

Seeking evidence for Finch and Crimmins's hypothesis of inflammatory exposure: the effect of canton of birth on Costa Rican elderly's health.

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### Abstract

In order to explain the secular decline in mortality due to cardiovascular illnesses, Finch and Crimmins (2004) propose that exposure to infectious diseases early in life increases the risk of chronic inflammation through life course. This paper seeks evidence for this hypothesis with data from a Costa Rican aging study, called CRELES. This country is ideal for studying the hypothesis because it has recently achieved very high life expectancy, but its current elderly population experienced a highly infectious environment early in life. The hypothesis is tested by studying the association of a highly infectious environment early in life with prevalence of chronic conditions, mortality, and biomarkers linked to inflammation. We find no conclusive evidence for Finch and Crimmins' hypothesis, because the measure for early inflammatory exposure is only associated with diabetes biomarker and hypertension. Results seem to provide evidence for Barker's hypothesis of early life programming of chronic diseases.

### Introduction

In a series of two articles, Finch and Crimmins (Finch and Crimmins, 2004; Crimmins and Finch, 2006) explain their hypothesis about the relationship between child mortality and adult mortality levels within the same cohort. They argue that the decrease in cardiovascular mortality in old age is positively associated with the decrease in exposure to infectious diseases early in life and subsequent decrement in infant and child mortality due to these causes; they call this association the “cohort morbidity phenotype” (Crimmins and Finch, 2006: 498). The authors try to prove their main argument with historical life tables from four European countries. Their data refer to mortality schedules for the 18<sup>th</sup> and 19<sup>th</sup> centuries. They study historical populations because

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“...the inflammatory mechanisms that we describe can only work when mortality from infection is high” (Crimmins and Finch, 2006: 499) and because they can parse out the effect of the popularization of smoking, a major factor of inflammation.

The main mechanism in this relationship relies on the idea that infections, even when latent or cured, produce chronic inflammation, as marked by C-reactive protein (CRP), interleukin 6 (IL-6), and fibrinogen. Chronic inflammation accelerates atherosclerosis, a risk factor for cardiovascular disease. The long-term role of infectious diseases in mortality change has been discussed by other authors as well (Elo and Preston, 1992; Leon and Davey Smith, 2000); it is also a key factor of Gersten and Wilmoth’s (2002) “Cancer Transition” framework, since death rates due to tumors linked with infections (gastric cancer, cervical cancer, hepatic cancer) have been declining over time during the last 100 years. All these hypotheses add to the increasing number of literature inspired on the “life course perspective in epidemiology” (Kuh and Ben-Shlomo, 1997); according to one of its variants, conditions early in life have deleterious effects on adult health (Barker, Eriksson, Forsén and Osmond, 2002; Doblhammer, 2004).

Infections are not the only mechanism that link early life conditions with health at old age. Other authors propose that malnutrition or extremely low caloric intake during gestation and infancy augment the risk of developing chronic diseases because organs were programmed *in utero* or at very young ages to certain conditions of low caloric intake, but during adulthood the same organs experience different conditions of normal or high caloric intake; this is the so called “Barker hypothesis” (Barker, 1998; Barker and Osmond, 1986; Barker, Osmond, Winter, Margetts and Simmonds, 1989; Barker,

Eriksson, Forsén and Osmond, 2002). Interestingly enough, Finch and Crimmins discuss that their explanation does not exclude Barker's hypothesis, because slowed growth *in utero* may be due to infections, and malnourished infants are more vulnerable to infectious diseases (Finch and Crimmins, 2004:1738). It is worth noting that diseases predicted by these two hypothesis (Barker's and Finch and Crimmins's) are roughly the same; however, there are some ailments that are particular to one or the other. For example, the evidence for "early programming" of stroke is not plenty (Barker, 1988), since research has documented the association for haemorrhagic stroke, but not always for occlusive stroke (Hypponen, Leon, Kenward and Lithell, 2001), and it is not clear whether the association is mediated by high blood pressure; however, the link between stroke and inflammation has been documented more thoroughly (Bos et al, 2006; Pepys et al, 2006). As well, Finch and Crimmins's hypothesis is adequate for explaining heart diseases linked to infections (rheumatic heart disease), but Barker's does not. Finally, on the other hand, diabetes has not been linked with infections, but the "early programming" of diabetes has been tested repeatedly (Barker, 1998; Barker et al, 2002; Hales and Barker, 2001). Differences in the sets of diseases that can be predicted by each hypothesis let testing the adequacy of each framework.

Even though the "inflammatory exposure" effect might be negligible in present day industrialized countries, the framework seems to be useful for exploring mortality change in less developed countries. Prentice and Moore (2005) explain that populations in the developing world might be strongly predisposed to developing certain chronic diseases associated with early life risk factors, because malnutrition during childhood is still pervasive in this part of the world; they argue that this condition might be stronger in

countries “... passing through a rapid economic and nutritional transition” (p.430). Palloni *et al* (2006) have pointed out that older adults in Latin America might be experiencing deleterious effects of adverse early life conditions, because poverty, malnutrition, and infectious diseases were very prevalent during the first part of the 20<sup>th</sup> century. Results from several research projects support the notion that the “Barker hypothesis” might hold in Latin America (Conlisk *et al*, 2004, Khan *et al*, 1995; Ramarkishnan *et al*, 1999; Martorell *et al*, 1998), although the size of the effects are sometimes rather small (Palloni *et al*, 2006). There is no scientific evidence that directly links conditions in the developing world with Finch and Crimmins’s hypothesis, probably because this hypothesis is relatively new. However, along this notion, Cubillos-Garzon, Casas, Morillo and Bautista (2004) suggest that there might be an epidemic of congestive heart failure in Latin America because of high prevalence of certain infectious diseases, such as rheumatic fever and Chagas disease (which is endemic to the region), in the recent past.

