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Supplementary Materials for

Urbanization and market integration have strong, nonlinear effects on cardiometabolic health in the Turkana

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Published 21 October 2020, *Sci. Adv.* **6**, eabb1430 (2020)
DOI: 10.1126/sciadv.abb1430

The PDF file includes:

Other Supplementary Material for this manuscript includes the following:

(available at advances.sciencemag.org/cgi/content/full/6/43/eabb1430/DC1)

Supplementary Materials and Methods

Study population

The Turkana are thought to be descendants of the Jie people of Uganda based on their linguistic and cultural similarity. The ancestors of the present day Turkana likely entered Kenya in the early 18th century, and expanded to their current range across Turkana county by ~1900 (30). Today, the Turkana represent the second largest pastoralist group in Kenya after the Maasai. Turkana county is a semi-arid desert characterized by low annual rainfall (~200 mm per year), frequent droughts, and high year round temperatures (mean day time high = 97F) (86). Most of the annual precipitation occurs only during the rainy season (March-May).

The Turkana are traditionally nomadic pastoralists; they herd five species of livestock (dromedary camels, zebu cattle, fat tailed sheep, goats, and donkeys) and rely on these animals as their main mode of subsistence (29). As a result of their pastoralist lifestyle, the Turkana have a remarkably protein-rich diet: 62% of calories are derived from milk or milk products, and 70-80% of calories are derived from animal products of some sort (29). Daily protein intake exceeds the FAO/WHO requirements by >300%, despite total caloric intake being limited (1,300–1,600 kcal/day) (85). Dietary items not derived from livestock are obtained through hunting and gathering, or through trade of animal products. For detailed descriptions of the diet, climate, and lifestyle experienced by traditional, pastoralist Turkana, see work from the South Turkana Ecosystem Project (summarized in (49)).

Over the last several decades, infrastructure in Turkana county has rapidly improved, primarily due to oil discoveries in South Sudan. As a result, this previously isolated region of Kenya has become more connected with the rest of the county, allowing market goods to flow into some regions of Turkana and allowing people from Turkana to move south into more

urbanized parts of Kenya. We focused on one region that has experienced an influx of Turkana people in the last few decades – Laikipia county. Laikipia is a cosmopolitan county near the equator with several large cities (Nanyuki, Nyahururu, and Rumuruti). The climate is generally cool and temperate, with rainfall throughout Laikipia county averaging from ~400-1100 mm per year depending on the specific location (87, 88). Importantly, because most of the migration between Turkana and Laikipia has occurred within the last few decades, and because it is rare for Turkana individuals to marry non-Turkana individuals, we expect very little population structure or genetic differentiation between Turkana individuals living in Turkana versus Laikipia county.

Interview and food frequency questionnaire data

Structured interviews were conducted with all participants, to collect basic information about demography, reproductive and health history, and lifestyle. All interviews were conducted in a language familiar to the participant (English, Turkana, or Swahili). The following pieces of information from the interviews, all of which were self-reported by participants, are relevant to the analyses presented in the main text:

- Sex
- Age
- Where the participant was born
- Main subsistence activity, chosen from the following categories: self-employment, formal employment, petty trade, farming, animal keeping, hunting and gathering, other.
- Occupation
- Highest education level

- Number of children
- Possession of the following items: finished floor, finished room, electricity, television set, mobile phone, flush toilet, gas cooking, indoor tap water, treated water. We asked about these items to quantify how urban or modernized each individual's life was, following previous work (10, 82, 83).
- Whether the participant was currently pregnant (for women only)
- Whether the participant was taking any medications (only 1.6% of study participants reported taking any medications, and no participants reported taking blood pressure or cardiometabolic medications, so this was not used as an exclusion criteria)
- Whether the participant was currently fasting (rather than excluding non-fasting individuals from our dataset, fasting status was noted and included as a covariate in downstream analyses)
- Number of meals eaten per day

Following previous studies (10), we also used a food frequency questionnaire to collect information about the use of a select items among the Turkana: alcohol, tobacco, meat, milk, blood, sugar, bread, salt, cooking oil, rice, ugali, potatoes, soda, fried foods, and sweets. We focused on these items because they reflect foods that are essential (meat, milk, blood) or uncommon (all carbohydrates as well as salt, and cooking oil) in the diet of pastoralist Turkana. The uncommon items can only be obtained through trade, and we therefore viewed these items as an indicator of market integration. Participants were asked how often a specific item was consumed and were given the following answer choices: never, rarely, 1-2 times per week, >2 times per week, or every day. Participants were instructed to provide information reflecting habits over the last year. For mediation analyses, these answers were recoded to a numeric scale

from 0-4. For mediation analyses, a 'carbohydrate score' was also created by summing up the number of carbohydrate items a given participant ate regularly (regularly was defined as more often than 'never' or 'rarely'). We note that the food frequency questionnaire was designed to provide general estimates of variation in diet between individuals, rather than exact caloric or nutritional estimates. Information about the consumption of each item among Turkana practicing different lifestyles can be found in Figure 1.

