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BIOLOGICAL HEALTH RISKS AND ECONOMIC DEVELOPMENT

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ABSTRACT

With populations aging and the epidemic of obesity spreading across the globe, global health risks are shifting toward non-communicable diseases. Innovative biomarker data from recently conducted population-representative surveys in lower, middle and higher income countries are used to describe how four key biological health risks – hypertension, cholesterol, glucose and inflammation – vary with economic development and, within each country, with age, gender and education. As obesity rises in lower income countries, the burden of non-communicable diseases will rise in roughly predictable ways and the costs to society are potentially very large. Investigations that explain cross-country differences in these relationships will have a major impact on advancing understanding of the complex interplay between biology, health and development.

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1. Introduction

Recent innovations in the measurement and interpretation of biological health risks in population-representative surveys provide unparalleled opportunities to substantially advance understanding of the relationships between economic development and the biological underpinnings of population health, health disparities and health transitions. With the epidemic of obesity spreading rapidly across the globe and no longer a major concern only in advanced countries, the pressing need for this improved understanding cannot be overstated. Increases in obesity are often accompanied by increases in the prevalence of a broad array of non-communicable diseases (NCDs), many of which can be controlled, albeit with high-cost treatments. At the same time, as life expectancy increases and fertility declines, populations are aging worldwide. The combination of increasing NCDs and greater shares of older adults is potentially a ticking time bomb that has critical implications for future economic development, the allocation of resources between generations and population well-being in the years ahead. In short, there is a compelling need from both a scientific and policy perspective for investment in innovative research that provides a fuller understanding of the complex interplay between biology, behavior, resources and the health of populations, and, thereby, the implications for poverty, inequality and public finances.

Because the most prevalent global health risks are shifting from infectious diseases and inadequate nutrition to NCDs, we focus on how metabolic-related biological health risks vary across developing and advanced countries, drawing out the implications for health and economic development. After laying the foundation with anthropometry and hypertension, about which a good deal is known at the population level, we examine blood-based health markers for which population-representative data are more scarce. Specifically, we examine biomarkers for cholesterol, blood sugar and inflammation, all of which have been implicated in major NCDs including cardiovascular disease, strokes and cancers. These biological risk markers are selected because, first, they are likely to play a key role in understanding the evolution of global health in the years ahead and, second, they underscore the value-added of integrating insights from biology with the behavioral sciences to understand that evolution.

In recent years, the population health literature has shifted from relying primarily on self-reported health status and anthropometrics to incorporate a broad array of physical health measures. Self-reports contain valuable information about one's own health status. Overall

general health status is arguably the best predictor of subsequent mortality. In part, this is because self-reports summarize an individual's entire health history, health behaviors and family health history. However, these advantages also complicate interpretation of self-reports since they reflect not only underlying health but also expectations about health, norms regarding health and information about health. The latter is often related to use of health care and, for example, randomized controlled studies have shown that individuals who are randomly assigned to a group that receives more health care are more likely to report themselves as being in poorer health. Inter-personal comparisons of health based on self-reported measures are, therefore, not straightforward (Idler and Benyamini, 1997; Frankenberg and Thomas, 2002; Dow et al, 2010.)

Biomarkers, in contrast, are quantified measures of general health and nutrition or measures of physiological states that represent the functioning of specific organ systems and physiological processes. In combination with self-reported health, biomarkers are valuable tools for understanding the current and likely future trajectory of population health across the globe. There are several important features of biomarkers. First, they are collected using standardized protocols, at least within a study, and do not rely on the respondent's knowledge of or willingness to report a health condition. Second, they provide evidence on the prevalence of specific risk factors and the underlying physiological mechanisms that affect population health as well as exposures to environmental challenges and genetic predispositions to disease. Third, biomarkers support estimation of sub-clinical risks in populations, that is, levels below cut-offs used to define diseases, which provide a rich picture of the distribution of risks at the population level. This is important for health policy planning and the design of forward-looking health programs. Fourth, in many low income settings, biomarker measures have identified high levels of undiagnosed, untreated and uncontrolled health conditions which significantly impacts understanding the state of global health and NCD prevalence, particularly in settings with limited health care access.

For all these advantages, it is important to underscore that much remains unknown about the optimal trade-off between the costs and benefits of collecting data on biological health risks in population studies. Biomarker measurement can be expensive and is not straightforward particularly in the context of complex population-based field studies that use different methods to collect, store and assay biological samples. Standardization of the resulting biomarker values so that they are comparable across studies remains a significant challenge. The development and validation of protocols to harmonize methods and assure results from different studies are

comparable is an active area of ongoing research. Biomarkers for several important domains of health, such as pain, are not fully developed and combining different biomarkers to construct a picture of overall health taking into account interactions within and across biological systems remains a challenge (McEwan and Stellar, 1993).

Anthropometric measures, such as height, weight and arm circumference, have been extensively used in the nutrition, health and economics literatures along with measures of nutrient intake and, in some studies, energy output. Physical performance measures, such as lung capacity assessments and grip strength have been included in some population surveys. Many studies have measured blood pressure. Until recently, the collection of biological samples in population-based field studies was rare because of costs, feasibility and perceived value of the markers. In recent years, however, there has been a revolution in the technology of collection and measurement of biomarkers, costs have fallen and a growing literature indicates that biomarkers are likely to be a powerful tool for health research. In short, information about biological health risks in population-based studies has the potential to dramatically transform the field and yield important new insights into the links between health and economic development.

2. Data

The relationship between life expectancy, one measure of overall population health, and per capita gross domestic product (GDP) is displayed in Figure 1 for eight countries. We use individual-level measures of health collected in population-representative surveys conducted recently in each of these countries to illustrate key points in the rapidly growing literature on the links between health and development. In the figure, GDP is measured in 2010 in purchasing power parity in US $ and life expectancy at birth is estimated for 2005-2010 by the United Nations Population Division. Three lower middle income countries, Ghana, India and Indonesia, are displayed in red, three upper middle income countries, China, South Africa and Mexico, are in green and two upper income countries, Russia, and the United States (U.S.) are in blue. GDP per capita ranges between $2,300 (Ghana) and $47,000 (U.S.) and life expectancy generally rises with per capita GDP except for the cases of South Africa (where HIV-related mortality is high) and Russia (where life expectancy is over 10 years lower for males than females). (Strauss and Thomas, 2006.)

The surveys were selected because they include multiple metabolic-related biomarkers for male and female adults of all ages. For the U.S., we use the 2009/10 wave of the National

Health and Nutrition Examination Survey (NHANES), a repeated cross-sectional survey that collects an extensive battery of health measures including bio-specimens for hundreds of assays. Data for Russia, Ghana and India are drawn from the first wave of the Study on Global Ageing and Adult Health (SAGE) surveys collected by the World Health Organization between 2007 and 2010. The surveys are designed to be representative of the adult population with an over-sample of adults age 50 and older (Kowal et al., 2012). The Mexican Family Life Survey is a nationally representative longitudinal survey of Mexicans, including those who move to the U.S.; we use those who were living in Mexico at the time of the third wave which was collected in 2007-2012 (Rubalcava and Teruel, 2014). The National Income Dynamics Survey (NIDS) is a nationally representative longitudinal sample of South Africans; we use the baseline survey collected in 2008 (Liebbrandt, Woolard, and de Villiers, 2009). Data on the health of Chinese is drawn from the 2009 and 2010 waves of the China Health and Nutrition Survey (CHNS), a longitudinal survey of respondents living in 9 provinces in China. The Indonesia Family Life Survey is a longitudinal survey that was representative of 83% of the Indonesian population at baseline (in 1993); we use the fourth wave collected in 2007 (Strauss et al. 2009). All samples of adults are restricted to those age 30 through 79 in each country. For recent reviews of the literature, see Crimmins et al, (2010), Popkin, Adair and Ng (2012), Crimmins (2014), Ng et al (2014) and Roth et al (2015).

3. Height, weight and body mass index

Height and weight have been widely used as markers of health and well-being in the nutrition, history and economic development literatures. Adult stature, an indicator of the "biological standard of living" (Komlos, 1985), is predictive of morbidity, mortality and economic prosperity, reaching back over time (in pioneering work by Fogel, 1994; Steckel and Floud, 1997; Komlos and Baten, 1998) as well as in contemporary societies, particularly in lower income settings (Strauss and Thomas, 1998; Batten and Blum, 2014). While part of height is inherited, attained adult stature also depends on phenotype influences with nutrition and disease insults during the first few years of life being pivotal (Martorell and Habicht, 1986). Adult stature is largely determined in the first 24 to 36 months of life in the absence of large nutrition or health shocks and so linear growth of young children has been a focus of a very large and rich literature in the health and social sciences. A key advantage of attained adult height is that it is fixed until older ages and so can be used to infer variation in health, nutrition and well-being

across cohorts. Among older adults, for whom shrinkage is important, leg length and arm length have been shown to be good proxies for attained adult stature (McDade and Hayward, 2009).

