

THE NATURAL SELECTION OF INFECTIOUS DISEASE RESISTANCE AND ITS EFFECT ON CONTEMPORARY HEALTH

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Abstract—This paper empirically tests the association between genetically determined resistance to infectious disease and cross-country health differences. A country-level measure of genetic diversity for the system of genes associated with the recognition and disposal of foreign pathogens is constructed. Genetic diversity within this system has been shown to reduce the virulence and prevalence of infectious diseases and is hypothesized to have been naturally selected from historical exposure to infectious pathogens. Base estimation shows a statistically strong, robust, and positive relationship between this constructed measure and country-level health outcomes in times prior to, but not after, the international epidemiological transition.

I. Introduction

PRIOR to the major medical discoveries associated with the international epidemiological transition, infectious diseases were a major determinant of mortality and subsequent differences in life expectancy across countries.¹ In 1940, a time prior to the transition, the average cross-country life expectancy at birth was 47 years with a standard deviation of 12 years; however, for 1980, a time after the transition, average life expectancy grew to 66 years, and the standard deviation across countries fell to 9 years. This growth and convergence of life expectancy is attributed to the eradication of many infectious diseases (Acemoglu & Johnson 2007), but what were the causes of the initial cross-country disparities in the virulence of infectious diseases?

In this paper, I address this question by empirically investigating the role of genetically determined differences in resistance to infectious diseases. The primary hypothesis is that country-level genetic differences that have been shown to provide resistance to infectious disease are tied to country-level health outcomes prior to, but not after, the international epidemiological transition. In order to better understand why cross-country genetic differences have arisen, I also discuss the origins of historic disease environments and the subsequent natural selection of resistance to infectious pathogens.

The measure of genetic resistance is found within the human leukocyte antigen (HLA) system, which comprises

239 genes located on the sixth chromosome (Shiina, Inoko, & Kulski, 2004). The HLA system is responsible for locating foreign proteins in order to direct cells of the immune system to initiate an immune response and is broken into two major classes, class I and class II, with both classes being associated with the recognition of certain pathogens (Piertney & Oliver, 2006).² Within this system of genes, diversity, or a lack of uniformity in regard to individual genetic loci, predominates, being the most diverse region within the human genome (Jeffery & Bangham, 2000).³ This high level of genetic diversity within the HLA system is hypothesized to provide increased resistance by increasing the number of potential immune responses to a foreign pathogen (Doherty & Zinkernagel, 1975). Uniform immune responses within a human population lead to the selection of pathogen variants that are able to overcome a common response (Black, 1992). As an example, individuals who obtain the measles virus from a relative are at least twice as likely to die from the infection as individuals who are infected through a nonrelative (Garenne & Aaby, 1990). The reason is that variants of the pathogen that have successfully infected the first host are able to survive the host's (genetically determined) immune response; since the second host's immune response is similar to the first host, the pathogen will be more successful in infecting the second host when compared to a pathogen that was successful in infecting an unrelated individual. Through the same process, populations that are genetically similar in regard to the HLA system are more susceptible to infectious pathogens, as a pathogen is better able to spread within a homogeneous population, increasing the rate of infection and virulence, and lowering life expectancy. Therefore, variation within the HLA system is hypothesized to provide population-level resistance. Indeed for modern human populations, resistance from variation in the HLA system has been shown for a number of infectious diseases, including HIV, malaria, and hepatitis B (respectively; Carrington et al., 1999; Trachtenberg et al., 2003; Hill et al., 1991; and Thursz, Thomas, Greenwood, & Hill, 1997). Additionally in mice studies, increased MHC diversity, the nonhuman version of HLA diversity, has been shown to provide resistance to multiple-strain infections (McClelland, Penn, & Potts, 2003; Penn, Damjanovich, & Potts, 2002).

Using country-level aggregations of ethnic-level genetic data, I construct a cross-country measure for diversity within the HLA system: HLA heterozygosity.⁴ I test the hypothesis

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¹ The discovery and widespread use of effective medicines (e.g., penicillin, streptomycin, a range of vaccines) in the late 1940s to early 1950s is labeled by Acemoglu and Johnson (2007) as the international epidemiological transition. I use this term throughout the paper.

² Class I molecules are expressed on nucleated cells and are associated with defense against viruses, while class II molecules are expressed on antigen-presenting cells and are associated with extracellular parasites, such as bacteria and protists (Piertney & Oliver, 2006).

³ Diversity is at the population level.

⁴ As explained in greater detail in section IIIA, a commonly used measure within population genetics for diversity is expected heterozygosity, defined as the probability that two randomly selected individuals differ in regard to

by estimating the association between country-level health measures (e.g., life expectancy at birth) and HLA heterozygosity in periods both prior to and after the international epidemiological transition.

While the within-population HLA variation is different across population groups, starting with the Columbian exchange, and accelerated by the mass development of roads, rail lines, and airports in the early twentieth century, the presence of infectious pathogens has become more homogeneous across countries (Crosby, 1972; Arroyo et al., 2006; Brownstein, Wolfe, & Mandl, 2006; Wilson, 1995). This rapid pace of globalization has created a global disease pool shared by all countries, resulting in the introduction of diseases into previously unexposed populations.⁵ Given the slow change of the human genome, country-level genetic resistance is reasonably assumed to be constant during this (short) period of globalization, resulting in a mismatch between the infectious disease environment and genetic resistance. The international epidemiological transition, however, provided technological advances that limit the virulence of this universal infectious disease environment and therefore limit the harms associated with the previously defined mismatch. In a sense, the primary hypothesis represents a gene-environment interaction, in which genetic diversity within the HLA system is hypothesized to be strongly associated with the virulence of the infectious disease environment after the globalization period and prior to, but not after, the international epidemiological transition.

Indeed, the measure of HLA diversity, or heterozygosity, is shown to have a strong and positive association with country-level health outcomes in periods prior to the international epidemiological transition. This positive relationship, however, becomes increasingly weakened for more contemporary periods, providing support for the main hypothesis: innate resistance did influence country-level response to infectious disease prior to the international epidemiological transition, but the effects of innate resistance are dissipated by more efficacious health technologies.

II. Background

This section provides details on the historical origins and selection of HLA diversity. Section IIA explains the role of agriculture, or the Neolithic revolution, in changing historic and contemporary disease environments. In section IIB, I discuss more of the state of the science on selection for variation within the HLA system as a resistance mechanism to

infectious pathogens. Finally, section IIC discusses the effect of early human migration patterns on overall levels of genetic diversity.

A. *Historic Differences in Infectious Disease Environments*

As reviewed by Wolfe, Dunavan, and Diamond (2007), the number of infectious diseases humans face increased substantially with the introduction of agriculture, commonly referred to as the Neolithic revolution.⁶ The conditions necessary for the rise of epidemic infectious diseases are dependent on agriculture. First, agriculture allowed the development of large, dense, and sedentary populations, which fostered an ease in the transmission of infectious diseases, as well as providing a large number of potential hosts. Second, the domestication of animals in the Neolithic provided closer contact between animals and humans. This close contact allowed zoonotic episodes in which pathogens from domesticate animals infected human hosts. The Neolithic revolution provided the conditions for the initiation and sustainability of novel infectious pathogens. Therefore, societies that domesticated animals earlier and developed large, dense populations also encountered a resulting increase in the infectious disease load at an earlier date.

Large, dense populations, a by-product of the adoption of agriculture, were necessary to sustain, or make endemic, the epidemic diseases resulting from zoonosis of domesticate animal pathogens (Dobson & Carper, 1996; Anderson & May, 1992; Wolfe et al., 2007). In order for a disease to persist within a population, the population must be large enough so that newly susceptible individuals, or hosts, are present. The infectious diseases resulting from the Neolithic revolution either kill the host or provide the host with antibodies so that he or she develops immunity to the disease. This implies that in small populations, all susceptible individuals will either die or become immune, causing the disease itself to die out. As an example, it has been shown that measles becomes endemic in island communities with populations roughly greater than 500,000 individuals (Black, 1966). If populations are insufficient in size, epidemics occur in which the disease sweeps through a population, leaving its members either dead or immune. Hunter-gatherer societies could not support large enough populations to sustain the epidemic diseases of the Neolithic revolution. Only the relatively large populations resulting from agriculture can supply hosts in such large numbers that allow the disease to be maintained. Eurasian countries contained an advantage in the initiation and use of agriculture, implying these states had the necessary population size to replenish hosts necessary for the endemicity of epidemic pathogens. Larger populations also led to greater rates of urbanization that facilitated the spread of disease through closer contacts and lower hygiene

genetic variants, or alleles, for a particular locus. Therefore, my focus is on expected heterozygosity within the HLA system, or HLA heterozygosity.

⁵ A notorious illustration is given by the numerous contacts between European explorers and native populations of the Americas and Oceania, in which previously unexposed native populations exhibited greater susceptibility and loss of life from many common European diseases. Another example is given by the greater loss of life by European settlers in tropical areas (Acemoglu, Robinson, & Johnson, 2001). In contrast, indigenous populations contain inherent resistance to tropical diseases, particularly malaria.

⁶ Other sources documenting the link between the Neolithic revolution and historic infectious disease environments include Dobson and Carper (1996), Aremelagos, Barnes, and Lin (1996), and Jared Diamond's seminal work, *Guns, Germs, and Steel: The Fates of Human Societies* (1997).

