SUPPLEMENTARY MATERIAL FOR ADDITIONAL RESULTS

Head-to-head comparison of the WHO STEPwise approach with immediate unattended and delayed unattended automated blood pressure measurements during household-based screening: a diagnostic accuracy study in Lesotho

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Contents

Table S1. Comparison of correlation coefficients of the screening measurements.

BP measurement	Systolic		Diastolic	
	Correlation with 24h-ABPM	P*	Correlation with 24h-ABPM	P*
Average 24h-ABPM				
SBPM	0·73(0·67 to 0·78)	-	0·67(0·60 to 0·73)	-
1st uABP	0·81(0·76 to 0·85)	0·0012	0·72(0·66 to 0·77)	0·13
2nd uABP	0·80(0·75 to 0·84)	0·011	0·69(0·63 to 0·75)	0·60
Daytime ABPM				
SBPM	0·70(0·64 to 0·76)	-	0·66(0·59 to 0·73)	-
1st uABP	0·81(0·76 to 0·84)	<0·0001	0·73(0·67 to 0·78)	0·024
2nd uABP	0·80(0·76 to 0·84)	0·00030	0·69(0·63 to 0·75)	0·44
Nighttime ABPM				
SBPM	0·61(0·53 to 0·68)	-	0·57(0·48 to 0·64)	-
1st uABP	0·68(0·61 to 0·74)	0·025	0·62(0·54 to 0·68)	0·18
2nd uABP	0·69(0·63 to 0·75)	0·015	0·59(0·50 to 0·66)	0·66

BP: Blood pressure;

24h-ABPM: 24-hour ambulatory blood pressure monitor;

SBPM: standard blood pressure measurement; uABP: unattended blood pressure.

**P is for test of difference between correlation coefficients. Correlation coefficient of SBPM with 24h-ABPM is compared with those of both uABPs with24h-ABPM.*

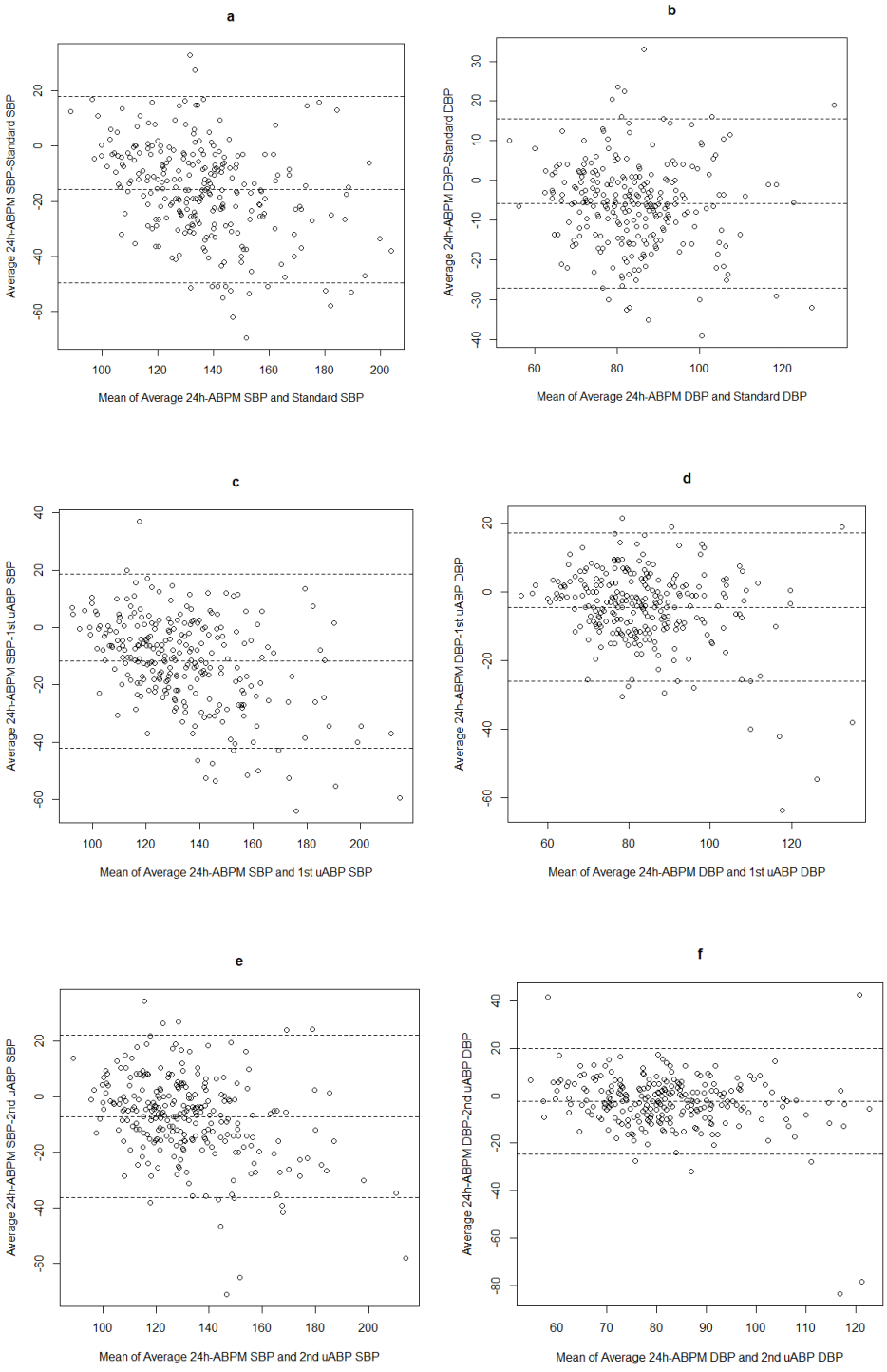


Figure S1. Bland-Altman plots showing levels of agreement between the three screening measurements and average ambulatory blood pressure monitor (24h-ABPM).

(a, c, e) show average 24h-ABPM systolic blood pressure (SBP) vs SBP of standard BP, 1st uABP and 2nd uABP respectively. **(b, d, f)** show average 24h-ABPM diastolic blood pressure (DBP) vs DBP of survey screen BP, 1st uABP and 2nd uABP respectively.

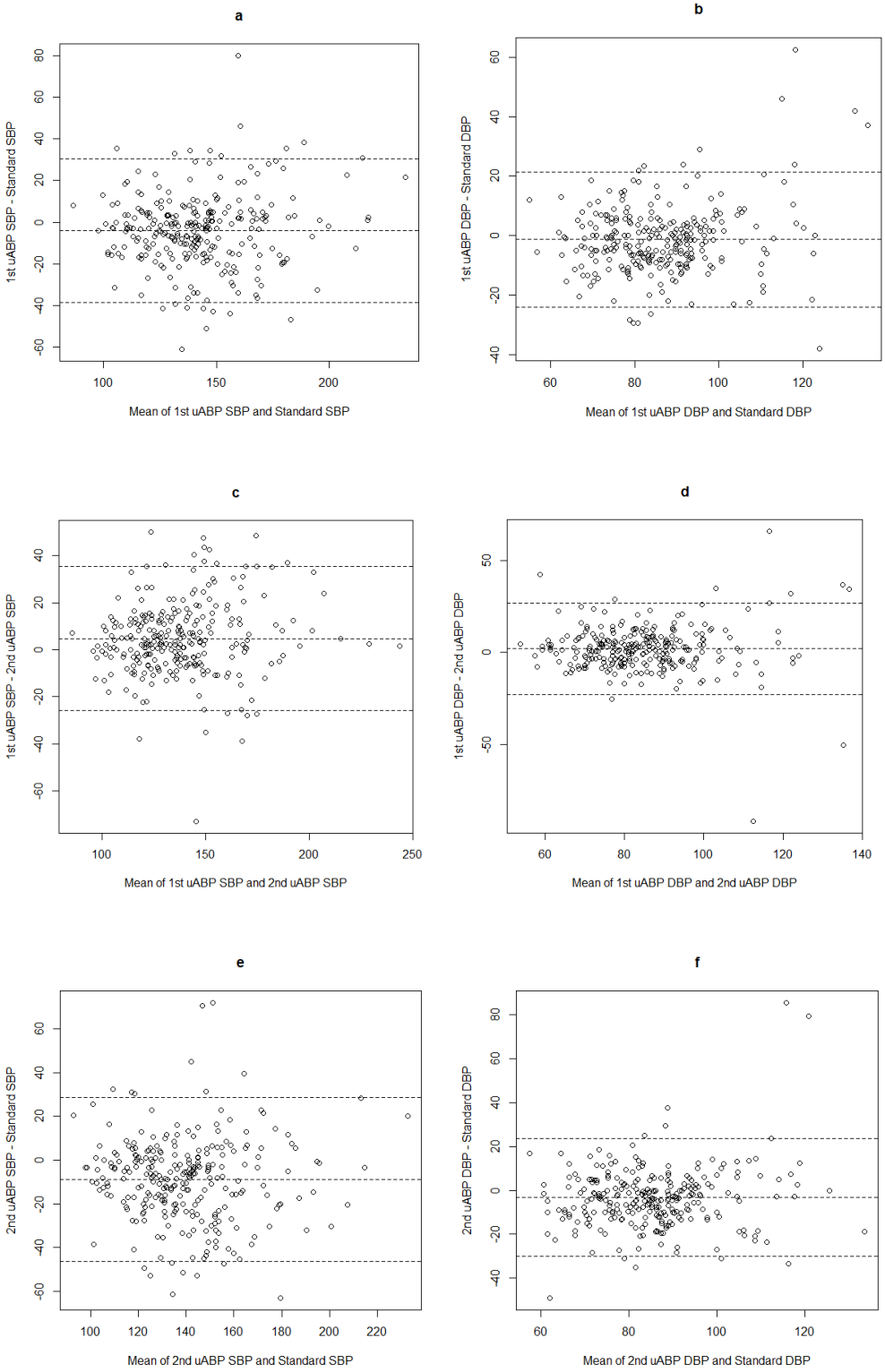


Figure S2. Bland-Altman plots showing levels of agreement among the three screening measurements.

(a, c, e) show systolic blood pressure (SBP) of 1st uABP vs standard; 1st uABP vs 2nd uABP; and 2nd uABP vs standard respectively. **(b, d, f)** show diastolic blood pressure (DBP) of 1st uABP vs standard; 1st uABP vs 2nd uABP; and 2nd uABP vs standard respectively

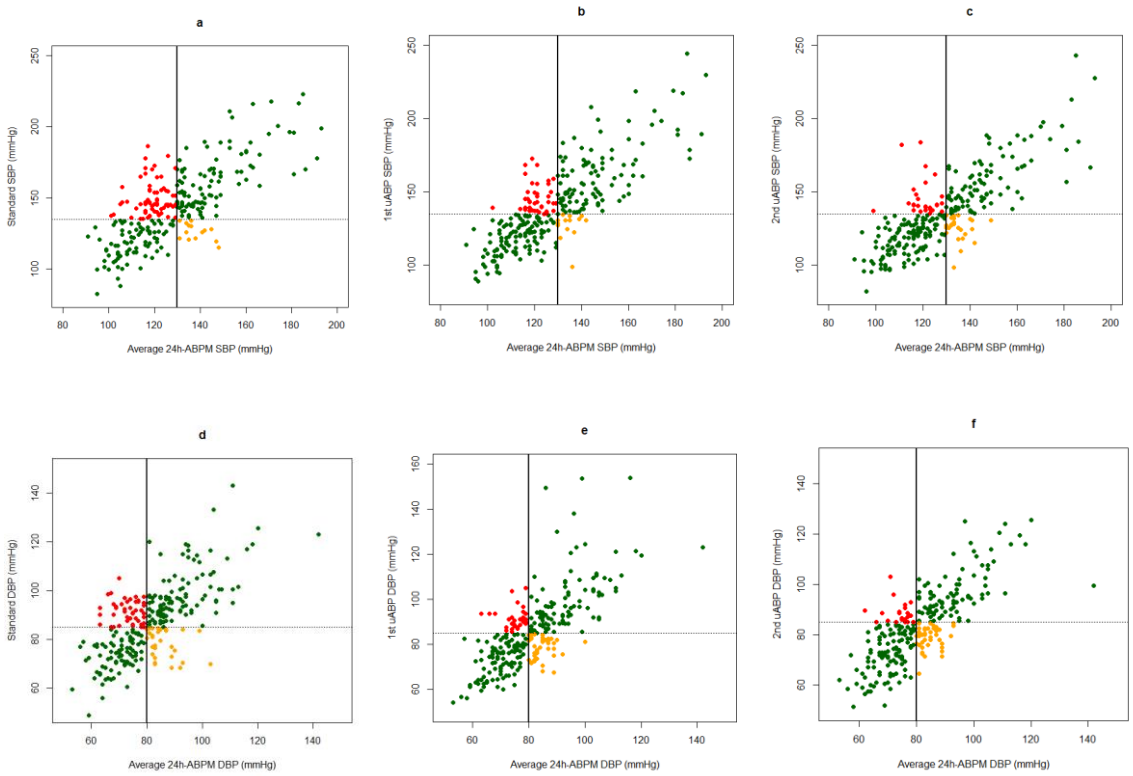


Figure S3. Scatter plot of average ambulatory blood pressure monitor (24-ABPM) vs standard BP, 1st unattended BP (uABP) and 2nd (uABP).

(a-c) show average 24h-ABPM systolic blood pressure (SBP) vs SBP of standard BP, 1st uABP and 2nd uABP respectively, using the cut off ≥ 135 mmHg . **(d-f)** show average 24h-ABPM diastolic blood pressure (DBP) vs DBP of standard BP, 1st uABP and 2nd uABP respectively, using the cut off ≥ 85 mmHg.

Black solid line is BP threshold for average 24h-ABPM (130 mmHg systolic, 80 mmHg diastolic); dash line is BP Threshold for screening measurements (135 mmHg systolic, 85 mmHg diastolic).Green colour- BP measurements match gold standard. Orange colour- masked hypertension. Red colour- white coat hypertension.

