ONLINE SUPPLEMENT

DOES BLOOD PRESSURE INEVITABLY RISE WITH AGE? LONGITUDINAL EVIDENCE AMONG FORAGER-HORTICULTURALISTS

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Short title: Blood pressure change with age and modernization

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METHODS

Village sample. Villages can be grouped based on decreasing access to market: Near Town (n=752 adults, 17 villages, average 18 km from San Borja), Lower Maniqui River (n=330, 6 villages, 23 km), Central River (n=261, 16 villages, 40 km), road to Rurrenabaque (n=70, 8 villages, 48 km), Forest (n=318, 11 villages, 56 km), Upper Maniqui River (n=276, 9 villages, 64 km), Mission (n=203, 1 village, 66 km), and Quiquibey River (n=59, 8 villages, 74 km). The following villages were added in 2010 and only sampled once: all villages along the road to Rurrenbaque, all villages along the Quiquibey River, 12 of the Near Town villages, one Forest village, 15 Near River villages, and one Lower Maniqui River village.

Medical rounds. Data were collected during annual medical exams of the Tsimane Health and Life History Project. From 2002 to 2004, a mobile medical team made annual visits to 18 villages, obtaining blood pressure measurements during routine medical exams. Efforts were made to sample all present individuals. An additional 7 villages were sampled from 2005 to 2009. From 2010 to 2011, medical exams on all adults age 40+ were conducted in a clinic in San Borja. An additional 45 villages were added to the sample in 2010. Adults from these 45 villages were only sampled once. Clinical exams are given by Bolivian physicians with the assistance of bilingual Spanish-Tsimane translators. Additional details are given here[1].

Age estimation. Ages were assessed by cross-checked demographic interviews, as has been described elsewhere[2]. These include using known ages from written records, relative age lists, dated events, photo comparisons of people with known ages and cross-checking of information from independent interviews of kin. In constructing relative age lists, multiple informants were used for each five year age grouping of individuals, and inconsistencies were investigated and resolved. The photo comparison method used a sample of 70 photos of individuals with known ages. For older individuals, 50 photos of men and women from ages 50-75 were used. Each of these methods provides a roughly independent age estimate. When all estimates yield a date of birth within a 3-year range, the average was used unless one or two estimates were judged to be superior.

DATA ANALYSIS

Estimation of individual rates of blood pressure change. To estimate individual longitudinal rates of change, BP values and time points were first centered on the mean blood pressure value and median time-point for a given individual, such that blood pressures were recoded as positive or negative changes from the subject's mean, and times were recorded as days before or after the subject's median reading date. Linear models were fit to blood pressure change including subject PID, a subject-by-time interaction, season of exam, and pregnancy status as control variables. Fitting all slopes in one model, instead of separate models for each subject, facilitated estimation of population values for control variables. Parameter values for rates of blood pressure changes were then obtained from the subject-by-time interaction parameters. Slopes based on only two data points had large variances and showed evidence of regression to the mean. In order to analyze these slopes we therefore had to determine how many data points were required for an accurate slope estimate. To examine the effect of number of measures on slope estimates we performed a simple simulation. Beginning with individuals with six or more observations we randomly sampled different numbers of consecutive observations from each individual. We then examined the standard deviation of the slopes obtained. The results show that the standard

deviation around the mean slope declines with increasing number of observations (Figure S7). For our data, however, requiring six or more observations would drastically decrease sample size. We therefore estimated the standard error of the mean that would be obtained from our sample, given different inclusion criteria to identify the "optimal" trade-off between accuracy and sample size. We found that the standard error was minimized by including only individuals with five or more observations. For longitudinal analyses we therefore use this inclusion criterion.

REFERENCES

1 Gurven, M., Kaplan, H., Winking, J., Rodriguez, D., Vasunilashorn, F., Kim, J., Finch, C., and Crimmins, E. Inflammation and infection do not promote arterial aging and cardiovascular disease among lean Tsimane forager-horticulturalists. *PLoS One*. 2009; 4:e6590.

2 Gurven, M., Kaplan, H. & Zelada Supa, A. Mortality experience of Tsimane Amerindians: regional variation and temporal trends. *American Journal of Human Biology*. 2007; 19:376-398.

Table S1. Number of repeat samples and hypertension diagnoses across repeat sampling

	# of Times Sampled									
Age Group	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Total**
20-29	193	164	122	105	54	33	11	7	0	689
30-39	61	51	67	96	52	36	28	5	3	399
40-49	236	24	43	47	74	32	22	11	2	491
50-59	120	16	18	28	28	17	16	5	0	248
60-69	108	12	24	11	22	9	8	2	0	196
70+	153	12	10	21	20	3	3	3	0	225
Total	871	279	284	308	250	130	88	33	5	2248
Total Obs.	871	558	852	1232	1250	780	616	264	45	6468
Never Hyper	92.2%	93.5%	88.4%	91.9%	86.4%	80.0%	84.1%	72.7%	40.0%	89.8%
Hyper Only Once	7.8%	6.5%	7.7%	6.2%	10.0%	16.9%	9.1%	18.2%	40.0%	8.5%
Hyper More Than	-	0.0%	3.9%	1.9%	3.6%	3.1%	6.8%	9.1%	20.0%	2.9%
Hyper Always	7.8%	0.0%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	3.1%

