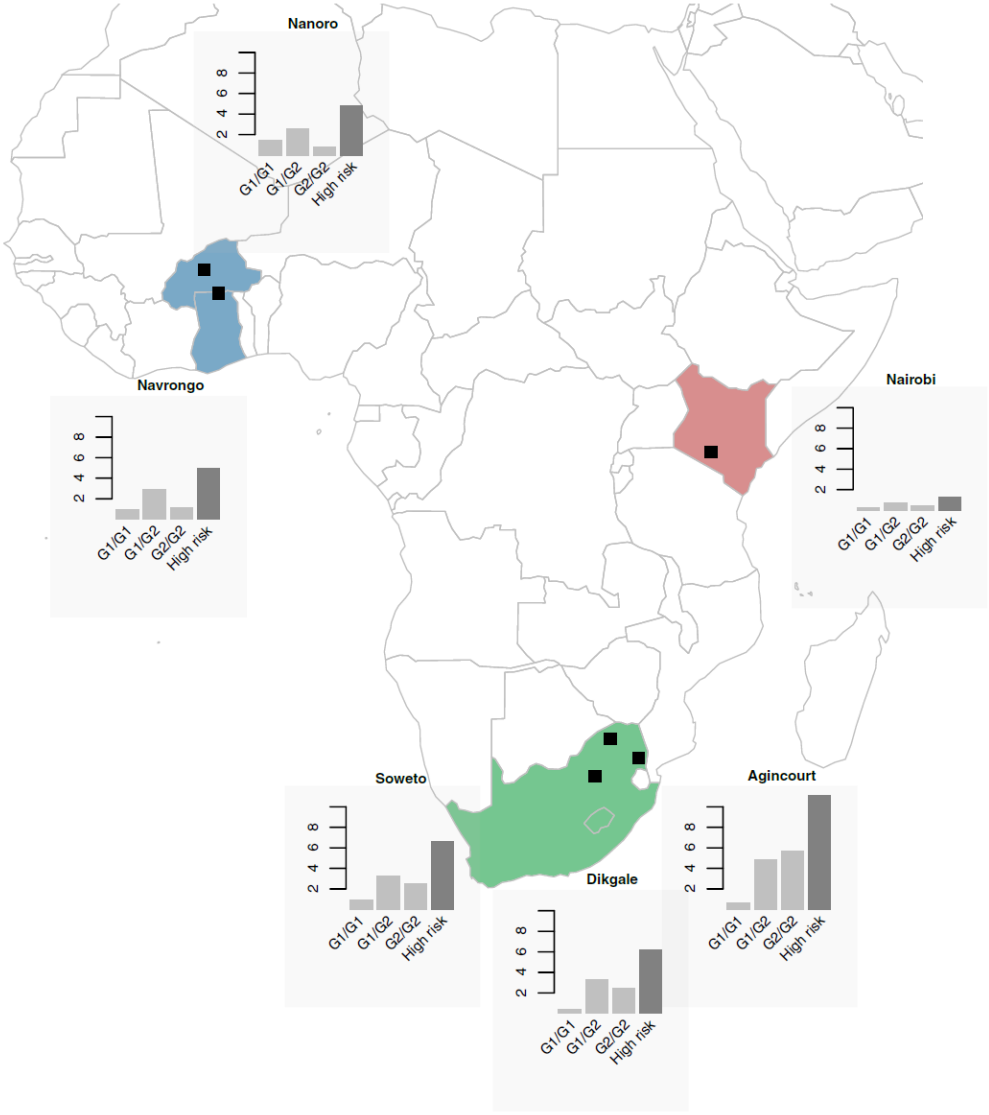


Figure 1. | Combined "high-risk" genotype frequencies are highest in West Africa or South Africa and lowest in East Africa, with distinct differences with regard to the G1/G1, G1/G2 and G2/G2 genotypes across regions. *APOL1* genotype (G1/G1, G1/G2, and G2/G2) frequencies (percentages) and combined "high-risk" genotypes (G1/G1, G1/G2, and G2/G2) for each sub-Saharan African region: Nanoro and Navrongo in West Africa; Nairobi in East Africa; and Soweto, Dikgale, and Agincourt study sites in South Africa.

Boua, Palwende Romuald, et al. "Genetic associations with carotid intima-media thickness link to atherosclerosis with sex-specific effects in sub-Saharan Africans." Nature communications 13.1 (2022): 855.