Biomarker measurements

Body mass index (BMI). Weight was recorded using a portable scale, which was always placed on a hard, flat surface. Height was recorded using a Seca 213 portable stadiometer; before height measurements were recorded, participants were asked to remove any hats or hair ornaments. Weight and height were recorded to the nearest kg and cm, respectively. BMI was calculated as weight (in kg) / height (in m)^2.

Waist circumference. Clothing was first removed from the waist line, and the participant was asked to stand with their feet shoulder width apart and their back straight. The top of the hip bone was located by the researcher, and measuring tape was aligned with the top of the hip bone and wrapped around the participant's waist. This procedure was completed three times, and three separate measurements of waist circumference were recorded to the nearest 0.5 cm. We considered the final waist circumference value for a given participant to be the average of the three measurements.

Lipid profiles. Approximately 8mL of intravenous blood was collected into an EDTA vacutainer tube. Immediately after collection, 40ul of each sample was used to conduct a lipid panel using the CardioCheck Plus (PTS Diagnostics) following the manufacturer's instructions.

Specifically, total cholesterol, HDL cholesterol, and triglycerides were measured for each participant, and LDL cholesterol was calculated by the CardioCheck Plus. Because the CardioChek Plus cannot read triglyceride values below 50 mg/dL, both triglyceride and LDL cholesterol values were not recorded for these individuals; this is because LDL cholesterol is estimated as a function of triglyceride, HDL cholesterol, and total cholesterol levels using the Friedewald Equation (LDL cholesterol = total cholesterol - HDL cholesterol – triglycerides/5). We found that alternatively setting incalculable triglyceride and LDL cholesterol values to the lowest possible value, rather than treating these values as missing, did not change our main results. Specifically, we still do not find any lifestyle effects on LDL cholesterol levels (all $p>0.05$ for the lifestyle effects from a linear model controlling for age and sex), and we still find differences in triglycerides levels between rural pastoralists and non-pastoralists versus urban individuals ($p=1.66x10^{-3}$ and $p=4.75x10^{-4}$, respectively).

Blood glucose levels. A drop of whole blood (~10ul) from a finger prick using a safety lancet was used to measure glucose levels. To do so, we used the OneTouch system following the manufacturer's instructions.

Body fat percentage. Body fat percentage was measured via bioelectrical impedance using the Omron HBF-306C Handheld Body Fat Loss Monitor according to the manufacturer's instructions.

Blood pressure. Arterial blood pressure was measured as systolic blood pressure and diastolic blood pressure. All participants sat in a relaxed position with their arm flat at a 90-degree angle, and with the arm relaxed and the wrist facing up. The cuff was placed around the participant's upper arm (approximately ½ inch above the elbow). Participants were asked not to

speak while a trained assistant used an Omron 10 Series Wireless Upper Arm Blood Pressure Monitor to collect a single measurement.

Composite measure. We also included a composite measure of health, which tallied the number of biomarkers above clinical cutoffs for a given individual. Specifically, we counted the number of biomarkers for each participant that met the following criteria: (i) waist circumference >89 cm for women or >102 cm for men; (ii) triglyceride levels >150 mg/dL; (iii) HDL cholesterol levels <40 mg/dL for men or <50 mg/dL for women; (iv) blood pressure >135/85; (v) fasting blood glucose levels >100 mg/dL; (vi) BMI >25; (vii) LDL cholesterol levels >100 mg/dL; and (viii) total cholesterol levels > 200 mg/dL. Cutoffs for BMI, LDL cholesterol, and total cholesterol were taken from CDC recommendations. Cutoffs for the remaining biomarkers followed the criteria used by the American Heart Association to define metabolic syndrome (33).

Correlations between measures. Controlling for age and sex, almost all biomarker measures are either moderately correlated (R^2<0.35 from a Pearson correlation, after age and sex were regressed out) or not correlated at all (53% of all possible pairs of measures are not significantly correlated at a 5% FDR). The strongest correlation we observed was between total and LDL cholesterol levels (R^2=0.762); however, lifestyle effects were not found for LDL cholesterol levels, suggesting that collinearity between measures does not produce false positive results.

Defining lifestyle categories

For analyses presented in the main text, individuals were binned into the following three categories based on their sampling location, diet, and self-reported subsistence activity: (i) pastoralist Turkana were defined as individuals that reported their main subsistence activity as

'pastoralism', that drink milk every day (i.e., that rely on their livestock for subsistence), and that live in Turkana county; (ii) non-pastoralist, rural Turkana were defined as individuals that live in Turkana county but did not meet the criteria for category (i); and (iii) non-pastoralist, urban Turkana were defined as individuals that live in Laikipia county.