(McNeil, 1976).⁷ Additionally, the sedentary lifestyle of the agricultural environment allowed for the contamination of water supplies and the collection of rodents and other pests that act as vectors for infectious disease.⁸

While large populations are necessary for the sustained presence of infectious diseases, they are not sufficient in accounting for the rise of infectious disease. This point is most apparent when considering the ruinous results infectious disease played on New World populations. The Mayans, Aztecs, Incas, and certain North Amerindian communities developed agriculture and had populations sufficient in size to support epidemic diseases, yet these populations were highly susceptible to European pathogens (Black, 1975). The primary reason for this disparity is in the lack of zoonotic episodes between domesticated animals of the New World and the civilizations in these areas. The domestication of animals created close contact between farmers and their animals, which allowed animal pathogens to infect new human hosts. Diphtheria, influenza A, measles, mumps, pertussis (whooping cough), rotavirus A, smallpox, and tuberculosis are similar to pathogens afflicting domesticated animals of Eurasia and “probably or possibly reached humans from domesticated animals” (Wolfe et al. 2007, p. 281). In comparison to populations from Eurasia, New World populations had fewer animals to domesticate, as well as a lower intensity of use (Hibbs & Olsson, 2004; Alesina, Guliano, & Nunn, 2013).⁹

The number of infectious diseases, and strains thereof, grew substantially as a by-product of the Neolithic revolution. Populations within Eurasia uniquely contained the necessary ingredients to both contract a large array of infectious pathogens at an earlier date from increased exposure to domesticated animals and to have a consistent presence of these infectious pathogens from large, dense, and sedentary societies. Given the link between HLA diversity and the number of infectious diseases (Fumagalli et al., 2011; Prugnolle et al., 2005) and the rise of infectious diseases from the Neolithic revolution, an obvious corollary is that the timing of the Neolithic revolution is associated with contemporary differences across populations in genetic diversity within the HLA system.¹⁰

Indeed, the role of the Neolithic revolution in shaping contemporary health outcomes from adaptations to differences in historical exposure is explored in the work of Galor and Moav (2007; hereafter GM). GM propose that societies that adopted agriculture at an earlier date have had an advantage in adapting to the new agricultural environment, and this

favorable adaptation has persisted into the present. To test this theory, GM use an ancestry-adjusted measure for the years a country has practiced agriculture. They find a strong, positive relationship between a prolonged history of agriculture and variations in health outcomes in the year 2000, which gives credence to theory of adaptation proposed by GM.¹¹ However, GM do not measure adaptation directly; millennia of agriculture is a proxy for adaptation. This paper advances both the theoretical and empirical findings of GM by measuring the effects of a specific genetic adaptation that is a by-product of the environment given by agriculture—that is, an increase in the prevalence and number of infectious diseases.

Furthermore, the use of genetic data allows us to measure, or quantify, the effects of historic environmental differences, implying the work explored in this paper is tied strongly to the literature that explores the role of history as a determinant of contemporary economic and health outcomes (see, e.g., Nunn, 2009; Putterman, 2008; Galor & Moav, 2007; Galor & Michalopoulos, 2011).

B. The Natural Selection of HLA Heterozygosity

The set of genes comprising the HLA system represents one of the most genetically diverse regions of the genome (Jeffery & Bangham, 2000), and this high level of diversity is hypothesized to have been naturally selected as a mechanism of resistance to infectious pathogens (Hughes & Yeager, 1997; Penman et al., 2013; Spurgin & Richardson, 2010). This natural selection for diversity within the HLA system is from balancing selection.¹² Balancing selection results from two distinct reasons: overdominance and frequency dependence (Slade & McCallum, 1992). Overdominance implies that heterozygotes, or individuals with differing alleles at a single locus, have an advantage compared to homozygotes, or individuals with identical alleles at a single locus.¹³ A prime example of overdominance is the advantage conferred by the sickle cell trait (Allison, 1954). Heterozygous individuals contain a greater resistance to malaria, while homozygotes either contain no resistance to malaria or are afflicted by

⁷ Genetic resistance to tuberculosis, the result of an airborne pathogen that spreads more easily within dense populations, is shown to occur in a greater frequency for individuals with a lineage of living within a city (Barnes et al., 2010).

⁸ Plague and typhus are primarily distributed through lice, which are native to rodents that can be supported only in large sedentary human settlements.

⁹ Countries within the Americas have a substantially lower number of potential domestic animals versus those within Eurasia (i.e., 0–1 to 7–9). Additionally, the use of animal husbandry is much lower for ethnicities within the Americas (Alesina et al., 2013).

¹⁰ This idea is empirically tested and discussed further within section IVA.

¹¹ A crucial difference between the current study and that of GM is that they find a statistically significant effect on life expectancy in 2000 CE. The use of years of agriculture by GM is intended to capture broad, general adaptations to agriculture, which includes adaptations to infectious disease as well as diet, noncommunicable disease, and other changes from the relatively new environment of agriculture. A critical point of this paper is that the measure of genetic adaptation, HLA heterozygosity, or diversity, has an insignificant effect on more contemporary health outcomes. As argued and shown empirically in section IVB, the international epidemiological transition substantially weakens the benefits of innate resistance to infectious disease. GM’s primary measure, however, encompasses other adaptations not tied strictly to the resistance of infectious disease and therefore remains a significant predictor of the variation in health disparities after the international epidemiological transition.

¹² For a fuller discussion see Bronson et al. (2013), Buhler and Sanchez-Mazas (2011), de Bakker et al. (2006), Jeffery and Bangham (2000), Meyer et al. (2006), Solberg et al. (2008), Traherne et al. (2006).

¹³ Individuals contain alleles at a gene locus from both the mother and father, implying two alleles at a given locus.

sickle cell anemia. This leads to the natural selection of variation at the gene locus responsible for the sickle cell trait.

Frequency-dependent selection results from a comparative advantage of rare alleles. Infectious pathogens are not a static selection pressure. Infectious pathogens (e.g., bacteria, viruses, protozoa) are undergoing natural selection.¹⁴ If a particular allele within a human host were to provide complete resistance to a certain pathogen strain, variants of the pathogen, which avoid resistance, would thrive. The relatively short time between generations of most pathogens also provides an advantage in adaptation. This implies that any genetic resistance to a particular pathogen, or strain, would be avoided by genetic mutations within the pathogen. In other words, infectious pathogens have greater defenses to more common HLA gene variants; therefore, rarer, or lesser frequent, HLA alleles are better able to recognize and dispose of a pathogen, implying a constant selection for rarer HLA alleles (Slade & McCallum, 1992). As a result, alleles associated with recognition will be in equal in frequency.

The precise mechanism, either heterozygote advantage or frequency-dependent selection, is still debated within the evolutionary biology literature (Spurgin & Richardson, 2010). However, the mechanism of balancing selection that leads to increased diversity within the HLA system is immaterial for the current work; of focus is simply the selection of diversity and its role in providing resistance to infectious pathogens.

As argued in section IIA, the Neolithic revolution changed the disease environment in which humans lived by increasing the number of pathogens and strains that early farmers and pastoralists faced. This change in disease environment serves as a likely candidate for an increase in pathogen-mediated selection and a resulting increase in HLA diversity (Fumagalli et al., 2011; Prugnolle et al., 2005). Further support is given by Prugnolle et al. (2005), who show a strong, positive association between pathogen richness, or the number of pathogens within a country, and HLA heterozygosity, and by the findings of Sabeti et al. (2007), who find evidence of recent selection of genetic variants within the HLA system.

C. Out-of-Africa Migration and Genetic Diversity

One further factor that is correlated with the level of genetic diversity within the HLA system is the overall level of genetic diversity within a population (Prugnolle et al., 2005; Qutob et al., 2012).¹⁵ The overall level of genetic diversity within a population has recently been shown to be a function of the population's migratory distance from East Africa (Ashraf & Galor, 2013; Ramachandran et al., 2005). Modern human populations originated within East Africa (roughly Ethiopia) and subsequently migrated to all other continents, excluding Antarctica. Given that the entire set of genetic diversity was contained within the initial East African population and that

migrating populations contain only a subset of this diversity, a strong, negative, and linear association exists between the distance along migration routes a country is from East Africa and the genomic diversity of populations within a country.

This implies that populations that are farther along migration routes from the initial point of Ethiopia have less overall genetic diversity, resulting in lessened diversity within the HLA system. As argued in sections IIA and IIB, however, differences in infectious disease environments also have an effect on the level of genetic diversity within the HLA system independent of migratory distance. Indeed, while roughly 80% of the variation in overall levels of genetic diversity is explained by the migratory distance from East Africa (Ashraf & Galor, 2013; Ramachandran et al., 2005), only 30% to 40% of the variation in HLA diversity is explained by out-of-Africa migratory distance (Prugnolle et al., 2005), implying that something other than the neutral genetic changes from migration out of Africa account for the population-level differences in HLA heterozygosity.

III. Data

This section provides a detailed discussion of the country-level measure of genetic diversity within the HLA system, as well as the country-level health outcomes to be used. Sources and definitions of all other variables are provided in the appendix of variables.

A. HLA Heterozygosity

In a recent work, Ashraf and Galor (2013; hereafter AG) explore the role of genetic variation in explaining historical and contemporary levels of development. In order to measure genetic diversity, they use a common measure within population genetics: expected heterozygosity, roughly defined as “the probability that two randomly selected individuals differ with respect to the gene in question” (AG, p. 3). Expected heterozygosity is calculated with the frequency of gene variants, or alleles, at a particular site on the genome, or locus. Mathematically, expected heterozygosity is defined by

$$H_{exp} = 1 - \frac{1}{m} \sum_{l=1}^m \sum_{i=1}^{k_l} p_i^2, \quad (1)$$

where p_i represents the fraction of allele i within each population and expected heterozygosity is found by the average across m loci.¹⁶

My measure of heterozygosity differs slightly from that found in AG. AG attempt to measure variation within the entire genome in order to measure the effects of fractionalization and creativity associated with high and low levels of genetic diversity, respectively. My work differs in that the use heterozygosity intends to capture balancing selection

¹⁴ Adaptation of infectious pathogens is routinely seen in the development of antibiotic resistance and the need for annual flu vaccines.