Table S2. Sample size for all variables by medical round

	Medical round and date (month/year)								
Variable	**(1) 8/03-12/03**	**(2) 1/04-6/04**	**(3) 7/04-12/04**	**(4) 1/05-8/05**	**(5) 10/05-7/06**	**(6) 8/06-8/07**	**(7) 9/07-8/08**	**(8) 10/08-10/09**	**(9) 12/09-12/10**
SBP	276	279	268	321	865	1117	1107	1186	1098
DBP	276	279	268	321	865	1117	1106	1186	1098
Pregnant	276	279	268	321	865	1117	1107	1186	1098
Height	184	143	250	115	840	1116	1104	1184	1057
Weight	184	142	247	115	852	1116	1103	1184	1057
BMI	183	141	246	115	839	1115	1102	1183	1056
Spanish fluency	193	201	210	247	658	863	945	1084	490
Years of schooling	192	197	209	241	648	851	934	1064	489
Smoking	179	182	172	199	586	759	700	712	508
Distance to San Borja	269	275	261	319	851	1100	1088	1168	1018

Table S3. Two-stage mixed models. Stage 1 models have a random slope and intercept for each individual in the study, with blood pressure (SBP, DBP, PP) as the dependent variable. Stage 2 models are generalized additive models that use the individual random-effect slopes plus population main effects from Stage 1 as the dependent variable to model associations with individual level slope, with the overall age-pattern in the slopes modeled with thin-plate splines. Parameter values are in units of change per decade. Only individuals with data for all variables and at least two observations were included (n=695 individuals, n=2,876 observations).

Stage 1 Main effects (mm Hg)		**SBP**			**DBP**			**PP**		
		B	**SE**	**p**	**B**	**SE**	**p**	**B**	**SE**	**p**
Constant		94.5	2.4	<0.01	57.6	1.6	<0.01	36.3	1.7	<0.01
Sex (Male)		2.7	1.0	<0.01	1.4	0.6	0.02	1.1	0.7	0.11
BMI		0.6	0.1	<0.01	0.4	0.06	<0.01	0.3	0.07	<0.01
Pregnant		-2.8	1.0	<0.01	-3.3	0.7	<0.01	0.4	0.8	0.63
Smoking tercile										
	1st	-1.2	0.9	0.21	-1.4	0.6	0.02	0.21	0.7	0.75
	2nd	1.1	1.2	0.34	0.5	0.8	0.55	1.1	0.8	0.21
	3rd	0.5	1.3	0.68	-0.4	0.9	0.62	1.2	0.9	0.19
Spanish fluency	None	0			0			0		
	Moderate	1.1	0.8	0.14	0.5	0.5	0.32	0.5	0.6	0.38
	Fluent	-1.1	1.0	0.27	0.4	0.7	0.51	-1.8	0.7	0.01
Years of Schooling		0.1	0.1	0.58	0.1	0.08	0.23	0.01	0.09	0.91
Distance to San Borja (per 10 km)		-0.3	0.1	0.04	-0.1	0.1	0.29	-0.2	0.1	0.13
Season	Wet	0			0			0		
	Dry	3.9	0.6	<0.01	2.8	0.4	<0.01	1.0	0.5	0.04
	Intermediate	-0.6	0.59	0.33	0.02	0.4	0.97	-0.6	0.5	0.26
		edf	**Ref.df**	**p**	**edf**	**Ref.df**	**p**	**edf**	**Ref.df**	**p**
Age Splines	Female	3.1	3.1	<0.01	1	1	<0.01	3.4	3.4	<0.01
	Male	3.4	3.4	0.03	2.6	2.6	<0.01	4.2	4.2	<0.01

Table S3 continued on next page

Table S3 continued

Stage 2 **BP slopes (mm Hg/decade)**		**SBP**			**DBP**			**PP**		
		B	**SE**	**p**	**B**	**SE**	**p**	**B**	**SE**	**p**
Constant		2.0	0.4	<0.01	0.9	0.2	<0.01	0.6	0.4	0.12
Sex (Male)		-2.7	0.1	<0.01	0.03	0.07	0.65	-3.0	0.1	<0.01
BMI		0.02	0.01	0.27	0.00	0.01	0.91	0.03	0.02	0.07
Smoking tercile										
	1st	-0.1	0.1	0.37	-0.03	0.07	0.63	-0.2	0.1	0.16
	2nd	-0.01	0.2	0.97	0.1	0.08	0.25	-0.1	0.2	0.41
	3rd	-0.02	0.2	0.90	0.05	0.09	0.59	-0.08	0.2	0.65
Spanish fluency	None									
	Moderate	0.05	0.1	0.65	0.07	0.06	0.26	0.01	0.1	0.93
	Fluent	0.08	0.1	0.55	0.06	0.07	0.41	0.2	0.2	0.28
Years of schooling		0.01	0.02	0.63	0.01	0.01	0.63	0.01	0.02	0.60
Distance to San Borja (per 10 km)		0.03	0.02	0.15	0.01	0.01	0.70	0.08	0.02	<0.01
		edf	**Ref.df**	**p**	**edf**	**Ref.df**	**p**	**edf**	**Ref.df**	**p**
Age Splines	Female	7.2	8.2	<0.01	6.1	7.3	0.184	7.5	8.4	<0.01
	Male	6.2	7.4	<0.01	2.7	3.4	<0.01	7.6	8.5	<0.01

Table S4. Variance in blood pressure and change in blood pressure by age and sex for Tsimane and NHANES 2005-2006. Cross-sectional (CS) Tsimane values are based only on the largest medical round; slopes were estimated from longitudinal (L) data on individuals with at least five years between first and last observations. P-values represent F-test comparison of variance with a Bonferroni correction for multiple comparisons. p<0.01 comparing Tsimane vs. NHANES BP variance, except for females aged 60+ (p=0.92).