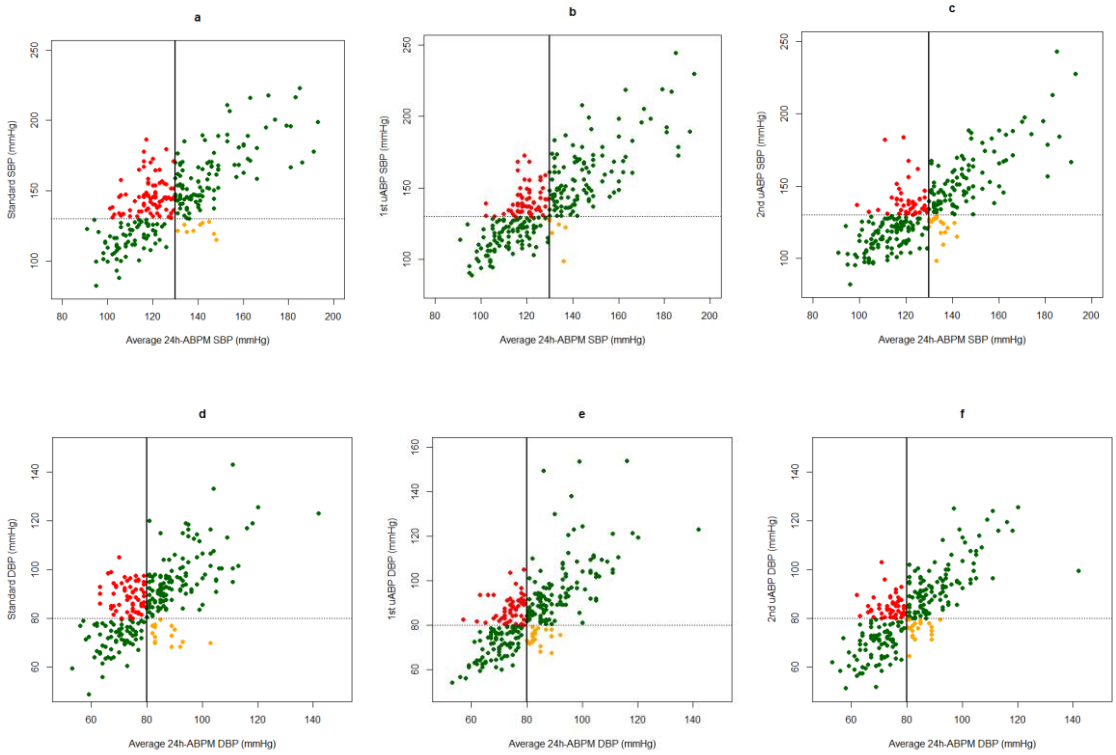


Figure S4. Scatter plot of average ambulatory blood pressure monitor (24-ABPM) vs standard BP, 1st unattended BP (uABP) and 2nd (uABP).

(a-c) show average 24h-ABPM systolic blood pressure (SBP) vs SBP of standard BP, 1st uABP and 2nd uABP respectively, using the cut off ≥ 130 mmHg . **(d-f)** show average 24h-ABPM diastolic blood pressure (DBP) vs DBP of standard BP, 1st uABP and 2nd uABP respectively, using the cut off ≥ 80 mmHg.

Black solid line is BP threshold for average 24h-ABPM (130 mmHg systolic, 80 mmHg diastolic); dash line is BP Threshold for screening measurements (130 mmHg systolic, 80 mmHg diastolic).Green colour- BP measurements match gold standard. Orange colour- masked hypertension. Red colour- white coat hypertension.

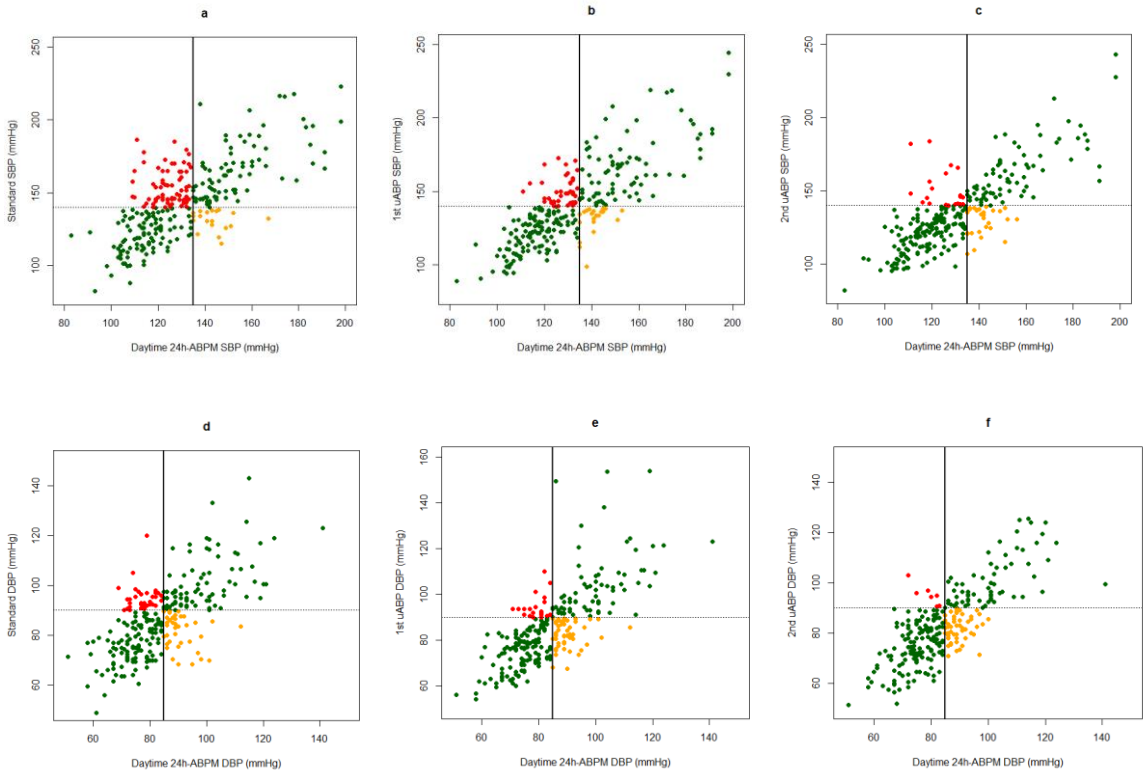


Figure S5. Scatter plot of daytime ambulatory blood pressure monitor (24-ABPM) vs standard BP, 1st unattended BP (uABP) and 2nd (uABP).

(a-c) show daytime 24h-ABPM systolic blood pressure (SBP) vs SBP of standard BP, 1st uABP and 2nd uABP respectively, using the cut off ≥ 140 mmHg . **(d-f)** show daytime 24h-ABPM diastolic blood pressure (DBP) vs DBP of standard BP, 1st uABP and 2nd uABP respectively, using the cut off ≥ 90 mmHg.

Black solid line is BP threshold for Daytime 24h-ABPM (135mmHg systolic, 85mmHg diastolic); dash line is BP Threshold for screening measurements (140 mmHg systolic, 90 mmHg diastolic).Green colour- BP measurements match gold standard. Orange colour- masked hypertension. Red colour- white coat hypertension

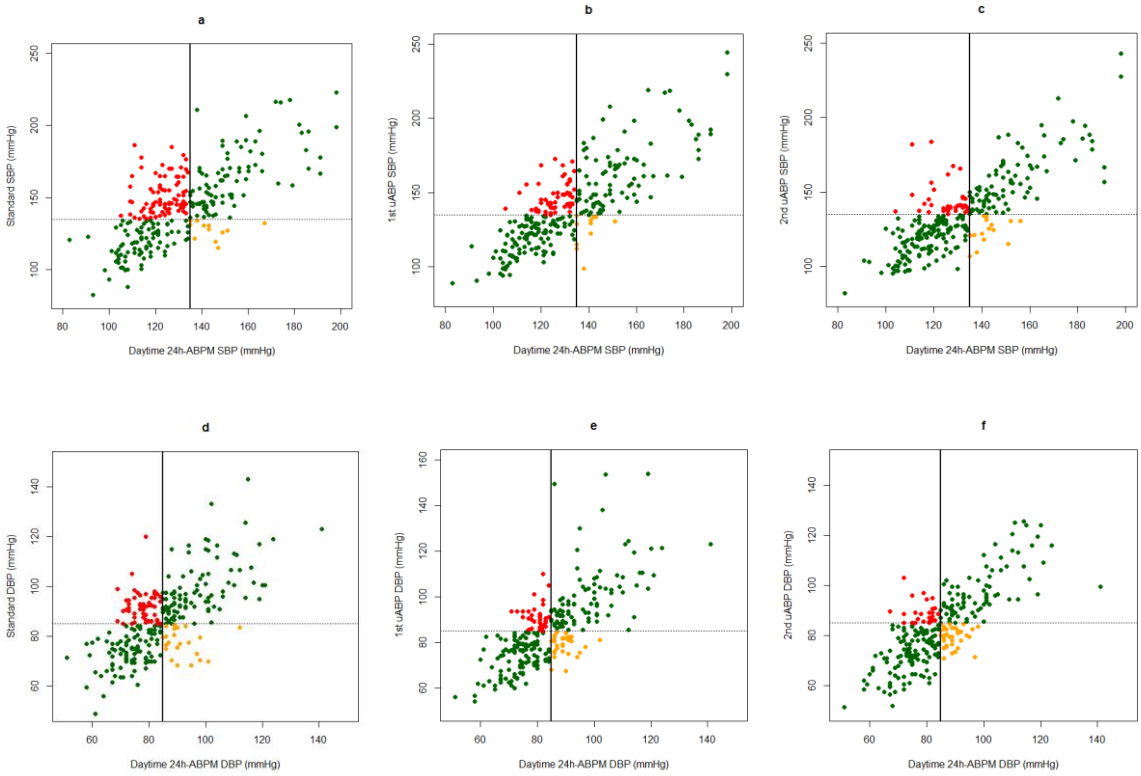


Figure S6. Scatter plot of daytime ambulatory blood pressure monitor (24-ABPM) vs standard BP, 1st unattended BP (uABP) and 2nd (uABP).

(a-c) show daytime 24h-ABPM systolic blood pressure (SBP) vs SBP of standard BP, 1st uABP and 2nd uABP respectively, using the cut off ≥ 135 mmHg . **(d-f)** show daytime 24h-ABPM diastolic blood pressure (DBP) vs DBP of standard BP, 1st uABP and 2nd uABP respectively, using the cut off ≥ 85 mmHg.

Black solid line is BP threshold for Daytime 24h-ABPM (135mmHg systolic, 85mmHg diastolic); dash line is BP Threshold for screening measurements (135 mmHg systolic, 85 mmHg diastolic).Green colour- BP measurements match gold standard. Orange colour- masked hypertension. Red colour- white coat hypertension

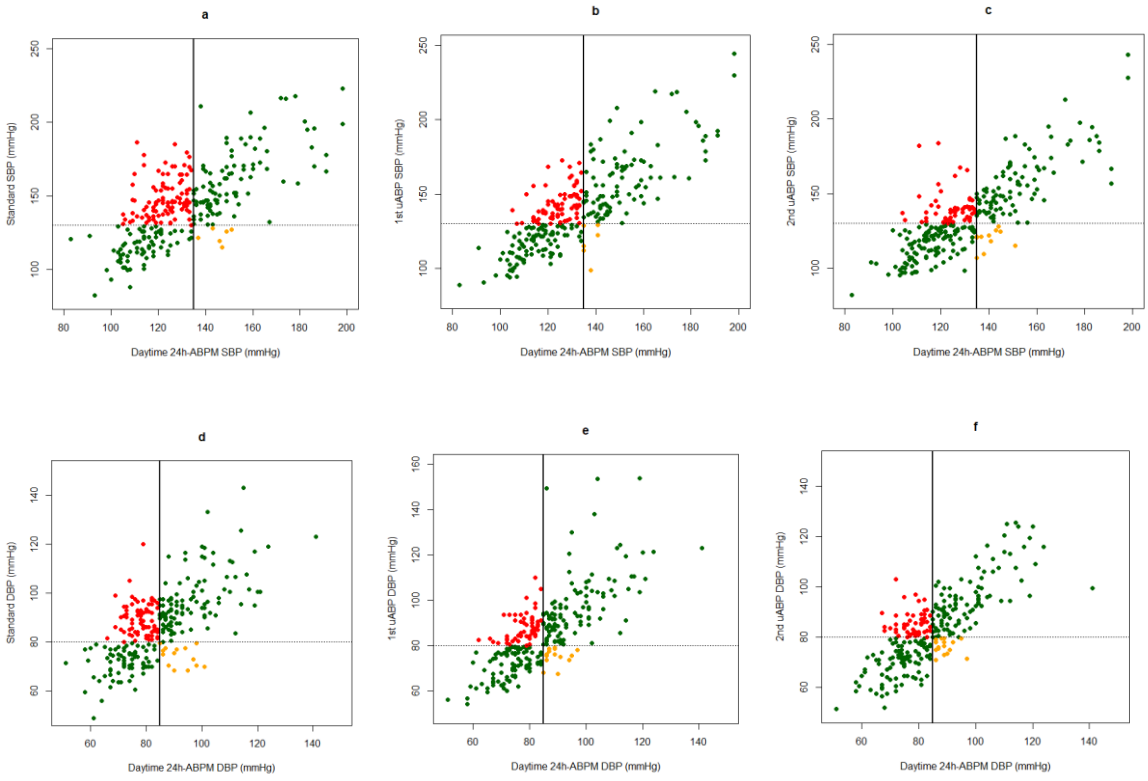
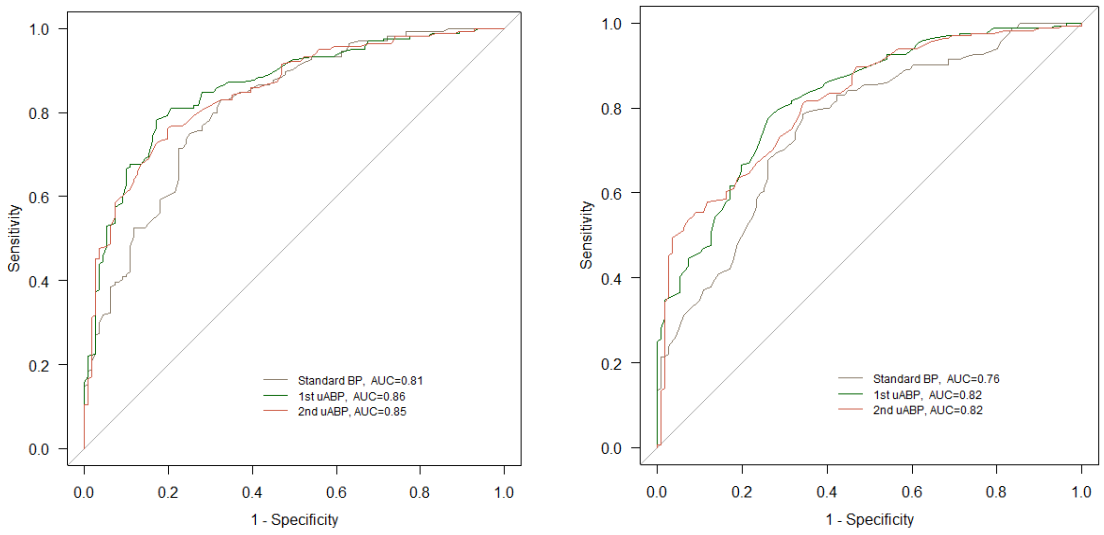


Figure S7. Scatter plot of daytime ambulatory blood pressure monitor (24-ABPM) vs standard BP, 1st unattended BP (uABP) and 2nd (uABP).