¹⁵ Empirical analysis exploring the determinants of HLA heterozygosity is given in section IVA.

¹⁶ An allele is a gene variant. As described in section IIIA, I use 156 differing loci, which can take one of two possible values. This implies that expected heterozygosity is maximized when each $p_i = 0.5$.

within the HLA system from historical exposure to infectious pathogens and is not representative of the entire genome.

My measure of interest is referred to as HLA heterozygosity. HLA heterozygosity is constructed with data on SNPs from the Allele Frequency Database at Yale University, referred to as ALFRED (Kidd et al., 2003). A SNP (single-nucleotide polymorphism, pronounced “snip”) is a single change along a strand of DNA. For example, if we consider two sample DNA fragments, ATA and ATC, the frequency of the A and C variants, or alleles, for the third nucleic base would be considered in constructing the measure of expected heterozygosity.¹⁷ ALFRED provides allele frequencies for anthropologically defined ethnicities, providing genetic data for 156 SNPs within 19 HLA genes for 51 distinct ethnic groups.¹⁸ Expected heterozygosity is calculated for each ethnicity. This gives HLA heterozygosity at the ethnic level; however, outcomes of interest are at the country level.

Allele frequency data are given by distinct ethnic groups; however, many (or most) relevant economic data are at the country level. This implies that an aggregation is needed in which countries are constructed of ethnic groups. Following Spolaore and Wacziarg (2009), I aggregate ethnic groups, and their respective measure of HLA heterozygosity, to the country level with the use of ethnic compositions found in Alesina et al. (2003).¹⁹ This implies that the country-level measure of HLA heterozygosity is the weighted average of ethnic-level HLA heterozygosities, where weights are determined by the fraction of the contemporary population associated with each ethnicity for which I have data.²⁰

The matching of ethnic groups from ALFRED to Alesina et al. (2003) is not perfect. ALFRED contains allele frequency data for 51 differing ethnic groups, while Alesina et al. (2003) contains hundreds of differing ethnic groups. In order to get around this problem, language classifications are used to match distinct ethnic groups in Alesina et al.

¹⁷ While four variants are possible (i.e., each nucleobase—C, A, T, and G), nearly all SNPs have only two variants. All SNPs under consideration have only two variants. Therefore, in calculating expected heterozygosity, the frequency of one allele is simply 1 minus the frequency of the alternative. This implies that expected heterozygosity for a single locus is maxed when the two possible variants of a SNP equal 50%.

¹⁸ A list of these ethnic groups is found in appendix table A1. The HLA system is associated with roughly 239 genes that are found on the sixth chromosome (Shiina et al., 2004).

¹⁹ The ethnic compositions found in Alesina et al. (2003) are from the 1990s. This creates an error in measurement for HLA heterozygosity, as I am interested in regressing aggregate health outcomes prior to the 1990s on the constructed measure. While it is safe to assume gene frequencies have remained relatively constant over this period (1940–1990), population compositions may have changed. I have no reason, however, to suspect a nonrandom error associated with population movements. Therefore, this measurement should lead to an attenuation bias, understating the true effect of HLA heterozygosity.

²⁰ This method assumes that there has been no admixture between ethnicities. In other words, this method assumes perfect inbreeding within ethnicities for a given country. Taking the opposite assumption of completely admixed populations within a country, which involves using country-level allele frequencies to calculate heterozygosity, does not change the main findings. The correlation between the isolated and admixed measures of HLA heterozygosity is 0.88. This is explored in appendix table A9.

(2003) to a similar ethnic group in ALFRED (Lewis, 2009). For example, Hutu from Alesina are classified as Bantu in ALFRED, Amayara are classified as Amerindian, and Polish are classified as Russian.²¹

In addition to the matching of ethnic groups, additional ethnic groups have been created through combinations found in ALFRED.²² The primary example of this is given by the ethnicity black in Alesina et al. (2003). The term *black* refers only to race, not ethnicity. Ultimately, black indicates a hereditary history from sub-Saharan Africa, but sub-Saharan Africa is not made up of a single ethnic group. In order to get around this problem, I first assign sub-Saharan African countries to one of three ethnic groups based on a map in Shillington (1989; Reader, 1998).²³ Next, using data on the transatlantic slave trade from Nunn (2009), I create a representative black ethnic group from the weighted average of the number of slaves from each African country, where each country is assigned to a representative ethnic group for which ALFRED has data. This leads to a symbolic black ethnic group of 49% Bantu, 12% Mandenka, and 39% Yoruba. Other notable combinations are white, which is 50% Italian and 50% French; mestizo, which is 50% white and 50% Amerindian or Mayan (depending on whether the respective country is in North or South America); and Germanic, which is 50% French and 50% Orcadian.

Through this method, I am able to construct genetic diversity scores for 175 countries, of which 131 are used in the baseline regression model. For the truncation, 17 countries contain no data for life expectancy in 1960, the primary dependent variable.²⁴ The additional 27 countries contain no data for at least one of the baseline control variables: 13 countries contain no data for (ancestry-adjusted) years since the Neolithic revolution, an additional 11 countries are missing data for the suitability of agriculture, and the remaining 2 countries are missing data for the fraction of the country that is arable.²⁵ Before the truncation, 24% of countries are from Europe, 24.57% are from Asia, 24% are from Africa, 20.57% are from the Americas, and 6.86% are from Oceania; after the truncation, 24.43% are from Europe, 26.72% are from Asia, 28.24% are from Africa, 18.32% are from the Americas, and

²¹ An analogous method is used in assigning ethnic data to modern countries in a similar paper by Alesina et al. (2013).

²² These combinations are not counted in the calculation of the heterozygosity score. HLA heterozygosity is calculated within each ethnicity. The combinations simply provide population weights.

²³ West African countries are assigned to Mandenka, countries around the Gulf of Guinea are assigned to Yoruba, and South African countries are assigned to Bantu. Note that most northeast African/Nilo-Saharan states are unused due to the lack of a close ethnic group in ALFRED.

²⁴ The seventeen countries: Bermuda, Dominica, Isle of Man, Iceland, Kazakhstan, Kyrgyzstan, St. Kitts and Nevis, Liechtenstein, Marshall Islands, Nauru, Palau, Russia, San Marino, Seychelles, Tuvalu, Taiwan, and Serbia.

²⁵ The thirteen countries: Antigua and Barbuda, Bahamas, Barbados, Brunei, Comoros, Fiji, Micronesia, Equatorial Guinea, Grenada, St. Lucia, North Korea, Solomon Islands, Suriname, Tonga, St. Vincent and the Grenadines, and Vanuatu. The eleven countries: Bahrain, Cape Verde, Cyprus, Hong Kong, Jamaica, Malta, Mauritius, Singapore, and Trinidad and Tobago. The additional two: Luxembourg and Slovakia.

TABLE 1.—SUMMARY STATISTICS: HLA HETEROZYGOSITY VERSUS AGGREGATE HETEROZYGOSITY

Variable	N	Mean	SD	Minimum	Maximum
HLA heterozygosity by continent	131	0.3183	0.0207	0.2347	0.3529
Europe	32	0.3343	0.010	0.3184	0.3529
Africa	37	0.3158	0.0176	0.2844	0.3352
Asia	35	0.3149	0.0146	0.2711	0.3298
Americas	24	0.3078	0.0253	0.2588	0.3503
Oceania	3	0.3022	0.0590	0.2347	0.3439
Overall heterozygosity by continent (Ashraf & Galor, 2013)	131	0.7248	0.0272	0.6279	0.7653
Europe	32	0.7342	0.0057	0.7217	0.7429
Africa	37	0.7444	0.0097	0.7282	0.7653
Asia	35	0.7208	0.023	0.682	0.7519
Americas	24	0.6912	0.0324	0.6279	0.7446
Oceania	3	0.6983	0.0360	0.6573	0.7248

HLA heterozygosity is a measure for genetic variation with the HLA system, which is responsible for the recognition of foreign pathogens. Overall heterozygosity is a measure for genetic variation across the entire genome. This measure is calculated with neutral genetic markers, or markers due to random genetic drift between isolated populations. Due to the origination of modern human populations within Africa, aggregate heterozygosity is a declining, linear function of the migratory distance from East Africa. Using genetic diversity data for 53 ethnic groups and the migratory distance from East Africa, Ashraf and Galor (2013) predict a country-level measure of heterozygosity. These variables are explained in greater detail in the appendix of variables.

2.29% are from Oceania. For my base estimation, continent fixed effects are used to account for any unobserved continent differences that may be associated with selection into the base sample.

Summary statistics for HLA heterozygosity are given within table 1 and a global cross-country plot is given in figure 1. As expected, countries with populations derived from Eurasia and Africa have higher levels of HLA heterozygosity, while those from the Americas and Oceania have lower levels.²⁶

B. Health Outcomes prior to the International Epidemiological Transition

The primary hypothesis is that genetic diversity within the HLA system should be positively associated with the resistance of a country's population to infectious disease prior to the international epidemiological transition. In other words, if a country's population has relatively low levels of HLA heterozygosity, then in periods prior to the international epidemiological transition, a greater fraction of the population will die from infectious diseases, thereby lowering life expectancy. In order to measure this relationship, I initially consider a number of country-level health outcomes prior to the discovery and diffusion of medical technologies associated with the international epidemiological transition. These include both predicted mortality from infectious disease and life expectancy in 1940, as well as life expectancy in 1960. The use of 1940s data, while truly before the epidemiological transition, is problematic due to a lack of data in relatively poor countries, leading to possible selection bias.²⁷ Therefore, the primary dependent variable is country-level life expectancy at birth in 1960. This time period is meant to capture health variations before the diffusion, not the discovery, of health technologies associated with the

international epidemiological transition (Acemoglu & Johnson, 2007). In other words, the use of 1960s data is seen as a viable trade-off between more global coverage and the precise timing of the introduction of the specified medical technologies.