This paper intends to look for evidence of the hypothesis of inflammatory exposure effects in one developing country: Costa Rica. This country is of particular interest because:

- Its epidemiological transition (Omran, 1971) occurred very recently and very fast; this implies that most of its older adult population experienced a very infectious environment during their younger years.
- It has the highest life expectancy at birth in Latin America, and is as high as in some developed countries (like the U.S.A.); this means that, if Finch and

Crimmins's hypothesis holds, the potential of improving life expectancy is higher than in developed countries.

#### Data source and methods

The Costa Rican Study on Longevity and Healthy Aging (CRELES, for its name in Spanish) is a on-going longitudinal study of a nationally representative sample of 2,827 adults born in 1945 or before (ages 60 and over at the first interview) and residing in Costa Rica by the year 2000, with over-sampling of the older old. For this analysis we use the data for the first wave of interviews, conducted from November 2004 through September 2006. This sample size was obtained from a two-step procedure. First, an original sample of 9,600 individuals was randomly selected from the 2000 census database with stratification by 5-year age groups. Sampling fractions ranged from 1.1% among those born in 1941-45 to 100% for those born before 1905. Next, for the in-depth longitudinal study we are analyzing here, a sub-sample of 60 "health areas" (out of 102 for the whole country) was taken with probability proportional to the population ages 60 and over. This sub-sample included near 5,300 individuals. The sub-sample, which covers 59% of Costa Rican territory, yielded the following non-response rates: 19% deceased by the contact date; 18% non-found in the field; 2% moved to other addresses; 2% rejected the interview; 2% pendant interviews after several visits (likely rejections). From those interviewed: 95% provided blood sample; 91% had anthropometric measures; 24% required a proxy to answer the questionnaire.

All data and specimens in the study were collected at the participants' homes, usually in two visits. In the first visit, participants provided informed consent and

answered a 90-minute long questionnaire (including some mobility tests and two blood-pressure measures) as well as a 10-minute frequency of tracer food consumption questionnaire. In a second visit early next day, fasting blood samples were collected by venipuncture: 1 EDTA purple top tube (for 3-4 ml. of whole blood) and 2 serum separating tubes (SST), with a clot activator (for 10-12 ml. of blood, to obtain 4-6 ml. of serum). In this visit the field team also picked up a cooler containing 12-hour overnight urine and took the anthropometric measures. All field data were collected using Personal Digital Assistants (PDAs), also known as palm computers, with software applications developed by CCP for this study.

Main response variables are recorded in two different ways. Prevalence of heart attacks (myocardial infarctions), other heart diseases, and strokes are reported by either the respondent or a proxy after corresponding questions of previous diagnoses. Prevalence of diabetes and hypertension are measured as a combination of self-reports and biomarkers: fasting serum glucose (FSG) levels for diabetes, and the mean of two blood pressure recordings for hypertension; therefore, an interviewee is classified as diabetic if the interviewee reported a previous diagnosis or if  $FSG \geq 126$  mg/dl; as well, a respondent is considered to have hypertension if either the respondent answered the question, or at least three of the four systolic/diastolic blood pressure readings were above 140/90 mm Hg. Two biomarkers serve by themselves, as well, as main response variables: Fasting serum glucose levels (FSG) and C-reactive protein (CRP). Both are estimated from fasting blood samples analyzed in clinical laboratories, and are operationalized in two ways: as continuous variables (in their own units of measurement), and as categorical variables that indicate high levels:  $FSG \geq 126$  mg/dl, and  $CRP \geq 3$

mg/L. CRP is available only for 703 individuals in the sample, because laboratories are still processing the information.

The main explanatory variable is a measure of historic child mortality levels in the canton where the person was born. The geographical unit called “cantón” in Costa Rica is approximately equivalent to the county level in the U.S.A. In the survey instrument, there is a question that asks respondents to report the place where they were born. Answers from this question were linked to historical information published by the Costa Rican Statistics Bureau during the first part of the 20<sup>th</sup> century. The measure used is the ratio of deaths at ages below 5 years divided by total births occurred in a specific year, and in this article it is called Child Mortality Index CMI. Infant mortality was not computed because official publications did not always contain the number of deaths at age below 1 year old. This information was initially recorded from 1907 on, therefore, people born before this year are excluded from the analysis; the Statistics Bureau did not publish the data by canton for three periods: between 1914-1915, because of economical hardships due to World War I; between 1917-1918, because a coup d’etat against President Gonzalez-Flores affected public finances; and between 1930-1931, because of the severe world economic crisis at that time (coincidental with the Great Depression in the U.S.A.); three dummy variables, one for each period, are included in the analysis, while zeroes are assigned instead of missing values in the main variable. One additional dummy variable is included for foreign-born respondents, who do not have information about CMI in their place of birth. Given the historical period, these ratios are affected by serious misreporting; this information will be compared with information from historical censuses to assess its quality.

Another problem of the dataset is that some people were born in cantones that were not yet founded at the moment of their birth. The CMI value for these places was made equal to the CMI values of the old cantones to which they belong as a subterritory. For example, the canton called Dota was segregated from the canton called Tarrazú in 1925; therefore, CMI values for Dota for the period 1907-1924 are the same as the values for Tarrazú during the same period. Two exceptions were made to this rule: a) three cantones that border with Nicaragua –Upala, Los Chiles, and Guatuso- belonged to the canton called Grecia, but they were closer to San Carlos, and their characteristics resemble those of San Carlos rather than those of Grecia; therefore, the CMI values for these three places are the same as those for San Carlos; b) Curridabat was an administrative district of the canton of San Jose, and was segregated from it in 1929; however, since it was a district of the capital, the Statistical Bureau published separate information for it; therefore, there was no need to apply the rule, because the information was available.

Data are analyzed with logistic and OLS regressions that take into account the clustering effect produced by the fact that the main explanatory variable is of geographical level rather than individual level; however, since the clusters are defined by time also (child mortality in each canton for each year of birth), the mean number of respondents per cluster (or second-level grouping) is relatively small ( $\bar{x}=3.2$ ; s.d.=2.5), which means that the clustering effect is not too strong. The regressions control for other risk factors of each disease, or other covariates related to the chosen biomarkers. Most control variables refer to information collected by questions in the interview.