Weight is difficult to interpret without adjusting for height. Body mass index (BMI), which is weight (in kilograms) divided by height (in meters) squared, has also been linked with mortality; Waaler (1984) documented that, among Norwegian adults, low BMI (below 18.5) and high BMI (above 28) are associated with elevated mortality risks. Similar patterns have been described for mortality and morbidity risks in populations around the globe with those who are overweight (BMI$\geq$25) and, especially, those who are obese (BMI$\geq$30) being at elevated risk of, *inter alia*, cardiovascular diseases, stroke, diabetes, cancers, muscular-skeletal problems and mortality (Dey et al., 2002; Must et al., 1999; WHO, 2000). Studies have shown that BMI affects economic prosperity, after controlling height and other human capital characteristics (Strauss and Thomas, 1997). BMI reflects the combination of energy expenditure (including types of physical activity), energy intake (taking into account diet composition), genetic factors and other lifestyle factors (such as stress exposures and smoking) and, for some, elevated BMI is indicative of greater muscle mass and may not indicate poor health. BMI is not indicative of a specific health risk but is a portmanteau proxy that may point to elevated risks and, on this score, has proved to provide valuable information about the evolution of population health.

Height and weight, which can be measured quickly and accurately in a field setting using a portable stadiometer and scale, respectively, have been included in population-based surveys for many decades. While measurement is straightforward, interpretation of BMI is complicated since it reflects the combination of fat, muscle and body type. Several alternative anthropometric indicators have been shown to provide useful additional information about health status including waist circumference (an indicator of central adiposity), the waist to hip ratio, arm circumference, leg and arm length and skinfold thickness. Recent technological innovations suggest that body composition may be estimated with bioelectric impedance analysis in field surveys.

One useful summary indicator for our cross-country comparisons is the percentage of the population that is overweight (BMI$\geq$25). It is displayed in Figure 2 by age and gender (in panel A) and by education and gender (adjusting for age, in panel B). Similar comparisons of average BMI and the fraction obese yield essentially the same overarching conclusions. The countries are arrayed by level of per capita GDP as in Figure 1. The figures by age are non-parametric estimates using locally weighted smoothed scatterplots (Cleveland, 1979). The estimates of the

association with education are predicted values from regression models that include linear splines in education, with knots at 6 and 12 years of completed schooling, as well as indicator variables for 10-year age groups. All models are estimated separately by gender for each country.

Generally, the fraction of adults who are overweight rises with GDP until countries enter into middle income and is essentially constant at higher levels of GDP. For example, among adults age 45 to 54, about 20% are overweight in India, 30% in Ghana and Indonesia, 40% in China, 60% in South Africa and over three-quarters are overweight in Mexico, Russia and the U.S., the three highest income countries. The fraction overweight is higher in the two African countries, given their GDP, particularly for females. Rates for females in Ghana are slightly higher than the rates in Indonesia and China (where GDP is two to four times higher) and rates for females in South Africa are close to those in the three high income countries (where GDP is two to five times higher).

In every country, the fraction overweight tends to rise with age to around 50 years and then declines, reflecting both life course and cohort effects with the latter being more important in middle-income countries like China that have enjoyed faster economic growth in recent decades. In all but the most advanced countries, females are more likely to be overweight than males. Figure 1a highlights two striking facts about gender differences. First, the female-male gap is very large in the African countries with females being almost twice as likely to be overweight as males which, along with the particularly high rates of BMI given GDP for females, suggests that factors over and above resources may affect BMI in these and other African societies as well as among African-Americans in the U.S. (Prentice, 2006; Flegal et al, 2010.) Second, the gender gap is small and possibly reversed among younger adults in the three highest GDP countries where BMI is high and does not rise with GDP.

Figure 2b displays the relationship between being overweight and education, a marker of longer-run socio-economic status (SES) so that the figure provides evidence on how biological health risks varies across the SES distribution, within each country, controlling age and gender. In every country other than the U.S, the best educated males are far more likely to be overweight than those with little education, even in countries where BMI is high. In South Africa and Mexico, over 80% of those with the most education are likely to be overweight. In the U.S., and most advanced countries, it is the less educated who are more likely to be overweight, as is the case for Russian females. In the upper middle income countries, South Africa, Mexico and China, the fraction of overweight females first rises with education and then falls. In the poorest

three countries, better educated females are more likely to be overweight than those with little education, as is the case for males. The pattern (across levels of GDP) of BMI and obesity first rising with education, then an inverted V shape and then declining and the pattern of females leading males in this transition in a country are well-documented (Popkin 2001; Popkin and Gordon-Larsen, 2004). While these comparisons of the shapes of the relationships are informative, comparisons of the fraction overweight for specific levels of education across countries is complicated since education levels do not have the same relative significance in every country.

Taking Figures 2a and 2b together, BMI and the fraction overweight tends to rise with overall economic prosperity but tapers off at high levels of BMI and GDP. Within the poorest countries, the fraction overweight rises with education for both males and females. In the richest countries, better educated females are more likely to adopt behaviors that limit BMI and the BMI-education profile is reversed. In the middle income countries this transition is evident among females but not among males: better educated females are on the vanguard of changing behavior in response to risks of being overweight. This, in conjunction with the fact that very large fractions of well-educated males in middle income countries are overweight suggests that there is both considerable scope and arguably an urgent need for programs that will stem the apparently inexorable march towards populations with high rates of overweight and the attendant metabolic disease burdens.

4. Hypertension

High blood pressure, or hypertension, is associated with several lifestyle factors including elevated BMI, greater stress, inadequate exercise, excess sodium in the diet, and tobacco consumption. High blood pressure usually develops over many years and prolonged exposure to elevated blood pressure can damage the inner lining of the arteries, leading to arteriosclerosis (hardening of the arteries) and atherosclerosis (narrowing of the arteries). Moreover, biological mechanisms underlying elevated blood pressure vary over the life course, with stiffness in the arteries playing an increasing role with age. Elevated blood pressure is a major risk factor for heart disease, stroke and kidney disease and has been implicated in later life cognitive decline (Kannel, 2000; Levy et al., 1996).

Blood pressure is straightforward to measure in a field setting.[1] Stage 2 hypertension is indicated when systolic pressure is 160 mmHg or higher or diastolic pressure is 100 mmHg or higher and stage 1 hypertension is indicated when systolic or diastolic pressure are 140 and 90 mmHg or higher, respectively. Figure 3 displays the percentage of males (in Figure 3a) and females (in Figure 3b) who are considered stage 2 hypertensive for each of three age groups in each country. The percentage whose blood pressure as measured in the survey exceeds at least one of the cut-offs for stage 2 hypertension is displayed by the solid dark bar for each age group. The percentage whose blood pressure is below the cut-off but report using medication to keep blood pressure low is displayed by the white bar. The sum of the heights of the solid and white bars indicates the percentage who are measured as hypertensive (i.e. uncontrolled hypertension) or on medication to lower blood pressure (i.e. controlled hypertension). This distinction between controlled and uncontrolled hypertension is important. In order to avoid long-term damage to the body system, clinical guidelines recommend that hypertension be controlled through lifestyle changes, medication or both. As is evident from the heights of the solid bars in Figure 3, for many people, hypertension is not controlled, particularly in lower income countries. This may reflect that hypertension is not diagnosed or not treated, or that treatment is ineffective.

Taking controlled and uncontrolled hypertension together, prevalence rises with age in every country. At younger ages, rates of hypertension are generally higher among males, relative to females but since the rate of increase with age tends to be faster for females, among older adults females are somewhat more likely to be hypertensive than males. These general patterns by age and gender are well-established for both developed and developing countries.

There are two striking additional features of Figures 3a and 3b. First, the variation across countries in the rates of hypertension, particularly rates of uncontrolled hypertension, is stunning. Second, levels of uncontrolled hypertension are extremely high in many developing countries and the vast majority of these cases are undiagnosed. This is profoundly troubling given the likely future impact on the lives of these people and their families as well as the impact on the public health sector.

[1] While measurement with a stethoscope and sphygmomanometer is considered the gold standard, the method requires considerable training. It is used in NHANES. In field settings, blood pressure has been measured using automated home monitors with an inflatable cuff placed around the bicep. The monitors are inexpensive, robust, well-validated and straightforward to use. In the Indonesian, Mexican, South African and SAGE surveys, blood pressure was measured using an Omron monitor with multi-size cuffs to allow for variation in bicep size in the study populations.

Moreover, South Africa stands apart from all other countries in the figure. In each age group, rates of uncontrolled hypertension are the highest among South Africans by a substantial margin: around 60% of South Africans age 60 to 79 are hypertensive (based on field-measurement) and another 10% report controlling hypertension with medication so that over 70% of this age group suffers from stage 2 hypertension: this is a staggering rate in the population. Even among adults age 30 to 44, almost 30% are hypertensive and less than 5% report taking medication. Since the impacts of hypertension cumulate over time, these high rates of hypertension and low rates of control raise serious concerns about the future health of the population which, taken in combination with the high rates of obesity, have powerful implications for the future burden of NCDs in South Africa and the concomitant demands on the health system and public finances supporting that system. This burden is exacerbated by the high rates of infectious disease, weak infrastructure and high rates of poverty in South Africa. While the figures are not as dramatic, similar concerns arise in the other African country, Ghana, where about 40% in the 60-79 age group are hypertensive and less than 10% are controlling their blood pressure. The data suggest that without significant changes in health care and lifestyles, the epidemic of obesity and hypertension that is sweeping through Africa will likely impose a heavy burden on future generations.