IV. Results

A. Explaining HLA Heterozygosity

In addition to summary statistics for HLA heterozygosity, table 1 also provides summary statistics for the overall level of genetic diversity from Ashraf and Galor (2013). In comparing the two measures of genetic diversity, African countries are found to have the highest levels of overall diversity, while countries from Europe contain the greatest amount of diversity within the HLA system. As explained in section IIC, the migratory distance from East Africa has a strong negative association with genomic diversity, and therefore diversity within the HLA system. Figure 2 plots the measure of diversity, HLA heterozygosity, as a linear function of migratory distance from East Africa. From figure 2, countries with a majority population from Europe and the Middle East tend to break from the linear association between HLA heterozygosity and migratory distance from East Africa, containing higher-than-predicted levels of HLA heterozygosity. As argued in section IIA, the Neolithic revolution, which led to the rise and sustained presence of many infectious pathogens, is hypothesized to contribute strongly to the overall level of genetic diversity within the HLA system. The higher level of heterozygosity for countries in Europe and the Middle East is hypothesized to be a product of the earlier and more widespread transition to agriculture. The Neolithic revolution facilitated the two necessary factors for increasing the infectious disease load: dense populations and close contact with domesticated animals. Therefore, I expect to see a positive association between societies that have practiced agriculture for longer periods; and have subsequently been exposed to infectious pathogens for a greater duration, and the level

²⁶ At the ethnic level, European and Middle Eastern populations contain the highest levels of HLA heterozygosity.

²⁷ For both 1940 measures, sub-Saharan African countries are mostly excluded.

FIGURE 1.—CROSS-COUNTRY HLA HETEROZYGOSITY

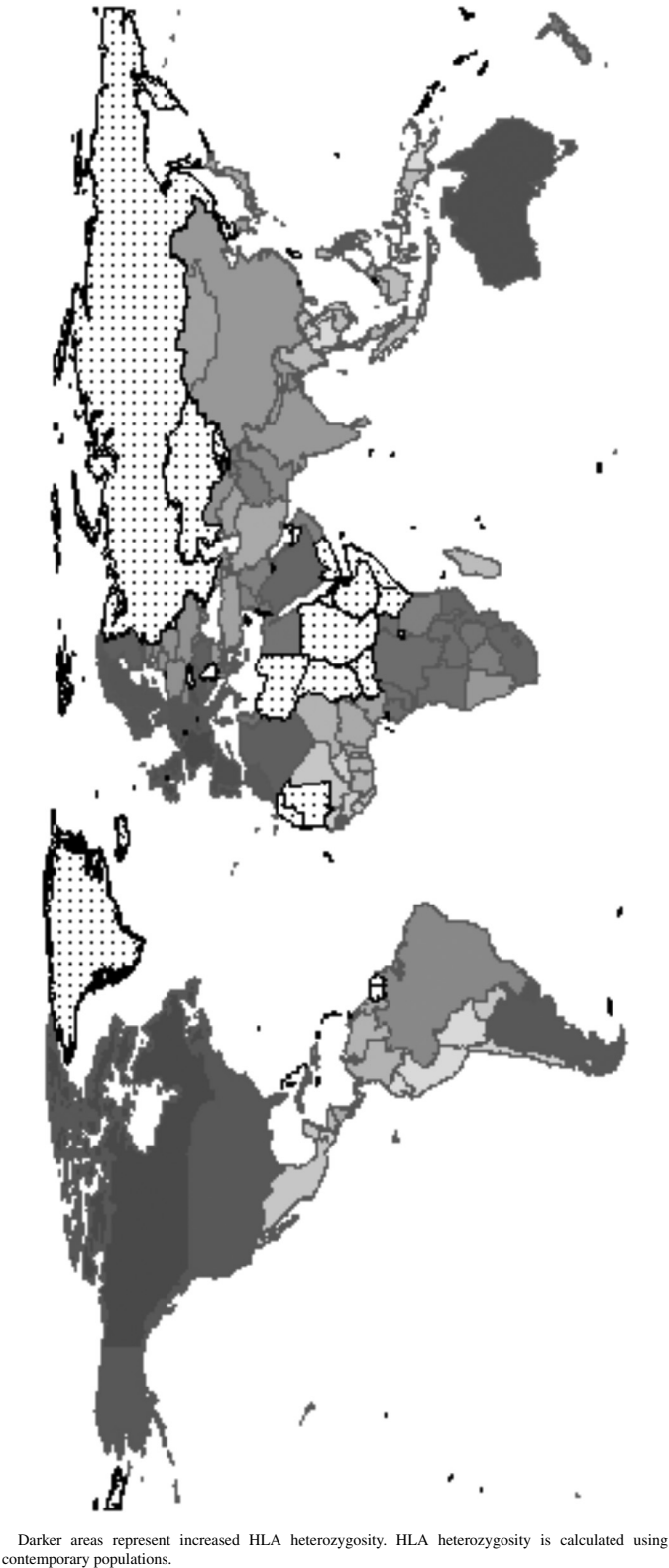
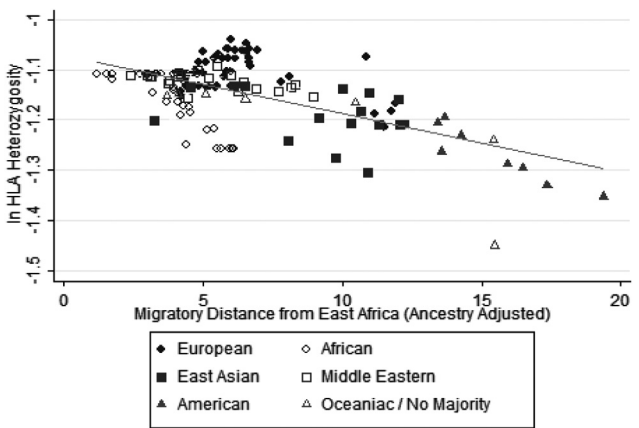


FIGURE 2.—HLA HETEROZYGOSITY AND MIGRATORY DISTANCE FROM EAST AFRICA



This figure displays the cross-country relationship between HLA heterozygosity and an ancestry-adjusted measure of migratory distance from East Africa. Countries are shaded by the majority of the population being from a noted region within the ALFRED data. Note that countries with populations from Europe and Middle East contain greater levels of HLA heterozygosity than is predicted by the linear trend.

of heterozygosity within the HLA system.²⁸ Furthermore, the more proximate determinants—population density and the number of domestic animals—should also be strongly associated with HLA heterozygosity.

The role of both the migratory distance from East Africa and the Neolithic revolution in explaining HLA heterozygosity is tested in table 2. The table regresses the log of HLA heterozygosity on the number of years since the Neolithic revolution, the number of potential domestic animals, population density in 1 CE, and migratory distance from East Africa.²⁹ Given that the relationship between overall levels of heterozygosity and migratory distance from East Africa has been established (Ashraf & Galor, 2013), I am interested in the role of the Neolithic revolution, and its more proximate effects, conditional on migratory distance. Consequently, the estimation in table 2 gives bivariate estimates for the years since the Neolithic revolution, the number of potential domestic animals, and population density in odd-numbered columns, while conditioning on migratory distance in even-numbered columns.

Columns 1 and 2 regress the natural log of HLA heterozygosity on the natural log of the years a country has practiced agriculture. Agriculture has a positive and significant effect on the main measure of heterozygosity in both the bivariate estimation and when controlling for migratory

²⁸ As a further test of the divergence between the neutral levels of genetic diversity from out-of-Africa migratory paths and the natural selection for diversity within the HLA system, appendix table A10 repeats the baseline estimation of table 3 while replacing the natural log of HLA heterozygosity with its ratio to overall levels of genetic diversity from Ashraf and Galor (2013). Results remain consistent with HLA heterozygosity relative to genome-wide heterozygosity being both positively and statistically associated with health outcomes prior to the international epidemiological transition.

²⁹ Given the absence of data on the numbers of actual domestic animals, I use the number of potential domestic animals as a proxy. This variable is used in similar research (see Ashraf & Galor, 2013).