Additionally, the ratio total cholesterol/HDL (High Density Lipoproteins) is assessed in clinical laboratories from fasting blood samples.

To test Finch and Crimmins's hypothesis, associations are studied through logistic regressions that have canton of birth's child mortality level (CMI) as main independent variable, and the following as dependent variables: high levels of CRP ( $CRP \geq 3$  mg/L), other self-reported heart disease, self-reported strokes, self-reported heart attacks, diabetes (self-reported + biomarker), hypertension (self-reported + biomarker), and high levels of FSG ( $FSG \geq 126$  mg/dl). If all the associations hold, except for the ones related with diabetes (diabetes and  $FSG \geq 126$  mg/dl), it would suggest that there is evidence for the "inflammatory exposure" framework. If the associations with diabetes hold, and some of the other associations do not -especially the ones relating CMI with CRP, other heart disease, and stroke- this would mean that there is more evidence for "Barker's hypothesis" than for Finch and Crimmins's. Additionally, two more OLS regressions are estimated to further explore the relationships under study; the two equations have biomarkers, measured in a continuous metric, as their dependent variables: CRP and FSG. All regression models take the complex sampling design into account.

Although the total sample size in CRELES is of 2827 individuals, some cases are excluded due to missing values. One of the most important exclusion (112 cases) was already described and refers to those born before 1907, when child mortality data were not published by the Statistics Bureau. Additionally, other excluded cases are all the individuals without FSG glucose or blood pressure information, those who reported not to be fasting when the blood sample was taken, and those who did not know whether they have a previous diagnosis of high blood pressure or diabetes (318 cases). After other

minor exclusions due to missing values in other covariates, the analysis sample is comprised of 2399 cases. In the analysis of CRP, given the lack of information on this biomarker for most of the cases, the sub-sample diminishes from 703 cases to 631.

## Results

The results section starts with a description of the main dependent variables in the analysis. Data show that some chronic illnesses among Costa Rican elderly are very common (Table 1). Diabetes and hypertension are the most frequent chronic conditions reported by interviewees: 3 out of every 5 elderly Costa Ricans have hypertension; while more than 26% can be considered to have diabetes (16% have FSG above 126 mg/dL, the threshold for defining diabetes according to fasting blood samples). Heart attacks, strokes and other heart diseases are not as prevalent, but it is important to acknowledge that diabetes and hypertension are typical risk factors for these cardiac and vascular diseases. On the contrary, only 1.3% has CRP levels above the cutoff point that defines high risk for cardiovascular diseases (Pearson et al, 2003). The relatively high standard deviation of CRP, with respect to its mean shows how skewed the distribution of this variable is. According to the data (bottom of Table 1), the death rate for the group 60 years old or above is near 0.045 (or 44.6 per thousand); according to official life tables in Costa Rica, this figure amounts to 0.043 (CCP, 2006). This resemblance suggests that the data source provides an acceptable representation of the country's mortality pattern at ages 60 and above. Finally, Table 1 provides a description of the main dependent variable: CMI. For every 100 births that occurred in the places where respondents were born, almost 24 children under 5 years old died. This figure appears to be high, since

nowadays in Costa Rica, this CMI is equivalent to 1.1 deaths of ages 0 to 4, for every 100 births.

Before computing association statistics between the dependent variables and the main independent variable, the natural logarithm of CMI –instead of the untransformed variable- is computed and used in the regression models, because the untransformed variable has a skewed distribution. In the first lines of Table 2, there are regression coefficients for CRP and FSG. Both are logged because they have each a skewed distribution, too. The coefficient for the FSG equation is significant at a 0.05 level, but the coefficient for CRP is not. Although there are problems of lower statistical power in the CRP regression, due to the smaller sample size, both coefficients can be considered to be in the same metric, due to the log transformation, and therefore they are comparable in this sense. Having this in mind, besides the significance level of the test, it can be observed that the magnitude of the association with FSG is larger than the magnitude for the CRP coefficient.

Regarding the analyses with categorical dependent variables, odds ratios are significantly different from one for FSG above 126 mg/dL and for hypertension. The odds ratio for diabetes is not significant, although it has the expected direction. On the contrary, the odds ratios for heart attack, stroke, and other heart diseases not only are non-significant, but their direction is the opposite of what is expected. This means that persons who were born in cantones with high child mortality are more likely to have hypertension and high glyceic values, but they are also less likely to have experienced the cardiac and vascular diseases under study.

These findings partially undermine Finch and Crimmins's hypothesis. However, there are two more associations that need to be observed and that are germane to their argument: the association between CMI on one side, and mortality and inflammation on the other side. Regarding mortality, the Gompertz regression hazard ratio is above one, but is not statistically significant, even to a 0.10 level. This figure means that people that were born in cantones with high child mortality are apparently more likely to die after age 60 than people born in cantones with lower child mortality; however, there is not enough statistical evidence to test whether this hazard ratio is different to one. In a similar fashion, people born in places with high child mortality have four times the odds of having high levels of CRP (OR=4.26), than people born in other places. However, again, there is not enough statistical evidence to test whether this odds ratio is significantly different from one. In both cases, this is a problem of statistical power. The test for the odds ratio depends on the sample size of the two groups that are compared, whereas the test for the hazard ratio depends on how many failures are observed in the survival analysis. In both cases, the needed sample size is not yet available, but will be in the near future; it is nevertheless unclear whether the direction of the association will remain the same. From a substantive point of view, these estimates suggest that Costa Ricans that were born in highly infectious settings have more evidence of physiological inflammation and are more likely to die, than people born in other places. This is consistent with Finch and Crimmins's hypothesis. However, the other equations discussed earlier do not show that this evidence of inflammation, theoretically related to an infectious environment, is necessarily translated into cardiovascular disease prevalence.

