Statistical analysis: SALT study

1. Implementation of the intervention

Salt replacement will be progressively implemented over six months in each village. The intervention will contemplate interactions with families as well as bakeries, community kitchens, food vendors including street vendors, and restaurants. Ideally, replacement will require a complete exchange of ordinary salt. The assessments of salt consumption will be carried out using questionnaires and weighing of salt containers at randomly selected households over time, and also by evaluating supply chain management indicators such as rate of delivery of the salt substitute to each family or food vendors.

Table 1: Stepped wedge design

	Time period						
Cluster	1	2	3	4	5	6	7
Village 1	0	1	1	1	1	1	1
Village 2	0	0	1	1	1	1	1
Village 3	0	0	0	1	1	1	1
Village 4	0	0	0	0	1	1	1
Village 5	0	0	0	0	0	1	1
Village 6	0	0	0	0	0	0	1

2. Structure of the data

Outcome variables: Systolic blood pressure (SBP), diastolic blood pressure (DBP), and body mass index (BMI)

Time: Time at each visit and time according to the stage (0,…, 6)

Intervention: Binary variable (intervention or control)

Clusters: Village, family and individual

3. Statistical Analysis

3.1 Primary outcomes: Systolic and diastolic blood pressure

We considered the following model

$$Y_{ijkl} = \mu + \alpha_i + \gamma_j + \varphi_k + \beta_l + \theta X_{kl} + \varepsilon_{ijkl} \qquad (1)$$

Where:

- Y_{ijkl} be the systolic blood pressure measured of individual i, in family j, at cluster k in time l
- μ is the mean outcome in the control group at time $T = 0$ (baseline)
- α_i is a random intercept of individual i ($\alpha_i \sim N(0, \tau^2)$)
- γ_j is a random intercept for family j ($\alpha_j \sim N(0, \omega^2)$)
- φ_k is a random intercept of cluster k ($\varphi_k \sim N(0, \vartheta^2)$)
- β_l is the fixed time effects corresponding to lag l ($l = 1, \dots, 6$)
- X_{ij} is an indicator for the treatment mode in village i at time j
- θ is the overall effect of the intervention

Stata code:

```
mixed sbp i.intervencion i.time || codvilla: || codhogar: || codigo:,
cov(uns) vce(cluster codvilla)
```

As a sensitivity analysis, we will consider three scenarios

a) <u>To test whether the effect of the intervention is different for each lag as described by Hughes et. al (2015)</u>

$$Y_{ijkl} = \mu + \alpha_i + \gamma_j + \varphi_k + \beta_l + \theta_m S_{klm} + \varepsilon_{ijkl} \qquad (2)$$

Where S_{klm} is equal to 1 if village l in time interval k has been in the intervention for m intervals since the introduction of the intervention and 0 otherwise.

Stata code:

```
mixed sbp i.Lag i.time || codvilla:  || codhogar: || codigo: , cov(uns)
vce(cluster codvilla)
```

Then, we evaluated the hypothesis that the effect of the intervention is the same regardless of the number of lags post intervention (i.e. H_0: $\theta_1 = \theta_2 = \theta_3 = \theta_4 = \theta_5$). This comparison did not consider the robust estimation of the variance.

Stata code:

```
mixed sbp i.Lag i.time || codvilla:  || codhogar: || codigo: , cov(uns)
estimate store sA
mixed sbp i.intervencion i.time || codvilla: || codhogar: || codigo:,
cov(uns)
estimate store sB
```

```
lrtest sA sB    // Hipotesis testing
```

b) To adjust for other covariates

To extend (1) by adjusting for sex, age, wealth index, education levels, and BMI at baseline

Stata code:

```
mixed sbp i.intervencion i.time sexo edad1 bmi0 i.eduacat i.xassets ||
codvilla:  || codhogar: || codigo: , cov(uns) vce(cluster codvilla)
```