		Variance						**P-value**		
		Tsimane				**NHANES**		**Males vs. Females**		
		Pressures (CS)		**Slopes (L)**		**Pressures (CS)**		**Pressure**	**Slopes**	**Pressure**
Measure	**Age**	**Females**	**Males**	**Females**	**Males**	**Females**	**Male**	**Tsimane**	**Tsimane**	**NHANES**
SBP	22 - 39	68.9	60.9	3.76	3.73	102.9	140.8	1.00	1.00	<0.01
	40-59	188.0	87.6	7.55	3.49	320.6	252.7	<0.01	<0.01	<0.01
	60+	454.7	115.7	11.52	8.55	600.4	426.9	<0.01	1.00	<0.01
DBP	22 - 39	46.3	70.1	2.12	3.31	119.4	167.8	<0.01	0.11	<0.01
	40-59	71.1	62.2	3.22	2.99	125.9	153.4	1.00	1.00	0.05
	60+	157.1	83.8	3.55	2.25	301.4	203.8	0.05	1.00	<0.01
PP	22 - 39	47.6	80.3	2.65	2.62	127.9	205.2	<0.01	1.00	<0.01
	40-59	95.1	69.0	4.55	2.30	241.2	189.3	0.17	<0.01	<0.01
	60+	190.5	89.7	6.27	5.46	685.1	444.5	0.01	1.00	<0.01

Table S5. Pairwise comparison of variance in blood pressure and change in blood pressure between age groups within each sex in the last medical round for Tsimane and NHANES 2005-2006. P-values represent F-test comparison of variance with a Bonferroni correction for multiple comparisons. CS refers to cross-sectional analysis and L refers to longitudinal analysis.

		p-value					
		Tsimane				NHANES	
		Pressures (CS)		Slopes (L)		Pressures (CS)	
Measure	Comparison	Females	Males	Females	Males	Female	Males
SBP	22 - 39 vs. 40 - 59	<0.01	0.03	<0.01	1.00	<0.01	<0.01
	22 - 29 vs. 60+	<0.01	<0.01	<0.01	0.02	<0.01	<0.01
	40 - 59 vs. 60+	<0.01	0.66	0.75	<0.01	<0.01	<0.01
DBP	22 - 39 vs. 40 - 59	<0.01	1.00	0.12	1.00	1.00	0.93
	22 - 29 vs. 60+	<0.01	1.00	0.36	0.87	<0.01	0.03
	40 - 59 vs. 60+	<0.01	0.54	1.00	1.00	<0.01	<0.01
PP	22 - 39 vs. 40 - 59	<0.01	1.00	0.04	1.00	<0.01	1.00
	22 - 29 vs. 60+	<0.01	1.00	0.02	0.04	<0.01	<0.01
	40 - 59 vs. 60+	<0.01	0.75	1.00	<0.01	<0.01	<0.01

TABLE S6. Probability of overweight or obesity (BMI>=25 kg/m2) and obesity (BMI>=30 kg/m2) in mixed-effects regression models with random intercept and age parameters, controlling for physician, medical round, season, and pregnancy status (n=3,411 observations for 1,136 individuals)

	Probability of overweight or obese				**Probability of obese**			
Predictor	Odds Ratio	95% Wald Confidence Limits		P	Odds Ratio	95% Wald Confidence Limits		p
Age	1.2			<0.01	1.2			<0.01
Age^2	0.99			<0.01	0.99			<0.01
Sex (Female)	1.8	1.4	2.5	<0.01	6.3	3.0	13.1	<0.01
Pregnant	1.7	1.2	2.5	<0.01	1.4	0.7	2.9	0.32
Region								
Downriver	1.7	1.3	2.4	<0.01	1.5	0.8	2.9	0.04
Mission	0.8	0.6	1.2	0.04	0.5	0.2	1.1	0.03
Forest	1.2	0.8	1.7	0.46	1.2	0.6	2.6	0.32
Upriver (vs. Near Town)	0.9	0.6	1.2	0.08	0.9	0.4	1.9	0.93
Spanish fluency								
None	0.5	0.4	0.7	<0.01	0.5	0.3	1.1	<0.01
Moderate (vs. Fluent)	1.1	0.8	1.4	<0.01	1.4	0.7	2.5	<0.01
Years of schooling	1.1	1.04	1.1	<0.01	1.1	1.01	1.2	0.03
Smoking								
Low	1.2	0.9	1.6	0.81	0.99	0.5	1.9	0.43
Moderate	1.1	0.8	1.6	0.77	0.5	0.2	1.5	0.03
High	1.1	0.8	1.6	0.66	1.3	0.5	3.3	0.8
Unknown (vs. None)	1.6	0.96	2.6	0.15	4.03	2.0	8.3	<0.01

TABLE S7. Regional differences in hypertension risk factors by sex. Yellow refers to region(s) with highest potential risk. Blue refers to region(s) with lowest expected risk.

