Population-level impact of adverse early life conditions on adult trajectories of morbidity, disability and mortality for low- and middle-income countries

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SHORT ABSTRACT

Evidence from theories of Developmental Origins of Health and Disease (DOHaD) suggest that experiencing adverse early life conditions subsequently leads to detrimental adult health outcomes. Most empirical DOHaD literature ignores the nature and magnitude of the impact of adverse early life conditions at the level of entire populations, the subsequent distortion of levels and patterns of adult health, and the ensuing load of disease and chronic illness and disability. In this paper, we use micro and macro simulation models combined with empirical estimates of incidence and prevalence of obesity, type 2 diabetes (T2D) and associated disability, to assess the magnitude of adult delayed effects on healthy life expectancy and life expectancy at older ages. Furthermore, we show how to use Age-Period-Cohort (APC) models to estimate the magnitude of delayed effects for older adults belonging to birth cohorts that experienced both adverse early conditions and rapid mortality decline.

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EXTENDED ABSTRACT

I. DOHaD

In the last decade or so research guided by the Developmental Origins of Health and Disease (DOHaD) paradigm and related theories has grown rapidly (Bateson and Gluckman 2011; Gluckman and Hanson 2005, 2006; Rosenfeld 2016). While the original idea of *delayed adult effects of* early conditions has been around for quite some time and in very disparate strands of literature (Derrick 1927; Frost 1939; Kermack, McEndrick and McKinlay 1934; Preston and Van de Walle 1978), it was Barker's work on "fetal programming" that provided the initial impetus for the creation of what is now a very active field of empirical research (Barker 1998; Barker 2012; Hales and Barker 2001; Lucas 1991). Although different strands of DOHaD theory invoke a vast array of mechanisms, they share an important trait: all invoke perturbations during critical periods of the development of a phenotype triggered by insults before conception, during embryonic and fetal life, perinatally, and across early stages of physical and cognitive growth. Early insults could lead to disruptions of processes of organ growth, differentiation and function, immune response, neurological development, metabolic regulation, and even the formation of adult preferences and behaviors. After prolonged latency periods, the disruptions could manifest themselves as delayed adult effects in the form of increased susceptibility to chronic illness, disability and mortality.

II. EMPIRICAL EVIDENCE

The empirical evidence generated in the last decade or so includes a bewildering variety of studies: from those resting on aggregate correlations (Barker and Osmond 1986) to those that follow cohorts of individuals exposed to adverse conditions *in utero* and in early life (Hoddinott et al. 2008; Lumey et al. 2012; Stanner et al. 1997; Stein and Lumey 2000; Tofail et al. 2008). The central objective of all these studies is to estimate the magnitude of effects of adverse early conditions (however measured) on multiple adult health outcomes, including adult mortality.

Missing from all these studies is treatment of the following problem: what does the empirical evidence for delayed adult effects *at the individual level* imply for levels, age patterns, and time trends of morbidity, disability and mortality for populations as a whole? How does the population-level impact of DOHaD mechanisms differ in low, middle and high-income populations? Can the recent demographic past and the resulting changes in the composition by early experiences of birth cohorts attaining older ages in low to middle have an influence on adult disease, disability, and mortality? How are levels and patterns of a region's or a country's adult health, disability, and mortality altered by the influx into older adult ages of birth cohorts whose members are scarred by

adverse early conditions? And, what exactly is the load of disease and disability that accompanies these cohorts as they transit through various stages in their life cycle?

Because of their implications for future trends of health and mortality and on private and governments' health expenditures, these issues should be at the forefront of population research. This paper begins to address some of these questions. To do so we focus on aggregate population outcomes and investigate the nature and quantitative importance of adult delayed effects implied by DOHaD for trajectories of morbidity, disability and mortality for entire populations.