In Russia and the U.S., about 60% of the 60-79 age group are hypertensive but over 80% of the Americans and over 50% of the Russians control hypertension with medication (Ikeda et al., 2014). Approximately 30% of the 60-79 age group are hypertensive in India, China and Mexico where about half of those people control blood pressure with medication. In Indonesia, the overall percentage of 60-79 year olds who are hypertensive is also about 30% but those who are not controlling blood pressure (the solid bar) is overwhelming relative to those who are controlling blood pressure (the white bar). This reflects two factors. First, diagnosis rates in Indonesia are exceptionally low. Only 5% of all males and females age 60-79 report having been diagnosed as hypertensive. Second, of that 5%, only one in three is actually keeping blood pressure below the cut-offs with medication; for the other two-thirds, either the medication is ineffective or the reports of using medication are wrong. (Franklin et al, 1999; Blacher et al., 2000; Izzo, Levy and Black, 2000; Kannel, 2000; Stevenson, 1999.)

The lower panels of the figure display the percentage of males (in Figure 3c) and females (in Figure 3d) who are hypertensive by three education groups. For males in all but the two highest income countries, the fraction controlling hypertension tends to rise with education while

the fraction that is measured hypertensive does not vary much with education and so, overall, total hypertension rates rise slightly with education. For females in the same countries, the fraction measured hypertensive is lowest among those with the most education but there is no consistent association between education and the fraction controlling hypertension or with total hypertension rates. In the U.S., better educated males and females are more likely to be taking medication and less likely to be measured hypertensive and so total hypertension rates decline with education. In contrast with the striking patterns linking education and being overweight in Figure 2, variation in hypertension with education is very modest. Public health programs that result in improved control of blood pressure will likely benefit populations across the entire spectrum of SES in many low income countries. (Addo, Smeeth and Leon, 2007; Busingye et al., 2014; Colhoun et al., 1998; Ibrahim et al., 1995; Lee et al., 2012; Steyn et al., 2008; Witoelar, Strauss and Sikoki, 2012; Wu et al., 2008).

In sum, in middle and low income countries, the pay-offs are likely to be substantial for policies that are effective in improving diagnosis and, when indicated, treatment of hypertension among adults across the entire age spectrum. The returns to programs and policies that result in lifestyle changes and medication use where appropriate are likely to be very high for individuals, their families and society.

5. Other non-invasive measures of health and nutrition

Some field surveys have included non-invasive activity-related measures in addition to anthropometry and blood pressure. Measures that are also simple, accurate and inexpensive to field include, for example, heart rate variability, lung capacity, grip strength, timed walks, timed repeated stands from a sitting position, observing a respondent perform specific activities such as walking in a straight line or standing on one leg and tests of fine motor skills. Accelerometers and pedometers are increasingly being adopted in population-based studies to measure energy expenditure over extended periods of time. While the link between many of these measures and underlying biology is indirect, the measures do contribute to a fuller representation of the physical health of an individual and, in many cases, provide a valuable complement to self-reported activities of daily living (ADLs) and instrumental ADLs. However, interpretation of activity-based measures can be complicated when they reflect both the capacity to perform the activity and the respondent's desire to perform. For example, the speed with which a respondent stands from a sitting position reflects not only musculo-skeletal difficulties but also exuberance,

energy and other, related traits. Similarly, converting accelerometer counts to energy expenditure is complicated by differences in body composition and variation in basal metabolic rates (Steptoe and Wilkins, 2011).

There is a long history of measurement of nutrient intake in field surveys. These studies have used individual food intake recalls, food consumption at the household level or measurement of food prepared and eaten in the home, converting food consumption to calories and nutrients. Each of these approaches is thought to be subject to substantial measurement error, albeit from different sources. Food recalls are usually asked of an individual respondent and typically span the preceding 24 hours. They miss day to day variation in diets which will be more important in higher income settings. Since extending the recall period is thought to result in a greater understatement of food intake, studies have suggested making daily visits to the same respondent for multiple days or asking respondents to complete food diaries over several days. An alternative that is less demanding of respondent time is the collection of food frequency diaries which typically focus on a specific set of food items (Wiehl and Reed, 1960). In general, these approaches tend to be associated with under-reporting of food intakes (Black, Welch and Bingham, 2000; Hill, 2001).

A key advantage of food recalls and food diaries is that it is possible, in principle, to obtain individual-specific measures of intakes. Since food consumption is typically measured at the household level, it is difficult to attribute consumption to an individual. The same concern arises with food that is weighed and measured since this is also typically conducted at the household level. Consumption data usually cover at least a week and in some cases longer periods of time and include food consumed at home and away from home. Respondents report the quantity of each specific item purchased or consumed out of own production. Converting consumption data to nutrient intakes relies on conversion tables that are not adjusted for quality (which tends to rise with income), wastage (which tends to increase with income) or food purchased but not yet consumed (which also tends to rise with income). The more aggregate the consumption data and the more diversity in foods within the aggregate, the greater the conversion error. Few surveys collect a roster of every person at each meal, including household members and guests, which complicates even per capita measurement of intakes.

Some studies have weighed and measured food by either visiting the household daily for up to a week or by providing scales and asking the respondent to measure all foods consumed. Food that is prepared and all leftovers are weighed and, in some cases, food consumed by each

individual is also weighed. This method is considered the most accurate method to measure intakes and addresses concerns with errors in recall and conversion to nutrients. However, it is extremely demanding of respondents and survey enumerators; in addition, it is difficult to measure food eaten out of the home which imparts a systematic bias.

The central issue for our purposes is that all these approaches to measurement of food intakes are subject to substantial error. An alternative approach measures energy expenditure using doubly-labelled water[2] or indirect calorimetry. However, measurement of specific nutrient intakes requires reliance on biochemical analyses of biological samples such as blood and urine.

6. Blood-based markers of health and health risks

In contrast with the markers discussed thus far, there has been a revolution in the collection and analysis of biological health risks in recent years. Whereas thirty years ago, very few large-scale household surveys collected any biomarkers over and above anthropometry, nowadays, biomarkers are routinely collected in many surveys across the globe. This reflects the combination of two complementary forces. First, understanding of health outcomes has been substantially enriched by the integration of insights from the health and social sciences with biologically-plausible models of causal mechanisms (McEwen, 1998; Crimmins and Seeman, 2004; Crimmins and Finch, 2006). These models have elucidated the complex biologic and socio-economic underpinnings of health inequalities, provided the foundation for models of health and health transitions over the life course and highlighted how, for some, the impact of health insults cumulate over the life course and may present as physiological deterioration at older ages. These insights have powerful implications for understanding the links between health and development.

The second force underlying this revolution in health measurement is the dramatic decline in the costs of collecting biomarkers in household surveys because of new technologies. There are four primary approaches to collecting and analyzing biological specimens to measure biomarkers. First, respondents are asked to visit a designated site where specimens are collected. A key challenge with this design is that the health of those who participate in the study may not be representative of the health of the entire target population. Of particular concern is that those in worst health may not be willing or able to travel to the site and those with the highest value of

[2] Doubly-labelled water contains a known concentration of stable isotypes of hydrogen and oxygen. As energy is expended, the body produces carbon dioxide and water and the differences in the isotype elimination rates provide an estimate of total energy expenditure.

time (who are also likely to be in good health) may be unwilling to travel to the site and participate. The distribution of health of those included in the sample is likely to be sparse in both the lower and upper extremes. Several studies have adopted this approach although few have described the likely implications of sample selectivity for population estimates of prevalence and associations with individual and community-level characteristics.

The second approach essentially takes the clinic to the respondent. NHANES, a pioneer of this approach, has been fielded since the early 1960s in the United States by the National Center for Health Statistics. A mobile examination center (MEC), comprising several large trailers equipped with state-of-the-art medical equipment are parked in a neighborhood and respondents undergo a complete physical examination in the MEC. Some biomarkers are assayed immediately; for others, specimens are stored for later analyses in a laboratory. All assays are conducted using best practices and, where necessary, are validated against an established reference laboratory. It is argued that NHANES provides the best estimates of population health in the U.S. although participant non-response is an ongoing challenge. A small number of studies have replicated the NHANES approach but a key impediment to widespread adoption of the model is the cost of the MEC.

The third approach collects specimens in the home and conducts assays at a later time. Collection, storage and analysis of urine and venous blood samples are relatively complicated. For some biomarkers, samples need to be assayed within a brief window after collection, samples needs to be fractionated with protocols depending on the target biomarkers and in some cases bio-specimens need to be collected over an extended period of time and thus involve multiple visits with the respondent. However, for several bio-specimens, such as saliva, hair and nail clippings, collection and transportation to a laboratory for analysis is inexpensive and straightforward in complex field studies and protocols have been established to measure many biomarkers with these specimens including, for example, endocrine and inflammatory responses, infections, exposures to toxins, markers associated with cancers and genetic material such as DNA and RNA.

In this vein, dried bloods spots (DBS) are a potentially powerful bio-specimen which have been collected in the home in several complex field studies in recent years and are being used to measure a rapidly growing number of biomarkers. Collection of DBS is simple: drops of whole blood are collected from a finger (or heel) prick onto absorbent filter paper which is then dried and stored. The cards are easy to transport to a laboratory where a disc is typically punched

out and an assay is conducted. DBS have been used to screen for diseases among newborn babies since the early 1960s (Guthrie and Susi 1963), have been used in many epidemiological studies and are increasingly adopted in population surveys (McDade, Williams and Snodgrass, 2007). A wide array of analytes have been measured using DBS including, for example, metabolic and nutrition-related markers, HIV, hepatitis and infectious diseases, inflammation markers, cortisol, testosterone, DNA and RNA. For some assays, the fact that each spot yields a relatively small volume of blood can be a challenge. In addition, widely-used protocols for cross-validation of assay implementation across different laboratories have not been fully established and comparisons of assay results across studies are not straightforward (Crimmins et al, 2014). However, progress is being made on both of these fronts.