We arrived at these category designations based on the following observations and analyses. First, based on our own observations and on comparisons of several commonly used measures of urbanicity (82, 83) (Figure 3), we considered all locations in Turkana county to be 'rural' and all locations in Laikipia county to be 'urban' and more industrialized or market-integrated. Second, based on studies from the South Turkana Ecosystem Project (49) and our own observations, we concluded that individuals practicing traditional pastoralism are only found in Turkana county. Based on these same sources (85), we also concluded that a major marker of traditional pastoralism was regular milk consumption, suggesting that individuals truly rely on their livestock for subsistence. While some individuals classified as rural non-pastoralists reported 'animal keeping' as their main subsistence activity, these individuals generally keep animals in a fixed location and use them for trade. Additionally, these non-nomadic animal keepers do not consume milk and blood from the animals on a regular basis (34% rarely consume milk and 66% consume milk 1-2 times per week); further, 75%, 63%, and 73% of these individuals use added sugar, salt, and cooking oil regularly, which also influenced our decision to not classify them as pastoralists. To ensure that our analyses were not biased by these decisions, particularly the classification of people who practice non-nomadic animal keeping within the general group of 'rural non-pastoralists', we repeated the analyses in the main text after assigning these individuals to their own, fourth category. Results were quantitatively similar

to what is reported in the main text and did not suggest that non-nomadic animal keepers should be considered a third group within the rural environment (Supplementary Table 2C).

Processing and analysis of publicly available datasets

Biomarker measurements from other populations

To compare biomarker levels in the Turkana to those reported for other small-scale and industrialized societies, we extracted summary data from published work for the following measures: BMI, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and body fat percentage. In particular, we collected biomarker information for small-scale agriculturalist and forager horticulturalist populations (Bantu, Tsimane, Shuar), other pastoralist populations or populations known to subsist on a high-protein diet (Evenki, Fulani, Masaai), and hunter-gatherers (Hazda) (6–12). We also compiled information on Turkana BMI from the 1980s, from work published by the South Turkana Ecosystem Project (34). For all biomarkers, we focused on data from adults and extracted sex-specific information where possible. We extracted the mean and standard deviation of each biomarker when reported, and in some cases, calculated the standard deviation from the reported standard error value and the sample size. All comparative data is presented in Supplementary Table 1B, and summaries are reported in Supplementary Table 1A.

To understand whether metabolic profiles in urban Turkana were as extreme as what is observed in the US, we downloaded raw data from the CDC's National Health and Nutrition Examination Survey (NHANES) (37). We used the R package "nhanesA" to download data collected in 2006, which is the default provided by this package (https://cran.r-project.org/web/packages/nhanesA/index.html). We filtered the data to include adults from 18-65

years of age, and combined these data with our biomarker values (see Table 1 for sample sizes). We then used linear models to test for effects of lifestyle (urban Turkana, rural Turkana, or US) on standardized values of each biomarker controlling for age and sex (similar to model (1)). For blood glucose and body fat percentage, which only show lifestyle effects in female Turkana, we analyzed females alone in the combined US and Turkana dataset. For the composite measure of health, which we calculated for the NHANES data in the same way as described in *Biomarker measurements*, we used generalized linear models with a binomial link function rather than linear models. For all 11 measures, we extracted the p-value associated with the lifestyle effect, and considered a given lifestyle contrast to be significant if the FDR-corrected p-value was less than 0.05.

For analyses of diastolic blood pressure, we repeated these analyses after excluding individuals on medications defined as 'cardiovascular agents' by NHANES (this includes vasodilators, ACE inhibitors, beta blockers, and diuretics commonly used to treat high blood pressure). For each biomarker, we repeated these analyses after subsampling the NHANES dataset to be the same size as our Turkana dataset. We repeated this subsampling 100 times to confirm that imbalanced sample sizes did not bias our estimates of effect size or our overall conclusions. Results from the subsampling analyses are summarized in Supplementary Table 2B.

Population density

Population density estimates were downloaded from NASA's Socioeconomic Data and Applications Center (SEDAC; https://doi.org/10.7927/H49C6VHW). Specifically, we used the Gridded Population of the World database (v4.11), which consists of estimates of human population density (number of persons per square kilometer) based on counts consistent with

national censuses and population registers. These data are available for the years 2000, 2005, 2010, 2015, and 2020. Data for all years were downloaded from SEDAC in GeoTiff format at 2.5 min resolution (equivalent to ~5km grids), and converted to GPS coordinates using the R package 'raster' (89).

To estimate the population density for a given sampling location, we calculated the distance between the GPS coordinates for the sampling location and all ~5km grids in Kenya using the haversine distance formula as implemented in the R package 'geosphere' (90). We extracted the $\log_{10}$ 2020 population density estimate for the grid with the shortest distance to the sampling location and used this value as a potential mediating variable in downstream analyses.