3.2. Secondary outcome: Time to hypertension

Let T be the time to hypertension diagnostic, then the instantaneous risk of hypertension (hazard) is

$$\lambda_{ij}(t) = \lambda_0(t)\alpha_i \exp(X_{ij}\beta)$$

where α_i is the village-level frailty and it is assumed to follow a gamma distribution, X_{ij} is whether or not village i receive the intervention in interval j

Computing code

```
keep if ht50 == 0                      // Keep persons without hypertension at baseline

stset dtime , id(codigo) failure(ht5)

xi:stcox i.intervencion, share(codvilla) hr
```

References

1. Scott, JM., decamp A., Juraska, M., Fay, MP., and Gilbert, PB. Finite-sample corrected generalized estimationg equation of population average treatment effects in stepped wedge cluster randomized trials. SMMR, 2017; 26(2): 583-597
2. Hughes, JP., Granston, TS., and Heagerty, PJ. Current issues in the Design and analysis of stepped wedge trials. Contemp Clin Trials. 2015; 45(0) 55-60.
3. Durovni, B., Saraceni, V., Moulton, L. H., Pacheco, A. G., Cavalcante, S. C., King, B. S., & Golub, J. E. (2013). Effect of improved tuberculosis screening and isoniazid preventive therapy on incidence of tuberculosis and death in patients with HIV in clinics in Rio de Janeiro, Brazil: a stepped wedge, cluster-randomised trial. *The Lancet infectious diseases*, *13*(10), 852-858.

Supplementary Table 1: Description of the study population at baseline by participating villages

	Village A (n=534)	Village B (n=449)	Village C (n=329)	Village D (n=414)	Village E (n=328)	Village F (n=322)
Sex						
Female	245 (45.7%)	221 (49.4%)	167 (50.8%)	224 (54.1%)	171 (52.1%)	169 (52.5%)
Age						
Mean (SD)	44.5 (16.8)	44.8 (18.8)	42.6 (16.8)	38.9 (14.5)	48.8 (18.4)	40.0 (15.9)
18-29 years	120 (22.4%)	121 (27.1%)	90 (27.4%)	131 (31.6%)	61 (18.6%)	110 (34.2%)
30-44 years	174 (32.5%)	133 (29.8%)	109 (33.1%)	162 (39.1%)	95 (29.0%)	107 (33.2%)
45-64 years	173 (32.3%)	121 (27.1%)	90 (27.4%)	98 (23.7%)	98 (29.9%)	76 (23.6%)
≥65 years	69 (12.9%)	72 (16.1%)	40 (12.2%)	23 (5.6%)	74 (22.6%)	29 (9.0%)
Wealth Index						
Bottom	185 (34.6%)	176 (40.7%)	111 (33.8%)	61 (15.2%)	84 (26.1%)	72 (23.1%)

Middle	177 (33.2%)	123 (28.5%)	123 (37.5%)	140 (34.8%)	113 (35.1%)	109 (35.1%)
Top	172 (32.2%)	133 (30.8%)	94 (28.7%)	201 (50.0%)	125 (38.8%)	130 (41.8%)
Education						
<7 years	191 (35.6%)	177 (39.6%)	108 (32.8%)	110 (26.6%)	136 (41.5%)	114 (35.4%)
7-11 years	238 (44.4%)	200 (44.7%)	155 (47.1%)	203 (49.0%)	132 (40.2%)	162 (50.3%)
≥12 years	107 (20.0%)	70 (15.6%)	66 (20.1%)	101 (24.4%)	60 (18.3%)	46 (14.3%)
BMI						
Mean (SD)	27.4 (4.9)	26.4 (4.3)	26.8 (4.5)	27.5 (4.4)	27.2 (4.9)	27.8 (4.6)
Normal Weight	173 (32.6%)	167 (38.5%)	115 (35.9%)	114 (28.1%)	104 (32.8%)	85 (27.5%)
Overweight	208 (39.3%)	189 (43.6%)	135 (42.2%)	182 (44.8%)	130 (41.0%)	141 (45.6%)
Obese	149 (28.1%)	78 (17.9%)	70 (21.9%)	110 (27.1%)	83 (26.2%)	83 (26.9%)
SBP [mean (SD)]	113.9 (15.7)	114.5 (15.9)	113.8 (18.4)	110.6 (16.2)	111.9 (19.3)	113.5 (17.2)