TABLE 2.—EXPLAINING HLA HETEROZYGOSITY

	Dependent Variable: ln HLA Heterozygosity					
	(1)	(2)	(3)	(4)	(5)	(6)
In Years since Neolithic Revolution (Ancestry Adjusted, 1500–1960)	0.0211** (0.0098)	0.0300*** (0.0086)				
In No. of Potential Domesticated Animals (Ancestry Adjusted, 1500–1960)			0.0266*** (0.0064)	0.0361*** (0.0051)		
In Population Density in 1 CE (Ancestry Adjusted, 1500–1960)					0.0144*** (0.0043)	0.0158*** (0.0033)
Migratory Distance from East Africa (Ancestry Adjusted, 1500–1960)		–0.0121*** (0.0014)		–0.0133*** (0.0015)		–0.0124*** (0.0015)
<i>N</i>	131	131	89	89	113	113
<i>R</i> ²	0.0217	0.4265	0.1176	0.5968	0.0626	0.4578

This table displays the relationship of factors associated with HLA heterozygosity. I consider four main determinants: the years a country has practiced agriculture, the availability of domesticated animals, the density of historic populations, and the migratory distance from East Africa. The Neolithic revolution is the ultimate cause of differential disease environments by providing dense populations and close contact with domesticated animals. Domesticated animals are associated with the initiation of many infectious diseases, whereas historically dense populations provide necessary hosts. Due to the serial founder effect, migratory patterns from East Africa have strong associations with overall genetic diversity. All coefficients are statistically significant with the expected sign. HLA heterozygosity is a measure for genetic variation with the HLA system, which is responsible for the recognition of foreign pathogens. Sources and definitions of all variables are given within the appendix of variables. Ancestry-adjusted measures use the matrix of migration between 1500 and 1960 from Chanda, Cook, and Putterman (2014). OLS coefficients are reported in each column. Significant *10%, **5%, ***1%. Robust standard errors are in parentheses.

distance. Using the estimated coefficient of column 2, a 10% increase in the years of agriculture is associated with a 0.3% increase in HLA heterozygosity.³⁰ If Angola, the most recent adopter of agriculture, adopted agriculture at a time consistent with France, then the HLA heterozygosity of Angola would be significantly higher than that of the average of countries composed entirely of European population.³¹

Columns 3 to 6 consider the more proximate determinants of HLA heterozygosity. Agriculture provided close contact with domesticated animals as well as large, dense populations, the two necessary factors that led to an increase in the infectious disease load within a country. A positive and statistically significant relationship between the number of potential domesticated animals and HLA heterozygosity is shown in columns 3 and 4, while the same relationship is exhibited with population density in 1 CE.

Conditional on migratory distance from East Africa, the Neolithic revolution and its by-products have a positive and significant effect on the measure of innate resistance to infectious disease. The revolution provided close contact between numerous domesticated animal species and humans, which facilitated the transmission of novel pathogens into human populations. This transmission was supported by the large, sedentary populations that also resulted from the Neolithic revolution. The prolonged exposure associated with these pathogens led to balancing selection for genes responsible in the recognition of foreign pathogens. Therefore, greater variation within the HLA system is observed for Eurasians, despite controlling for differences in geographical distance from East Africa. Section IVB explores my

primary hypothesis of whether this inherent genetic variation can explain differences in health outcomes prior to the international epidemiological transition.

B. HLA Heterozygosity, Country-Level Health Outcomes, and the International Epidemiological Transition

The primary hypothesis of this paper is that genetic resistance to infectious disease, measured by HLA heterozygosity, is positively associated with country-level health outcomes prior to the international epidemiological transition. To test this hypothesis, I use the following estimating equation,

$$\ln y_i^{t < i.e.t.} = \alpha + \beta_1 (\ln \text{HLA}_i) + \beta_2' \mathbf{X}_i + \beta_3' \mathbf{I}_i^c + \epsilon_i,$$

where i is a country indicator, $y_i^{t < i.e.t.}$ represents aggregate health outcomes prior to the international epidemiological transition, and β_1 measures the effect of HLA heterozygosity and is the coefficient of interest throughout the paper. \mathbf{X}_i is a vector of country-level controls, including ethnic fractionalization, agricultural productivity, geography, and an ancestry-adjusted measure for the agricultural transition, \mathbf{I}_i^c is an indicator variable as to whether country i is within continent c , and ϵ_i is the cross-country error term. The baseline controls are adopted from similar estimation in Ashraf and Galor (2013) and are intended to control for the persistent effects of historical development. Additionally, controlling for ethnic fractionalization is intended to capture any unseen effects from using the ethnic compositions found in Alesina et al. (2003).

Table 3 gives estimates from the baseline estimating equation. The estimates consider three alternatives for measuring country-level health outcomes prior to the epidemiological transition: the mortality rate from fifteen infectious diseases in 1940, life expectancy at birth in 1940, and life expectancy at birth in 1960. Column 1 shows the bivariate relationship between HLA heterozygosity and predicted mortality from infectious diseases in 1940. The coefficient is negative and statistically significant at the 1% level, indicating that

³⁰ The standard deviation of HLA heterozygosity is relatively small; 1 SD represents 6% of the mean.

³¹ All analysis is done with contemporary populations. The construction of HLA heterozygosity gives a measure based on contemporary populations (e.g., the United States is composed primarily of European populations). Consequently, all historic regressors and controls have been adjusted by migration movements, or “ancestry adjusted.” In adjusting populations by migration movements, I use the matrix of migration from 1500 to 1960 (Chanda, Cook, & Putterman, 2014), which is partially derived from the 1500–2000 migration matrix of Putterman and Weil (2010).

TABLE 3.—THE EFFECT OF HLA HETEROZYGOSITY PRIOR TO THE INTERNATIONAL EPIDEMIOLOGICAL TRANSITION

Dependent Variable	ln Predicted Mortality in 1940		ln Life Expectancy in 1940		ln Life Expectancy in 1960	
	(1)	(2)	(3)	(4)	(5)	(6)
ln HLA Heterozygosity	−5.0080*** (0.7117)	−3.8610*** (1.1282)	2.1436*** (0.3310)	1.0771*** (0.3771)	1.6200*** (0.2455)	1.0151*** (0.1899)
ln Ethnic Fractionalization		−0.3970 (0.3961)		0.0724 (0.1338)		−0.1210 (0.0927)
ln Years since Neolithic Revolution (Ancestry Adjusted, 1500–1960)		0.5975** (0.2358)		−0.0031 (0.0549)		0.0370 (0.0397)
ln Fraction of Arable Land		0.0449 (0.1220)		−0.1060*** (0.0366)		−0.0087 (0.0160)
ln Suitability of Agriculture		0.0362 (0.0844)		0.0530** (0.0238)		0.0080 (0.0128)
ln Abs. Latitude		−0.3260** (0.1297)		0.0980** (0.0410)		0.0199 (0.0156)
Continent fixed effects	No	Yes	No	Yes	No	Yes
N	73	73	71	71	131	131
R ²	0.3488	0.5133	0.3329	0.7192	0.2271	0.7446

This table displays the relationship between HLA heterozygosity and Acemoglu and Johnson's (2007) measures of health before the epidemiological transition as well as the baseline estimation, which uses life expectancy at birth in 1960 as the main dependent variable. The use of 1960 data is intended to increase the sample in terms of both size and global representation. Odd-numbered columns provide the simple bivariate relationship between HLA heterozygosity and the alternative measures of premedicinal health, and even-numbered columns include baseline controls and continent fixed effects.

HLA heterozygosity is a measure for genetic variation with the HLA system, which is responsible for the recognition of foreign pathogens. Sources and definitions of all variables are given within the appendix of variables. Continent fixed effects consist of dummies for Africa, the Americas, Asia, and Europe. Ancestry-adjusted measures use the matrix of migration between 1500 and 1960 from Chanda et al. (2014). OLS coefficients are reported in each column. Significant *10%, **5%, ***1%. Robust standard errors are in parentheses.

greater variation within the HLA system is associated with lower mortality from infectious disease in 1940. In particular, a 1% increase in HLA heterozygosity is associated with a 5% decline in mortality rates. When baseline controls are included in column 2, the coefficient slightly attenuates in magnitude but remains both negative and statistically significant. Columns 3 and 4 perform estimates similar to those of columns 1 and 2 with life expectancy in 1940 as the dependent variable. Columns 3 and 4 show that HLA heterozygosity has a positive and strong statistical relationship with life expectancy before the epidemiological transition. The estimated coefficient of interest in column 4, which comprises the baseline regression, implies roughly a unit elastic relationship between HLA heterozygosity and life expectancy in 1940; for mean HLA heterozygosity, a 1 standard deviation increase in heterozygosity is associated with roughly a 6% to 7% increase in life expectancy. If Vietnam, the country with the lowest life expectancy in 1940, contained the levels of HLA of New Zealand, the country with the highest life expectancy in 1940, the average person from Vietnam would be expected to live three additional years.

The use of 1940s health data is ideal; however, data are relatively sparse for this period.³² Therefore, life expectancy at birth for 1960 is used as the main dependent variable, potentially sacrificing the benefits of using a time period prior to the epidemiological transition in order to have a more general sample. Given that many medicines and vaccines were discovered in the late 1940s and early 1950s, the use of data from the 1960s is meant to capture the effects of inherent resistance before the widespread distribution of these medical technologies.

Column 5 of table 3 gives the bivariate regression of 1960 life expectancy on HLA heterozygosity. The coefficient of HLA heterozygosity is positive and significant at the 1%

level, implying that greater genetic diversity within the HLA system is associated with a higher life expectancy in 1960. As with life expectancy in 1940, a unit elastic relationship exists between HLA heterozygosity and life expectancy in 1960 for the baseline estimate of column 6. The estimated coefficient of column 6 confirms that the effect of HLA heterozygosity is not accounting for the persistence of historical development, as measured by the years of agriculture and exogenous agricultural controls, the ethnic composition of a country, or absolute latitude, which can be seen as a broad measure for climate and geography. Additionally, the estimation of column 6 controls for unobserved factors across continents. Considering two countries with similar income levels in 1960, Venezuela and France, the coefficient of column 6 implies that if Venezuela's population contained HLA variation similar to the population of France, Venezuela's life expectancy would increase by roughly ten years, which would eliminate the difference in life expectancy between the two countries.

The use of 1960 life expectancy is seen as a data trade-off, where the more prominent coverage and more accurate measures of 1960 are used in place of Acemoglu and Johnson's (2007) 1940 data, which is indeed prior to the set of technologies developed from the international epidemiological transition. The complicating factor with the use of data from the 1960s is that the presence of medicine should dissipate any effect of inherent genetic resistance to infectious disease. In an environment absent medicine, innate resistance is hypothesized to have a strong effect on the virulence of infectious disease; however, with the discovery of medicines and vaccines, access to medicines should nullify the effect of innate resistance. To confirm this idea and show that 1960 is an early enough period to capture the effects of innate resistance, table 4 explores the effects of HLA heterozygosity on life expectancy in more contemporary periods. If HLA heterozygosity does represent genetic resistance to infectious

³² Most sub-Saharan African countries have missing data for this period.