To estimate the population density of each individual's birth location around the time they were born, we first assigned GPS coordinates to each birth location using Google Maps. We note that for some individuals we could not identify the reported birth location on a map, but importantly these individuals have similar health profiles as individuals for whom GPS coordinates could be assigned (all FDR>5% for linear models testing for an effect of birth location missingness on each biomarker, controlling for age, sex, and lifestyle). For individuals with assigned GPS coordinates, we next found the ~5km grid closest to the birth location using the procedure described above. Next, we estimated the population density of the grid during the year the individual was born, by fitting a linear model of $\log_{10}$ population density as function of year (using all available data, from 2000, 2005, 2010, 2015, and 2020). We extracted the beta and intercept from this linear model, and calculated $\log_{10}$ population density for the individual's birth year as intercept + beta x birth year.

Distance to closest major city

Population estimates in 2019 for major cities in Kenya were downloaded from the World Population Review (http://worldpopulationreview.com/countries/kenya-population/cities/). We considered major cities to be those with population counts >10,000 and extracted GPS locations for these cities from Google Maps. Using GPS coordinates for each sampling location, we calculated the distance between all major cities and the sampling location using the haversine distance formula as implemented in the R package 'geosphere' (90). We used the shortest distance (in kilometers) from each sampling location to a major city as potential mediating variable in downstream analyses.

Translating estimates of effect size into percentages

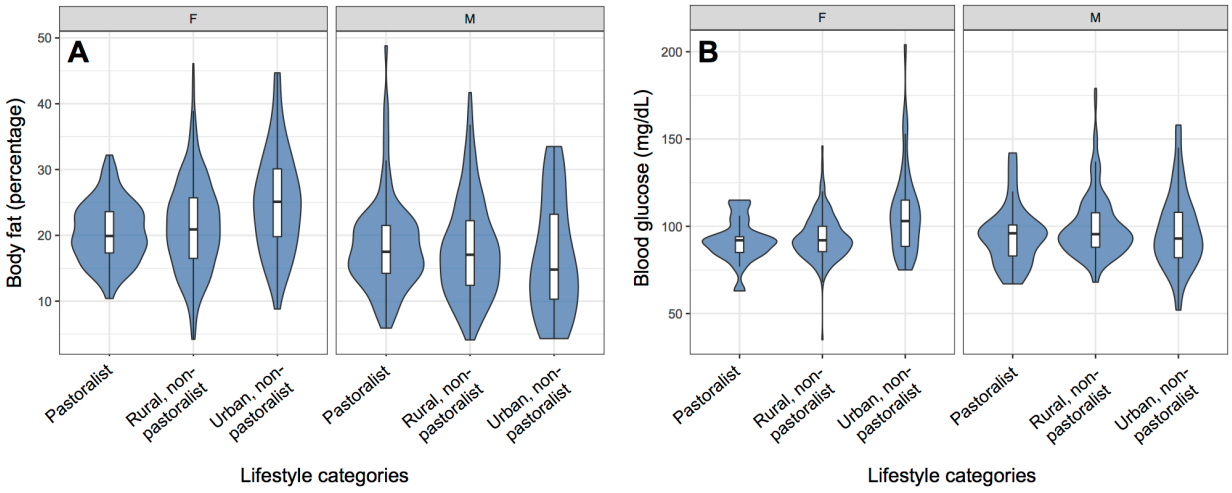
In the main text, we report model fitted estimates of several biomarkers (in Figure 2) as well as estimates of effect size expressed as the percent difference between lifestyle categories (or between individuals born in different types of early life environments). To estimate the percent difference in, for example, BMI between an individual living in a rural versus urban location, we reran model 1 without normalizing the outcome variable. We then extracted the fitted model estimates (for $\beta_0, \beta_l, \beta_a, \beta_s$) and used them to calculate BMI for an 'average' individual in the population by summing the fitted effect sizes multiplied by average values from the dataset (a_i=40.4 years; s_i=0 (indicating female)). To isolate how lifestyle influenced BMI, we performed these calculations after setting $l_i = 1$ (indicating rural, Turkana county) or $l_i = 0$ (indicating urban, Laikipia county). Where percentages are reported, we then calculated the percent difference between the two BMI estimates. For results pres nted in Figure 2, we did not translate biomarker estimates into percentages; to obtain the error bars presented in Figure 2, we

performed the summations described above after the standard error of the estimate of β_l had been added to or subtracted from β_l, to get the upper and lower bound of each error bar, respectively.