Following on the use of CRP, it is important to have in mind that there are other physiological processes that affect its level in blood samples, since there are other inflammatory processes and agents besides atherogenesis (Pearson et al, 2003). Table 3 records how the coefficient for lnCMI changes after sequentially controlling for these other confounding factors: age and sex (original equation); total cholesterol/HDL ratio; caloric, carbohydrates and fat intake; obesity and overweight; statin medication; arthritis; smoking history; and other covariates (living in Metropolitan Area, schooling, low current income, and history of alcohol intake). In the set of equations that assess the impact on CRP as a continuous variable, the adjustments that produce the largest changes in the regression coefficients, are: Total cholesterol/HDL ratio, food intake, and smoking history. The first two increase the magnitude of the coefficient; since cholesterol and food intake have a positive association with CRP, this means that people born in cantones with higher CMI have on average lower cholesterol and lower caloric intake. On the contrary, after adjusting for smoking, the coefficient diminishes in magnitude (from 0.026 to 0.006). Again, since smoking is positively associated with CRP, people born in high CMI cantones are more likely to smoke. The other set of sequential equations contain odds ratios generated with logistic regressions, where the outcome variable is having  $CMI \geq 3$  mg/dL. Caloric, carbohydrates and fat intake are the variables that have the largest impact on the odds ratio, which changes from 2.91 to 4.12 after controlling for these food variables. The inclusion of smoking history in the equations also changes the odds ratio, but in the opposite direction as the one observed in the OLS regressions; in this case, the odds ratio augments from 4.24 to 5.06. This means that the three-way association among smoking, lnCMI and CRP levels varies according to whether the latter

variable is observed as a continuous or as a categorical variable. Again, none of the coefficients observed in Table 3 are statistically significant (not even at a 0.10 level), mainly because of problems of statistical power.

Besides statistical power, there is another potential limitation in the analysis: the quality of the data about historical child mortality. Nowadays, under-registration in birth and death records in Costa Rica is very rare (CCP-INEC, 2002), but the most effective measures to improve Vital Statistics and the Civil Registry occurred during the 1940's and the 1960's decades. Since the CMI information is based on Vital Statistics from the first part of the 20<sup>th</sup> century, there is considerable measurement error in the variable. Vital Statistics are compared with information from the 1927 and the 1950 censuses in order to assess the measurement error magnitude. It is quite large especially in 1927; in most of the subregions, underreporting is larger than 30%. However, in 1950, underreporting was lower than 10%, except in three very rural subregions: Guapiles-Sarapiquí, San Carlos, and Eastern Cartago. How to counterbalance the effect of this measurement error? Two strategies are pursued. The first one is based on the notion that the degree of underreporting is differential across sub-regions. The same models are estimated 14 times, each one excluding a different subregion each time (results not presented). The direction in the coefficients does not change, except when coefficients are close to zero. The only coefficient that is sometimes significant and sometimes not, is the one in the logistic regression for diabetes, but this happens because its Wald test z-coefficient varies around the 1.6 value. This strategy was not pursued for CRP variables because of the small sample size.

The other strategy is based on the notion that there are historical explanations underlying the magnitude of the CMI across space and time. The variable CMI was categorized in three categories:  $CMI \leq 18.0$ ,  $18.0 < CMI < 31.0$ , and  $CMI \geq 31.0$ . The cutoff points, 18.0 and 31.0 are roughly equivalent to the percentiles 20 and 80 for CMI in the dataset. These categories were then mapped in four different years: 1915, 1925, 1935, and 1945 (See Figure 2). One of the most obvious and expected results in this mapping is that cantones in the lowest CMI categories start to be more frequent through time; in 1945, there are no cantones in the upper CMI category any more. One of the most important results observed in the maps is that there are certain cantones that are in the lowest CMI category during most of the period. Among them, the ones around Santa Cruz and Carrillo in the Northern Pacific, as well as certain mountainous towns in the outskirts of the Central Valley (Poás, Alfaro Ruiz, Dota). These places have in common that they have settlements established before the 20<sup>th</sup> century, but they have not been densely populated. Another possible explanation regarding the Northern Pacific is that it is located in the Dry Tropical Forest region, which has a very mild climate.

On the other hand, regions with high child mortality vary throughout the period. However, particularly before the 1940s, there are two areas where high child mortality was commoner during the period. The first area is comprised by province capital towns and some other more urban cantones (Goicoechea, Tibás, Alajuelita). Although Costa Rica did not have densely populated cities at the beginning of the 20<sup>th</sup> century (like Mexico City or Lima, Peru), towns in the Central Valley were denser than the rest of the country. Population density favored the spread of infectious diseases before vaccination and other public health measures were carried on. Also, a report from the Health

Secretariat (Luros, 1942) noticed that water pollution due to coffee processing (a very important industry in the Central Valley) increased the incidence of diarrheas and other infectious diseases. The second area with high CMIs groups the cantones in the Turrialba-Limón axis. This subregion was the main way of communication between the Central Valley and the Port of Limón. It has a very rainy climate, which favors certain infectious agents (especially, water-born or mosquito-transmitted, like malaria).

From a methodological point of view, the mapping roughly agrees with a historical explanation about why child mortality due to infectious diseases was high or low in certain areas. Given these results, the CMI categorization is transformed into two dummy variables –one for low CMI and the other for high CMI-, and the models are estimated again but with these two dummy variables instead of using the continuous variable ( $\ln\text{CMI}$ ). This decision reduces the explanatory richness of using a continuous variable, but it apparently reduces the measurement error given that the new variables have not only a quantitative explanation, but also a substantive justification. The new coefficients and odds ratios are presented in Table 4. Results are consistent with the ones obtained in the models that have CMI as a continuous variable. Moreover, there is even more information to interpret. One of the most important and consistent results across equations is that the coefficients that are statistically significant are not the ones for CMI above 31.0 deaths per 100 births, but the ones for low CMI ( $\text{CMI} \leq 18.0$ ). This possibly means that differences between cantones with high and with middle-range child mortality levels do not indicate a more infectious environment; but when CMI is under certain threshold seems to indicate better control of infections.