TABLE 4.—THE EFFECT OF HLA HETEROZYGOSITY AFTER THE INTERNATIONAL EPIDEMIOLOGICAL TRANSITION
Dependent Variable: In Life Expectancy

	1960 (1)	1970 (2)	1980 (3)	1990 (4)	2000 (5)	2010 (6)
In HLA Heterozygosity	1.0151*** (0.1899)	1.0405*** (0.1696)	0.8421*** (0.1700)	0.5490*** (0.1798)	0.2512 (0.1541)	0.1788 (0.1335)
Baseline controls	Yes	Yes	Yes	Yes	Yes	Yes
Continent fixed effects	Yes	Yes	Yes	Yes	Yes	Yes
<i>N</i>	131	131	131	131	131	131
<i>R</i> ²	0.7446	0.7340	0.6995	0.6886	0.7683	0.7480

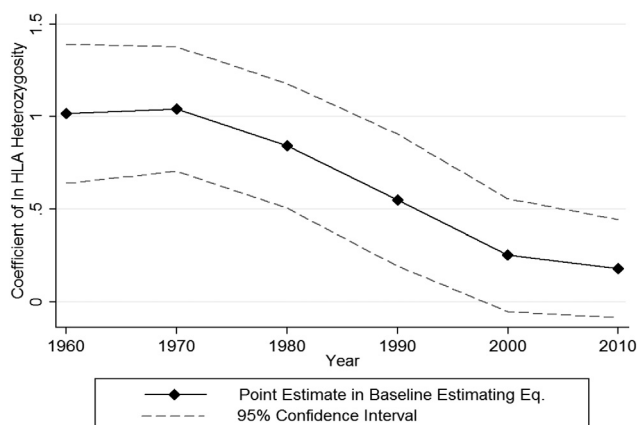
This table provides support for the lessened benefit of genetically determined resistance following the international epidemiological transition and for the use of 1960 data as a valid proxy for health outcomes prior to the diffusion of health technologies associated with epidemiological transition. More contemporary periods are associated with a greater prevalence and use of medical technologies of the epidemiological transition; therefore, the effect of inherent resistance on life expectancy lessens in magnitude, becoming insignificantly different from zero in 2000 CE.

HLA heterozygosity is a measure for genetic variation with the HLA system, which is responsible for the recognition of foreign pathogens. Baseline controls include ethnic fractionalization, an ancestry-adjusted measure for the years a country has practiced agriculture, the fraction of arable land within a country, the suitability of agriculture within a country, and absolute latitude. Continent fixed effects consist of dummies for Africa, the Americas, Asia, and Europe. OLS coefficients are reported in each column. Significant *10%, **5%, ***1%. Robust standard errors are in parentheses.

disease, the effect should be more pronounced in earlier periods in which medical technologies associated with the international epidemiological transition are rare or nonexistent. However, in more contemporary periods, which are assumed to have benefited from the diffusion of these technologies, the benefits of resistance from HLA heterozygosity, and therefore the coefficient representing its relationship with life expectancy, should be weakened.

Table 4 explores the effect of HLA heterozygosity on life expectancy from 1960 to 2010 and tests the effect of HLA heterozygosity, or innate resistance, in postepidemiological transition environments. Column 1 reproduces the baseline regression. Columns 2 to 6 regress life expectancy at birth in 1970 to 2010 (by decade) on HLA heterozygosity, respectively. As the set of technologies that comprise the international epidemiological transition becomes more widely distributed over time, the coefficient of HLA heterozygosity is hypothesized to move to 0. Comparing columns 2 to 6, the magnitude of the coefficient of HLA heterozygosity remains roughly constant between 1960 and 1970. Starting in 1980, however, the magnitude of the coefficient of HLA heterozygosity begins to lessen and becomes insignificantly different from 0 in the year 2000 and remains so. This finding is shown graphically in figure 3.³³ The effect of HLA heterozygosity becomes insignificantly different from 0 as we move forward in time, supporting both the role of HLA heterozygosity as a measure of innate resistance and the use of 1960 as a period before the diffusion of technologies associated with the epidemiological transition.

The estimated effects of tables 3 and 4 provide strong support for the main hypothesis of this paper: long-running genetic differences within the immune system, measured by the expected heterozygosity of HLA genes, have an effect on health outcomes before the use (or distribution) of medical technologies associated with the epidemiological transition. Prior to the transition, the country-level differences in HLA heterozygosity are shown to be strongly associated with the mortality rate from infectious diseases and

FIGURE 3.—THE EFFECT OF HLA HETEROZYGOSITY FOLLOWING THE
DIFFUSION OF HEALTH TECHNOLOGIES FROM THE INTERNATIONAL
EPIDEMIOLOGICAL TRANSITION

This figure displays the point estimates for the coefficient of HLA heterozygosity in table 4. Note that the effect of HLA heterozygosity declines over time. A key hypothesis is that this decline is due to the diffusion of medical technologies associated with the international epidemiological transition.

resulting differences in life expectancy at birth. However, as the set of technologies is diffused, the effect of HLA heterozygosity is lessened and ultimately becomes statistically indistinguishable from 0.

C. Robustness

Controlling for regional ethnic differences. One potential source of bias associated with the measure of HLA heterozygosity lies within the aggregation from ethnic groups to the country level. Given the limited number of ethnic groups from which HLA heterozygosity is constructed, the aggregated measure may simply be accounting for the fraction of a country's population derived from a region. Specifically, populations from Europe have been shown to have favorable institutions and human capital (Easterly & Levine, 2012). In other words, the relationship between HLA heterozygosity and life expectancy in 1960 may reflect some underlying role of European populations in promoting greater health outcomes. In addition, other populations may have unobserved effects that are also correlated with both HLA heterozygosity and life expectancy in 1960. Therefore, it is worthwhile

³³ Using the 71-country sample of columns 3 and 4 of table 3, the same lessening role of HLA heterozygosity is seen between 1940 and 2010. This is given by appendix table A8 and shown in appendix figure A2.

TABLE 5.—ROBUSTNESS TO THE INFLUENCE OF REGIONAL POPULATIONS
Dependent Variable: ln Life Expectancy in 1960

	% European = 0 (1)	% European ∈ (0,1) (2)	% European = 1 (3)	Full (4)
ln HLA Heterozygosity	0.7241* (0.3623)	0.8049*** (0.2923)	0.7281** (0.3111)	0.8870*** (0.2872)
Baseline controls	Yes	Yes	Yes	Yes
Continent fixed effects	Yes	Yes	No	Yes
Population fixed effects	No	No	No	Yes
N	55	52	24	131
R ²	0.4183	0.5891	0.5162	0.7891

This table performs both a sample truncation and the inclusion of population fixed effect to control for any potential health benefits associated with populations from a particular region. Easterly and Levine (2012) argue that European populations contained both human capital and institutional advantages in accumulating wealth. I therefore restrict the sample based on the fraction of the contemporary population that is from Europe in columns 1 to 3. Column 4 includes population fixed effects; that is, we control for the contemporary fraction of each regional population within each country. Controlling for regional populations, with special attention given to populations from Europe, does not alter the main finding.

HLA heterozygosity is a measure for genetic variation with the HLA system, which is responsible for the recognition of foreign pathogens. ALFRED data provide six regions: Africa, the Americas, East Asia, Europe, the Middle East, and Oceania. The country-level population fraction from each region is calculated using ethnic compositions from Alesina et al. (2003) matched to the ethnic groups of ALFRED. Baseline controls include ethnic fractionalization, an ancestry-adjusted measure for the years a country has practiced agriculture, the fraction of arable land within a country, the suitability of agriculture within a country, and absolute latitude. Continent fixed effects consist of dummies for Africa, the Americas, Asia, and Europe. OLS coefficients are reported in each column. Significant *10%, **5%, ***1%. Robust standard errors are in parentheses.

to explore the effect of HLA heterozygosity in countries with differing concentrations of European descent as well as controlling for the fraction of the population from each region. This is shown in table 5.

In order to account for the fraction of a country's population being from each region (the Americas, Europe, East Asia, the Middle East, Oceania, and sub-Saharan Africa), I create an indicator variable for each ethnic-specific region for which there are HLA genetic data in ALFRED. This indicator is then aggregated to the country level using the matrix of ethnic compositions, giving the fraction of each country's population from the specified region. If, for example, a country is composed equally of the French and Yoruba ethnic groups, the country is assigned a 50% fraction from Europe and 50% fraction from Africa.

Columns 1 through 3 of table 5 restrict the sample by the fraction of country's contemporary European population. Column 1 considers countries with no fraction of the population from Europe, column 2 considers counties with a partial fraction from Europe, and column 3 considers only countries for which the entire population is from Europe. For each sample, the effect of HLA heterozygosity on life expectancy at birth in 1960 is consistent. While the point estimates of the coefficient are slightly smaller in magnitude when compared to the base estimate of column 6 in table 3, the effect of HLA heterozygosity remains both positive and significant at conventional levels, indicating that the portion of the population from Europe is not substantially altering the protective effect of genetic variation within the HLA system.

The estimations of columns 1 to 3 are extended within column 4, which controls for the portion of the population from each region. This in effect represents population fixed effects and corrects for any unobservable association between the region an ethnicity is from, its level of heterozygosity within the HLA system, and life expectancy in 1960. The magnitude of the coefficient of HLA heterozygosity in column 4 is statistically indistinguishable from the base estimate and remains positive and statistically significant at the 1% level. The estimations of table 5 give no reason to suspect

that either the portion of European or any other regional ethnicity's population fraction is driving the link between HLA heterozygosity and life expectancy prior to diffusion of the epidemiological transition.