DBP [mean (SD)]	73.3 (9.8)	73.1 (9.5)	73.6 (9.9)	71.8 (9.8)	71.3 (10.8)	72.1 (11.2)
Hypertension						
Yes	91 (17.1%)	90 (20.5%)	59 (18.2%)	56 (13.6%)	79 (24.8%)	53 (16.9%)
Type 2 diabetes						
Yes	23 (4.3%)	10 (2.2%)	11 (3.3%)	13 (3.1%)	15 (4.6%)	15 (4.7%)

* For comparison between villages (study sites).

Supplementary Table 2: Effect of the intervention on blood pressure evaluating a lag (delayed) effect

	Systolic blood pressure		Diastolic blood pressure	
	Coefficient (95%CI[a])	**p-value**	**Coefficient (95%CI[a])**	**p-value**
Lag				
1	-1.29 (-2.01; -0.57)	<0.001	-0.82 (-1.37; -0.27)	0.004
2	-1.42 (-2.54; -0.31)	0.012	-0.65 (-1.39; 0.08)	0.081
3	-1.56 (-3.01; -0.04)	0.044	-0.95 (-1.83; -0.07)	0.034
4	-1.93 (-3.15; -0.04)	0.002	-0.95 (-1.71; -0.19)	0.014
5	-2.37 (-3.64; -1.10)	<0.001	-1.27 (-2.17; -0.37)	0.006
6	-1.26 (-2.81; 0.29)	0.112	-0.68 (-1.72; 0.36)	0.200

We evaluated the hypothesis that the effect of the intervention is the same regardless of the number of lags post intervention (i.e. H_0: $\theta_1 = \theta_2 = \theta_3 = \theta_4 = \theta_5$).
[a] Robust: The standard error allow for intra-class correlation

Supplementary Table 3: Effect of the intervention on hypertension incidence

	Control period*	Intervention period*	Time and cluster adjusted model† HR (95% CI)	Fully adjusted model†** HR (95% CI)
Hypertension (new cases)[1]	79	102		
Time at risk	1983.3 person-years	2777.8 person-years		
Incidence rate	3.98	3.67		
Intervention			***	0.41 (0.27 – 0.62)
p-value			-	< 0.001
Hypertension (as in baseline)[2]	107	133		
Time at risk	1961.1 person-years	2712.3 person-years		
Incidence rate	5.46	4.90		
Intervention			0.49 (0.34 – 0.71)	0.45 (0.31 – 0.66)
p-value			< 0.001	< 0.001

Cox proportional hazard modeling on a calendar time axis to account for secular trends with gamma-distributed random effects for village-level shared frailty was conducted to compare the instantaneous risk of hypertension in those who received a salt substitute with that in the control period

*Does not account for observations nested within households and villages

†Only accounts for clustering at the village level

**Adjusted by age, sex, education, wealth index, and body mass index
*** Non convergence of the optimization
[1] Hypertension was defined according to blood pressures measurements only.
[2] Hypertension was defined according to blood pressures measurements and considering the diagnosis of a physician and current treatment.

Supplementary Table 4: Details 24-hour urine samples

	Sample at baseline (n = 602)	**Sample at the end** (n = 605)
Sex female (%)	334 (55.5%)	315 (52.1%)
Age, in years (Mean ± SD)	45.5 (17.0)	47.5 (16.9)
Village		
A	138 (22.9%)	124 (20.5%)
B	123 (20.4%)	122 (20.2%)
C	71 (11.8%)	75 (12.4%)
D	91 (15.1%)	102 (16.9%)
E	90 (15.0%)	97 (15.9%)
F	89 (14.8%)	85 (14.1%)
Sodium, in gr (Mean ± SD)	3.94 (1.86)	3.95 (1.83)
Potassium, in gr (Mean ± SD)	1.97 (1.20)	2.60 (1.20)
Creatinine, in mg (Mean ± SD)	1119.6 (442.5)	1255.4 (525.2)