Another important result is that odds ratios for prevalence of cardiac diseases (heart attack and other heart diseases) have the opposite direction of what would be predicted from Finch and Crimmins's hypothesis. People that were born in places with high CMI are less likely to have such ailments; coefficients for the low CMI dummy variable are not statistically significant in these same equations. Finally, it is worth to say that the equation with lnCRP as a dependent variable does not show any clear evidence for the inflammatory exposure framework; however, there are again obvious limitations due to very low statistical power.

### Conclusions

The main goal of this article was to find evidence for Finch and Crimmins's hypothesis of inflammatory exposure using a new dataset about aging in Costa Rica, called CRELES. According to Finch and Crimmins, this hypothesis should be useful for explaining the secular mortality decline in the world. However, they do note that the process that they describe might have happened in developed countries in the past, but not in present days, because mortality transition in these countries was already started before any of the living cohorts were born. However, the hypothesis should theoretically be fruitful in explaining mortality patterns and health among the elderly in nowadays developing countries, because vaccination and other public health measures became common some time after they were born and therefore, infectious diseases were very prevalent when they were children. Besides, analyzing the topic with data on elderly's health has a close agreement with Finch and Crimmins's arguments, since they link infant and child mortality ( $q_0, q_{1-4}, q_{5-9}, q_{10-14}$ ) with mortality at older ages ( $q_{70}$ ) within the same

cohort. Besides, Costa Rica is an interesting case for testing the hypothesis because it has achieved life expectancy levels comparable to industrialized countries.

Past child mortality is associated positively and significantly only with hypertension and fasting serum glucose levels. Only when CMI is categorized, there are significant associations with heart attacks and other heart diseases, but the association has the inverse direction. For the inflammatory exposure hypothesis to hold, all of these associations should have been significant and positive, except for glucose (a marker for diabetes), even though the relationship found with high blood pressure would have been predicted by Finch and Crimmins's framework. The evidence resembles more the "early programming" hypothesis because the significant effect observed for diabetes and  $FSG \geq 126$  mg/dL.

In order to use Barker's hypothesis as the main explanatory framework for the findings, it is necessary to make the assumption that child mortality in Costa Rica during the early 20<sup>th</sup> century is a good surrogate for malnutrition levels. This assumption is reasonable because child mortality in Costa Rica during the early 20<sup>th</sup> century was mostly due to infections and diarrheas, which were also linked to malnutrition (Mata, 1980; Muller and Krawinkel, 2005; Pelletier, Frongillo, Schroeder and Habicht, 1995).

Regardless of whether it is Barker's or Finch and Crimmins's hypothesis the one that best fits the data, their relevant consequence is that historical events and conditions might be accounting for part of the chronic disease burden in developing countries (Palloni et al, 2006; Prentice and Moore, 2005). If it is not possible to avoid these risk factors because they happened in the past, it is important to take them into account in projections of disease burden and mortality, in order to assess its future impact on health

services. Furthermore, the presence of this risk factor is almost non-existent in industrialized countries (Crimmins and Finch, 2006), but it is probably very common in developing countries where resources for chronic disease treatments are more limited. This paper's results suggest that Costa Rica should plan for the "stickiness" (Palloni *et al*, 2006) of diabetes and hypertension prevalence until current elderly cohorts are replaced by the ones born after the 1940's.

As for additional results not yet commented, the association between lnCMI and mortality, and between lnCMI and CRP have the expected direction, according to Finch and Crimmins's hypothesis. However, in this case, the analyses performed in this paper have very low statistical power. Had they been significant, they would have provided evidence for certain mechanisms described by these authors<sup>2</sup>. The analyses would have been richer if information on other biomarkers had been available. Fibrinogen and IL-6 are also good markers of inflammation, and are mentioned in Finch and Crimmins's papers. CRELES does not have funding for generating these data from stored plasma, yet.

Besides low statistical power, another limitation faced in the analyses is the measurement error in child mortality statistics, due to Vital Statistics misreporting in Costa Rica during the first part of the 20<sup>th</sup> century. Although categorization of extreme values does not completely solve the measurement error problem, it might have reduced it, given that cantones classified in the extreme categories have certain historical characteristics in common that justify their classification.

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<sup>2</sup> The CRELES project expects to have enough CRP laboratory results and enough mortality data in a year from now to reduce the statistical power problem.

Another possible limitation in the analysis is selection due to differential survival. The inverse direction in the association between lnCMI and cardiovascular diseases might have occurred because people with such diseases might have died more often than people without them, and therefore, the pool of survivals is composed mainly of people with less “frailty”. The selection effect might not be too strong given that the estimated risk ratio from the Gompertz hazard model is not too large. The availability of the data from CRELES second wave (in mid-2008) will let controlling selection, because information will not be prospective rather than just retrospective.

To summarize, regardless of the limitations commented above, the paper does not find strong evidence for Finch and Crimmins’s hypothesis. The results suggest that Barker’s “early programming” hypothesis is more likely to be occurring in Costa Rica. These findings agree with results by other authors who have investigated the effect of early childhood conditions on health in Latin America (Conlisk *et al*, 2004; Khan *et al*, 1995; Martorell *et al*, 1998; Palloni *et al*, 2006; Ramarkishnan *et al*, 1999).

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TABLES.

Table 1. Descriptive statistics for dependent variables and main explanatory variable. Proportions for categorical variables, and mean (and  $\pm$  standard deviation) for interval or ratio scale variables (Results weighted by sampling weights).