	Females						Males					
Variable	Forest (57 km)	Upriver (62 km)	Downriver (22 km)	Fatima (66 km)	Near Town (18 km)	p	Forest (57 km)	Upriver (62 km)	Downriver (22 km)	Fatima (66 km)	Near Town (18 km)	p
Age (years)	38.6	37.2	38.5	37.0	38.3	ns	38.9	38.5	40.7	38.4	40.4	*
Height (cm)	151.0	150.4	150.9	150.9	150.9	ns	162.2	161.7	162.2	163.7	163.2	‡
Weight (kg)	54.3	52.2	55.6	53.7	54.8	‡	61.0	61.0	61.8	63.7	63.5	‡
Body fat (%)	25.7	24.1	26.3	24.8	24.9	‡	16.6	16.4	17.3	18.1	16.4	‡
BMI (kg/m^2)	23.8	23.1	24.4	23.5	24.0	‡	23.2	23.3	23.5	23.8	23.8	‡
Schooling (years)	0.2	0.8	0.8	2.3	2.1	‡	0.9	1.9	1.9	3.0	4.5	‡
Spanish fluency (%)												
None	88.5	71.3	65.4	49.9	30.2	‡	55.4	23.1	19.3	16.7	8.9	‡
Moderate	10.8	25.1	29.0	33.3	36.1		35.8	46.0	43.0	58.3	31.4	
Fluent	0.7	3.6	5.7	16.9	33.7		8.9	30.9	37.7	25.0	59.7	
Smoking (%)												
None	66.4	71.2	70.4	80.5	83.3	‡	4.2	21.0	14.8	16.8	12.6	‡
Low	22.9	13.5	13.2	7.1	8.3		17.8	21.6	19.6	12.4	25.0	
Moderate	7.3	5.5	6.4	3.7	5.0		33.0	17.7	30.7	23.5	33.5	
High	2.0	4.9	0.0	0.0	1.2		42.1	35.1	22.6	46.0	25.9	
SBP (mm Hg)	110.0	103.2	108.1	108.0	106.9	‡	113.9	110.3	113.3	113.0	112.0	‡
DBP (mm Hg)	68.5	64.2	66.4	68.1	66.1	‡	70.4	67.5	68.6	70.8	67.7	‡
PP (mm Hg)	41.5	39.0	41.7	39.9	40.9	‡	43.5	42.8	44.6	42.2	44.2	†
n (cases)	492	515	471	463	939		434	467	463	417	817	

*p<0.05, †p<0.01, ‡p<0.001, ns=not significant

Table S8. Blood Pressure at average U.S. and Tsimane body mass index (BMI), estimated from models in Table 2 and Figure 2.

Calculated With Tsimane Average BMI					
	Average	**NHANES**		**Tsimane**	
Sex/Age	**BMI**	**SBP**	**DBP**	**SBP**	**DBP**
Female					
Age 40	24.29	113.29	70.25	112.73	70.03
Age 70	23.07	135.98	65.99	117.02	70.99
Male					
Age 40	24.15	120.22	73.85	112.63	69.97
Age 70	23.20	131.02	67.76	117.11	71.05

Calculated With US Average BMI					
	Average	**NHANES**		**Tsimane**	
Sex/Age	**BMI**	**SBP**	**DBP**	**SBP**	**DBP**
Female					
Age 40	28.56	114.96	70.79	115.72	71.98
Age 70	29.66	138.56	66.82	121.64	74.01
Male					
Age 40	29.35	122.26	74.50	116.27	72.35
Age 70	28.55	133.11	68.43	120.86	73.50