(a-c) show daytime 24h-ABPM systolic blood pressure (SBP) vs SBP of standard BP, 1st uABP and 2nd uABP respectively, using the cut off ≥ 130 mmHg . **(d-f)** show daytime 24h-ABPM diastolic blood pressure (DBP) vs DBP of standard BP, 1st uABP and 2nd uABP respectively, using the cut off ≥ 80 mmHg.

Black solid line is BP threshold for Daytime 24h-ABPM (135mmHg systolic, 85mmHg diastolic); dash line is BP Threshold for screening measurements (130 mmHg systolic, 80 mmHg diastolic).Green colour- BP measurements match gold standard. Orange colour- masked hypertension. Red colour- white coat hypertension

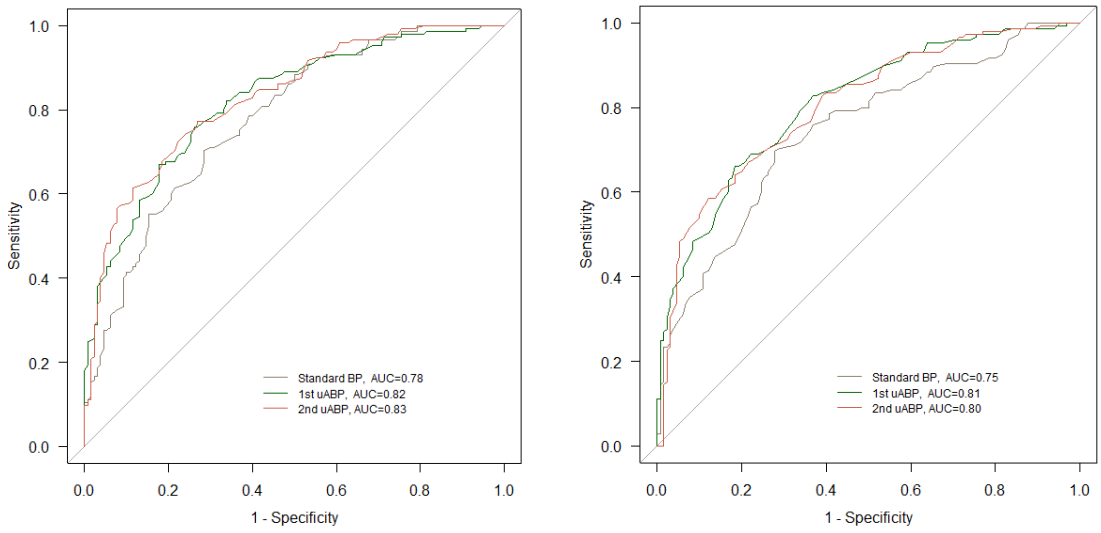


(a) (b)

Figure S8. ROC curve using average 24h-ABPM (≥130/80 mmHg) as reference.

a) Reference vs systolic values of standard BP, 1st uABP, and 2nd uABP. *P*= 0.047 for AUC difference between 1st uABP and standard BP; *P*= 0.18 for AUC difference between 2nd uABP and standard BP; *P*= 0.65 for AUC difference between 1st uABP and 2nd uABP;
b) Reference vs diastolic values of standard BP, 1st uABP, and 2nd uABP. *P*= 0.011 for AUC difference between 1st uABP and Screen BP; *P*= 0.048 for AUC difference between 2nd uABP and Screen BP; *P*= 0.87 for AUC difference between 1st uABP and 2nd uABP.

ROC= receiver operating characteristics; AUC= area under the curve; uABP= unattended blood pressure; 24h-ABPM= 24 hour ambulatory blood pressure monitoring.



(a) (b)

Figure S9. ROC curve using daytime 24h-ABPM (≥135/85 mmHg) as reference.

a) Reference vs systolic values of standard BP, 1st uABP, and 2nd uABP. *P*= 0.067 for AUC difference between 1st uABP and standard BP; *P*= 0.046 for AUC difference between 2nd uAOBP and standard BP; *P*= 0.65 for AUC difference between 1st uABP and 2nd uABP;
b) Reference vs diastolic values of standard BP, 1st uABP, and 2nd uABP. *P*= 0.012 for AUC difference between 1st uABP and standard BP; *P*= 0.043 for AUC difference between 2nd uABP and standard BP; *P*= 0.87for AUC difference between 1st uABP and 2nd uABP.

ROC= receiver operating characteristics; AUC= area under the curve; uABP= unattended blood pressure; 24h-ABPM= 24 hour ambulatory blood pressure monitoring.

Table S2. Diagnostic categories at 140 mmHg systolic and 90 mmHg diastolic cut offs for screening measurements, using average 24h-ABPM thresholds (130 mmHg systolic, 80 mmHg diastolic) as reference.

Category	Systolic			Diastolic		
	Standard BP N(%)	1st uABP N(%)	2nd uABP N(%)	Standard BP N(%)	1st uABP N(%)	2nd uABP N(%)
White coat hypertension	55(20)	27(9.8)	18(6.5)	30(10.9)	19(6.9)	6(2.2)
Masked hypertension	21(7.6)	25(9.1)	44(16)	52(18.9)	68(24.7)	70(25.5)
Sustained hypertension	99(36)	95(34.5)	76(27.6)	89(32.4)	73(26.5)	71(25.8)
Sustained normotension	100(36.4)	128(46.5)	137(49.8)	104(37.8)	115(41.8)	128(46.5)

BP= Blood pressure; uABP= unattended blood pressure; 24h-ABPM= 24 hour ambulatory blood pressure monitor

Table S3. Diagnostic categories at 135 mmHg systolic and 85 mmHg diastolic cut offs for screening measurements, using average 24h-ABPM thresholds (130 mmHg systolic, 80 mmHg diastolic) as reference

Category	Systolic			Diastolic		
	Standard BP N(%)	1st uABP N(%)	2nd uABP N(%)	Standard BP N(%)	1st uABP N(%)	2nd uABP N(%)
White coat hypertension	69(25.1)	42(15.3)	29(10.5)	46(16.7)	30(10.9)	22(8.0)
Masked hypertension	15(5.5)	15(5.5)	28(10.2)	32(11.6)	40(14.5)	49(17.8)
Sustained hypertension	105(38.2)	105(38.2)	92(33.5)	109(39.6)	101(36.7)	92(33.5)
Sustained normotension	86(31.3)	113(41.1)	126(45.8)	88(32.0)	104(37.8)	112(40.7)

BP= Blood pressure; uABP= unattended blood pressure; 24h-ABPM= 24 hour ambulatory blood pressure monitor

Table S4. Diagnostic categories at 130 mmHg systolic and 80 mmHg diastolic cut offs for screening measurements, using average 24h-ABPM thresholds (130 mmHg systolic, 80 mmHg diastolic) as reference

Category	Systolic			Diastolic		
	Standard BP N(%)	1st uABP N(%)	2nd uABP N(%)	Standard BP N(%)	1st uABP N(%)	2nd uABP N(%)
White coat hypertension	84(30.5)	59(21.5)	46(16.7)	61(22.2)	50(18.2)	48(17.5)
Masked hypertension	10(3.6)	6(2.2)	19(6.9)	17(6.2)	22(8.0)	24(8.7)
Sustained hypertension	110(40.0)	114(41.5)	101(36.7)	124(45.1)	119(43.3)	117(42.5)
Sustained normotension	71(25.8)	96(34.9)	109(36.9)	73(26.5)	84(30.5)	86(31.3)

BP= Blood pressure; uABP= unattended blood pressure; 24h-ABPM= 24 hour ambulatory blood pressure monitor

Table S5. Diagnostic categories at 140 mmHg systolic and 90 mmHg diastolic cut offs for screening measurements, using daytime 24h-ABPM thresholds (135 mmHg systolic, 85 mmHg diastolic) as reference

Category	Systolic			Diastolic		
	Standard BP N(%)	1st uABP N(%)	2nd uABP N(%)	Standard BP N(%)	1st uABP N(%)	2nd uABP N(%)
White coat hypertension	71(25.8)	41(14.9)	20(7.3)	35(12.7)	20(7.3)	9(3.3)
Masked hypertension	19(6.9)	21(7.6)	28(10.2)	42(15.3)	54(19.6)	58(21.1)
Sustained hypertension	83(30.2)	81(29.5)	74(26.9)	84(30.5)	72(26.2)	68(24.7)
Sustained normotension	102(37.1)	132(48.0)	153(55.6)	114(41.5)	129(46.9)	140(50.9)

BP= Blood pressure; uABP= unattended blood pressure; 24h-ABPM= 24 hour ambulatory blood pressure monitor

Table S6. Diagnostic categories at 135 mmHg systolic and 85 mmHg diastolic cut offs for screening measurements, using daytime 24h-ABPM thresholds (135 mmHg systolic, 85 mmHg diastolic) as reference

Category	Systolic			Diastolic		
	Standard BP N(%)	1st uABP N(%)	2nd uABP N(%)	Standard BP N(%)	1st uABP N(%)	2nd uABP N(%)
White coat hypertension	84(30.5)	56(20.4)	35(12.7)	53(19.3)	36(13.1)	27(9.8)
Masked hypertension	12(4.4)	11(4.0)	16(5.8)	24(8.7)	31(11.3)	39(14.2)
Sustained hypertension	90(32.7)	91(33.1)	86(31.3)	102(37.1)	95(34.5)	87(31.6)
Sustained normotension	89(32.4)	117(42.5)	138(50.2)	96(34.9)	113(41.1)	122(44.4)

BP= Blood pressure; uABP= unattended blood pressure; 24h-ABPM= 24 hour ambulatory blood pressure monitor

Table S7. Diagnostic categories at 130 mmHg systolic and 80 mmHg diastolic cut offs for screening measurements, using daytime 24h-ABPM thresholds (135 mmHg systolic, 85 mmHg diastolic) as reference

Category	Systolic			Diastolic		
	Standard BP N(%)	1st uABP N(%)	2nd uABP N(%)	Standard BP N(%)	1st uABP N(%)	2nd uABP N(%)
White coat hypertension	98(35.6)	77(28.0)	56(20.4)	75(27.3)	58(21.1)	56(20.4)
Masked hypertension	6(2.2)	6(2.2)	11(4.0)	16(5.8)	15(5.5)	17(6.2)
Sustained hypertension	96(34.9)	96(34.9)	91(33.1)	110(40.0)	111(40.4)	109(39.6)
Sustained normotension	75(27.3)	96(34.9)	117(42.5)	74(26.9)	91(33.1)	93(33.8)

BP= Blood pressure; uABP= unattended blood pressure; 24h-ABPM= 24 hour ambulatory blood pressure monitor

Table S8. Accuracy of hypertension diagnosis at different blood pressure cut offs using average 24h-ABPM as reference

BP cut off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR (+) (95% CI)	LR (-) (95% CI)	AUROC (95% CI)
Standard BP measurement							
≥140/90	86(79-91)	66(56-75)	79(72-85)	76(66-84)	2.5(1.9–3.3)	0.2(0.1-0.3)	0.76(0.70-0.81)
≥135/85	90(84-94)	57(47-67)	76(69-82)	79(68-88)	2.1(1.7-2.6)	0.2(0.1-0.3)	0.73(0.68-0.79)
≥130/80	94(89-97)	45(35-55)	72(65-78)	84(72-92)	1.7(1.4-2.0)	0.1(0.1-0.3)	0.69(0.64-0.75)
1st uABP							
≥140/90	72(65-79)	82(73-89)	86(78-91)	67(58-75)	4(2.6.6.1)	0.3(0.3-0.4)	0.77(0.72-0.82)
≥135/85	84(77-89)	71(61-79)	81(74-87)	75(65-83)	2.8(2.1-3.9)	0.2(0.2-0.3)	0.77(0.72-0.82)
≥130/80	92(87-96)	59(49-69)	77(70-83)	84(73-91)	2.3(1.8-2.9)	0.1(0.1-0.2)	0.76(0.71-0.81)
2nd uABP							
≥140/90	60(52-68)	94(88-98)	94(87-98)	62(54-69)	11(5-23)	0.4(0.4-0.5)	0.77(0.73-0.82)
≥135/85	76(68-82)	76(67-84)	83(75-88)	68(59-76)	3.2(2.2-4.5)	0.3(0.2-0.4)	0.76(0.71-0.81)
≥130/80	89(82-93)	58(48-68)	76(69-82)	77(66-86)	2.1(1.7-2.7)	0.2(0.1-0.3)	0.73(0.68-0.79)

BP= Blood pressure; uABP= unattended blood pressure; 24h-ABPM= 24 hour ambulatory blood pressure monitor; CI= confidence interval; PPV= positive predictive value; NPV= negative predictive value; LR= likelihood ratio.

Table S9. Optimal cut points for screening measurements using average and daytime 24h-ABPM.