The fourth approach to biomarker measurement exploits recent advances in the technology of point-of-care monitors. These portable monitors are usually battery-powered and typically use capillary blood from a finger prick – thereby exploiting the advantages of the third approach to biomarker measurement – while also providing information to the respondent at the time of the assessment – a key advantage of the second approach, bringing the clinic to the home. This is a significant and important advantage during a lengthy interview and is especially valuable in settings where health service use is constrained by price, access, quality or respondents' resources. Regular measurement of known levels of the biomarker using quality control strips provided by the manufacturer assures the monitor is accurate and measures do not drift during the field period. The key limitation is that there are relatively few portable point-of-care monitors that are robust enough and have been validated for complex field settings (as opposed to a doctor's office).

The HemoCue photometer is a point-of-care monitor that has been successfully used in numerous studies to measure hemoglobin (Hb) in the home. It is one of the earliest point-of-care monitors developed and has been used since the late 1980s (Bridges, Parvin and van Assendorf, 1987). It requires only a small sample of blood from a finger stick; it is inexpensive, very robust and portable; does not require electricity or refrigeration, displays the measure within seconds and has been shown to have high levels of specificity and sensitivity in very diverse settings. Indeed, the HemoCue photometer has provided important population-representative evidence on the prevalence of this indicator of iron deficiency in populations across the globe.

We examine three biological risk factors that have been implicated in cardiovascular disease, stroke and premature mortality: total cholesterol and glycosylated hemoglobin (HbA1c)

are indicative of metabolic functioning while C-reactive protein (CRP) is a marker of inflammation that has broader implications for health and well-being. All three are measured using blood samples although the measurement strategy varies across countries and biomarkers.

Total cholesterol

High levels of cholesterol put individuals at risk for cardiovascular disease. Total serum cholesterol levels are related to coronary heart disease and, at some age, tend to increase the risk of cardiovascular and all-cause mortality (Anderson, Castelli, and Levy, 1987; Weverling-Rijnsburger et al., 2003). The three components of cholesterol are low density lipoprotein (LDL), very low density lipoprotein (VLDL) and high density lipoprotein (HDL) cholesterol. HDL cholesterol has antioxidant and anti-inflammatory functions and its benefits include the removal of excess cholesterol from blood vessels, prevention of blood vessel blockages, promotion of blood flow and improved innate immunity (Toth, 2005; Feingold and Grunfled, 2011). Low levels of HDL cholesterol are associated with an increased risk of cardiovascular disease incidence and mortality including coronary heart disease, coronary artery disease and stroke (Barter and Rye, 1996; Castelli et al., 1986; Gordon et al., 1989; Weverling-Rijnsburger et al., 2003). In contrast, LDL cholesterol deposits on the inside of blood vessels and creates plaque. Whereas HDL and total cholesterol are not affected by whether an individual has fasted prior to measurement, this is not the case for LDL. Since requiring study participants to fast, and monitoring their fasting behavior, substantially complicates field work, most studies have measured only HDL and total cholesterol.

We focus on total cholesterol which has been measured in four of the studies we examine using three of the different methods described above. In the United States, NHANES brought the clinic to the respondent. In China, after an overnight fast, blood was drawn in the home, frozen, and transported to a national central lab in Beijing. In Indonesia and Mexico, a point-of-care monitor, the CardioChek Analayzer, was used to measure total cholesterol in the home. Recent advances have established that total cholesterol can be measured in DBS.

Results are presented for the percentage of the adult population age 30 through 80 years for whom measured total cholesterol indicates a high risk of heart disease (240mg/dl or higher). (Jellinger et al., 2012). Since cholesterol can be controlled with medication, this percentage is adjusted to include the percentage of the population who report themselves as being on such medication and whose measured total cholesterol indicates successful control (<240 mg/dl). This

adjustment is made for the United States and Indonesia; medication use to control cholesterol is not reported in the China or Mexico studies. The fraction of the population on medication is tiny in Indonesia (less than ½%) and the adjustment makes no difference in the figures. It is, however, an important adjustment in the U.S., as explained below.

Percentages with high total cholesterol (or on medication) are displayed by age in Figure 4a and by education in Figure 4c, estimated separately for males and females. Among females, the levels and variation with age are remarkably similar in Indonesia, China and Mexico. The percentage rises steeply with age from age 30 to around 50. Among females age 50 and older, about one in five have high total cholesterol, and, among these older females, the percentage does not vary with age. Among males, only about one in ten has high total cholesterol or is on medication and the link with age is muted, rising slightly to around age 50 in China and Mexico and not varying much with age in Indonesia. In the U.S., the patterns are completely different in two key dimensions. First, the percentage with high total cholesterol or on medication rises dramatically with age from about one in 10 among younger adults (age 30-39 years) to over half of older adults (age 70-79 years). The majority of this age gradient reflects higher rates of medication among older adults: among those who either have high total cholesterol or are on medication, 15% of those in their thirties and 80% of those in their seventies are controlling cholesterol with medication. Second, the female disadvantage in total cholesterol in Indonesia, China and Mexico is not apparent in the U.S.

The optimal cut-off to identify elevated health risks is not clear and it is not obvious that a single cut-off is appropriate across all settings included in the figure. We present estimates using a cut-off rather than levels of measured total cholesterol because methods for adjusting measured levels for medication use have not been established. Selecting a lower cut-off ($\geq$200mg/dL) increases the percentage of the population with elevated risks to between 35 and 40% in Indonesia, China and Mexico and to about 60% in the United States (including those on medication) but has little impact on the comparisons across countries and demographic groups.

The relationships between high total cholesterol and education, adjusted for age, are displayed in Figure 4c. For males and females in China and the U.S., the education gradients are not significantly different from zero. In Indonesia, for both males and females, the percentage of the population with high total cholesterol rises with education (by 0.7 percentage points for each year of education). In Mexico, the percentage rises at lower levels of education for females but rises very dramatically at higher levels of education among males. Controlling for age, one-

quarter of Mexican males has high levels of total cholesterol.[3] (Perova et al, 2001; Witeolar, Strauss and Sikoki, 2012; Yan et al, 2012.)

Glycosylated hemoglobin (HbA1c)

The prevalence of diabetes mellitus, which is indicated by poor control of blood glucose levels, is thought to be growing rapidly in both developed and developing countries. This reflects, in part, aging of populations (since the prevalence of type 2 diabetes rises with age) and the worldwide epidemic of obesity (a powerful diabetes risk factor). The majority of population-based estimates of glucose metabolism have relied on fasting blood samples which are complicated to collect in a field setting. Several recent studies have relied on glycosylated hemoglobin (HbA1c) which can be assessed without fasting. HbA1c is a measure of plasma glucose concentration which, in turn, is indicative of average blood glucose levels over the previous three months. HbA1c levels are elevated when blood glucose levels are not controlled and are used to indicate diabetes mellitus which is associated with cardiovascular disease, kidney disease and retinopathy (Rohlfing et al., 2000; Selvin et al., 2010; Khaw et al., 2004; Selvin et al., 2010).

Figures 4b and 4d display the percentages of the population with measured HbA1c that is elevated ($\geq$6.5%) or who report being on medication to control blood sugar in China, Mexico and the United States. Assays were conducted immediately after collection of blood in China and the U.S. using high-performance liquid chromatography (HPLC) and were conducted in the home using the in2it A1c Analyzer in Mexico. Measures using the in2it A1c analyzer have been shown to correlate well with HPLC assessments (Martin et al., 2010).

Diabetes is usually indicated when two recordings of HbA1c are at least 6.5%; however, the data used here are based on a single measure for each respondent. Nonetheless, the first and most striking fact is that rates of elevated HbA1c are extremely high in Mexico: fully one-third of adults age 30 through 79 are likely to suffer from diabetes. This is about twice the rate in the

[3] Using data from the same four countries, we have also explored levels of HDL cholesterol, the "good" cholesterol, low levels of which are risk factors for poor health outcomes. Using 40g/dL as a cut-off, about one-quarter of Chinese and one-half of Americans have low levels of HDL (or cholesterol is controlled with medication). In Indonesia and Mexico, over two-thirds of the population is estimated to have low levels of HDL. While it is possible that this reflects high levels of infection in Indonesia and Mexico; the estimate for Mexico is higher than other estimates from that country. The fact that both the Mexican and Indonesian studies used the CardioChek Analyzer and blood was analyzed in the lab in the Chinese and American studies suggests the differences may reflect differences in measurement protocols and underscores the importance of future research that validates biomarker measurement protocols in field settings taking account of variation in temperature, humidity and handling of materials.

United States which, in turn, is about twice the rate in China. In all three countries, elevated HbA1c rises with age although the rates decline at older ages among Mexican and American males. Other than for older Mexicans, there are no differences between males and females. Only a small fraction of adults who report themselves as controlling blood sugar with medication do not have elevated HbA1c: 1% in China, 2% in Mexico and only 4% in the U.S. In fact, over 70% of the people who have elevated HbA1c in the U.S. also report taking medication and they account for over two-thirds of those who are on medication. Clearly, rates of elevated blood sugar levels are very high in Mexico and the U.S., even in the presence of diagnoses and medication. Moreover, clinical trials have not demonstrated clear benefits to lowering glycosylated hemoglobin using diabetes medications among diabetic patients (Action to Control Cardiovascular Risk in Diabetes Study Group, 2008; Selvin et al., 2008).