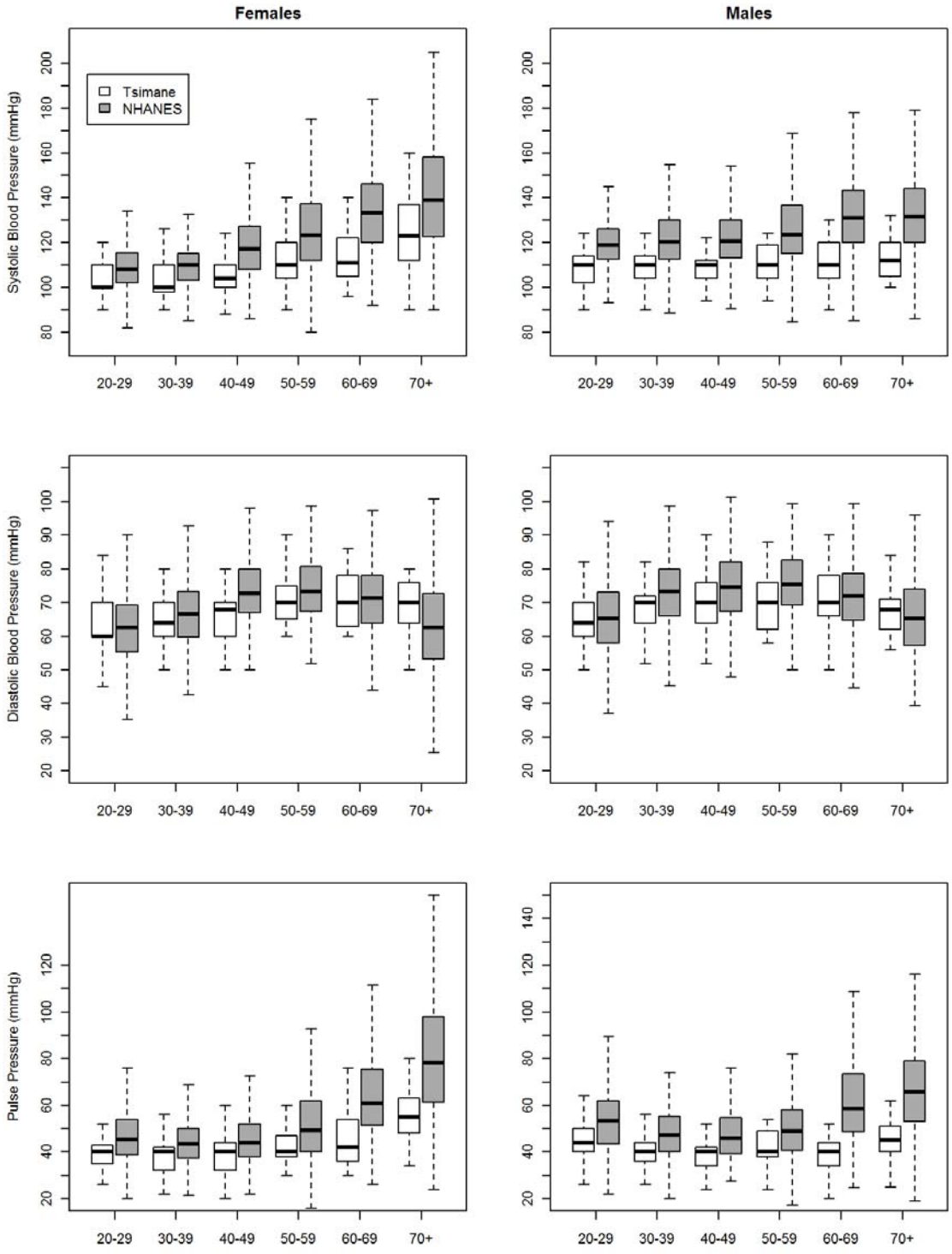

Figure S1. SBP, DBP and PP for last Tsimane medical round (Oct. 2008-2009) and NHANES 2005-2006 for females and males. Boxes encompass the 25th- 75th percentiles, lines indicate the median, and whiskers indicate either the extreme data points or 1.5 times the interquartile range, whichever produces a shorter whisker. Outliers are not shown.

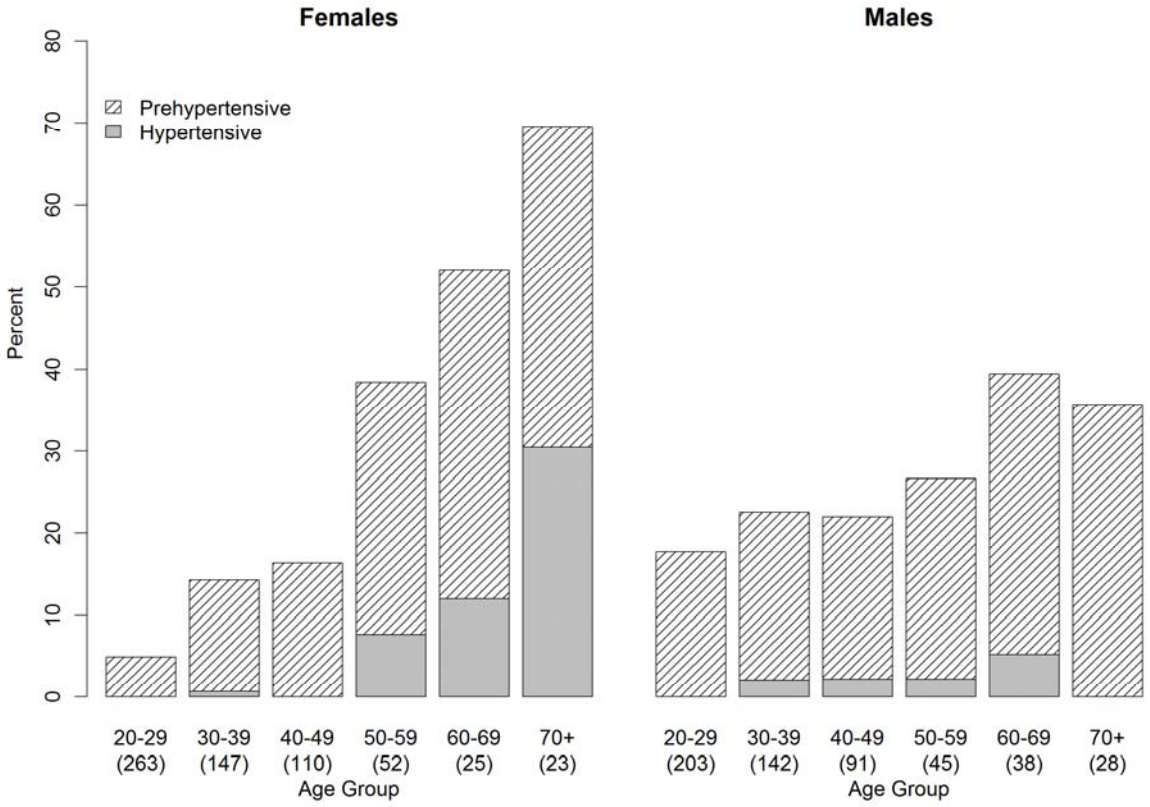

Figure S2. Prevalence of hypertension, pre-hypertension and normal tension among (a) females and (b) males during the last medical round (n=1,186 individuals). Sample sizes are in parentheses below age categories.