Screening measurement	**Cut point based on average 24h-ABPM**			**Cut point based on daytime 24h-ABPM**		
	Cut point (mmHg)	**Sensitivity (%)**	**Specificity (%)**	**Cut point (mmHg)**	**Sensitivity (%)**	**Specificity (%)**
Systolic						
SBPM, mmHg	140	75	75	143	70	72
1st uABP, mmHg	135	78	83	136	76	74
2nd uABP, mmHg	130	76	80	130	77	73
Diastolic						
SBPM, mmHg	83	79	66	87	70	72
1st uABP, mmHg	81	79	73	87	66	82
2nd uABP, mmHg	79	81	66	83	67	78

BP= Blood pressure; uABP= unattended blood pressure; 24h-ABPM= 24 hour ambulatory blood pressure monitor

Table S10. Search for evidence before this study

Search string	Result
(‘Unattended blood pressure*’ OR ‘Unattended automated blood pressure*’ OR ‘Automated blood pressure*’ OR ‘uABP*’ OR ‘uAOBP*’ OR ‘AOBP*’ OR ‘Out-of-office blood pressure*’) AND (‘Office blood pressure*’ OR ‘Standard blood pressure*’) AND (‘Ambulatory blood pressure monitoring’ OR ‘Blood pressure monitoring, ambulatory’ OR ‘Ambulatory blood pressure*’) AND (‘Survey’ OR ‘WHO steps survey’)	PubMed = 61 Embase= 20
(‘Unattended blood pressure*’ OR ‘Unattended automated blood pressure*’ OR ‘Automated blood pressure*’ OR ‘uABP*’ OR ‘uAOBP*’ OR ‘AOBP*’ OR ‘Out-of-office blood pressure*’) AND (‘Office blood pressure*’ OR ‘Standard blood pressure*’) AND (‘Ambulatory blood pressure monitoring’ OR ‘Blood pressure monitoring, ambulatory’ OR ‘Ambulatory blood pressure*’) AND (‘Survey’ OR ‘WHO steps survey’) AND (‘sub-saharan Africa’ OR ‘Africa South of the Sahara’ OR ‘subsaharan Africa’)	PubMed= 3 Embase= 0

Panel S1. Full study protocol

Community-Based chronic disease Care Lesotho (ComBaCaL): Baseline Survey to Assess Non-Communicable Disease Burden

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Research legislation:	Ordinance on human research with the exception of clinical trials (HRO) [1].
Type of Research Project:	Research project involving human subjects
Risk Categorisation:	Risk category A
Project Leader:	Prof. Niklaus Labhardt, Assistant Professor, Research Group Leader, Swiss Tropical and Public Health Institute (Swiss TPH), Socinstrasse 55, +41 79 8701859, n.labhardt@unibas.ch

PROTOCOL SIGNATURE FORM

Study Title	**Community-Based chronic disease Care Lesotho (ComBaCaL): Baseline Survey to Assess Non-Communicable Disease Burden**

The project leader (main center) and the investigator (at the local center/site) have approved the protocol version ***01 (dated 16.08.2021)***, and confirm hereby to conduct the project according to the protocol, the Swiss legal requirements [1,2], the current version of the World Medical Association Declaration of Helsinki [3] and the principles and procedures for integrity in scientific research involving human beings.

Project leader (lead center/site)

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Local Project Leader at local center/site:

Site: SolidarMed, House 3A Happy Villa Maseru, Lesotho

Name of Local Project Leader: **Ravi Gupta, MD**

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Study Co-Investigators

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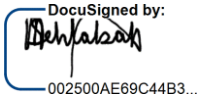
Name: **Moelo Sehlabaka**, Lesotho Ministry of Health, Maseru, Lesotho

Date: 30-Aug-2021 | 14:17:16 CEST Signature:



Name: **Madavida Mphunyane**, Lesotho Ministry of Health, Maseru, Lesotho

Date: 26-Aug-2021 | 17:29:38 CEST Signature:

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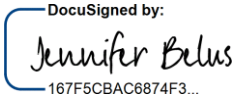
Date: 19-Aug-2021 | 12:24:23 CEST Signature:



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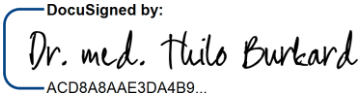

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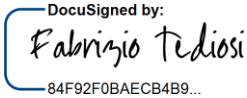

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1. GLOSSARY OF ABBREVIATIONS

ABPM	*Ambulatory blood pressure measurement*
ACR	*Albumin creatinine ratio*
aHT	*Arterial hypertension*
ASSIST	*Alcohol, Smoking and Substance Involvement Screening Test*
BMI	*Body mass index*
BP	*Blood pressure*
CI	*Confidence interval*
CMD	*Common mental disorder*
CRF	*Case report form*
CSI-D	*Community Screening Instrument for Dementia*
CVD	*Cardiovascular disease*
CVDRF	*Cardiovascular disease risk factor*
DALY	*Disability-adjusted life-years*
DHS	*Demographic and Health Survey*
DM	*Diabetes mellitus*
DNA	*Deoxyribonucleic acid*
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders-5*
eCRF	*Electronic case report form*
eGFR	*Estimated glomerular filtration rate*
EKNZ	*Ethikkommission Nordwest- und Zentralschweiz*
FRS	*Framingham Risk Score*
GAD-2	*Generalized Anxiety Disorder-2*
GAD-7	*Generalized Anxiety Disorder-7*
HBV	*Hepatitis B virus*
HBsAg	*Hepatitis B surface antigen*
HFIAS	*Household Food Insecurity Access Scale*
HIV	*Human immunodeficiency virus*
HRA	*Human Research Act*
HRO	*Ordinance on Human*
IASP	*International Association for the Study of Pain*
ICF	*Informed consent form*

IPAQ-SF	*International Physical Activity Questionnaire Short Form*
MoH	*Ministry of Health*
MNSI	*Michigan Neuropathy screening instrument*
NCD	*Non-communicable disease*
ODK	*Open Data Kit*
PCR	*Polymerase chain reaction*
PHQ-2	*Patient Health Questionnaire-2*
PHQ-9	*Patient Health Questionnaire-9*
PSU	*Primary sampling unit*
PTSD	*Post-Traumatic Stress Disorder*
PTSD-PC	*Primary Care Post-Traumatic Stress Disorder screener*
RBG	*Random blood glucose*

SSU	*Secondary sampling unit*
STEPS	*STEP wise approach to Surveillance*
T2DM	*Type 2 diabetes mellitus*
TB	*Tuberculosis*
WHO	*World Health Organization*
YLD	*Years lived with disability*

2. BACKGROUND AND PROJECT RATIONALE

Non-communicable chronic diseases (NCDs), which include cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), and common mental disorders (CMDs), are the number one cause of death and disability globally[1]. Historically, in the sub-Saharan Africa region, there has been a focus on infectious diseases, particularly HIV and tuberculosis (TB)[2]. However, the burden of disease profile has rapidly shifted in the last decades, particularly since the introduction of highly efficient ART, and is now dominated by NCDs[3,4]. The growing importance of NCDs is attributable to demographic ageing, rapid urbanization, and the expansion of unhealthy lifestyles, such as physical inactivity, unhealthy diets, and tobacco consumption[5-7]. At the same time, countries in this region continue to struggle with a high burden of communicable diseases[1]. As a result, health systems are faced with a "double burden," arising from the health and economic impact of both NCDs and communicable diseases.

As the burden of disease due to NCDs in sub-Saharan Africa is relatively new, little research has been conducted on how to provide pragmatic and scalable prevention and treatment models for NCDs in the context of a high communicable disease burden and chronic health system underfunding leading to poor health system infrastructure and shortage of trained health personnel. Before research on relevant treatment models can be tested in this context, it is necessary to understand the intersection of NCDs (i.e., NCD comorbidity) in a population already burdened with communicable diseases, and the arising complications, which will change the landscape of treatment provision for NCDs.

In sub-Saharan Africa, the proportion of disability-adjusted life-years (DALYs) that resulted from NCDs increased from 37.8% in 1990 to 66.0% in 2019[1]. Adult CVD was estimated to contribute 22.9 million DALYs[2]. Arterial hypertension (aHT), defined as above 140/90 mmHg, is the most prevalent CVD[8-12]. Diabetes mellitus (DM) is characterized by chronic hyperglycemia resulting from defects in insulin secretion and or action. Approximately 90% to 95% of cases are due to T2DM, which is associated with lifestyle risk factors such as obesity and physical inactivity. The prevalence of T2DM in adults varies significantly across the region from 2.0% in Gambia to as high as 14.8% in Mauritius[13-16]. Overall, in sub-Saharan Africa approximately 20 million people live with T2DM and this figure is projected to increase to 47 million people in 2045. Despite this rising prevalence, an analysis of the care cascade reveals that about 50% of persons remain undiagnosed. In the field of mental health, it is estimated that CMDs, which includes depression, anxiety, and substance use, account for 19% of all years lived with a disability (YLD) in the region. Data on risk factors for development of CMDs includes family diagnosis of a mental health problem and experiences of trauma[17-19]. However, the vast majority of this data comes from high-income countries and the extent to which such risk factors are relevant in sub-Saharan Africa is largely unknown. If unaddressed, CMDs are predicted to lead to 45 million YLDs in sub-Saharan Africa by the year 2050.[2,20,21]

In addition to understanding risk factors for NCDs, which can aid in prevention, it is also necessary to investigate associated end-organ damage. The prevalence of CVD and T2DM continues to rise in sub-Saharan Africa, but there is very little high-quality data in the region regarding the prevalence of complications from these diseases[22]. Data is especially lacking in rural regions. For CVD, one study from Nigeria estimated the prevalence of complications, including left ventricular hypertrophy, nephropathy, and retinopathy to be 27%, 12% and 2% respectively, among people with newly diagnosed aHT[23] For T2DM, one review from 2003 suggests that up to 25% of people in Africa with T2DM at diagnosis already had retinopathy. Between 5% to 28% had nephropathy and micro-albuminuria within a year of diagnosis; after 5-10 years of diagnosis these estimates are between 32-57%.[24] Non-standardized diagnostic algorithms, late diagnosis, and substandard treatment regimens likely contribute to reported complications[24-26]. Awareness of the burden of end-organ damage in newly diagnosed individuals will allow for a more accurate representation of the NCD problem in sub-Saharan Africa, and inform the design and implementation of relevant interventions.

Previous studies in various settings have shown that NCD burden is often unevenly distributed among different socioeconomic groups depending on their behavioral risk factors such as quality of diet. [27-29] However, there is currently a dearth of data on the association of socioeconomic status and NCD prevalence, food security, healthcare access highlighting the need for studies in this field.

Lesotho, a landlocked country within South Africa, is a typical example of an African low-income country with growing prevalence of NCDs that are overtaking HIV and other infectious diseases as the major cause of disability, morbidity, and early death[30]. According to World Health Organization (WHO) estimates, 22% of the adult population suffers from aHT, 6% from diabetes, and 5% from depression.[30,31] Due to social and economic determinants, women are often most affected by the lack of access to NCD prevention and care.[30] The Ministry of Health (MoH) of Lesotho has therefore proposed an NCD strategic plan where delivery platforms should provide integrated HIV and NCD services.[32]

In order to provide enough service coverage for disease diagnosis and treatment at the population level, it is necessary to map the relevant steps of the treatment cascade. For NCDs, this includes the determination of the number of patients affected by the condition and the subsequent proportions of patients who are aware of their diagnosis, receive treatment, and have achieved their relevant treatment targets. Several other countries in sub-Saharan Africa have begun documenting the treatment cascades for CVD and T2DM, including South Africa and Tanzania.[16,33,34] These countries show large gaps in diagnosis and treatment. Finally, there is very limited data examining co-occurring NCDs (e.g., the prevalence of having both a CMD and DM) and the burden of NCDs in a population with a high prevalence of infectious diseases, such as HIV and TB. This knowledge will be essential to determine how prevention and treatment services can be provided in countries with limited health infrastructure and financial resources and in particular in Lesotho, where the MoH intends to integrate HIV and NCD services.

Our larger goal is to design and test a pragmatic and integrated model of care for NCDs and infectious diseases in Lesotho, which will be developed in a subsequent randomized, village-based, interventional trial. This current protocol is the formative work necessary to prepare for this future trial. We will conduct a population-based survey in Lesotho for a variety of NCDs and infectious diseases, assessing prevalence of diseases, risk factors, complications, and treatment engagement.

3. PROJECT OBJECTIVES AND DESIGN

3.1 Aim and objectives

Aim

The overall aim of this population-based survey is to assess the prevalence and morbidity, as well as the impact of socioeconomic factors, on a selection of non-communicable diseases and their risk factors, as well as to characterize the gaps in their treatment cascade in Lesotho.

Specific objectives

The specific objectives of this population-based survey are:

1. To assess the prevalence of the following non-communicable conditions:
    a. CVDs and CVD risk factors (CVDRFs): aHT, dyslipidemia, hyperglycemia, overweight/abdominal obesity, nicotine use, physical inactivity, unhealthy diet
    b. Mental health: Depression, anxiety (generalized anxiety disorder (GAD) and post-traumatic stress disorder (PTSD)), substance use, dementia, and chronic pain

c. To estimate the 10-year risk of CVD among participants using both the Framingham Risk Score and WHO cardiovascular disease risk score. The Framingham Risk Score is mostly used in high-resource settings, but requires more detailed clinical information. The WHO cardiovascular disease risk charts allow for the calculation of cardiovascular risk in lower-resource settings.

2. To describe the treatment cascade for the measured risk factors and health conditions
3. To determine the association between socioeconomic status and the prevalence of the non-communicable conditions, the level of food security, and healthcare access
4. To describe health-related quality of life of the sampled population
5. Furthermore, we plan to conduct six sub-studies nested within the overall survey. The objectives of these nested studies are outlined below:
   a. Objective nested study 1
      To assess prevalence of end-organ damage in individuals diagnosed with DM and/or aHT and to compare it to individuals with normal BP and normal blood glucose.

   b. Objective nested study 2
      To evaluate a pragmatic approach of community-based screening for aHT and to evaluate a novel 24-hour BP measuring bracelet device.

   c. Objective nested study 3
      To examine the sensitivity and specificity of shortened screening tools for depression and anxiety.

   d. Objective nested study 4
      To assess linkage to clinic-based care and outcomes after community-based diagnosis of DM and/or aHT.

   e. Objective nested study 5
      To assess linkage to care and outcomes among individuals who report suicidality during the survey and are referred to mental health care.

   f. Objective nested study 6
      To measure the prevalence of hepatitis B virus (HBV) infection. Of those who screen positive for HBV, determine the level of liver cirrhosis and treatment eligibility according to the current WHO guidelines.

3.2 Primary variables of interest

Primary variables of interest are the prevalence of the selected chronic conditions. To meet objective 2 (description of the treatment cascade of the selected chronic conditions) we will further collect information on awareness of the conditions, access to care and clinical control of the conditions. For objective 3 and 4 (association of socioeconomic factors with selected chronic conditions and the determination of quality of life), we will collect demographic and socio-economic information of participants and assess their quality of life.

Table 1 on page 15 provides an overview of the variables collected and the device/questionnaire used for each variable. We will make use of already established and validated questionnaires or a modified form, where needed. Below, we describe in more detail the measures included in the study.