As shown in Figure 4d, conditional on age, uncontrolled blood sugar or being on medication tends to decline with education among females, particularly in the U.S. and among Mexican females with at least primary schooling. Among males, the rates rise with education among Chinese, are unrelated to education among Mexicans with high school education or less and then decline, and decline with education among Americans. These patterns are similar to those observed for BMI. Specifically, elevated health risks switch from rising with education to declining with education as levels of development increase and females tend to be on the vanguard of this switch (Barquera et al., 2013; Yan et al., 2012.)

The extremely high levels of elevated HbA1c among Mexicans adults, particularly those in their forties and fifties, and among those with less education is profoundly troubling. Diabetes ranks among the top three causes of death in Mexico (Sistema Nacional de Información en Salud, 2007). Given the close link between diabetes and both age and obesity, as developing countries like Mexico age and as obesity levels also rise in other countries that are aging, diabetes is likely to become a very serious burden on individuals, their families, the health system and the public sector budget. It is not too early to experiment with and evaluate policies that have the potential to affect these patterns.

C-Reactive Protein (CRP)

Our final biological risk factor is a marker of inflammation, C-reactive protein. Inflammation arises whenever there is an infection or injury and is a defensive response to a potentially harmful challenge. Acute inflammation occurs when increased blood and leukocytes

are transported to the tissues that are under assault and the biological system returns to its normal state within a few days. Prolonged or chronic inflammation occurs when acute inflammation persists rather than resolving, which typically results in tissue damage or destruction. Acute inflammatory processes have been implicated in atherosclerosis and the pathogenesis of cardiovascular disease. Chronic inflammation reflects disease history and risks for future disease, as chronic activation of inflammatory pathways may be set off by early exposure to infectious diseases (Crimmins and Finch, 2006). Inflammation is also elevated among those who are overweight and obese as well as those who are currently exposed to an infection or injury. Inflammation is, therefore, a general marker of health and may be a valuable complement to BMI and self-reported health status to indicate overall population health.

CRP is one of many potential markers of inflammation. It is an acute phase protein that reflects general systemic inflammatory response. Part of the immune response to infection, tissue damage and injury involves increases in circulating levels of CRP. Elevated levels of CRP have been found to be positively associated with cardiovascular disease incidence including myocardial infarction, stroke and peripheral arterial disease; diabetes; metabolic syndrome; and mortality in adults (Jenny et al., 2007; Kuller et al., 1996; Pradhan et al., 2001; Ridker et al., 2000, 2003).

Since chronic inflammation occurs over the entire life course, we present CRP levels for all ages for the countries with CRP measures, Indonesia, China, and the U.S., in Figure 5a. The percentage of the population with CRP $\geq$ 3 mg/L, a cut-off indicating chronic inflammation, is displayed. In each country, elevated CRP rates decline during the first few years of life and then rise after around age 10. In China, the rise is steep throughout the life course and in the U.S., the increase tapers off in early middle age but remains elevated. In Indonesia, there is much less variation with age. At each age, the probability of elevated CRP is similar in China and America, but is substantially lower in Indonesia. Overall, only 10% of the Indonesian population has elevated CRP whereas in China and the U.S., the rates exceed 25% and peaks for American females around age 65 when half suffer from elevated inflammation.[4]

Gender differences in CRP are relatively small in Indonesia and China, but high levels of CRP are much more common among female adults relative to males in the U.S. Patterns by

[4] The substantially lower rates of elevated inflammation in Indonesia relative to China and the U.S. are surprising given that overall infection rates are higher in Indonesia. They may reflect collection and assay differences; while the reported estimates are designed to be translated into comparable units, CRP is measured from plasma in China and the United States but from DBS in Indonesia..

education are displayed in Figure 5b, controlling age and gender, restricting the sample to adults age 30 through 79 (to assure education has been completed). Elevated inflammation declines substantially with education in the U.S., modestly in China and is essentially unrelated to education in Indonesia. (Nazmi and Victora, 2007; Yan et al, 2012).

7. BMI and the other biomarkers

As the epidemic of obesity spreads across the globe, increases in BMI will likely be accompanied by higher rates of NCDs. It is, therefore, of substantial interest to compare the associations between BMI and the other biomarkers across countries. Non-parametric estimates of the associations for each country are presented for hypertension in Figure 6 and for elevated HbA1c, total cholesterol and CRP in Figure 7. The estimates, which adjust for age and gender, are displayed for adults age 30 through 79. For hypertension, total cholesterol and HbA1c, the percentages include those who report being on medication to control the risk factor. Generally speaking, as BMI increases, the fraction of the population with elevated levels of each of the four biological risks also increases for every country. Consequently, the global epidemic of obesity is likely to be accompanied by elevated rates of hypertension, metabolic health problems and inflammation.

As shown in Figure 6, as BMI increases, hypertension rates rise at roughly the same rate in each country so that, for example, if average BMI for a country increases from 25 to 30, it will be accompanied by a 10 percentage point increase in the share of the population that is hypertensive. In part, the slopes reflect biological links between BMI and hypertension.

Another striking feature of the figure is the tremendous heterogeneity across countries in the level of hypertension for any particular BMI. There are three main groups of countries. First, for any BMI, adults in Indonesia and Mexico are the least likely to be hypertensive: as an example, among those whose BMI is 30 kg/m^2, about 20% are hypertensive. Second, in the U.S., India and China, hypertension rates are higher with the risk rising to 30% for those with BMI of 30 kg/m^2. Third, in Ghana, Russia and South Africa, hypertension rates are very high with the risk being around 50% at this BMI level. These very large gaps across countries likely reflect variation in lifestyle such as diet, exercise and stress, use of health care and possibly genetic differences. Patterns in China suggest lifestyle differences are central. At low levels of BMI, hypertension rates in China are very similar to those in the lowest group, Mexico and Indonesia, but at high levels of BMI, hypertension rates are as high as in the second group, the U.S. and

India. The rapid rise in hypertension among heavier Chinese is a serious concern and presumably reflects the impact of lifestyle differences among those who are overweight and obese relative to those who are not. Moreover, the dual burden of elevated BMI and hypertension in the third and possibly second group of countries will elicit a heavy price in terms of population well-being, health care costs and, possibly, economic productivity in the years to come.

As shown in Figure 7a, HbA1c also rises with BMI. The rate of increase is essentially identical for all three countries -- Mexico, China and the U.S. -- except, perhaps, at very high levels of BMI in Mexico where the curve is much flatter. A one unit increase in average BMI for a country is associated with a one percentage point increase in the share of the population with elevated HbA1c. Conditional on BMI, rates of elevated HbA1c are the same in China and the U.S. but about twice as high in Mexico. This is not likely to be driven by genetic differences since, controlling BMI, there are only small differences in the incidence of elevated HbA1c among white Americans and Mexican-origin Americans in NHANES. To the extent the gap is not due to differences in measurement, it is likely that diet, behavior and lifestyle factors play a role. As BMI rises in Mexico, this evidence suggests it will be accompanied by high rates of diabetes which will likely impose a very large burden on the society.

The relationship between elevated total cholesterol and BMI is displayed in Figure 7b. As BMI increases, elevated cholesterol rates rise and then decline; the point of inflection is at lower levels of BMI in China, Indonesia and Mexico (between 25 and 30 kg/m^2) than in the U.S. (30 kg/m^2). At every level of BMI, cholesterol rates are much higher in the U.S. and lowest in China and Mexico, with Indonesia lying between these extremes.

Finally, Figure 7c displays the relationship between BMI and inflammation. In all three countries, the relationship is flat until BMI reaches 25 and then rises. Given BMI, the rates of inflammation are essentially identical in the U.S. and China but much lower in Indonesia. It is not clear what explains this difference and it is possible that it reflects differences in measurement.

8. Conclusions

The evidence summarized in the figures suggests three main conclusions. First, as the epidemic of obesity reaches more and more parts of the globe and as levels of BMI rise in lower income countries, the burden of non-communicable diseases will also rise in roughly predictable ways. The costs to individual, families and society are likely to be very large indeed. There is an

urgent need for a co-ordinated global effort to design, implement and evaluate programs and policies that will forestall those costs.

Second, there are important cross-country differences in the relationships among these biomarkers which likely reflect differences in health conditions, the costs and organization of health care services and possibly socio-economic, demographic and genetic heterogeneity. Understanding the factors that underlie these differences remain important open questions and new insights into these factors and mechanisms have the potential to yield powerful scientific and policy conclusions regarding population health.

Third, the technology exists to measure major biological markers of health and well-being in even complex field studies but there is only limited evidence on these risk factors in population-based studies. To be sure, there are significant measurement challenges and there is considerable work to be done to cross-validate different measures in different settings. Such investments are likely to have a major impact on scientific understanding of the complex interplay between biology, health and development.