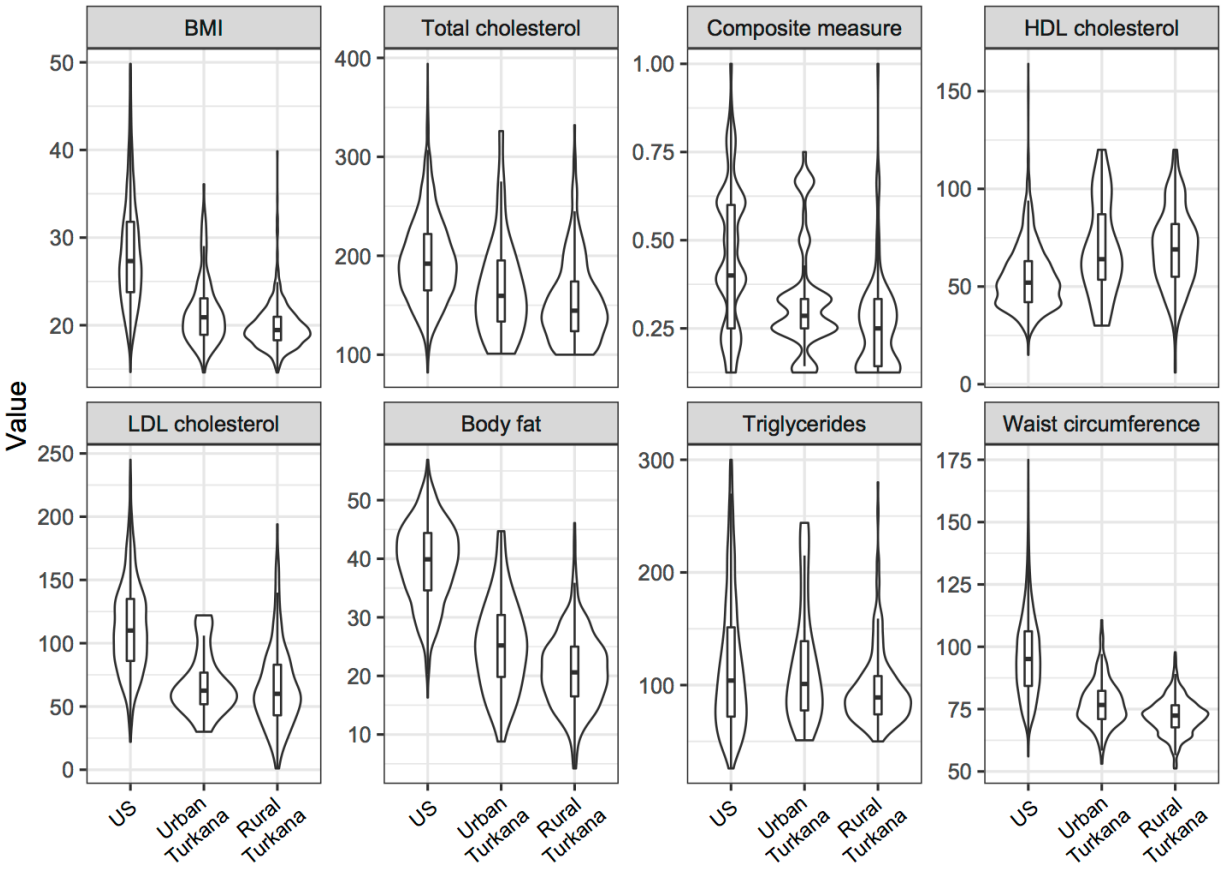
We performed similar calculations using the fitted model estimates from model (5), in order to understand the relative impact of early life versus adult environmental conditions. Here, we extracted the estimates for $\beta_0, \beta_l, \beta_a, \beta_s, \beta_d$, and varied d_i or l_i to isolate the effects of early life population density or adult lifestyle, respectively. For calculations involving early life population density, l_i was set to 1, and d_i was varied between 0.504 and 1.360, which represent the 25th and 75th percentiles of $\log_{10}$ early life population densities. We calculated percent differences in health biomarkers in this manner for the biomarkers with significant early life effects as estimated in model (5), namely: average waist circumference, BMI, diastolic blood pressure, body fat percentage, and the composite measure of health (Supplementary Table 4A). For body fat percentage, where environmental effects are only observed in females, all models focused on this sex alone and did not include the effect of β_s.