- Objective 1a: Demographic and CVDRF information questionnaires are based on STEPS (STEP wise approach to Surveillance)[35]. STEPS is a WHO-developed, standardized but flexible framework to monitor the main NCD risk factors through questionnaire

assessment and physical and biochemical measurements for country-level estimates. It is usually coordinated by national authorities of the implementing country. The STEPS surveys are generally household-based and interviewer-administered, with selected samples of around 5000 participants. Lesotho had its last STEPS survey in 2012.[36]

- Objective 1a: Physical inactivity will be measured using the validated International Physical Activity Questionnaire Short Form (IPAQ-SF)[37], which has been adapted to the local context and language according to the IPAQ recommendations.[38]

- Objective 1a: Nutritional CVDRFs will be measured using two questionnaires assessing junk food and salt intake. The salt intake questionnaire is adapted from the STEPS survey, whereas the junk food questionnaire is a shortened unquantified food frequency questionnaire adapted from an assessment tool for obesity used in South Africa.[39]

- Objective 1b: For depression screening, we will use the Patient Health Questionnaire-9 (PHQ-9). PHQ-9 is a questionnaire that measures symptoms of depression over the past two weeks based on criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5). Each item is scored on a 4-point Likert scale ranging from “0” (not at all) to “3” (nearly every day). The PHQ-9 has been widely used in clinical practice and research in sub-Saharan Africa.[40-42]

- Objective 1b: Screening for anxiety will be conducted with the Generalized Anxiety Disorder-7 (GAD-7) and the Primary Care Post-Traumatic Stress Disorder screener (PC-PTSD-5) scales. The GAD-7 is an easy to use 7-item scale based on the DSM-5 criteria for identifying likely cases of generalized anxiety disorder. Each item is scored on a 4-point Likert scale ranging from “0” (not at all) to “3” (nearly every day). GAD-7 has been validated and used extensively in sub-Saharan Africa[43-45] in a variety of contexts including remote health surveys, epidemiologic studies, and primary care settings. The PC-PTSD-5 is a brief screener for PTSD and aligns with the DSM-5 criteria for the disorder. It assesses whether an individual has experienced a lifetime traumatic event, and if so, assesses an individual’s response to five items (yes/no) assessing the hallmark symptoms of PTSD [46]. It is one of the few brief screeners available for PTSD[47] and has been used successfully in sub-Saharan Africa.[48]

- Objective 1b: Substance use (including alcohol use) will be derived from Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)[49]. It is a WHO-developed questionnaire that screens for levels of risky substance use in adults. ASSIST consists of eight questions covering tobacco, alcohol, cannabis, cocaine, amphetamine-type stimulants, inhalants, sedatives, hallucinogens, opioids and 'other drugs'. A risk score is provided for each substance, and scores are grouped into 'low risk', 'moderate risk,' or 'high risk'. The risk score determines the level of intervention recommended (brief intervention or brief intervention plus referral to specialist treatment). ASSIST takes approximately 5 to 10 minutes to administer and has been validated in similar settings for adults. A modified version is available for adolescents from ages 10-14 and ages 15-17.[50-53] We also include a few additional questions regarding history of substance use problems, primary substances used, amount of money spent on substances, and previous treatment for substance use.

- Objective 1b: Screening for dementia will be conducted using the brief version of the Community Screening Instrument for Dementia (CSI-D). It is a tool that was developed specifically for use in low- and middle-income countries. It combines culture and education-fair cognitive testing of the participant (seven items) and an informant interview enquiring the participant's daily functioning (six items). The measure can be scored with or without the informant responses.[54]

- Objective 1b: Chronic pain will be assessed using an adapted questionnaire based on the International Association for the Study of Pain (IASP).[55,56] The questionnaire has five items and assesses the presence of chronic pain, its location, severity and impact.

- Objective 1c: Estimating the CVD risk among participants, we will follow the WHO cardiovascular disease risk chart, as well as the Framingham Risk Score (FRS), which have both been validated.[57-59] These CVD risk prediction approaches determine the 10-year risk of developing CVD in relevant target populations using different calculation methods. We will compare the population CVD long-term risk using both scores.

- Objective 2: The treatment cascade for measured risk factors and health conditions will be assessed by measuring whether participants who meet criteria for a given health condition were previously aware of their condition, whether they are currently engaged in care for the condition, and whether their health condition is currently well controlled. This is a common approach to measuring treatment cascades for health conditions.[33,60]

- Objective 3: The socioeconomic status will be computed for each household using the Demographic and Health Survey (DHS) Program wealth index questions for Lesotho.[61] The DHS wealth index is an approximately 15-item questionnaire that assesses household assets and utility services, including country-specific assets that are viewed as indicators of economic status. This measurement also accounts for differences in economic status indicators in rural versus urban areas. The data from the questionnaires is then used to construct cut points to form wealth quintiles

- Objective 3: Food security is a household-level measure assessed using the Household Food Insecurity Access Scale (HFIAS) for Measurement of Food Access. The questionnaire consists of nine questions that assess the severity of food insecurity and a further accompanying nine questions that assess the frequency of a food insecurity-related occurrence[62].

- Objective 3: Healthcare access is assessed using questions taken from various validated questionnaires, as no single validated questionnaire assesses the three main components of healthcare access: availability, physical affordability and acceptability of healthcare services[63].

- Objective 4: Health-related quality of life will be measured using the EuroQol EQ-5D-3L instrument.[64] The instrument assesses five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The dimensions are assessed by asking the respondents to rate different aspects of their health on the day using a three-point set of response options. The EQ-5D-3L instrument has been validated and used in a number of countries in sub-Saharan Africa[65-67]. The South African Sesotho validated version of the questionnaire will be used in the current study[68].

- Nested study 1: Presence of aHT or DM associated end-organ diseases like nephropathy, retinopathy, hypertensive cardiomyopathy and peripheral neuropathy will be assessed using point of care serum creatinine measurements and albumin creatinine ratio(ACR)[69], Welch Allyn iExaminer™[70] for fundoscopy, Phillip's Lumify™ portable ultrasound for echocardiography[71] and a 10g microfilament[72] for sensitivity assessment of the foot respectively. These devices and examinations are validated and have been used in sub-Saharan Africa.

- Nested study 2: Accuracy of pragmatic approaches to community-based BP measurements will be assessed by measuring standard office BP, unattended automated 24-hour BP with Aktiia™ bracelet, all evaluated against a 24-ambulatory BP measurement. The Aktiia™ bracelet measures optical photo-plethysmographic signals on

the wrist and calculates systolic BP and diastolic BP values using pulse wave analysis technique. [73,74]

- Nested study 3: To assess the sensitivity and specificity of the shortened screening tools PHQ-2 and GAD-2 for depression and anxiety, they will be administered to all participants and their results will be compared to the full-length PHQ-9 and GAD-7 tools. The PHQ-2 is comprised of the first two items of the PHQ-9 and inquires the degree to which an individual has experienced depressed mood and anhedonia over the past two weeks (the hallmark symptoms of depression). Similarly, the GAD-2 contains the first two questions of the GAD-7. Both are typically used as screening tools to establish whether additional assessments of depression or anxiety are needed. A few studies in low- and middle-income settings have validated the PHQ-2 and GAD-2. [75,76]

- Nested study 4: To assess whether participants who are diagnosed with aHT or diabetes are linked to care, we will use medical record extraction. Because clinics in Lesotho do not use routine medical records for these kind of conditions, participants' clinic visits will be documented in a study-specific health linkage visit log at the clinic.

- Nested study 5: To assess whether participants at moderate or high-risk of suicidality return to the clinic for follow-ups on their mental health problems, we will use medical chart extraction. Because clinics in Lesotho do not use routine medical records for these kind of conditions, participants' clinic visits will be documented in a study-specific health linkage visit log at the clinic.

- Nested study 6: Hepatitis B surface antigen (HBsAg) will be assessed using the Determine™ HBsAg point-of-care test.[77] Treatment eligibility for those testing HBsAg-positive will be assessed during a follow-up at one of the three hospitals using the aspartate aminotransferase to platelet ratio index, as well as HBV DNA and fibroscan (if possible).

3.3 Study design

We will conduct a population based cross-sectional survey in randomly selected villages in urban and rural areas in Butha-Buthe and Mokhotlong districts in Lesotho. We will conduct a multistage cluster sampling, where village clusters will be our primary sampling unit (PSU) and household members will be our secondary sampling unit (SSU). The level in between (households) will not be randomly sampled. Instead, all households in a sampled village cluster will be visited and enrolled (if consent is provided by the head of household, see Section 4.2 for details on informed consent process). An equal number of PSUs for urban and rural areas will be allocated in order to ensure sufficient precision for both urban and rural settings.

For each PSU, a sampling frame will be created comprising the number of households within the village, district of the village (Butha-Buthe vs Mokhotlong), and the village's accessibility to the corresponding health facility. Village accessibility to heath center will be categorized as easy vs hard; hard is defined as needing to cross a mountain or river or travel more than ten kilometers. We will ensure that PSUs are of similar size (number of households). Small villages will be clustered with other villages. An independent statistician will provide a computer-generated random sample that is proportional to the sampling frame factors so that village clusters are representative.

The SSU sampling frame will be compiled during the electronic data collection in each household and will entail gender and age. Individuals will then be randomly drawn by the data collection tool, the Open Data Kit (ODK), using probability proportional to target sample size sampling (see Table 2 under Section 5.1. Statistical Analysis Plan).

On the day, the survey team visits a PSU (i.e., village cluster), all households within the cluster will be visited. All household members, both absent and present, will be enumerated. All eligible present household members will be invited to participate in the study. All study participants aged 18 years and older will receive basic screening for DM, aHT, and HIV (if eligible as per Lesotho MoH risk assessment). All study participants aged 10-17 years will receive screening for HIV (if eligible as per Lesotho MoH risk assessment). Within each household, any eligible individual who falls into any of our strata of interest based on age, gender, and location (see Table 2 and 3), may be randomly selected by the data collection tool to participate in further assessments until each stratum is filled.

3.4. Scientific justification of study population

The study is a population-based survey in Lesotho, which aims to produce a representative sample of the population in the two districts of Mokhotlong and Butha-Buthe, where recruitment will take place, as well as the country overall. Recruitment will be divided equally between rural and urban settings in order to ensure a sufficient sample in each setting so that outcomes can be compared across the two settings.

1. Overview of variables and measurement strategies

Objective	Variable/Domain	Population group	Measurement tool	Measurement thresholds or strategy
Objective 1a	Blood pressure	≥18 years	Calibrated sphygmomanometer	European recommendations: • Optimal: <120/80 mmHg • Normal: 120-129/80-84 mmHg • High normal:130-139/85-90 mmHg • Grade 1 aHT:140-159/90-99 mmHg • Grade 2 aTN:160-179/100-109 mmHg • Grade 3 aTN:>180/110 mmHg
Objective 1a	Lipid profile	≥30 years	Cholesterol Total Cholesterol HDL	Normal < 200 mg/dL (5.2 mmol/L) Normal> 40 mg/dL (1 mmol/L) in men and > 50 mg/dL (1.3 mmol/L) in women
Objective 1a	Blood glucose	≥18 years	Random blood glucose (RBG) Hb1Ac	Normal: <126 mg/dL (7.0 mmol/L). Normal: ≤200 mg/dL (11.1 mmol/L) Normal: <6.5% (48 mmol/mol) * Diabetes mellitus will be defined as HbA1c ≥ 6.5%
Objective 1a	Overweight/ abdominal obesity	≥10 years	Weight, height	Adults >18 y: BMI • <18.5- underweight • 18.5-24-9 normal • >=25-29.9-overweight • >30 obesity Children/adolescents 10-18y: z-score • < 2 SD classify low weight-for-age (underweight), low height-for-age (stunting) and low weight-for-height (wasting). • >2 SD classify high weight-for-height (overweight).[78]

Objective 1a	Nicotine use	≥10 years	See substance use (objective 1b) for measurement strategy	See substance use (objective 1b) for measurement thresholds
Objective 1a	Physical activity	≥10 years	International Physical Activity Questionnaire Short Form (IPAQ-SF)	N/A
Objective 1a	Nutrition	≥10 years	Questionnaire assessing junk food and salt intake	N/A
Objective 1b	Depression	≥10 years	Patient Health Questionnaire-9 (PHQ-9)	Mild ≥ 5 Moderate ≥ 10 Severe ≥ 15
Objective 1b	Anxiety	≥10 years	Generalized Anxiety Disorder (GAD-7) and Post-Traumatic Stress Disorder in Primary Care (PTSD-PC)	For GAD-7 Mild ≥ 5 Moderate ≥ 10 Severe ≥ 15 For PTSD-PC PTSD likely: ≥4
Objective 1b	Substance use	≥10 years	WHO Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) Additional substance use questions about history of use and prior treatment	For alcohol: Low risk: 0-10 Moderate risk: 11-26 High risk: 27 For tobacco and other substances: Low risk: 0-3 Moderate risk: 4-26 High risk: 27
Objective 1b	Dementia	≥50 years	Community Screening Instrument for Dementia: CSI-D	Dementia likely: <6 (respondent score), <5 (respondent and informant score)

Objective 1b	Chronic pain	≥18 years	Questions based on the definition of chronic pain according to the International Association for the Study of Pain (IASP)	Severity and impact on an 11-point Numerical Rating Scale (NRS) proposed by the IASP
Objective 1c	CVD risk index(es)	≥30 years	Framingham Risk Score WHO Cardiovascular Risk Charts	Low risk <10% Intermediate risk 10-20% High risk ≥20%[79]
Objective 2	Treatment cascade for measured risk factors and health conditions	≥18 years	Individual items assessing awareness of health condition, engagement in care for health condition, and health condition status	N/A
Objective 3	Socioeconomic status	Head of household only	Demographic and Health (DHS) Program wealth index questions for Lesotho	N/A
Objective 3	Food security	Head of household only	Household Food Insecurity Access Scale (HFIAS) for Measurement of Food Access	N/A
Objective 3	Healthcare access	≥18 years	Tool designed to assess three components of healthcare access: availability, physical affordability, acceptability of healthcare services	N/A
Objective 4	Health-related quality of life	≥18 years	EuroQol (EQ-5D-3L), a validated assessment tool assessing 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.	N/A
Nested study 1	Kidney disease	Participants with aHT and/or DM	Estimated glomerular filtration rate (eGFR) based on serum creatinine calculated using CKD-EPI formula, albumin creatinine ratio (ACR)	eGFR < 60mL/min/1.73m2 and/or ACR ≥30mg/g: Chronic kidney disease