Variables	<i>(sample size)</i>	Descriptive statistics
<i>(Means and SD)</i>		
C-reactive protein concentration (mg/L)	631	0.58 ( $\pm$ 0.77)
Fasting serum glucose (FSG) (mg/dL)	2399	107.87 ( $\pm$ 39.48)
<i>(Proportions)</i>		
CRP $\geq$ 3 mg/L	631	1.3
FSG $\geq$ 126 mg/dL	2399	16.3
Prevalence of heart attack (%)	2399	4.6
Prevalence of strokes (%)	2399	3.6
Prevalence of other heart disease (%)	2399	11.7
Prevalence of diabetes (self-reported + biomarker) (%)	2399	26.5
Prevalence of hypertension (self-reported + biomarker) (%)	2399	59.5
Child mortality index (CMI) (deaths per 100 births)	1954	23.71 ( $\pm$ 9.08)
One-year mortality rate (per 1000)	2399	44.64

Table 2. Association between health variables and natural logarithm of child mortality index (lnCMI). Odds ratios per 1-unit increase in lnCMI for disease prevalence, regression coefficient for biomarkers, and Gompertz regression hazard ratio for death rate.

Variables	Sample size	Association statistic		
		Adjusted only by age and sex	Adjusted by other covariates †	
<i>(Linear regression coeff)</i>				
ln of C-reactive protein ††	631	0.014	0.006	
ln of FSG	2399	0.063 **	0.060 **	
<i>(Odds ratios)</i>				
C-reactive protein ≥3 mg/L	626	2.95	4.26	
FSG ≥126 mg/dL	2399	1.84 ***	1.81 ***	
Prevalence of heart attack (%)	2399	0.68	0.63	
Prevalence of strokes (%)	2399	0.84	0.80	
Prevalence of other heart disease (%)	2399	0.69	0.71	
Prevalence of diabetes (%)	2399	1.37	1.36	
Prevalence of hypertension (%)	2399	1.54 **	1.54 **	
<i>(Gompertz reg hazard ratio)</i>				
Mortality hazard	2399	1.18	1.29	

† Confounding variables include: sex, age, living in Metropolitan Area, obesity, overweight, education (6 years of schooling or more), low income, history of smoking, history of alcohol intake, and nutritional variables (More than 3000 daily calories, more than 40 g of daily saturated fat, more than 400 g of daily carbohydrates).

†† Adjusted also by ratio of HDL/total cholesterol and arthritis in the second equation.

\*: p<.10

\*\* : p<.05

\*\*\*: p<.01

Table 3. Change in the association between C-reactive protein and natural logarithm of child mortality index (lnCMI), after controlling for other risk factors. Regression coefficients for ln C-reactive protein (as a continuous variable). Odds ratios per 1-unit increase in lnCMI for C-reactive protein  $\geq 3$  mg/L.

Variables	Sample size	Association statistic
<i>(Linear regression coeff)</i>		
Adjusted only by age and sex		0.014
+ Adjusted by Total chol/HDL ratio (ln)		0.022
+ Calories, carbohydrates and fat intake †		0.029
+ Obesity and overweight		0.025
+ Statin medication		0.025
+ Arthritis		0.026
+ Smoking history		0.006
+ Other covariates ††		0.011
<i>(Odds ratios)</i>		
Adjusted only by age and sex		2.95
+ Adjusted by Total chol/HDL ratio (ln)		2.91
+ Calories, carbohydrates and fat intake †		4.12
+ Obesity and overweight		4.04
+ Statin medication		4.25
+ Arthritis		4.24
+ Smoking history		5.06
+ Other covariates ††		4.96

† Dummy variables for nutritional characteristics. Caloric intake=More than 3000 daily calories; Fat intake=More than 40 g of daily saturated fat; Carbohydrates intake=More than 400 g of daily carbohydrates).

†† Confounding variables include: living in Metropolitan Area, education (6 years of schooling or more), low income, history of alcohol intake.

\*:  $p < .10$

\*\* :  $p < .05$

\*\*\*:  $p < .01$

Figure 1. Estimated underreporting of child death records (relative to underreporting in birth records) in Costa Rica, based on census information, by sub-region, 1927 and 1950.