III. OBJECTIVES OF THE PAPER

To do the above we generalize and improve upon an existing model (Palloni and Beltrán-Sánchez 2016, 2017) that formalizes relations predicted by DOHaD between exposure to adverse early conditions, on one hand, and adult health, disability, and mortality on the other. The current model emphasizes the impact of early life conditions on adult mortality and suggests that when mortality declines in populations affected by detrimental early life conditions, average adult mortality may go through stages in which mortality will decline more slowly than background mortality rates, remain steady, or even increase (Palloni and Beltrán-Sánchez 2016, 2017; Palloni and Souza 2013). We make two major improvements to this model to incorporate chronic diseases and disability and an accounting of healthy life expectancy. In addition, we evaluate the performance of a statistical tool to estimate adult delayed effects associated with early conditions from empirical data on morbidity, disability and mortality. We describe these three goals below.

First, the existing model focuses on mortality only. In this paper we include consideration of chronic illness and disability status as outcomes that are highly sensitive to adverse early conditions. In particular, we use empirical estimates of the incidence and prevalence of obesity and type 2 diabetes (T2D), as well as associated disability, to assess the magnitude of adult delayed effects on healthy life expectancy and life expectancy at adult and older ages. This extension serves as a tool to understand relations involving the two health conditions that figure most prominently in DOHaD-related research, obesity and T2D, and the onset of deleterious early conditions. In addition, by including ill-health and disability we contribute to the literature on compression of morbidity and mortality introducing an entirely novel perspective that considers explicitly adverse early conditions of birth cohorts as a potentially significant determinant of health and mortality at older ages. Thus, for example, we will be able to determine whether or not the existence of delayed effects in a population produces oscillations in trends of illness, disability and mortality that lead to alternating periods of compression and expansion of morbidity or mortality depending on the composition of cohorts attaining older ages. This is relevant for low- to middle-income countries

currently experiencing rapid growth of obesity and T2D prevalence while still in the midst of a yet unfinished epidemiological transition. As we argued elsewhere (Palloni and Beltrán-Sánchez 2016, 2017), the very nature of past mortality decline experienced by these countries makes them more susceptible to the influence of changes in older cohorts composition by early experiences as they could have significant impact on the population's future health and mortality.

The **second** improvement consists of translating the formal model (Palloni and Beltrán-Sánchez 2016, 2017) into a microsimulation model with the power of generating scenarios including combinations of different classes of mortality decline and diverse nature of delayed effects. As is the case in all microsimulation models, we assess magnitudes of uncertainty associated with parameter estimates. Thus, for example, an important input are estimates of rates of obesity and obesity-specific T2D incidence. The corresponding incidence functions, however, depend on population data subject to sampling and other classes of errors. By integrating measures of such errors, the microsimulation produces outcomes with known boundaries of uncertainty.

Although we do not do implement systematic empirical applications, we demonstrate that the microsimulation model offers ample room for specifying multiple mediating pathways conjectured by DOHaD. We introduce two mediating paths. The first involves physiological as well as molecular processes that occur early in life and are the result of deleterious early conditions. Thus, we illustrate how to integrate parameter estimates from clinical studies relating changes in early nutritional deficiencies into epigenetic marks (excess methylation of CpG islands) that, in turn, increase the propensity to develop child and adult obesity (and other metabolic disorders). Second, we consider how the inclusion of events experienced across the life course may modify (reduce, amplify) the impact of early conditions. This feature is of strategic importance as it is known that some of the impacts of adverse early conditions are indeed reversible

The third contribution of the paper is an evaluation study of the power of Age-Period-Cohort (APC) methods to identify consistent estimates of the delayed adult impact of early conditions. These methods are employed to retrieve unbiased and consistent estimates of age, period and cohort effects on mortality data. In this paper we answer the following question: do APC methods retrieve consistent effects when older adult populations experience delayed effects due to adverse early conditions and, simultaneously, rapid mortality declines? To assess APC methods robustness we use the alternative scenarios in the microsimulation and two large mortality data bases, the Human Mortality Database (HMD) and the Latin American Mortality Database (LAMBdA).

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