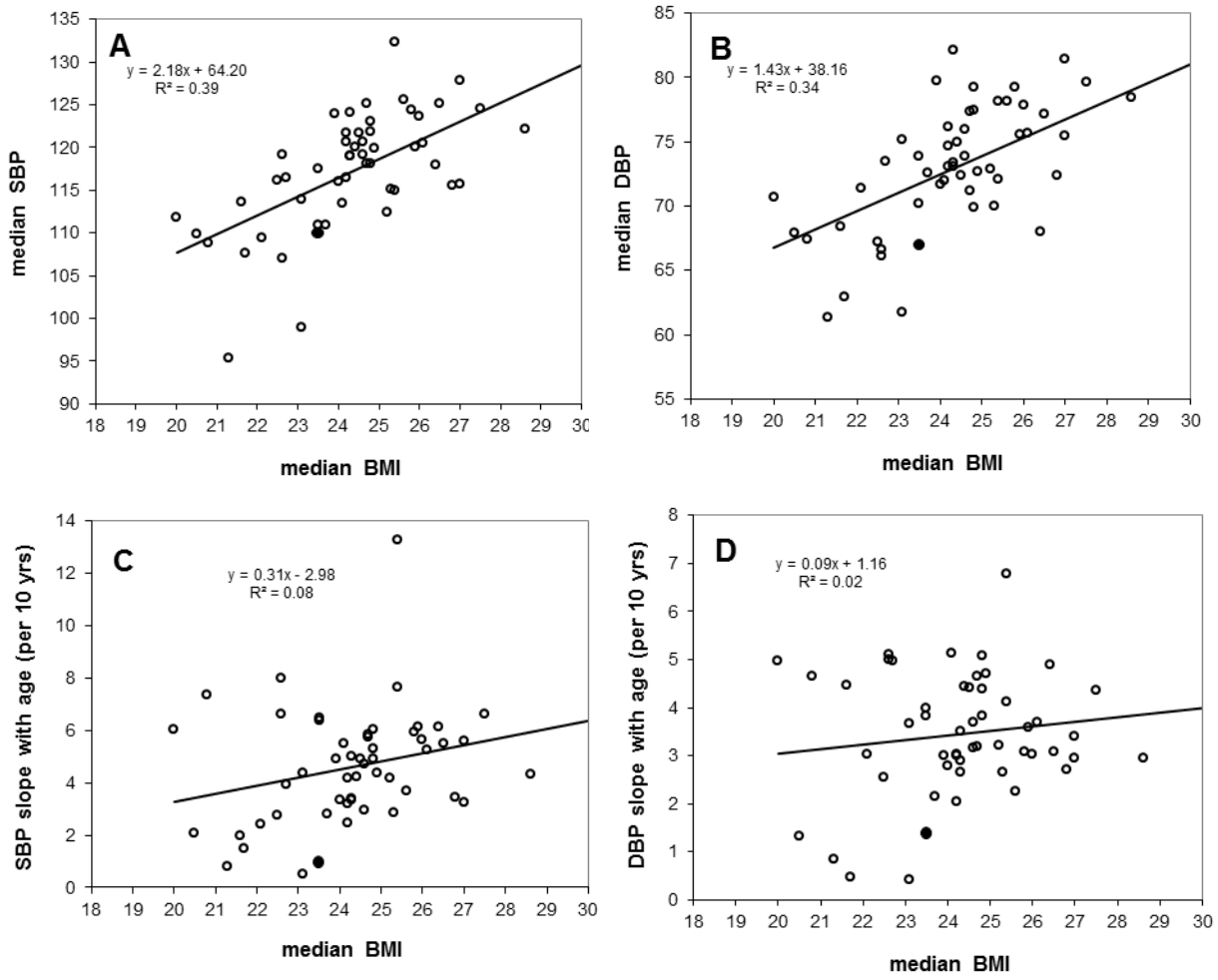

Figure S3. Effects of median adult body mass index (BMI) on median levels of (a) SBP and (b) DBP, and on age-related increases per 10 years of adult age in (c) SBP and (d) DBP, using INTERSALT study (ages 20-59). Tsimane estimates are represented as black dots.

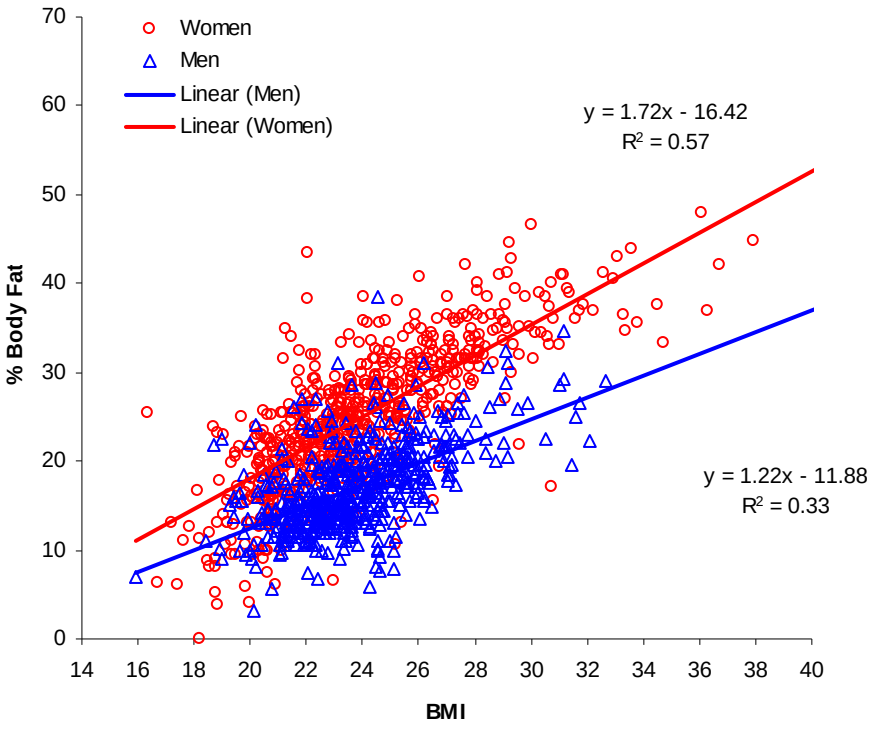

FIGURE S4. Body fat percentages as a function of body mass index (BMI) for women and men in largest medical round (Oct. 2008-2009).