	Diabetic retinopathy	Participants with diabetes only	Welch Allyn iExaminer™[80]	Presence of at least one microaneurysm. Severity will be based on International Clinical DR Disease Severity Scale[81]
	Hypertensive retinopathy	Participants with aHT only	Welch Allyn iExaminer™	Minimum criterion of arteriolar constriction. Further staging will be according to Mitchel-Wong's grading system[82]
	Peripheral neuropathy	Participants with diabetes only	Using a 10-g monofilament	Presence of sensation in 8 or more sites will be considered normal. Absence of sensation in 3 or more sites will be indicative of peripheral neuropathy
	Hypertensive cardiomyopathy	Participants with aHT only	Phillip's Lumify™ Ultrasound	Left ventricular mass and function above the upper limit of normal for sex and age according to the European Association of Cardiovascular imaging
Nested study 2	Diagnostic accuracy of three BP measurement approaches	Consenting adults sampled	WatchBP® office device, Optical Aktiia™ bracelet, 24-h ambulatory BP measurement (ABPM) device	N/A
Nested study 3	Screening scores and total scores for depression and anxiety	≥18 years	PHQ-9/PHQ-2 and GAD-7/GAD-2	N/A
Nested study 4	Linkage to care for diabetes and/or aHT	All participants diagnosed with diabetes and/or hypertension	Study-specific health linkage visit log at the clinic	Marked attendance in the study-specific health linkage visit log at relevant time periods.
Nested study 5	Linkage to mental health care for patients with suicide risk	All participants who are at moderate or	Study-specific health linkage visit log at the clinic	Marked attendance in the study-specific health linkage visit log at the clinic at relevant time periods.

		high-risk of suicide		
Nested study 6	Hepatitis B	≥ 10 years old	HBsAg Determine™ point-of-care test. Treatment eligibility for those testing HBsAg-positive will be assessed during a follow-up at one of the three hospitals using the aspartate aminotransferase to platelet ratio index, as well as HBV DNA and fibroscan (if possible).	N/A

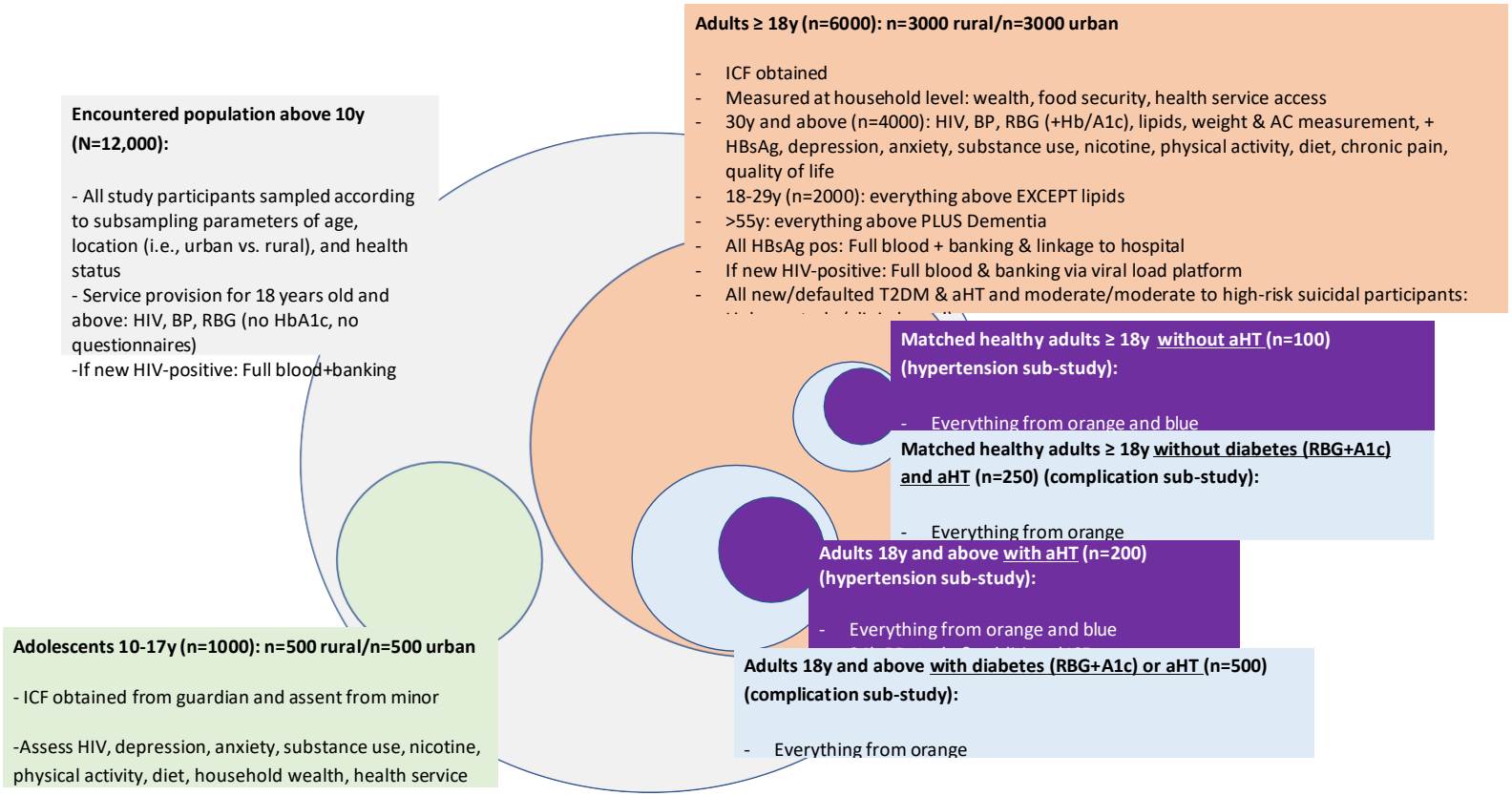

Figure 1. Estimated number of households and inhabitants from the selected villages.

4. PROJECT POPULATION AND STUDY PROCEDURES

4.1 Project population, inclusion and exclusion criteria

Villages situated in the Butha-Buthe and Mokhotlong districts in Lesotho will be randomly selected and all eligible households within each village will be invited to participate (see Section 3.3). The population of interest consists of all household members aged 10 years or older from households in these two districts. The estimated number of households and inhabitants from the selected villages is presented in Figure 1.

A household is defined as one or more individuals who reside in a physical structure (e.g., compound, homestead) and share housekeeping arrangements. A household member is defined as an individual who is acknowledged by the head of household as a household member. Household members who are 10 years or older are eligible to participate (see detailed inclusion and exclusion criteria under Section 4.1.)

Eligibility criteria are as follows:

Inclusion criteria village/cluster:

- Located in Butha-Buthe or Mokhotlong districts
- Village chief gives verbal consent for his/her village to participate

Inclusion criteria household:

- Adult household head or representative (≥ 18 years old) gives verbal consent to include the household in the survey

Inclusion criteria individual:

- Individual who is acknowledged by the head of household as a household member
- At least 10 years of age and provides written consent (or consent of guardian) to participate. Minors provide assent.

4.2 Recruitment, screening and informed consent procedure

Community sensitization activities will take place before recruitment to maximize community support and participation in the survey. The mobilization will begin with a district launch meeting that will include key leaders, local mass media, and other stakeholders. The study teams will contact local village chiefs and other stakeholders where appropriate (e.g., local government officials, religious and community leaders) prior to initiation of data collection. Further mobilization activities may include community sensitization meetings.

After community sensitization, recruitment into the study will take place at the households of the selected village clusters. All occupied households within a selected village will be approached by trained fieldworkers to ask permission to speak with the head of household. If the head of household is not available at that time, fieldworkers will ask for another adult (≥18 years old) who is willing to serve as a representative for the head of household in his/her absence. If the head of household (or a representative) is available, fieldworkers will provide a brief explanation of the study and ask for verbal consent to allow household members to participate. After verbal consent has been given by the head of household or representative, all household members will be asked about their sex and age and the household-level questionnaires (household wealth, health service

access and food security) will be administered. Those individual household members who meet study eligibility (as defined under Section 4.1), are present in the home at the time of recruitment, and are randomly selected to participate by the data collection tool will be invited to participate in further assessments. For these participants, a written informed consent form (ICF) will be sought from those. The consent form (see ICF attachment) will be explained in a summarized manner and household members will be given an opportunity to ask questions. Once the informed consent process is complete, a signed copy of the consent form will be retained by study staff and a copy given to participants. Each consenting household member will subsequently complete the study interview and related procedures by a trained fieldworker (described in Section 4.3). As specified in the ICF, participants agreeing to participate in the study will not receive any remuneration, as this is standard research procedure in Lesotho.

For minors (<18 years old), a guardian provides written informed consent and the minor provides verbal assent to participate. For illiterate participants, a witness chosen by the participant provides written informed consent and the participant provides a thumbprint. The number of participants who are eligible for study participation but decline participation will be also be recorded.

Persons who are part of a surveyed household but reject study participation or are ineligible for study participation will be offered BP, RBG and HIV status assessment (and testing if eligible according to Lesotho HIV testing guidelines) as part of routine service provision and will be referred for further care to the corresponding health facility if deemed necessary by the study nurse in charge. For individuals who receive the routine service provision and test positive for HIV, we will get their consent to biobank their blood samples and add their data to the Lesotho HIV biobank database using our team's standard consent form (see Biobank ICF).

4.3 Study procedures

Data collection is estimated to take approximately 12 months to reach the desired sample size of 7000 participants and is scheduled to begin in September 2021 and to end August 2022. All data collection will take place in Lesotho. SolidarMed Lesotho is the implementing partner of this study and will oversee data collection and study implementation. Trained fieldwork teams will be deployed to communities and conduct data collection. Each fieldwork team will consist of approximately six team members and one driver who will escort the fieldwork teams to the villages. Fieldwork teams will consist of one nurse and five nursing assistants and will include both male and female staff members who speak Sesotho and are familiar with the local communities. Data will be collected electronically using the Open Data Kit (ODK) platform. ODK allows for offline data collection by multiple users. Data collected during the study will be uploaded to a protected server in Switzerland, such as Switchdrive, once an internet connection is available. Only staff members who are part of the research team and study investigators will have access to the data.

The survey time with participants who are randomly selected by the ODK data collection tool according to the sample sizes needed to fill the study strata (see Table 2) to complete the full protocol is estimated to be up to 1.5 hours, including time to consent. Interviews will be conducted in or near the household in a private space. The questionnaires will first be administered, followed by physical and biochemical measurements.

Table 1 provides a detailed description of all domains and assessment tools used for variables of interest, including eligibility criteria for certain assessments. Briefly, questionnaires will be used to assess demographics, health economics, nutrition and physical health, and mental health, including CMDs, dementia, and chronic pain, among others. This will take approximately 30 minutes and be conducted by the nursing assistant. The clinical and laboratory assessments will also take approximately 45 minutes and cover the following domains: height, weight, RBG, BP,

lipids, confirmatory assessments (HbA1c), and infectious disease (HIV, Hepatitis B). For blood sugar assessment, only participants with RBG ≥ 5.6mmol/L will undergo the HbA1c confirmatory test. The nursing assistant will conduct the clinical assessments. HIV testing will be offered according to Lesotho MoH guidelines. For some participants, an end-organ complication assessment (foot, eye, heart, and renal) will be conducted by the nurse of the field team (see details in nested study 1, Section 5.3.1). The end-organ complication assessment will take approximately 45-60 minutes. Definitions for aHT and diabetes are provided in Table 1.

For laboratory assessments, we will perform a venipuncture. A maximum of 7.5 mL of venous blood will be drawn by qualified survey staff from consenting participants aged 18 and older. A second sample will be collected for participants who test positive for HIV and/or Hepatitis B for further virological analyses (PCR viral load and genotype sequencing) and liver function assessment. Blood samples will be labelled with the study identification number and stored in temperature-controlled cooler boxes. Samples will be transported to the respective district hospital within 2 days for short-term storage. All samples will be stored for the duration of the study in a -80°C biobank freezer at Seboche Hospital Laboratory (for HIV and Hepatitis B positive participants).

The venous blood will be used to perform all point-of-care tests (RBG, HbA1c, lipid profile, serum creatinine, HIV test, HBs Ag test). In case venous blood draw is unsuccessful, capillary blood from finger-prick test may be used for point-of-care tests. To estimate the ACR, spot urine sample will be obtained from eligible participants to be analyzed using relevant point of care device.

Some results will be available to participants during the home visit. These results include BP, RBG, HbA1c, HIV test, and HBsAg. The survey staff will ensure that the results are communicated to the participants and attached to their personal health record ("bukana"), for further use by their routine health providers. Any other relevant medical information that is deemed clinically relevant will also be added into the personal health record and communicated verbally to participants.

4.4 Withdrawal and discontinuation

Participants are only excluded from the study if they withdraw their informed consent. The consent form states that participants may withdraw their consent at any time. Withdrawing consent means that the participant's data will be destroyed. All electronic data will be deleted from the server and device storage and any hardcopy data will be shredded prior to being disposed of. The informed consent states that if participants withdraw their consent, any prior use of the data by the research team cannot be altered.

5. STATISTICS AND METHODOLOGY

5.1. Statistical analysis plan

Participant characteristics will be described by summary statistics using means, standard deviations, medians, interquartile ranges, and percentages, as appropriate.

Objective 1 of this study is to calculate prevalence of non-communicable conditions, including risk factors and diseases. To do so, we will calculate the percentage of the sample meeting criteria for each risk factor and disease category. We will compare proportions by gender, age, and setting (urban vs. rural) using Chi-square test and test for associations using uni- and multivariate logistic regression. Further, we will calculate the FRS and WHO CVD risk score to estimate the 10-year risk for a CVD event in different subgroups.

For objective 2, to develop treatment cascades for the measured health conditions, we will use descriptive statistics. Based on the total number screened for the disease, we will calculate the following: the proportion of individuals who meet the criteria for the respective condition; of those who meet criteria, the proportion previously aware of their condition; of those aware of their condition, the proportion currently engaged in care; of those engaged in care, the proportion meeting the treatment target.

Objective 3 is to measure the association of socioeconomic factors with selected chronic conditions and risk factors. The sample for this analysis will include all households visited. To examine the association of household socioeconomic status with chronic health conditions and risk factors, we will conduct uni- and multivariate logistic regression analyses. Concentration curves and indices will be computed in order to determine the prevalence of food (in)security in the different socioeconomic groups. If food (in)security is dominant in one group, a decomposition analysis will be performed to determine the main drivers that contribute to the socioeconomic inequalities associated with food security.

Objective 4 is to assess the health-related quality of life in the overall study population and in population subgroups affected by diabetes, aHT, CVDRFs and CMDs, including differentiation between new diagnosis versus already enrolled in care, and well-controlled in care versus badly controlled in care. The value sets describe the health status of the different sets of population. The values will be measured according to a cardinal scale ranging from 0 (death) to 1 (perfect health). The value sets will be compared according to gender, setting (rural vs. urban) and NCD status using Chi-square test.