Supplementary Figures

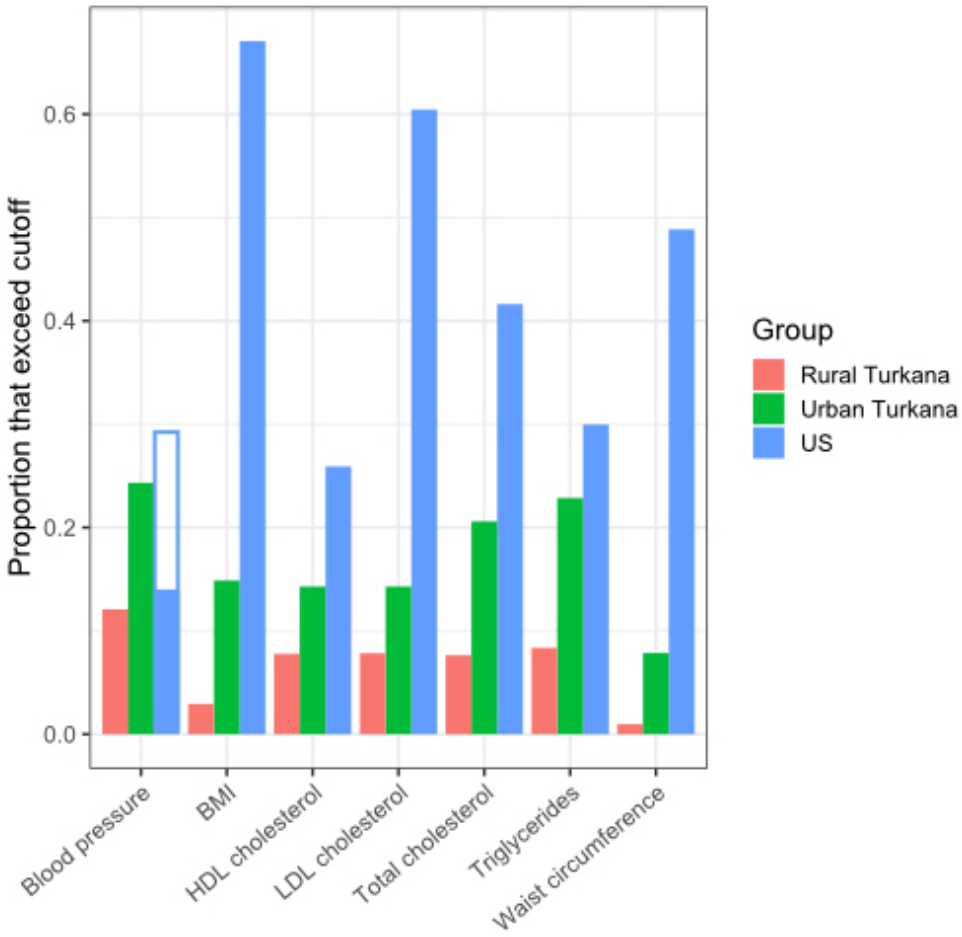
Supplementary Figure 1. Mean biomarker values for measures with a significant sex x lifestyle interaction. Using likelihood ratio tests, we determined that (A) body fat and (B) blood glucose had significant sex x lifestyle interactions, such that lifestyle effects were observed in females, but not males. Raw data are shown to support this conclusion, all contrasts between the three lifestyle categories analyzed for males alone were not significant (linear model controlling for age, all $p>0.05$, sample sizes as in Table 1). Contrasts between the three lifestyle categories analyzed for females alone showed a similar pattern to what is described in the main text for other biomarkers (Figure 2). Specifically, no significant differences were observed between body fat ($p=0.391$) and blood glucose levels ($p=0.629$) for pastoralist versus rural, non-pastoralist Turkana; however, strong differences were observed between both of these groups and urban, non-pastoralist Turkana (contrast between pastoralists and urban non-pastoralists: body fat, $p=4.660\times10^{-5}$, blood glucose: $p=2.179\times10^{-7}$; contrast between rural and urban non-pastoralists: body fat, $p=3.194\times10^{-5}$, blood glucose: $p=4.030\times10^{-4}$).