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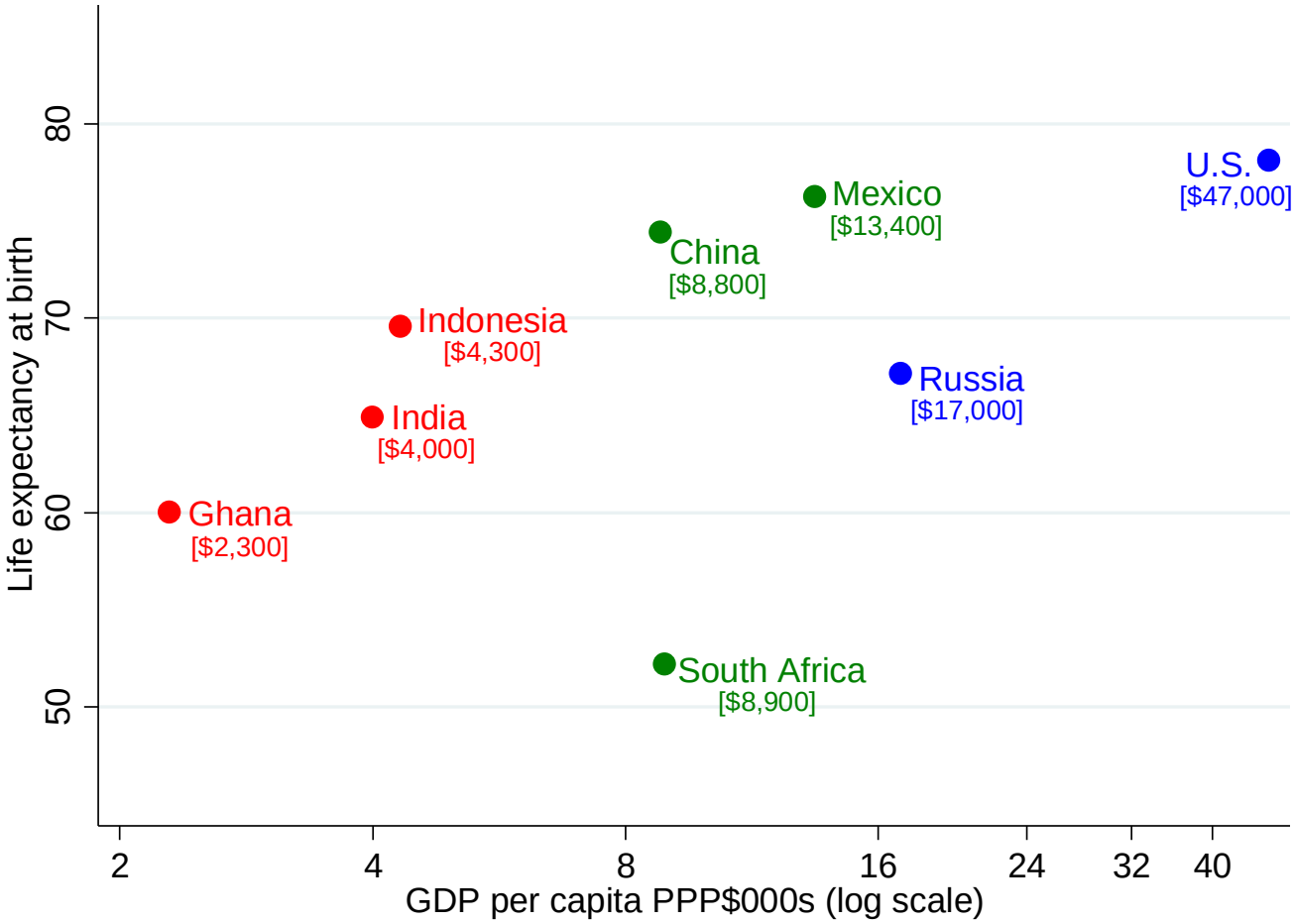
Figure 1: GDP per capita and life expectancy at birth



Note: GDP per capita is measured in 2010 purchasing power parity dollars (which are in brackets below each country name) from the Penn World Tables, version 6.3. Life expectancy at birth estimates are for 2005-2010 from the United Nations Population Division.

Figure 2: Percent overweight (BMI≥ 25) by gender, age and education

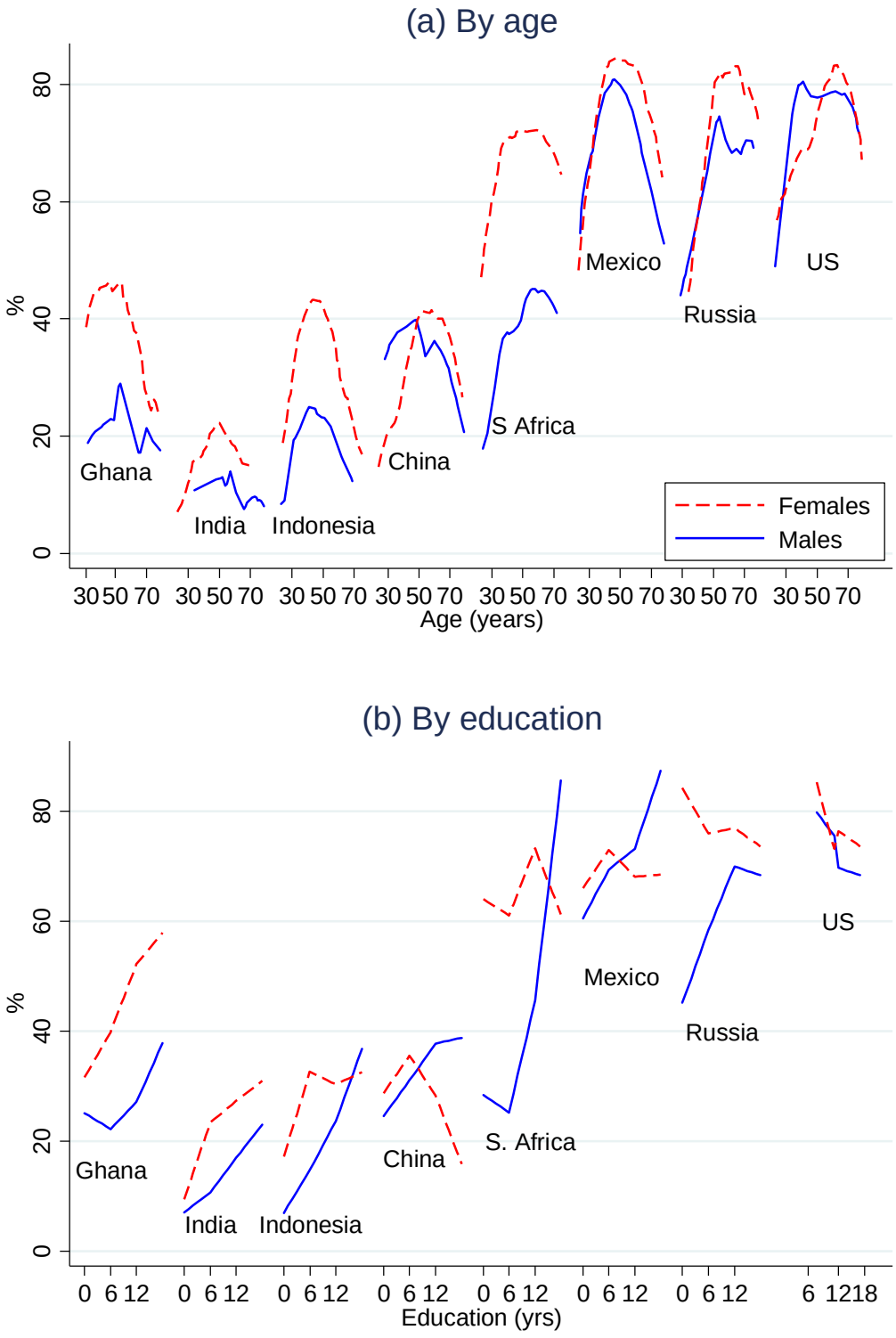
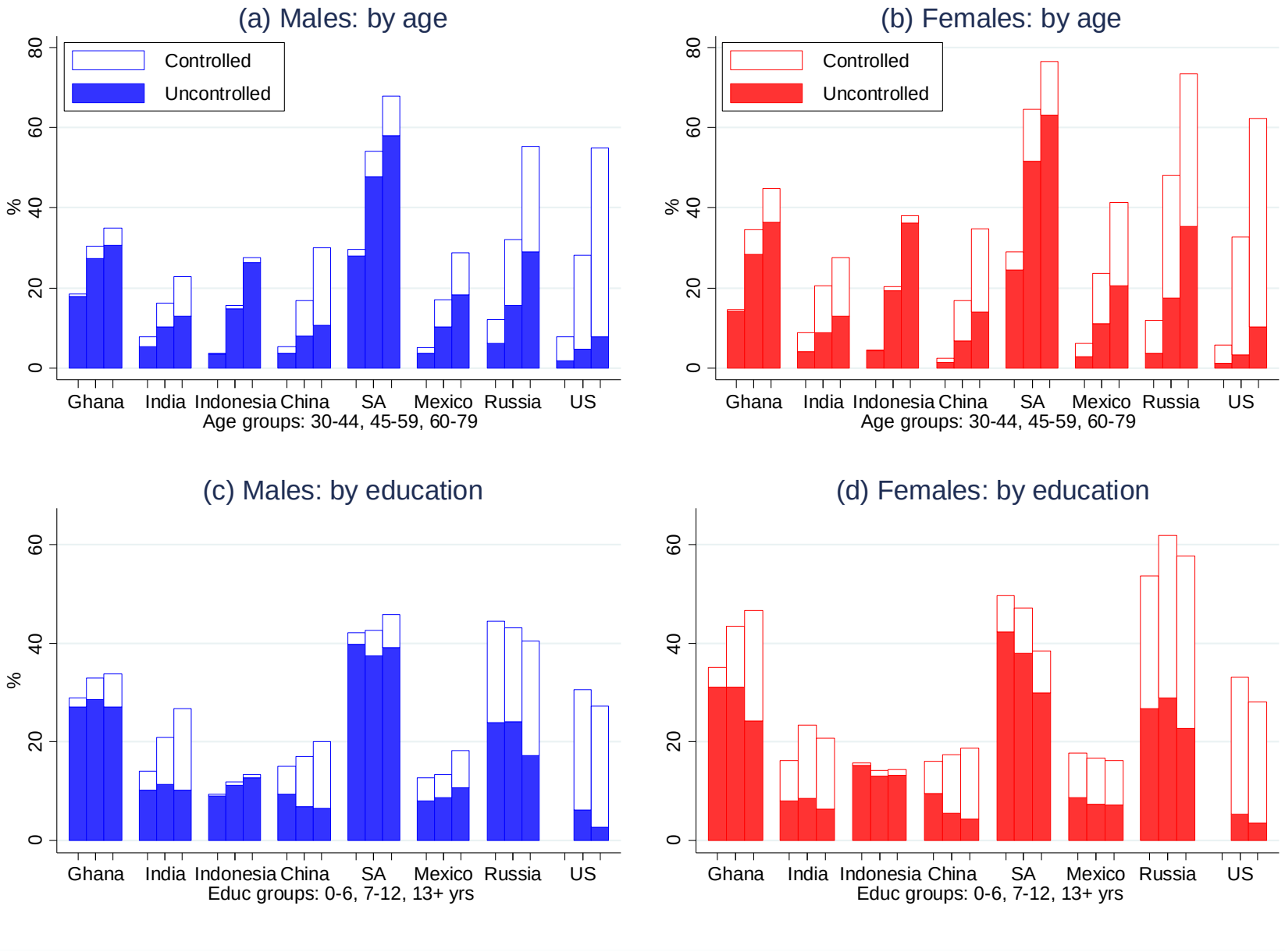