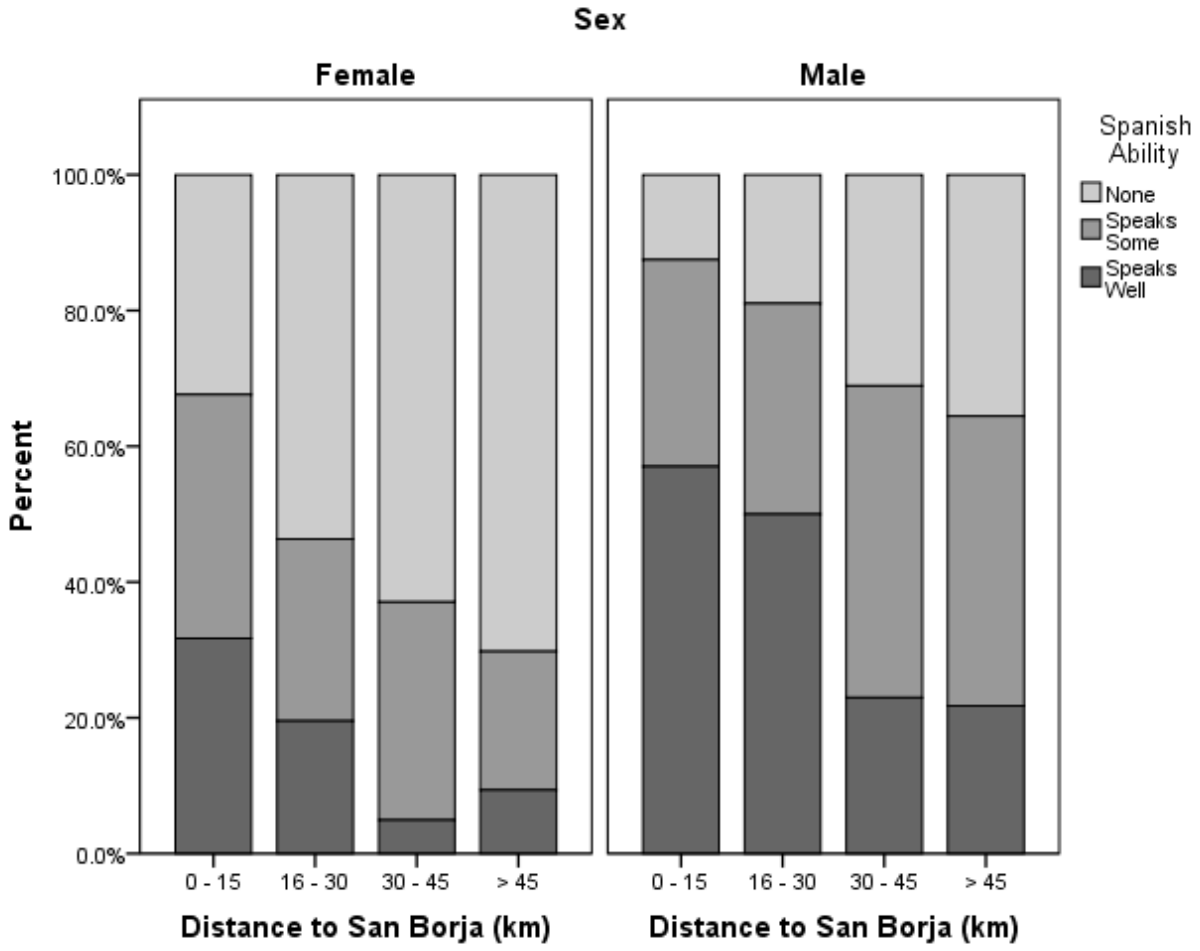

Figure S5. Spanish ability by sex and distance to San Borja

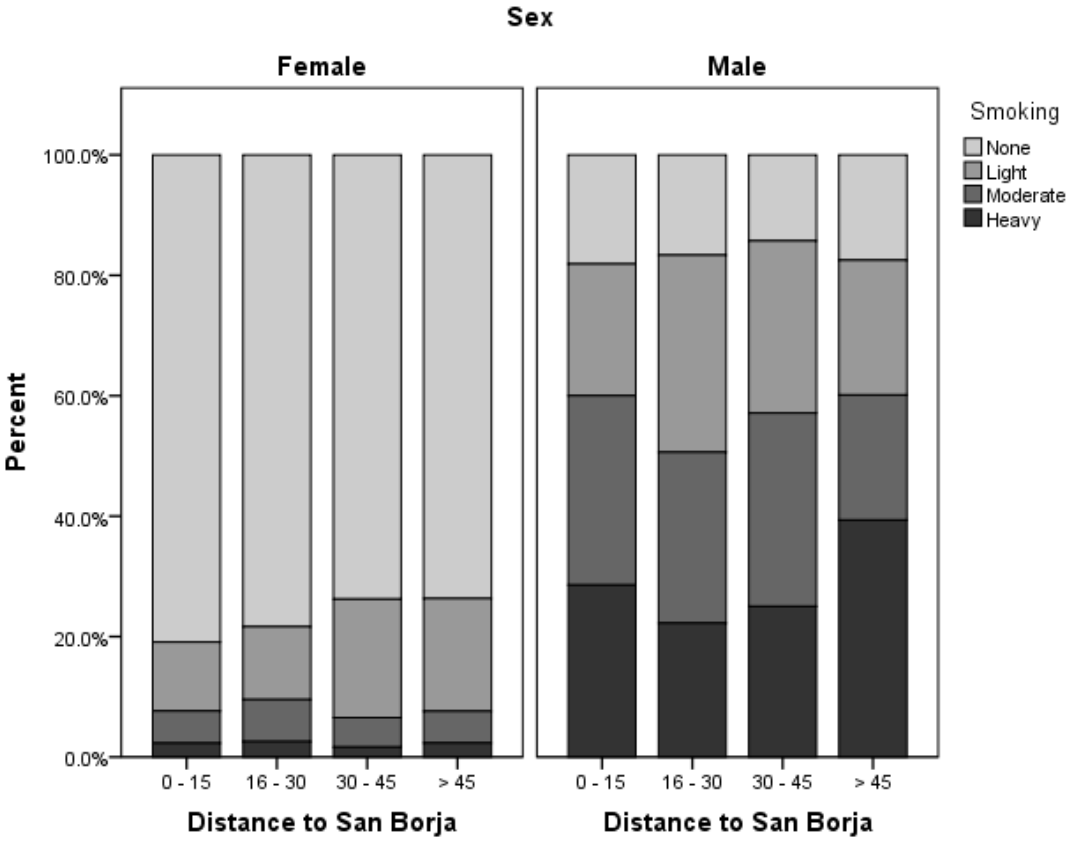

Figure S6. Smoking by sex and distance to San Borja

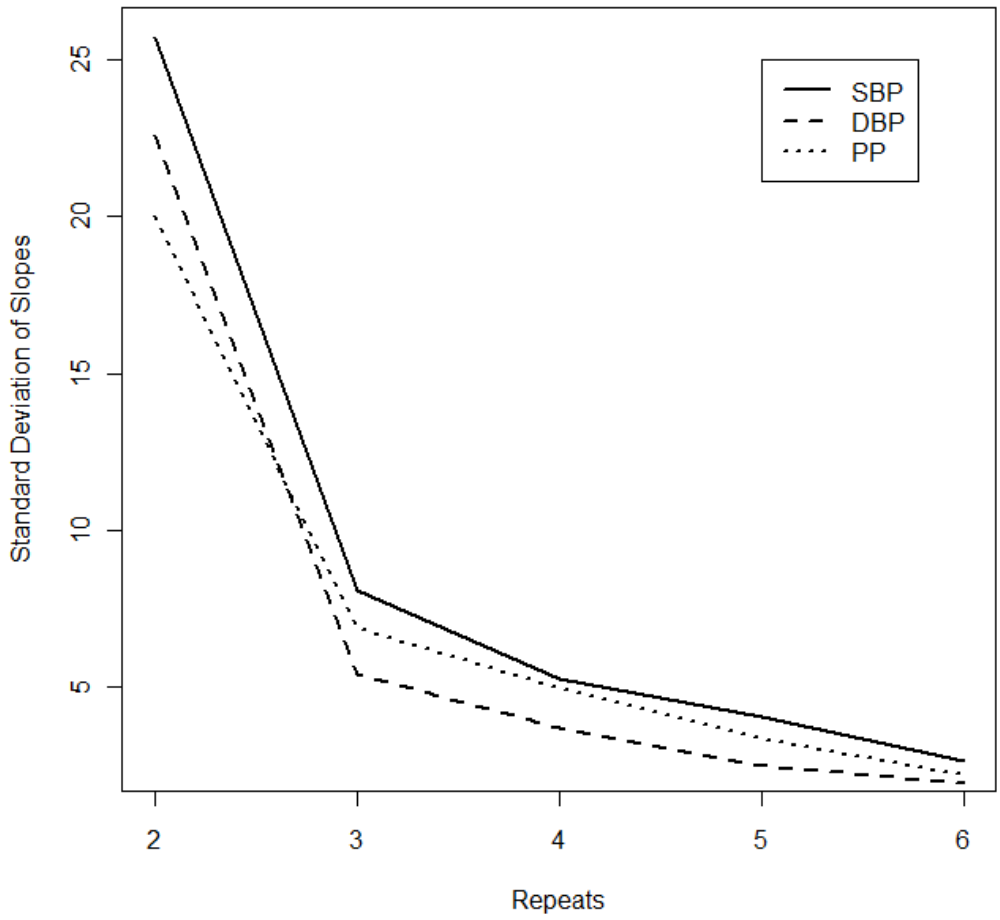

Figure S7. More observations lead to lower deviation in slope estimates. Pressure values from individuals with six or more observations were randomly resampled for 2-6 consecutive observations and a linear line was fit for each individual slope. The graph shows the sample standard deviation in slope estimates for a given number of observations. Note that sample size and subject identities are held constant.