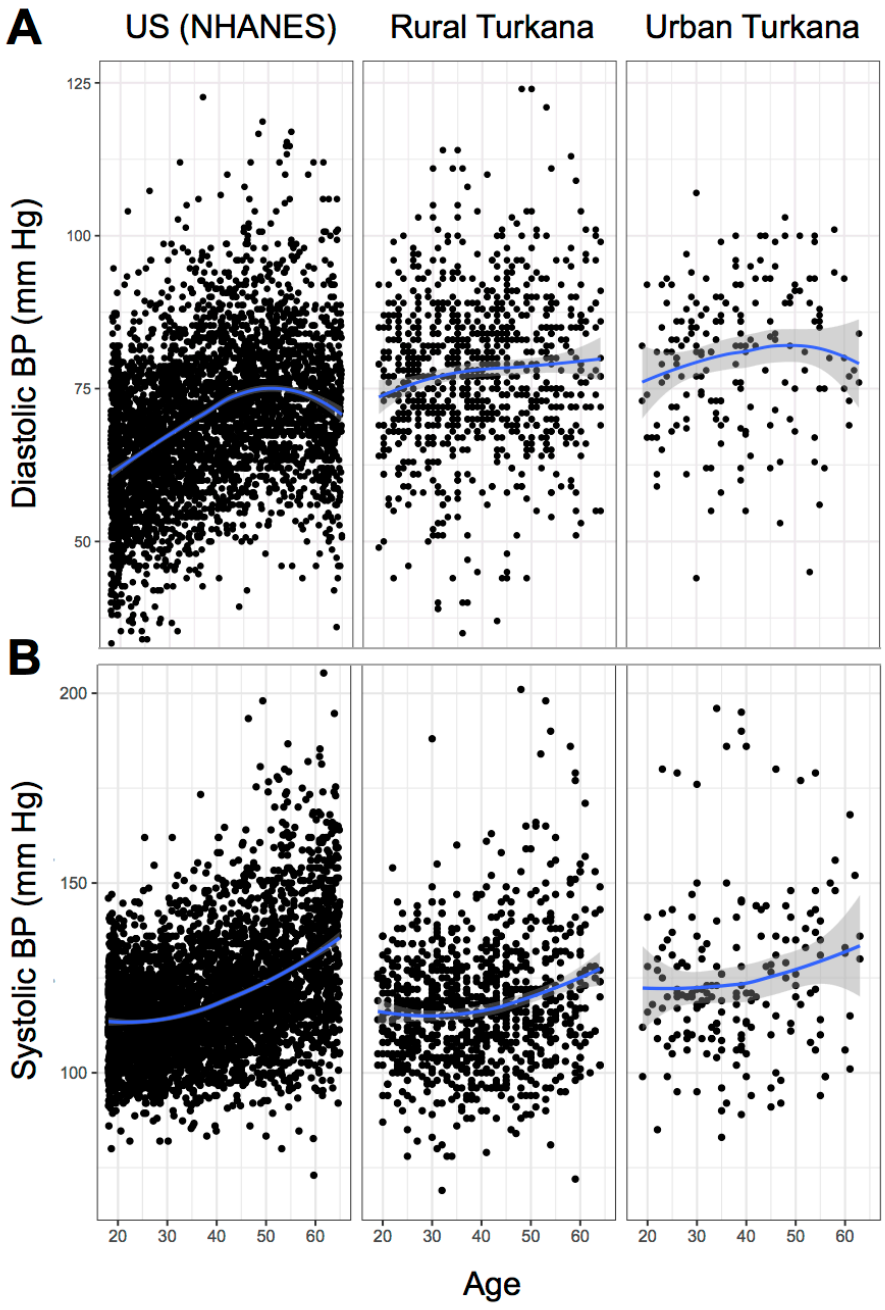
Supplementary Figure 2. Mean biomarker values for Turkana individuals versus the US (NHANES). Raw data for 8 measured biomarkers are shown for the NHANES dataset (filtered to include individuals aged >18 and <65 years old) versus rural and urban Turkana. Raw data for the two blood pressure measures are shown in Supplementary Figure 4, and data for blood glucose are not shown as no significant differences between groups were found (Figure 2). Outliers in the most extreme 1% of the dataset for BMI, total cholesterol, triglycerides, and waist circumference are not shown to aid visualization. For body fat, where only females were analyzed, only data for this sex is plotted. Units of measure are as follows: BMI (kg/m^2); composite measure (proportion); HDL, LDL, triglycerides, and total cholesterol (mg/dl); body fat (percentage); and waist circumference (cm).