Figure 3: Percent hypertensive or on medication by gender, age and education



Note: Hypertensive is stage 2 hypertensive, defined as systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 100 mmHg.

Figure 4: Percent with high total cholesterol and high glycosolated hemoglobin by gender, age and education

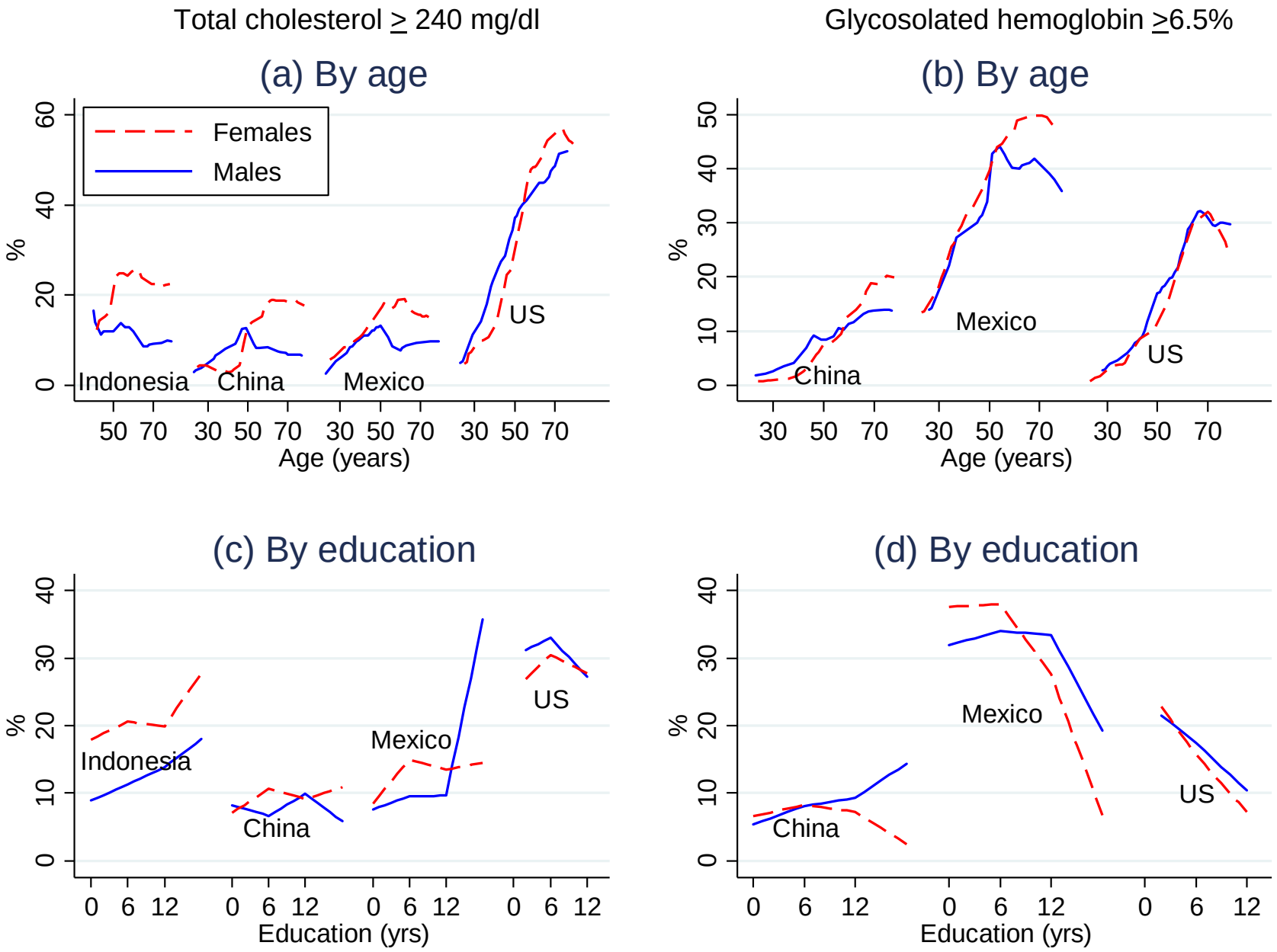


Figure 5: Percent with high levels of inflammation by gender, age and education (C-reactive protein ≥ 3 mg/dl)