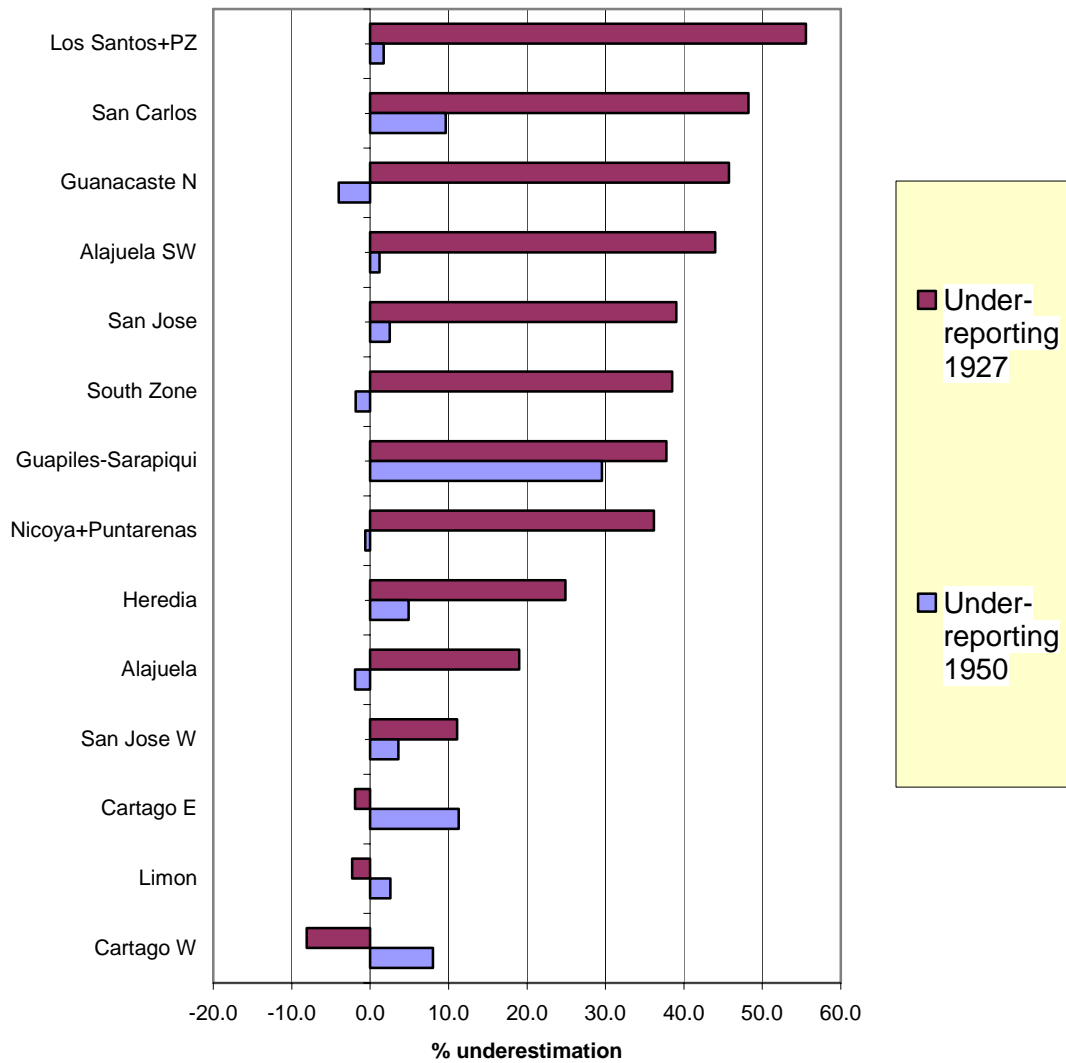
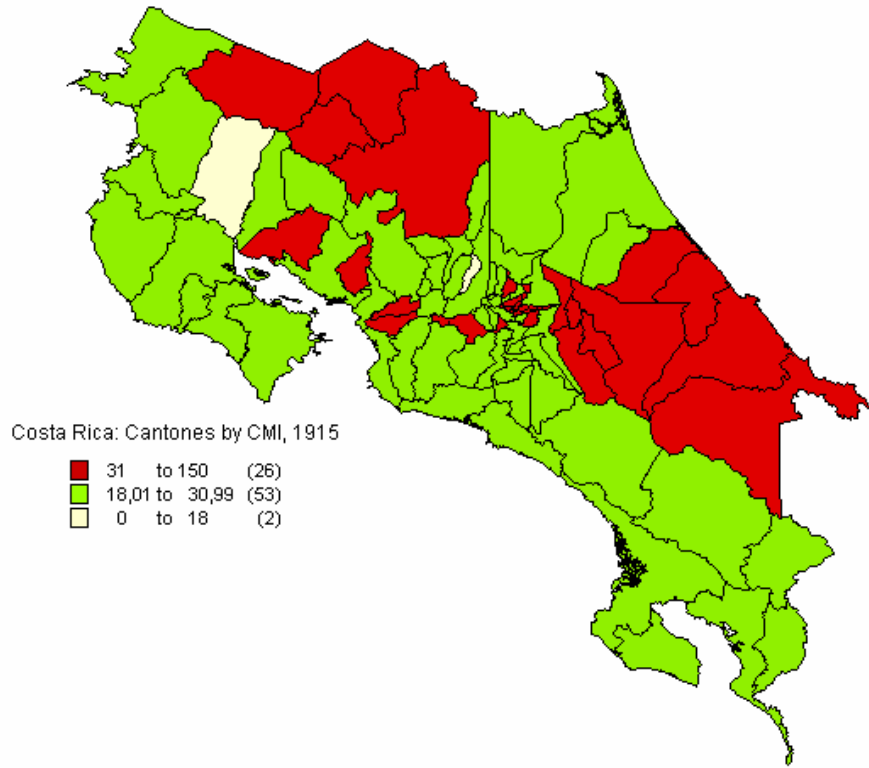




Figure 2. Costa Rica: Child Mortality Index (CMI) by canton: 1915, 1925, 1935 and 1945.

**1915**



**1925**

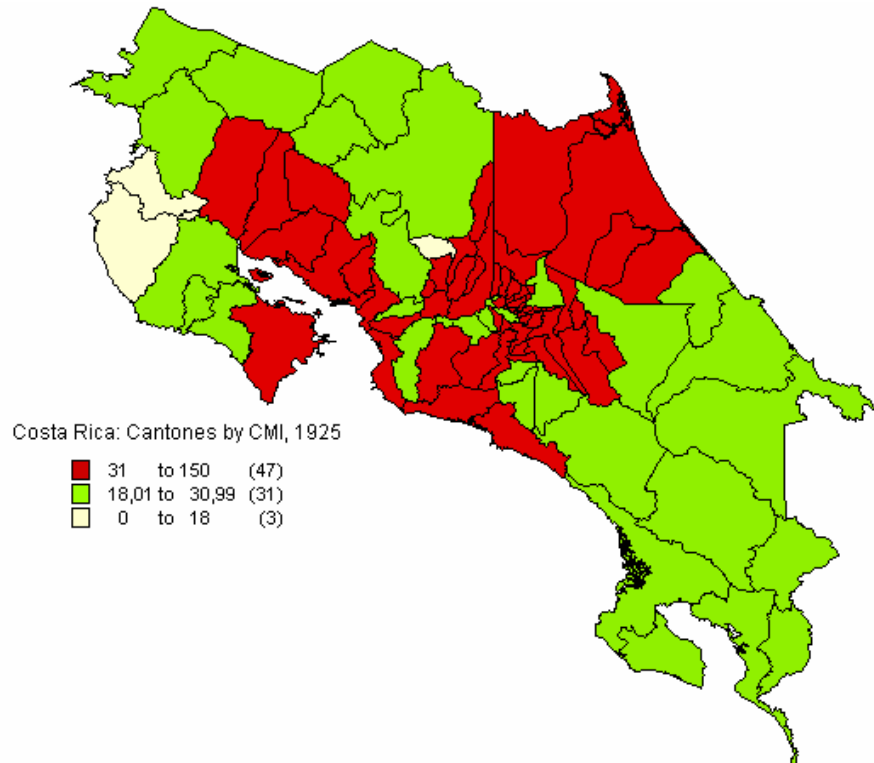
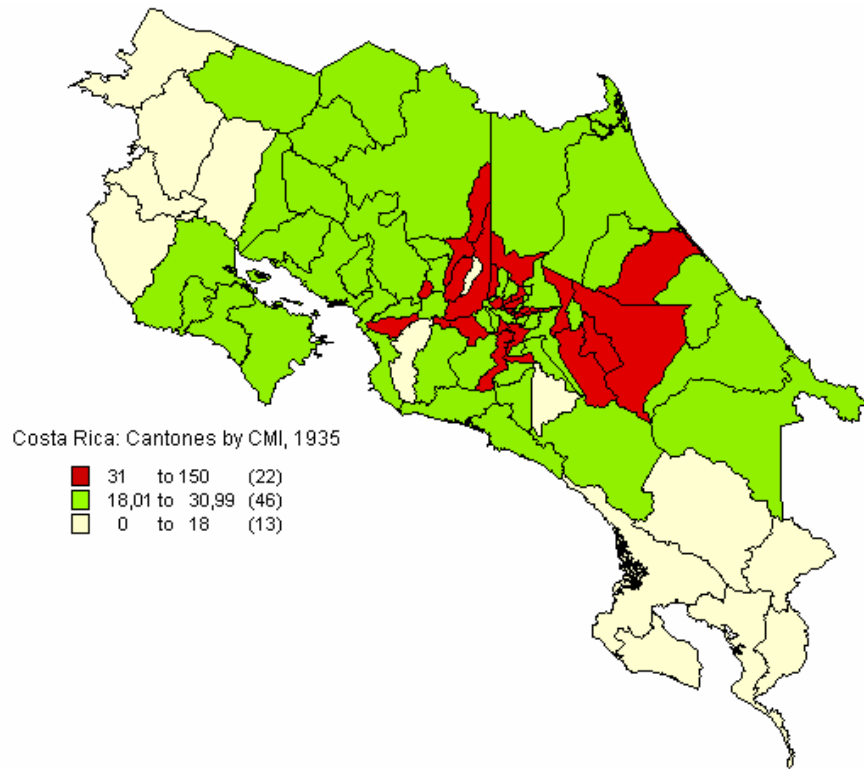