Sample-size

Sample size calculation was based on the estimated proportion of the population who would meet criteria for the primary NCDs of interest (CVD, DM, and CMDs) using the methods recommended in the WHO's step-wise approach to chronic diseases risk factors surveillance (STEPS). For each NCD, a representative sample based on a priori stratification variables will be selected from the population of the villages that comprise the two districts. For adults, the stratification variables are the following: gender (men vs. women), age (18 to <30 vs. ≥30), and setting (urban vs. rural). For minors (ages 10 - 17), we stratify by gender and setting only. Our sample size calculation accounts for the following factors: prevalence rate for each CVD (by gender, location and age, if available), level of precision of the estimate, confidence interval (CI), a design effect that accounts for multi-stage sampling design, and an anticipated non-response rate. The sample size calculator of the WHO STEPS survey was used[83], whereby all calculations assumed a 95% level of confidence and a design effect of 1.50.

Table 2 provides the detailed sample size calculations for each stratum of the main conditions to be assessed in this survey among the adult population. A total of 120 village-clusters (60 in rural areas and 60 in urban areas) are feasible to visit within the given timeframe and all will be visited during the study. The largest sample size required is for depression with 3040 adults needed in each setting (Table 2). We will therefore need to enroll approximately 50 adults per village sampled.

Table 2. Sample size calculation for the adult survey population

Condition by location	Sub-stratum 1: Gender	Sub-stratum 2: Age group	Estimated prevalence	Margin of error	Adjusting for anticipated non-response	Estimated sample size	Sample size per condition by setting
DM in urban	male	18-30y	0.02	0.02	0.95	**298**	1619
	male	above 30y	0.03	0.02	0.95	**441**	

	female	18-30y	0.02	0.02	0.95	**298**	
	female	above 30y	0.04	0.02	0.95	**582**	
DM in rural	male	18-30y	0.01	0.02	0.95	**150**	1039
	male	above 30y	0.02	0.02	0.95	**298**	
	female	18-30y	0.01	0.02	0.95	**150**	
	female	above 30y	0.03	0.02	0.95	**441**	
aHT in urban	male	18-30y	0.10	0.05	0.95	**218**	1141
	male	above 30y	0.15	0.05	0.95	**309**	
	female	18-30y	0.12	0.05	0.95	**256**	
	female	above 30y	0.18	0.05	0.95	**358**	
aHT in rural	male	18-30y	0.09	0.05	0.95	**199**	1071
	male	above 30y	0.14	0.05	0.95	**292**	
	female	18-30y	0.11	0.05	0.95	**238**	
	female	above 30y	0.17	0.05	0.95	**342**	
Substance use in urban	male	18-30y	0.15	0.05	0.90	**327**	2643
	male	above 30y	0.18	0.05	0.90	**378**	
	female	18-30y	0.05	0.02	0.90	**760**	
	female	above 30y	0.08	0.02	0.90	**1178**	
Substance use in rural	male	18-30y	0.15	0.05	0.90	**327**	2643
	male	above 30y	0.18	0.05	0.90	**378**	
	female	18-30y	0.05	0.02	0.90	**760**	
	female	above 30y	0.08	0.02	0.90	**1178**	
Depression in urban	male	18-30y	0.05	0.02	0.90	**760**	3040
	male	above 30y	0.05	0.02	0.90	**760**	
	female	18-30y	0.05	0.02	0.90	**760**	
	female	above 30y	0.05	0.02	0.90	**760**	
Depression in rural	male	18-30y	0.05	0.02	0.90	**760**	3040
	male	above 30y	0.05	0.02	0.90	**760**	
	female	18-30y	0.05	0.02	0.90	**760**	
	female	above 30y	0.05	0.02	0.90	**760**	
Anxiety in urban	male	18-30y	0.03	0.02	0.90	**466**	1864
	male	above 30y	0.03	0.02	0.90	**466**	
	female	18-30y	0.03	0.02	0.90	**466**	
	female	above 30y	0.03	0.02	0.90	**466**	
Anxiety in rural	male	18-30y	0.03	0.02	0.90	**466**	1864
	male	above 30y	0.03	0.02	0.90	**466**	
	female	18-30y	0.03	0.02	0.90	**466**	
	female	above 30y	0.03	0.02	0.90	**466**	
HepB in urban	Male	18-30y	0.07	0.03	0.90	**463**	1852
	male	Above 30y	0.07	0.03	0.90	**463**	
	female	18-30y	0.07	0.03	0.90	**463**	
	female	Above 30y	0.07	0.03	0.90	**463**	
HepB in rural	male	18-30y	0.07	0.03	0.90	**463**	1852
	male	Above 30y	0.07	0.03	0.90	**463**	

	female	18-30y	0.07	0.03	0.90	**463**	
	female	Above 30y	0.07	0.03	0.90	**463**	

Our approach to sample all households within a village will likely lead to oversampling. We nevertheless retain this approach for several reasons including the fact that having a larger number of clusters (i.e., villages) will ensure that the sample is more representative of the population. Furthermore, this survey aims to provide basic screening services for aHT and DM to all individuals who reside in the selected villages, therefore allowing us to provide services to a greater number of people. BP and blood glucose measurement will thus be offered to all adult individuals encountered during the campaign. HIV testing will be offered according to national Lesotho guidelines.

Based on the above sample size calculations (Table 2), but accounting for the imprecision in assumptions, including the different prevalence rates, we opt for the following target sample sizes with equal distribution between rural and urban setting:

Adults 18-30y: aim 2000 participants

Adults ≥30y: aim 4000 participants

Children/adolescent all 10-17y, aim ≥1000 participants (500 in rural and 500 in urban)

5.2. Handling of missing data

Analyses will use all available data, where possible. Our sample size estimates assume a small proportion of data (5 to 10%, depending on the measure) will be missing due to participants declining to answer or interviewer error. We plan to implement several data quality measures to reduce the number of missing responses (see Section 8.1).

5.3. Nested studies

5.3.1 Nested study 1

Objective: To assess the prevalence of sub-clinical end-organ damage in individuals diagnosed for DM and/or aHT and to compare it to individuals with normal blood pressure and normal blood glucose.

Rationale: As the prevalence of CVDRFs continues to rise in sub-Saharan Africa with its attendant morbidity and mortality, awareness of the proportion of newly diagnosed individuals already with sub-clinical end organ damage will contribute to a more complete documentation of the nature of the NCD burden in sub-Saharan Africa and inform the design and implementation of relevant interventions.

Participants: Among individuals participating in the survey, a subsample will be randomly selected for assessment of end-organ damage
Eligible are:

- Individuals who screen positive for at least one of the following conditions: DM or aHT
- “Controls”: Individuals screened negative for DM and aHT

Main outcomes: Prevalence of kidney disease, peripheral neuropathy, hypertensive heart disease and retinopathy. These outcomes are defined in Table 1 and described in Section 3.2 of the protocol.

Study design: Design will be cross-sectional. Participants will be randomly selected by the data collection software ODK to complete the assessments after information about DM and aHT diagnoses is available.

Sample size: This is an explorative study and there is no data that allows to anticipate the prevalence of end-organ damage in this population. We will use convenience sampling aiming for an end-organ damage assessment in ≥500 participants with aHT and/or DM and ≥100 participants without aHT or DM. Depending on interim-analyses the sample-size may be adjusted during the survey.

Measurement of end-organ damage

Kidney Disease (both for DM/aHT and controls): A spot urine sample as well as a venous blood sample obtained will be collected for point-of-care analysis of ACR in mg/g, and serum creatinine in µmol/l. Estimated glomerular filtration rate (eGFR) will be calculated electronically using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation based on serum creatinine, age, and sex.

Retinopathy (both for DM/aHT and controls): Using the Welch Allyn iExaminer System™, a non-mydriatic fundus photographic instrument, photographs of the optic disc, macular, blood vessels and the rest of the retina will be taken from both eyes. Ophthalmologists will examine these photographs, and stage retinopathy, where present, according to the International Clinical Diabetic Retinopathy Disease Severity Scale or Mitchel-Wong classification for diabetic and hypertensive retinopathy, respectively.

Peripheral neuropathy (only for DM and controls): Peripheral neuropathy will be assessed using a 10g monofilament. Five sites on both feet will be assessed: the plantar surfaces of the hallux and third toe, as well as the first, third and fifth metatarsal heads. Presence of sensation to the monofilament on examination will be scored 1, absence 0, for a maximum score of 10 and a minimum score of 0. Peripheral neuropathy will be considered present at a score of eight (8) or less.

Hypertensive heart disease (only for aHT and controls): The Philips Lumify Ultrasonography device will be used by trained research nurses in a focused echocardiographic procedure on individuals with hypertension to detect signs of hypertensive heart disease. A predefined set of images including measurements of size and function will be taken and stored in an external drive. Afterwards, they will be transmitted to a cardiologist for analysis. Assessment of left ventricular (LV) mass and dimensions will be performed according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging.

Data Analysis: Descriptive summary statistics such as mean, standard deviations, median, interquartile range and percentages will be used, as appropriate, to describe prevalence of end-organ damage among those with raised blood glucose or aHT, as well as among the controls. Inferential statistics will be conducted using logistic regression models to estimate odds ratios for development of end organ damage in the groups.

5.3.2 Nested study 2

Objective: To evaluate different pragmatic approaches for community-based arterial hypertension (aHT) screening:

i. To evaluate unattended automated blood pressure (BP) vs traditional BP measurement.
ii. To evaluate a novel 24-hour blood pressure measuring bracelet device (Actiia)™.[84]

Rationale: During community-based surveys, the prevalence of aHT tends to be overestimated because obtaining a second set of readings at a different time for confirmation of aHT for those with raised BP is often not practical. To obtain a more accurate picture, there is the need to develop an accurate, pragmatic screening protocol that accounts for the survey conditions and cultural context.

Main outcomes: Three pragmatic BP measurement approaches will be compared against a gold standard. The three approaches are: 1) traditional BP measurement approach, 2) automated BP measurement, and 3) using a novel 24-hour Aktiia bracelet. The gold standard will be a 24-hour ambulatory blood pressure measurement (ABPM). The outcome of this study will be measures of diagnostic accuracy, such as sensitivity, specificity, and positive and negative predictive values (see data analysis section).

Study design and sample size: For this nested study, we will use a cross-sectional design. Sample size is calculated using the sample size calculation methods of Buderer et al.[85] Based on presumed sensitivity of 84%, specificity of 79% of self-measurement methods,[86] and prevalence of hypertension of 30%, we estimate that a minimum of 172 people with aHT and 91 participants without would be required. Accounting for a non-response rate of 20% including for non-compliance during ABPM or device malfunction, 207 participants with aHT and 110 participants without aHT will be needed (317 in total).

Inclusion criteria: Adults with aHT and those with normal BP using traditional automated BP measurement devices, who live in urban/peri-urban areas (for feasibility of collecting devices the following day), will be randomly selected to participate in the study until the necessary sample size is achieved.

Data collection: First, informed consent will be sought from participants sampled for this sub-study (see ICF for blood pressure sub-study). Enrolled participants will have their BP measured using: 1) the traditional measurement approach, where three readings are obtained by a study research assistant, after 15 minutes of rest, and each subsequent reading taken two minutes apart. The average of the last two BP readings will be recorded. 2) An unattended automated device will be used to collect three serial blood pressure readings, one minute apart. 3) The Actiia™ bracelet and ABPM will be respectively applied to the wrist and upper arm of the participant for 24 hours. The unattended automated device will be used to collect further readings after retrieving the 24-hour devices. We will counterbalance the order in which the various BP readings are taken to mitigate an order effect.

Data Analysis: Data from ABPM will only be included in the analysis if a minimum of 20 daytime readings and seven nighttime readings are available. Daytime readings will be defined as occurring between 7am to 7pm; nighttime readings will be defined as occurring between 9pm to 6am (if participant is unsure of their awake and sleep times, after being asked initially). Participants will be considered to have raised BP if systolic BP is ≥ 140mmHg or diastolic BP is ≥ 90mmHg on automated BP measurement device; systolic BP ≥ 135mmHg, or diastolic BP is ≥ 85mmHg on unattended automated BP measurement. Participants will be considered confirmed as having aHT if present with at least one of the following:
i) ABPM average of ≥130/80mmHg; ii) daytime average of ≥135/85 mm Hg; or iii) nighttime average of ≥120/70 mm Hg).[87]

Participants' characteristics will be described using summary statistics such as mean, standard deviations, median, interquartile range and percentages, as appropriate. Using ABPM and the screening methods, participant BP will be categorized for each screening method into normotension, where the screening method is negative and ABPM normal; sustained hypertension, where screening

method is positive and ABPM positive; masked hypertension, where screening method is negative and ABPM positive; and white coat hypertension, where screening method is positive and ABPM negative. Measures of diagnostic accuracy (sensitivity, specificity, positive and negative predictive values, and area under the receiver operating characteristic curve) will be calculated using ABPM as gold standard.

5.3.3 Nested study 3

Objective: To examine the sensitivity and specificity of using shortened screening tools for depression and anxiety.

Rationale: The health system in Lesotho (as well as other low-resource settings) is overburdened with high patient volumes and limited number of providers. At the same time, there is growing global recognition that CMD assessment and treatment must be incorporated into primary health care. This will only be possible with short, validated screening tools for CMDs. In Lesotho, no such screening tools for depression and anxiety have been validated yet, though there is a growing trend to do so in other sub-Saharan African countries.[88]

Main outcomes: Full versions of the Patient Health Questionnaire-9 (PHQ-9) to assess depression and the Generalized Anxiety Disorder-7 (GAD-7) to assess for anxiety will be administered. The shortened versions of these questionnaires are the PHQ-2 and GAD-2, which are comprised of the first two items of each questionnaire and assess the hallmark symptoms of each disorder (i.e., feeling sad and anhedonia for depression and feeling nervous and uncontrolled worry for anxiety). The outcome of this study will be measures of diagnostic performance of the PHQ-2 and GAD-2, as compared to the PHQ-9 and GAD-7, respectively.

Study design and sample size: The sample size enrolled will depend on the prevalence of disorders observed. When we assume a depression prevalence of 5% with a precision of 3% and a screener sensitivity of .91 and specificity of .70, we would need a sample size of 6992 adult participants (≥ 18 years old). We will thus continually enroll all participants into this substudy (i.e., all participants will be administered the full GAD-7 and PHQ-9) and we will monitor the observed prevalence rate to determine the final sample size collected. Once we have our final sample, we will assess the predictive ability of using the first two items from each scale to identify participants who likely meet criteria for clinical levels of depression or anxiety.

Data analysis: Total scores on the PHQ-9 and GAD-7 will be considered the gold standard for assessing clinical levels of depression and anxiety, respectively. The screening results of the PHQ-2 and GAD-2 (positive vs. negative) will be compared against the total scores on PHQ-9 and GAD-7. Measures of diagnostic performance will then be assessed including sensitivity, specificity, positive and negative predictive values, and accuracy.