Omitted variables. Tables 6 and 7 include omitted variables that may be associated with either the measure of HLA heterozygosity or life expectancy in 1960. The additional variables are broken into two classes: endogenous and exogenous. The additional exogenous variables, found in table 6, include genetic, geographic, and historic population controls, while the endogenous controls of table 7 consist of income, human capital, and demographics in 1960.

The first column of table 6 includes the measure for overall genetic diversity into the baseline estimating equation. Ashraf and Galor (2013) show that genetic diversity has a nonlinear association with economic development: societies with too little genetic diversity lack innovation, whereas societies with too much heterozygosity have increased conflict. Therefore, the measure of HLA heterozygosity may be accounting for the indirect effect of overall heterozygosity on income. Additionally, historically rich societies may have attracted an increased number of migrants, thereby increasing total genetic heterozygosity within an ethnic population. Conversely, historically rich societies had the means to prevent migration, thereby lowering ethnic heterozygosity. Given this potential relationship to historical development, HLA heterozygosity may be accounting for the persistence of historical development within populations. Therefore, controlling for AG's overall heterozygosity, which is more influenced by historic migrations and ethnic mixing, also controls for this potentially confounding association with historic development. When controlling for overall diversity within the genome, the coefficient of HLA heterozygosity remains consistent in both magnitude and significance.³⁴

³⁴ For the base sample, the correlation between aggregate heterozygosity and HLA heterozygosity is 0.61. Given the collinearity between the two measures of heterozygosity, the standard error on the coefficient of interest increases by roughly 50%.

TABLE 6.—ROBUSTNESS TO EXOGENOUS OMITTED VARIABLES
Dependent Variable: In Life Expectancy in 1960

	(1)	(2)	(3)	(4)
In HLA Heterozygosity	1.0771*** (0.3401)	0.7713*** (0.2040)	0.8699*** (0.2239)	0.5373* (0.3093)
Aggregate heterozygosity (Ancestry adjusted, 1500–1960)	–0.2784 (1.1998)			0.1385 (1.0280)
Fraction of population at risk of contracting malaria		–0.1613*** (0.0481)		–0.1730*** (0.0487)
% within tropics		–0.0003 (0.0006)		–0.0003 (0.0006)
% within desert		–0.0016 (0.0015)		–0.0013 (0.0014)
Mean distance to coast or river		0.0116 (0.0385)		0.0299 (0.0381)
Fraction of nonindigenous population			0.0982 (0.0632)	0.1203 (0.0734)
Baseline controls	Yes	Yes	Yes	Yes
Continent fixed effects	Yes	Yes	Yes	Yes
N	131	131	131	131
R ²	0.7449	0.7741	0.7504	0.7824

A number of potentially confounding exogenous omitted variables are included in the table: aggregate genetic diversity, a measure for the suitability of malaria, the fraction of a country within the tropics, the fraction of a country that is desert, the average distance within a country to a coast or river, and the fraction of the population that has migrated into the country as of 1960. The inclusion of these controls, both piecemeal and jointly, does not alter the positive, statistically significant effect of HLA heterozygosity, although in the joint estimation of column 5, the coefficient is lessened in magnitude and significance falls to the 10% level.

HLA heterozygosity is a measure for genetic variation with the HLA system, which is responsible for the recognition of foreign pathogens. Sources and definitions of all variables are given within the appendix of variables. Baseline controls include ethnic fractionalization, an ancestry-adjusted measure for the years a country has practiced agriculture, the fraction of arable land within a country, the suitability of agriculture within a country, and absolute latitude. Continent fixed effects consist of dummies for Africa, the Americas, Asia, and Europe. OLS coefficients are reported in each column. Significant *10%, **5%, ***1%. Robust standard errors are in parentheses.

TABLE 7.—ROBUSTNESS TO ENDOGENOUS OMITTED VARIABLES
Dependent Variable: In Life Expectancy in 1960

	(1)	(2)	(3)	(4)	(5)
In HLA Heterozygosity	1.0000*** (0.2118)	0.6575*** (0.2124)	0.6127*** (0.1633)	0.7529*** (0.1944)	0.5296*** (0.1673)
In GDP per Capita in 1960		0.0977*** (0.0221)			0.0280* (0.0167)
In Avg. Years of School in 1960			0.1320*** (0.0195)		0.1037*** (0.0190)
In Population Density in 1960				0.0002 (0.0152)	0.0063 (0.0126)
In Urbanization Rate in 1960				0.1137*** (0.0223)	0.0343* (0.0195)
In Fraction of Population under 15 Years in 1960				–0.0614 (0.0887)	–0.0148 (0.0685)
Baseline controls	Yes	Yes	Yes	Yes	Yes
Continent fixed effects	Yes	Yes	Yes	Yes	Yes
N	109	109	109	109	109
R ²	0.7378	0.8062	0.8727	0.8256	0.8897

This table controls for a number of potentially endogenous controls: income, human capital, and demographics in 1960. Given the relationship between income and genetic diversity (Ashraf & Galor, 2013), controlling for income and related variables is intended to dispel the effect of HLA heterozygosity working through an income channel. When controlling for these additional measures, the effect of HLA heterozygosity remains both positive and significant at the 1% level; although, as with joint inclusion of all endogenous omitted variables, the coefficient on HLA heterozygosity is reduced in magnitude in column 5.

HLA heterozygosity is a measure for genetic variation with the HLA system, which is responsible for the recognition of foreign pathogens. Sources and definitions of all variables are given within the appendix of variables. Baseline controls include ethnic fractionalization, an ancestry-adjusted measure for the years a country has practiced agriculture, the fraction of arable land within a country, the suitability of agriculture within a country, and absolute latitude. Continent fixed effects consist of dummies for Africa, the Americas, Asia, and Europe. OLS coefficients are reported in each column. Significant *10%, **5%, ***1%. Robust standard errors are in parentheses.

Column 2 of table 6 includes a number of environmental and additional geographic controls. These include the percentage of a country's population that is at risk of contracting malaria, the fraction of a country within either a tropic or desert climate, and the mean distance to a navigable river or coast. The prevalence of malaria, and tropical diseases in general, is strongly related to contemporary, aggregate health outcomes, implying it is necessary to control for this difference across countries. Furthermore, tropical disease environments represent a barrier to entry for European populations that contain the greatest amount of HLA diversity (Acemoglu et al., 2001), implying the potential

for bias from the previously omitted tropical environments. As seen in column 2, the inclusion of a control for the malarial environment within a country, as well as other environments, lessens the magnitude of the coefficient of interest, but the effect of HLA heterozygosity on 1960 life expectancy remains positive and significant at the 1% level.³⁵

Migrating populations also have the potential to bias both life expectancy and heterozygosity. A population with

³⁵ The piecemeal inclusion of the environmental controls does not change the results.

more migrants will contain greater mixing between the populations, leading to increased heterozygosity.³⁶ Migrant populations may also contain increased human capital or better institutions, which indirectly affect health. Controlling for the 1960 portion of the migrant population since 1500 CE in column 3 does not alter the main finding associated with HLA heterozygosity. The elasticity of life expectancy in 1960 in regard to HLA heterozygosity remains roughly one-to-one, implying that historic migration movements are not the cause for the positive relationship between heterozygosity within the HLA system and life expectancy in 1960.

All exogenous omitted variables are included in column 4 of table 6. The inclusion of all controls leads to a reduction in the point estimate of the coefficient of HLA heterozygosity, while significance remains at the 10% level.³⁷ When conditioning on relevant controls for genetics, environments, and population movements, the estimated effect of HLA heterozygosity is reduced but remains positively associated with life expectancy prior to the international epidemiological transition.

Additional controls are considered in table 7. These include income, human capital, and demographics in 1960. The additional variables of Table 7 constitute more endogenous controls, as the effect of HLA heterozygosity may be associated with some general level of economic development, which is correlated with health, human capital, and income. Controlling for these alternative channels of economic development allows for a greater focus on the relationship between HLA heterozygosity, which represents innate resistance, and aggregate health.

Column 1 reestimates the baseline regression with the reduced sample for which data exist for endogenous controls. The reduced sample does not alter the estimated effect of HLA heterozygosity on life expectancy in 1960, and a unit elastic relationship remains. Column 2 includes GDP per capita in 1960. Health and income are strongly correlated; more developed states are better able to provide greater nutrition, sanitation, and care to the sick (Bloom & Canning, 2000). It is therefore necessary to control for income in order to more accurately account for the effect of innate resistance on life expectancy. Additionally, given the strong correlation between HLA heterozygosity and the overall heterozygosity measure of Ashraf and Galor (2013), the measure of heterozygosity may be accounting for income differences, which are creating a spurious relationship with life expectancy. The inclusion of income in column 2 does lead to a reduction

in the magnitude of the coefficient, but the effect of HLA heterozygosity on life expectancy in 1960 remains positive and significant, implying the measure of innate resistance has an effect on health outside the income channel.

Due to the strong relationship between human capital, particularly education, and health (Baker et al., 2011), column 3 includes a control for the average years of school within a country in 1960. As with income in column 2, the inclusion of years of schooling results in an attenuation in the coefficient, but the effect of HLA heterozygosity again remains both positive and significant. Column 4 includes a number of demographic controls for 1960, which consists of the fraction of the population living in an urban area, the population density, and the fraction of the population between the ages of 0 and 14 in 1960. Population density and urbanization are intended to control for the ease in transmission of the infectious crowd diseases under consideration, while the fraction of the population aged between 0 and 14 is used to account for young populations, which may be more vulnerable to infectious diseases. The inclusion of demographic controls does not alter the sign or significance of the coefficient of HLA heterozygosity.