Figure 2. Costa Rica: Child Mortality Index (CMI) by canton: 1915, 1925, 1935 and 1945 (Continue).

**1935**



**1945**

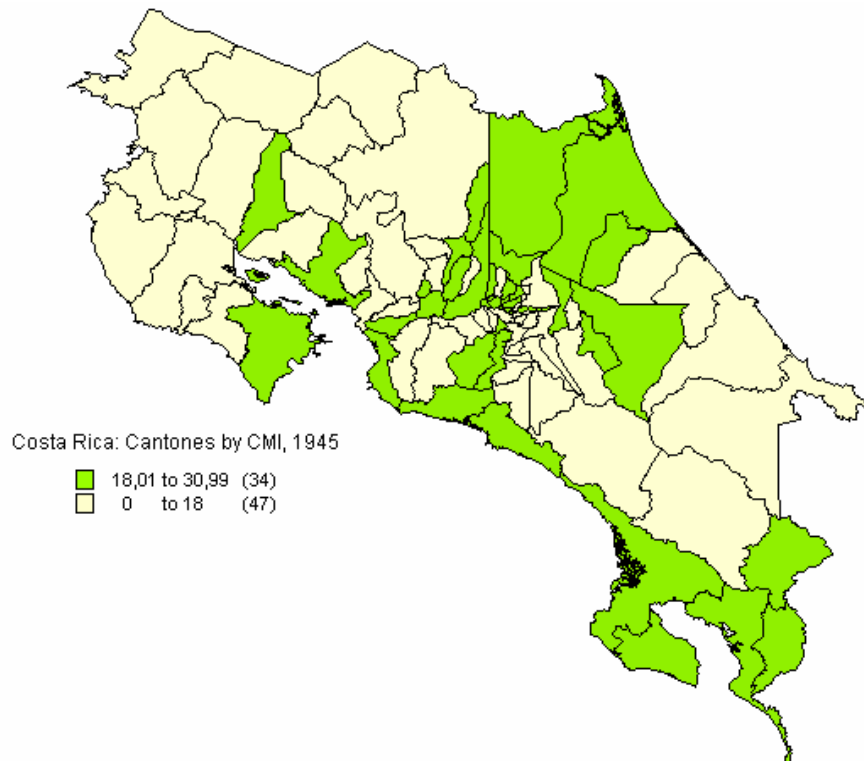


Table 4. Association between health variables and categories of child mortality index. Odds ratios for disease prevalence, and OLS regression coefficients for biomarkers.

Variables	Sample size	CMI ≤18.0 deaths per birth	CMI ≥31.0 deaths per birth
<i>(Linear regression coeff)</i>			
ln of C-reactive protein	631	0.041	0.034
ln of FSG	2399	-0.040 **	0.015
<i>(Odds ratios)</i>			
C-reactive protein ≥3 mg/L	631	††	††
FSG ≥126 mg/dL	2399	0.60 **	1.24
Prevalence of heart attack (%)	2399	1.07	0.61 **
Prevalence of strokes (%)	2399	0.91	1.00
Prevalence of other heart disease (%)	2399	1.12	0.63 **
Prevalence of diabetes (%)	2399	0.74 *	1.07
Prevalence of hypertension (%)	2399	0.63 ***	0.97
<i>(Gompertz reg hazard ratio)</i>			
Mortality hazard	2399	0.61	1.12

† Controlling for confounding variables include: sex, age, living in Metropolitan Area, obesity, overweight, education (6 years of schooling or more), low income, history of smoking, history of alcohol intake, ratio total cholesterol/HDL, and nutritional variables (More than 3000 daily calories, more than 40 g of daily saturated fat, more than 400 g of daily carbohydrates).

†† Not enough cases for logistic regressions to be estimated.

\*: p<.10

\*\* : p<.05

\*\*\*: p<.01

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