5.3.4 Nested study 4

Objective: To assess linkage to care and follow-up among participants found living with DM or aHT and not in care during the survey (new diagnosis as well as previously diagnosed but not in care).

Rationale: Linkage to care has been shown to be very low after community-based screening for chronic health conditions.[89]

Study design, participant inclusion and procedure: Survey participants who screen positive for DM or aHT, or previously diagnosed but are currently not in care, will be followed up at the health facilities to assess the proportion who are linked to care within 30 days after the survey and engagement in care over six months. Based on available

registers and a simple study documentation tool, the study team will assess who linked to care at the clinics within 30 days after the survey and engagement in care at six months. At 12 months, participants will be re-contacted and will be asked to complete several of the same assessments conducted at baseline to understand the degree to which their DM and/or aHT are well-controlled. Assessments will include blood pressure, RBG, HbA1c, serum creatinine, ACR, focused echocardiography, and eye examination.

Main outcome: Linkage to care, defined as attendance at one of the clinics in the two study districts within 30 days of referral. Engagement in care is defined as the maintenance of healthcare following initial linkage and requires adherence to scheduled clinic visits over six months. Follow-up assessment is the change between blood pressure and/or RBG from baseline to follow-up.

Secondary outcomes: Association between relevant participant socio-demographic and clinical characteristics and linkage to care.

Data analysis: The linkage to care will be described as a proportion. Uni- and multivariate logistic regression will be used to assess for potential associations between participant socio-demographic and clinical characteristics and linkage to care. Change in blood pressure and RBG will be modeled using longitudinal analyses such as mixed modeling or another appropriate statistical technique.

5.3.5 Nested study 5

Objective: To assess mental health linkage to care and follow-up for participants who report suicidality.

Rationale: There is currently limited data on whether referral procedures to provide mental health treatment to reduce risk for patients with moderate or high suicide risk are adequate.

Study design, participant inclusion, and procedure: Observational study of standard of care procedures. All enrolled participants in the parent study (≥ 10 years) who are deemed to be at moderate or high-risk of suicide based on clinical assessment will be enrolled. Participants who are at high-risk for suicide will be immediately transported to the nearest healthcare facility. High-risk participants are those that present with immediate risk to harm to self, due to high suicidal intent, access to means, and/or a suicide plan. Patients at moderate risk will be provided with a referral to the local psychiatric nurse. Moderate risk patients, though not in immediate danger to themselves, present with thoughts of self-harm and are judged to be at some risk for self-harm and/or suicide. Based on available registers and a simple study documentation tool, the study team will assess number and timing of patient follow-up visits for mental health care within 90 days after the survey. At 12 months, participants will be re-contacted and will be asked to complete several of the same assessments conducted at baseline to assess their mental health status, including depression and suicide risk, anxiety, and substance use.

Main outcomes: The primary outcomes are: whether the patient was linked to mental health care (yes/no) within 90 days, number of days to clinic attendance, number of follow-up visits, and whether patient was lost to follow-up within a three-month follow-up window. Follow-up assessment is the change in depression and suicide risk, anxiety, and substance use from baseline to follow-up.

Data analysis: Summary statistics such as mean, standard deviations, median, interquartile range and percentages will be used to summarize the main outcomes of the study. Descriptive statistics will be compared to available data from similar settings to

determine the adequacy of standard of care. Change in mental health measures will be modeled using longitudinal analyses such as mixed modeling or another appropriate statistical technique.

5.3.6 Nested study 6

Objective: To estimate the prevalence of active hepatitis B virus (HBV) infection, and to determine among those screened positive for HBs Ag, the level of liver cirrhosis using non-invasive markers of hepatic fibrosis (such as aspartate aminotransferase to platelet ratio index and fibroscan) and HBV replication to determine treatment eligibility according to the current WHO guidelines.

Rationale: Sub-Saharan Africa is increasingly affected by HBV-related morbidity and mortality. Contributing to this are high costs of diagnosis, lack of screening programs for early diagnosis and treatment, as well as insufficient data for adequate planning of resources, despite treatment options being available.

Study design, sample size and procedure: Design will be cross-sectional. Sample size is calculated based on an estimated prevalence of 7% according to currently modelled data for Lesotho by the Institute of Health Metrics and Evaluation.[90] Using an error margin of 3%, and anticipated non-response rate of 10%, a minimum of 1852 adults in urban and 1852 adults in rural areas will be required. However, we all participants who are enrolled in the full survey will complete the HBV testing.

The study procedure will be carried out as described under Section 4.3, and detailed on Table 1. Eligible participants are household members from a household of the surveyed area ≥10 years of age. From all eligible participants, the data collection tool will randomly select the needed sample size. Participants will be screened for HBsAg using a validated point-of-care device (Determine™ HBsAg point-of-care test).[77] From those participants that screened positive, venous blood will be collected, cooled and transported to the district hospital within 2 days and stored in a -80°C freezer for HBV viral load assessment at a later stage. Additionally, these participants will be referred to the district hospitals for appropriate work-up and care such as the assessment of the aspartate aminotransferase to platelet ratio index and fibroscan (if possible). The clinics providing follow-up support to participants enrolled in the study (as part of standard of care) will receive training and support by ComBaCaL. Participant medical records will be reviewed within 12 months to assess care outcomes (defined below).

Main outcomes: Population prevalence of HBsAg-positivity and prevalence of HBsAg positivity with eligibility for treatment in Lesotho.

6. REGULATORY ASPECTS AND SAFETY

6.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [3], the Human Research Act (HRA) and the Human Research Ordinance (HRO) [1] as well as other locally relevant regulations. The Project Leader acknowledges his responsibilities as both the Project Leader and the Sponsor.

The study research protocol and all associated documents will be submitted to the ethics board in Switzerland for initial review and to the Lesotho Ethics Committee. All future amendments will be submitted to the Ethikkommission Nordwest- und Zentralschweiz (EKNZ) and Lesotho Ethics Committee.

6.2 Notification of safety and protective measures (HRO Art. 20)

The project leader is promptly notified (within 24 hours) if immediate safety and protective measures have to be taken during the research project. The Lesotho Ethics Committee will be notified of these measures and of the circumstances necessitating them within seven days.

6.3 Serious events (HRO Art. 21)

If a serious adverse event occurs, the Lesotho Ethics Committee will be notified within seven days. The fieldwork staff will notify the study PIs of such an event within 48 hours and a report will be written to document the event, the severity and seriousness of the event, and its possible relationship to the study.

6.4 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval before implementation. Exceptions are measures that have to be taken immediately in order to protect participants or staff.

6.5 End of project

Upon project completion or discontinuation, the Ethics Committee is notified within 90 days.

7. FURTHER ASPECTS

7.1 Overall ethical considerations

By providing evidence on NCD burden and care, this project will inform program implementers and policy makers in Lesotho. The initial population-based survey will provide an overview of the NCD burden, evidence which will be essential for national NCD care planning. A carefully planned and executed multi-staged cluster sampling will be undertaken to ensure that study units are representative of the population in the two districts.

Participation in the study will be voluntary. Before entering a household to explain the study, study teams will ask for oral consent from the head of household or his/her representative. After entry, informed consent will be sought from all eligible and interested household members. Adequate time will be given and the project staff will be available to answer questions. Each member of the household agreeing to participate will provide written consent.

Individuals encountered who are not members of the household, or household members who are not randomly selected to take part in the survey, but who wish to receive some of the provided services (i.e., blood sugar, BP measurement, or HIV testing) will receive these services as part of a general service provision. However, they will not be included in the study. Participants who test positive for HIV as part of general service provision will be asked to sign a consent form to biobank their blood (see Biobank ICF).

Standard operating procedures will be developed to provide clear guidance to fieldwork teams to address any medical emergencies, such as hypertensive emergencies or severe hypoglycemia. Each fieldwork team will have a trained nurse who will promptly administer any initial life-saving care, after which the participant will be transported to a nearby clinic in a project vehicle. To ensure a thorough evaluation of the health of each participant, survey time for each participant is expected to take up to 1.5 hours (if participants are selected for the various sub-studies). Participants will be informed of their health parameters, with standardized medical counseling

offered, and referral made to a nearby clinic for appropriate care and follow-up where deemed necessary by the study clinical staff. Participants do not receive any remuneration for their participation in the study.

7.2 Risk-Benefit Assessment

We do not guarantee that participants will experience any direct health benefits from participation. However, we anticipate identifying newly diagnosed cases of NCDs and infectious diseases. Any newly diagnosed cases, or previously diagnosed cases which are not currently involved in care, will be referred to local health services. Participants are required to cover any costs of care (including transportation) provided outside of the study, including costs of follow-up visits after referral by the study team. Furthermore, although not a direct benefit of participation, we will inform participants that we plan to develop community-based treatment options that will improve care in the community for a variety of health concerns. Thus, participation in this study will help to achieve this goal.

The primary risks of study participation and corresponding mitigation strategies are outlined below.

Domain	Risk	Mitigation
Psychological	Psychological distress resulting from (1) screening positive to a disease or (2) being asked sensitive questions about psychological health	Study staff will be trained on asking questions and delivering screening results in a sensitive, non-judgmental manner. Study staff will refer participants to receive appropriate medical or psychological support for diagnosed conditions.
Social	Household disagreements from divulging of information by household members	All household members will be told that each person's interview is private and must be conducted individually. Interviews will be conducted in a private space to avoid other household members accessing information.
Medical	Bleeding, infection, pain, bruising after venous blood draw	Appropriate infection prevention and control measures such as use of gloves and disinfectant. Only staff with appropriate level of training will be involved (e.g., blood draws only performed by trained nurses).
Data	Threats to participant confidentiality	All staff will be trained in procedures to mitigate loss of participant confidentiality. These procedures include safe storage of data (e.g., data stored on a secure server in Switzerland), limited access to identifiable data, and strategies for contacting and interacting with study participants that maintains their confidentiality.

7.3 Rationale for the inclusion of vulnerable participants

We are enrolling minors aged 10 to 17 in the study to understand early risk for NCDs, including lifestyle factors such as nutrition, exercise, and substance use. NCDs in adolescents, particularly obesity and diabetes, is a growing global epidemic.[91] Understanding the prevalence of NCDs and

relevant risk factors is essential to design effective interventions for adolescents to address these concerns.

8. QUALITY CONTROL AND DATA PROTECTION

8.1 Quality measures

We have several strategies to ensure collection of high-quality data. All survey data collected in the field will be directly entered using a tablet and transmitted to the server regularly. The data will be stored on a server in Switzerland. The use of a direct entry technology (rather than copying paper-based source data onto another platform) reduces errors. We will ensure that the fieldwork teams have adequate supplies and materials so that data collection and safe transportation of collected blood samples will be possible.

The data will be monitored regularly by trained staff in Lesotho with additional data quality checks from senior data managers in Switzerland. Each participant record will be checked for accuracy and consistency. Any aberrant response or unjustified missing data will be identified. These queries will be taken to the fieldwork teams and any data errors corrected. Furthermore, Lesotho-based monitoring teams will visit field activities on a regular basis and provide direct supervision to ensure accuracy of data entry in the field. Switzerland-based project staff will review data on a bi-weekly basis and provide reports on data quality. All staff will be trained according to study specific standard operating procedures. Weekly meetings will be held between fieldwork teams and monitoring teams to identify and rectify issues with regard to study implementation.

Our team will use an electronic dashboard system to monitor the progression of data collection. The dashboard will provide daily summaries of the data uploaded to the server. The dashboard will track coverage and completion of data collection by district, village, and participant demographics (i.e., age group, gender, rural vs. urban). The dashboard will also allow monitoring of data completion by individual participants. This will allow us to quickly identify if there is missing data at the item level for a given participant and recontact the participant if needed.

8.2 Data recording and source data

All data, including household and individuals' information will be collected and recorded on mobile tablet devices using an application programmed in Open Data Kit (ODK), an open-source mobile data collection application. The source data will be compiled through the questionnaires and field laboratory tests. The information will be recorded in preprogrammed electronic Case Report Forms (eCRFs). All data fields have been designed for purposes of the survey and will contain original records.

8.3 Confidentiality and coding

Project data will be handled with the utmost discretion and will only be accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. Participants in the survey will be assigned a unique survey identification number (survey ID). The investigators will keep a separate confidential subject identification list that matches identifying codes with the participants' names, phone numbers, and other identifiable information (ID log). Survey information will be collected on the digital Case Report Forms (CRFs), identified with the participant survey ID.

Digital CRFs will be kept in password-protected tablets. Only trained research staff on the study will have a password. When not in use, these will be kept in locked cupboards. All paper forms,

including hardcopies of the ID log and the ICFs, will be filed in locked cabinets in the SolidarMed research office in Lesotho.

Samples for laboratory testing and biobanking at the Seboche Hospital Laboratory will be labelled according to local requirements and transported to the laboratory in cooler boxes, where they will be processed within 48 hours. Samples for Hepatitis B DNA viral load and genotyping will be shipped in batches to Applied Microbiology Research Laboratory at University Hospital Basel. Before shipment, a Material Transfer Agreement will be submitted to the Lesotho ethics board.

Stored plasma from participants screened positive for HIV and Hepatitis B will be stored at the -80 degrees freezer at Seboche Hospital Laboratory. Stored samples will be labelled with the unique participant number only. The -80 degrees freezer is located in a restricted area, which is only accessible to authorized personnel.

8.4 Retention and destruction of study data and biological material

An anonymized dataset will be deposited in an open-access data repository at the end of the project and once the objective specified in the protocol have been addressed. The ICFs and ID log will be kept in Lesotho at the SolidarMed office in a locked cupboard for at least ten years. The serum tubes may be kept up to a maximum of 5 years inside the -80 freezer at Seboche Hospital Laboratory to allow for further serological, virological or biochemical analyses. No human DNA will be stored/analyzed.

8.5 Translations and reference language

The reference language for all study documents is English. Study documents requiring translation (e.g., consent form, certain questionnaires in the CRF) will be translated to Sesotho by a bilingual English and Sesotho speaker, back-translated into English, and the two versions compared to ensure appropriate translation.

9. FUNDING / PUBLICATION / DECLARATION OF INTEREST

9.1. Funding

This survey is funded by the Swiss Development Cooperation, through a grant issued to SolidarMed. Findings of the survey will be shared at relevant stakeholder meetings in Lesotho as well as at national and international scientific conferences.

9.2. Publication and dissemination of results

Results of this study will be submitted to peer-reviewed journals and conference presentations. Preference will be given to journals with an open access publication model. All investigators and collaborators listed on the research protocol will have the opportunity to contribute to the publication of results. To facilitate capacity building and foster academic careers in Lesotho, the study team commits to encourage and support publications by Basotho collaborators.

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