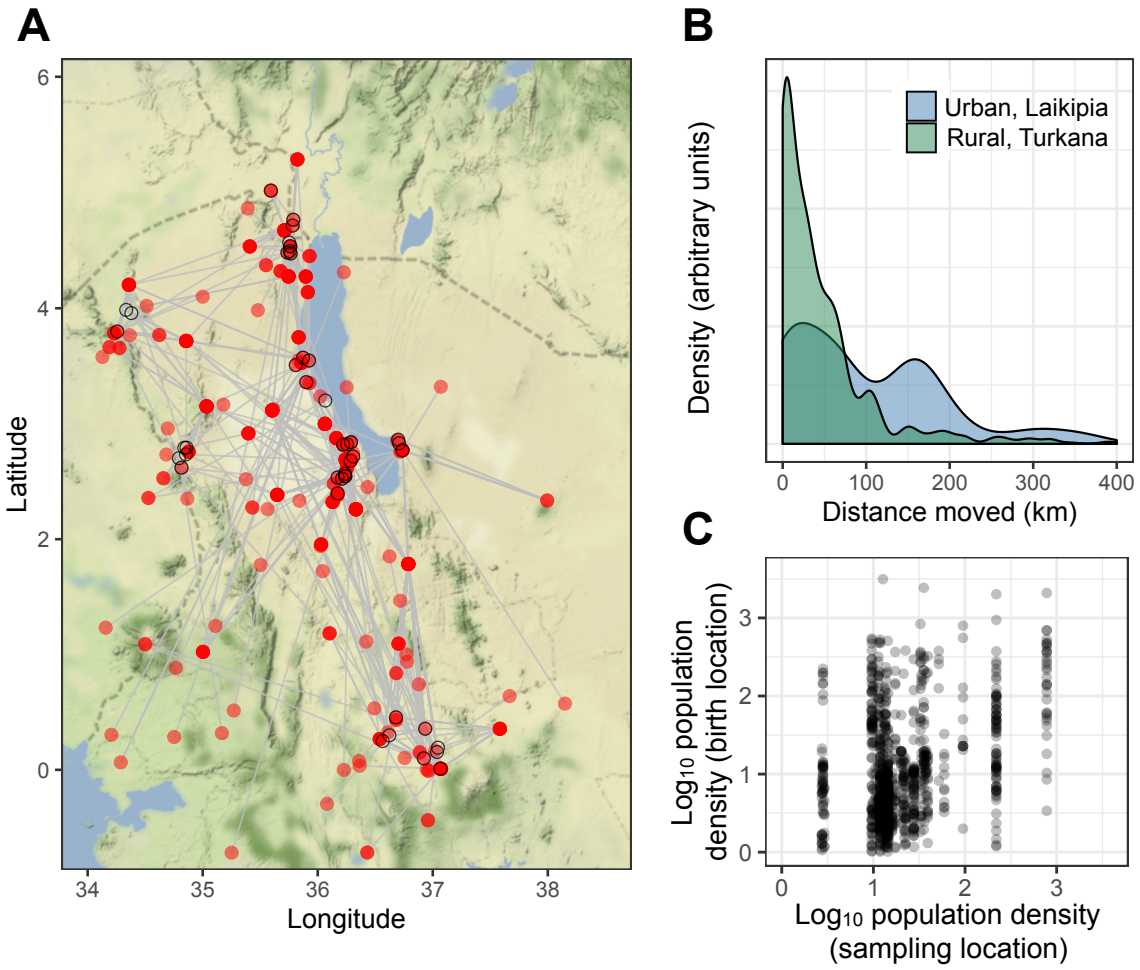
Supplementary Figure 3. Proportion of Turkana versus US (NHANES) individuals whose biomarker values exceed clinical cutoffs. Cutoffs were defined as follows: (i) waist circumference >89 cm for women or >102 cm for men; (ii) triglyceride levels >150 mg/dL; (iii) HDL cholesterol levels <40 mg/dL for men or <50 mg/dL for women; (iv) blood pressure >135/85; (v) BMI >25; (vi) LDL cholesterol levels >100 mg/dL; and (vii) total cholesterol levels > 200 mg/dL. Cutoffs for BMI, LDL cholesterol, and total cholesterol were taken from CDC recommendations. Cutoffs for the remaining biomarkers followed the criteria used by the American Heart Association to define metabolic syndrome (33). For blood pressure, we also show hypertension prevalence in the US when we expand our definition to include individuals taking medications used to treat high blood pressure (14.85% of US individuals, shown as open bar extension); no Turkana reported being on high blood pressure medications. Only biomarkers that exhibited significant differences between the US and Turkana are shown.



Supplementary Figure 4. Blood pressure values for Turkana individuals versus the US (NHANES). Raw data for (A) diastolic and (B) systolic blood pressure are shown for the NHANES dataset (filtered to include individuals aged >18 and <65 years old) versus rural and urban Turkana. Outliers in the most extreme 1% of the dataset are not shown to aid visualization. Loess curves against age are shown for each population.



Supplementary Figure 5. Relationship between birth location and location at time of sampling. (A) Red points denote birth locations of study participants, open circles denote sampling locations, and grey lines connect each participant's birthplace with the location at which they were sampled in adulthood. No lines are drawn for participants that were born and sampled in the same location. (B) Distance between birth location and sampling location for participants sampled in urban, Laikipia county versus participants sampled in rural, Turkana county. Participants sampled in Laikipia county are more likely to be living far from their birth location (Wilcoxon test, $p=1.364 \times 10^{-15}$). (C) There is minimal correlation between the population density of each individual's birth and sampling locations, suggesting that effects of urbanicity across the life course can be considered independently ($R^2 = 0.115$, $p<10^{-16}$).



Supplementary Table 1: **A**. Summarized comparisons of health biomarkers measured in Turkana versus other subsistence-level populations (focusing on females, or both sexes if sex-specific data were not reported). **B**. Biomarker datasets compiled for comparative analyses.

Supplementary Table 2: **A**. Results for models used to test for lifestyle effects on health within the Turkana (red shading highlights significant results). **B**. Results for models used to test for lifestyle effects on health, comparing urban and rural Turkana to the US (NHANES; red shading highlights significant results). **C**. Results for models used to test for lifestyle effects on health within the Turkana, when 4 lifestyle categories rather than 3 were used (red shading highlights significant results).

Supplementary Table 3. Results from mediation analyses, shown as the proportion of 1000 bootstrap iterations for which the effect of lifestyle was reduced when the potential mediating variable was taken into account (red shading highlights significant results).

Supplementary Table 4: **A**. Results for models used to test for early life effects on adult health (red shading highlights significant results). **B**. Results for models used to test for early life effects on adult health (when the adult environment was defined by log10 population density; red shading highlights significant results). **C**. Results for models used to test whether individuals with versus without birth location data had similar health profiles.

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