All endogenous controls are included in the baseline regression in column 5. As with the piecemeal inclusion, the coefficient of HLA heterozygosity is reduced but remains positive and significant. Once these additional correlates of development are controlled for, the positive effect of HLA heterozygosity on life expectancy prior to the international epidemiological transition remains, providing further support for the role of HLA heterozygosity in measuring genetically determined resistance to infectious disease, mortality rates thereof, and resulting life expectancy differences across countries prior to the international epidemiological transition.

V. Conclusion

This work empirically establishes a link between genetically determined resistance to infectious disease and country-level health outcomes prior to the international epidemiological transition. In doing so, I create a novel measure of resistance, HLA heterozygosity, that has a positive, statistically significant, and robust relationship with life expectancy at birth in 1960, a period argued to be before the diffusion of health technologies associated with the international epidemiological transition. This estimated relationship is robust to controlling for relevant factors that may be associated with both the level of diversity within the HLA system and contemporary economic and health outcomes; broadly, these include geographic, socioeconomic, historic, ethnic, and genetic differences across countries. After the diffusion of medical technologies, however, the effect of HLA heterozygosity on life expectancy becomes insignificantly different from 0. The strong statistical relationship between HLA heterozygosity and life expectancy is substantially lessened by the introduction of medicines and vaccines, which dissipate any benefits from genetically determined resistance.

³⁶ The base measure of HLA heterozygosity considers populations to be isolated. In supplementary analysis, a measure of heterozygosity that assumes complete mixing for populations within a country is constructed. The correlation between the two ways of calculating heterozygosity is 0.88, with the effect of the mixed HLA heterozygosity on life expectancy in 1960 being similar to the isolated measure. This is given by appendix table A9.

³⁷ The increased standard error associated with the inclusion of overall heterozygosity is one factor for the reduction in significance. The exclusion of overall heterozygosity from the estimation of column 4 reduces the standard error by roughly one-third, increasing statistical significance to the 5% level, while not altering the magnitude of the coefficient.

The paper also explores the origins and selection of differences in HLA heterozygosity across populations and countries. As argued in sections IIA and IVA, an important source of the variation in HLA heterozygosity is the differential timing date of the Neolithic revolution, which provided the means of development for a much more severe infectious disease environment. This focus on the importance of agriculture relates strongly to the work of Galor and Moav (2007) but also ties the effects of differential infectious disease resistance to other works within economics that focus on the importance and persistence of historical events in explaining contemporary outcomes (see Chanda et al., 2014; Nunn, 2009; Galor & Moav, 2007; Galor & Weil, 2000).

Although I find a strong association between HLA heterozygosity and country-level health outcomes prior to the epidemiological transition, this association may be under-reporting the effect due to likely measurement error in the construction of HLA heterozygosity. This measurement error is primarily due to the use of only 51 ethnicities in creating the global data set, which results in an absence of distinction between different ethnicities within the same language group. In other words (due to data constraints), I am using very broad ethnic classifications. A more nuanced approach (per Ashraf & Galor, 2013) that generates a greater distinction between peoples of differing regions should more accurately measure the effects of HLA heterozygosity on health. But even with large measurement error, the coefficient of HLA heterozygosity remains statistically significant, indicating that a strong relationship exists with premedicinal health. A further concern involves the potential endogeneity of HLA heterozygosity. As argued in section IVC, ethnic-level heterozygosity may be associated with the historical development of the ethnicity, implying HLA heterozygosity is accounting for unobserved benefits of historic economic development. This potential endogeneity, however, is accounted for when controlling for aggregate heterozygosity in column 2 of table 6. Additionally, the inclusion of region-specific population controls in table 5 accounts for the source of this endogeneity.³⁸

In closing, this research sheds new light on the role and origin of genetic differences in explaining contemporary cross-country health outcomes. It provides a unique measure of genetically determined resistance to infectious disease that is strongly associated with country-level health outcomes prior to, but not after, the international epidemiological transition and provides support for the persistent effects of

environments and history in explaining contemporary health and economic outcomes.

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³⁸ The migratory distance from East Africa and its square have been considered as a potential instrument; this is addressed in appendix table A12. These variables, however, may not satisfy the exclusion restriction, as migratory distance from East Africa is indirectly related to productivity through the overall level of genetic diversity, as Ashraf and Galor (2013) showed. However, when conditioning on income, which is intended to capture the effects of migratory distance on output, the 2SLS estimated coefficient of HLA heterozygosity is roughly identical in magnitude of that found in column 2 of table 7, indicating that the relationship between HLA heterozygosity and life expectancy in 1960 is unlikely the by-product of historical development.

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APPENDIX

Absolute latitude

The absolute value of a country's representative latitude. Representative latitude is given by the centroid latitude of a country from *The World Factbook* (2011).

Aggregate heterozygosity (or predicted diversity)

A country-level measure of genetic diversity calculated using neutral (i.e., not shaped by natural selection) genetic variants. These data are constructed from the expected heterozygosity measures of 53 ethnicities in

Ramachandran et al. (2005). Using this observed ethnic data and the strong linear association between expected heterozygosity and the migratory distance from East Africa, Ashraf and Galor (2013) predict a global data set for historic, country-level heterozygosity. These data are from Ashraf and Galor (2013).

Ancestry adjusted, 1500–1960

A matrix that gives the share of a country's 1960 population from 1500 CE populations. This matrix is constructed from the Putterman and Weil (2010) 1500–2000 CE migration matrix and data on migration between 1960 and 2000 from Ozden et al. (2011). The construction of this matrix is described in detail in Chanda et al. (2014).

Ethnic fractionalization

An index from Alesina et al. (2003) that represents the probability of two randomly selected individuals belonging to different ethnicities.

Fraction within desert

The fraction of a country with a Koppen-Geiger desert climate. These data come from Nunn and Puga (2012).

Fraction within tropics

The fraction of a country with a Koppen-Geiger tropical climate. These data come from Nunn and Puga (2012).

Fraction of young population in 1960

The fraction of a country's population that is aged 0 to 14 years in 1960. This variable is included in the vector of demographic controls and comes from *World Development Indicators* (World Bank 2012).

GDP per capita in 1960

Maddison estimates for PPP converted GDP per capita in constant 2007 constant dollars. Found in Avakov (2010).

Fraction of nonindigenous population in 1960

The fraction of a country's 1960 population that is derived from outside the country since 1500 CE. These data are found using the 1500–1960 migration matrix of Chanda et al. (2014).

HLA heterozygosity

This measure is discussed in detail in section III and represents the main measure of innate, genetic resistance to infectious pathogens. In short, genetic variation, which is measured by expected heterozygosity, is calculated for 156 SNPs found within genes associated with the HLA system (Kidd et al., 2003). These ethnic data are then aggregated to the country level by matching ethnic compositions within Alesina et al. (2003) to those within ALFRED by language (Lewis 2009).

Life expectancy in 1940

Life expectancy at birth in 1940. These data come from historic UN and League of Nations reports by way of Acemoglu and Johnson (2007).

Life expectancy in 1960–2010

Life expectancy at birth for each year (i.e., 1960–2010 by decade). These data come from *World Development Indicators* (World Bank, 2012).

Mean distance to coast of navigable river

The average distance (in kilometers) of GIS coordinates within a country to a navigable river of ice-free coast. These data are from Gallup, Sachs, and Mellinger (1999).

Migratory distance from east africa

The distance (in kilometers) along proposed migratory routes from the expansion of modern human populations out of East Africa (i.e., Addis Ababa, Ethiopia). These data are from Ashraf and Galor (2013).

Number of potential domesticate animals

The number of prehistoric native animals that were a potential source of domestication within a country. These data are from Hibbs and Olsson (2004).

Percentage of arable land

The fraction of a country's land area suitable for growing crops. These data are from *World Development Indicators* (World Bank, 2012) by way of the data set of Ashraf and Galor (2013).

Percentage of population derived from Europe and other regions

Using the ethnicities for which I have data on HLA heterozygosity, ethnic groups are ascribed to the region (Africa, the Americas, East Asia, Europe, the Middle East, and Oceania) in which they are found. Using a matrix of ethnic composition, which gives contemporary ethnic compositions in terms of the 51 ethnicities from ALFRED, I compute the fraction of a country's population from each region.

Percent of population at risk of contracting malaria

The fraction of a country's 1994 population living in malarial regions multiplied by the prevalence of *P. falciparum*. These data are from Gallup and Sachs (2001).

Population density in 1 CE

Population data for 1 CE come from McEvedy and Jones (1978). Land area for each country is based on contemporary borders and is from *World Development Indicators*. These data are adopted from Ashraf and Galor (2011).

Population density in 1960

The number of persons per square kilometer for a country in 1960. This variable is included in the vector of demographic controls and comes from *World Development Indicators* (World Bank, 2012).

Suitability of agriculture

A measure for the suitability of agriculture based upon climatic and soil conditions. A geospatial data set of this variable is constructed by Ramankutty et al. (2002), which is aggregated to the country level (averaged across area within a country) by Michalopoulos (2012). The data are by way of Ashraf and Galor (2013).

Urbanization in 1960

The fraction of the population living within an urban area in 1960. This variable is included in the vector of demographic controls and comes from *World Development Indicators* (World Bank, 2012).

Years of schooling 1960

Years of schooling measures the average years of schooling for a country's age 15 and over population. These data come from Barro and Lee (2010).

Years since the Neolithic revolution

The number of years a country has practiced agriculture until the year 2000. These data are from Putterman and Trainer (2006).

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