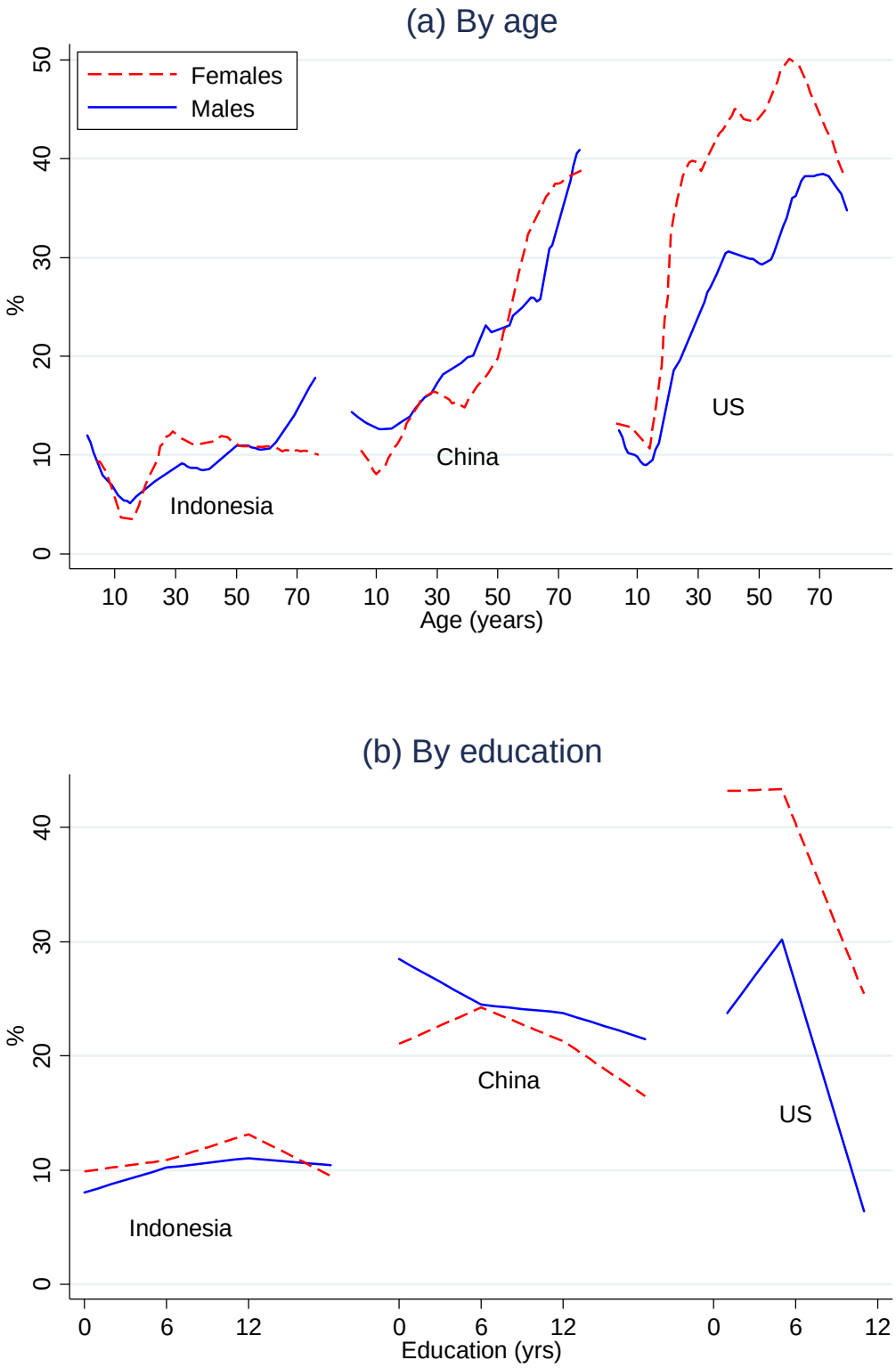
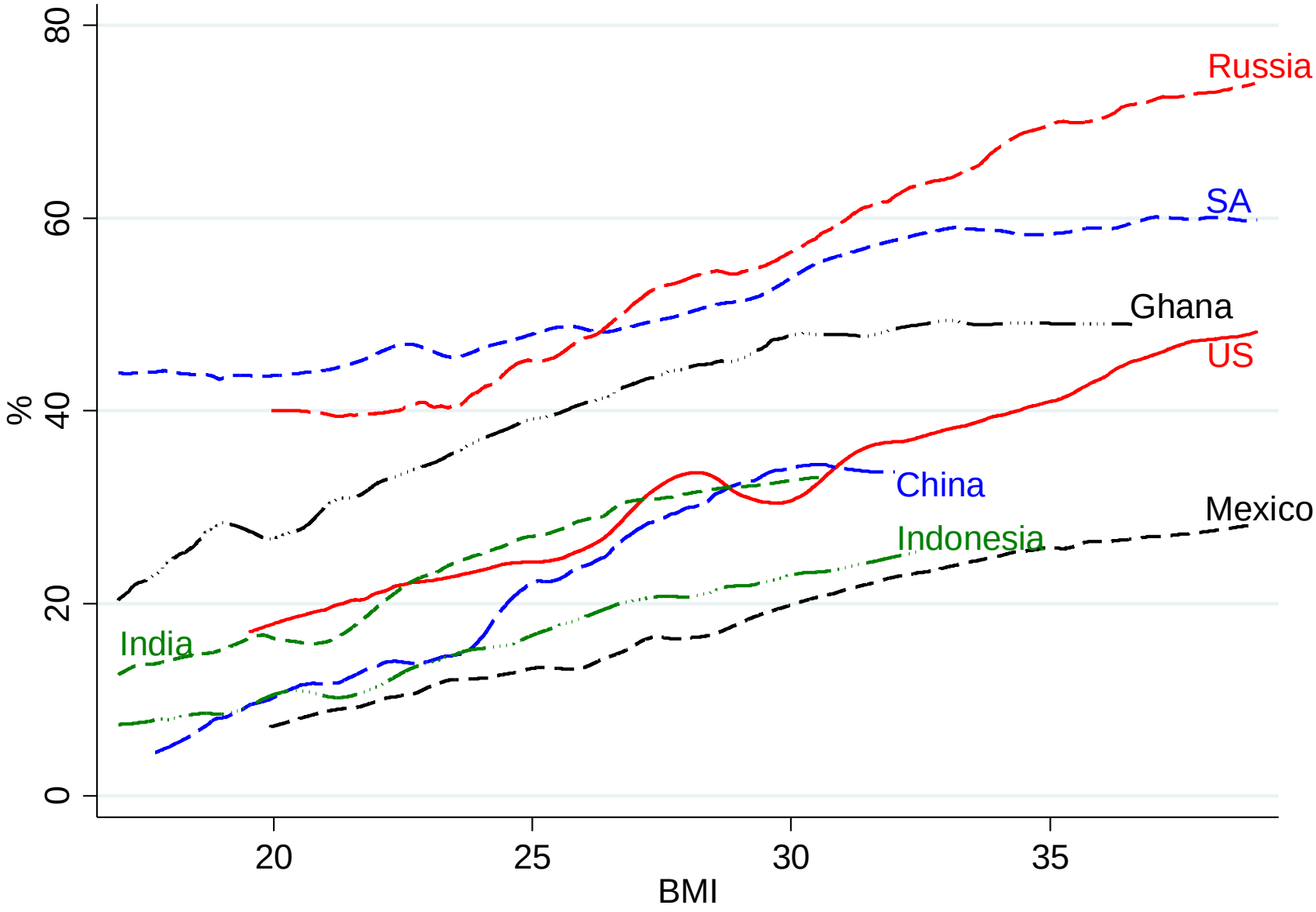


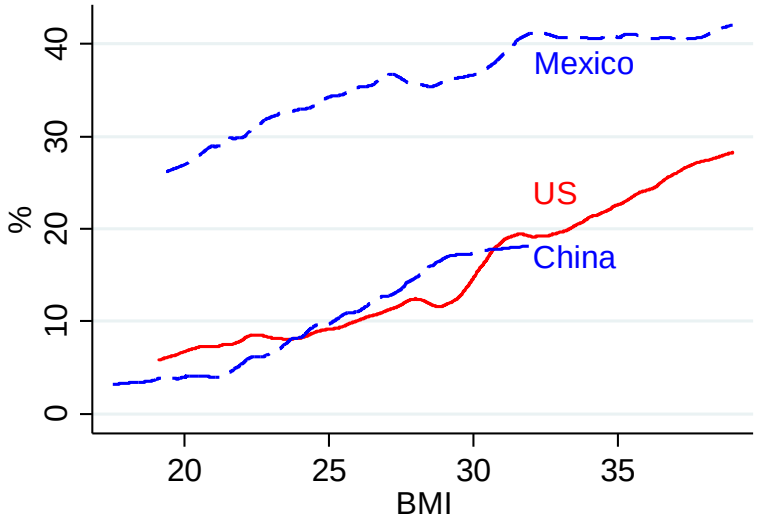
Figure 6: Relationship between percent hypertensive and BMI



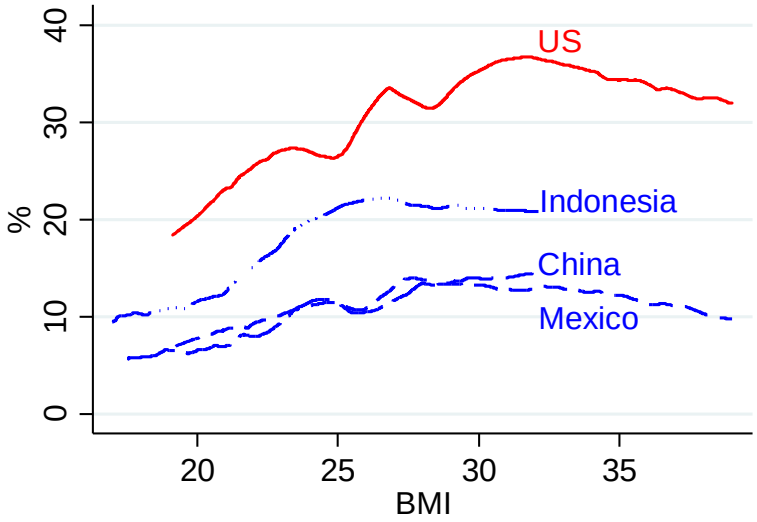
Note: Hypertensive is stage 2 hypertensive, defined as systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 100 mmHg.

Figure 7: Relationship between blood-based biomarkers and BMI

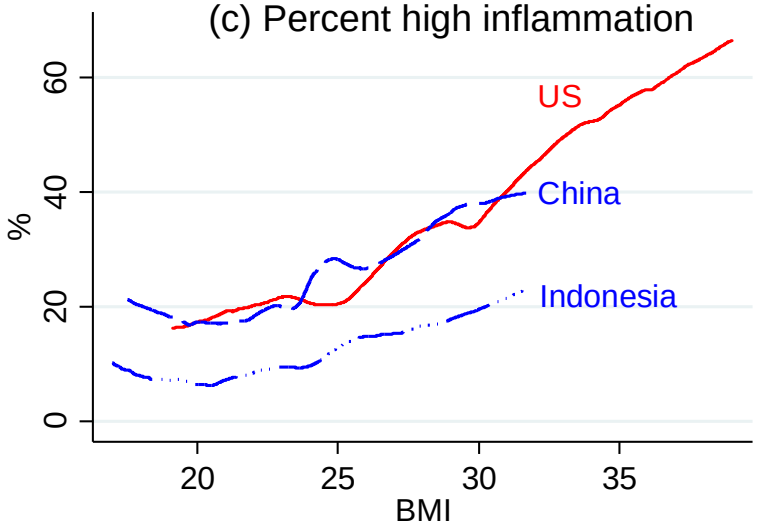
(a) Percent high glycosolated hemoglobin



(b) Percent high total cholesterol



(c) Percent high inflammation



Note
High glycosolated hemoglobin (HbA1c): ≥6.5%
High total cholesterol: ≥240mg/dl
High inflammation: C-reactive protein≥3mg/dL