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Research proposal [Part B2]
(not evaluated in Step 1)

Part B2: *The scientific proposal* (max. 15 pages)

Section a. State-of-the-art and objectives

1 BACKGROUND

Over the past two decades there has been massive growth of research on the nature of delayed adult effects of early conditions. We refer to this field of research as the **Developmental Origins of Health and Disease (DOHaD)** [42a–44, 58][1]. A rapidly growing body of evidence strongly suggests that key pathways that 'translate' early experiences into adult health outcomes are epigenetic in nature. They are part of a complex epigenomic machinery evolved in mammals and some plants to flexibly respond and accommodate to ecological changes and to optimize fitness under rapidly changing environmental conditions [110, 13, 14].

DOHaD is bound to revolutionize the study of health, disability and human mortality and if population health sciences conducts business as usual and ignores the research front opened up by DOHaD it will do so at its own peril. Integration of standard population health sciences and DOHaD will generate new hypotheses and shed light on a number of phenomena that are now considered puzzling. It is likely that the new, refreshed approach will identify causal mechanisms that are quite different from those considered in traditional population health sciences and, if so, it will inevitably have important effects on the design of health interventions. For example, the incidence patterns and severity of modern metabolic disorders appear to be set early in life and, if so, health interventions may be redirected and target children and adolescents instead of older adults.

The most exciting possibility is that advances in the understanding of the epigenetic mechanisms (principally via methylation of CpG islands, histone modifications and disruptive microRNA) and the environmental conditions that trigger (or erode) epigenetic signatures will shed light on pathways linking early exposures and delayed adult health responses. If so, the integration of DOHaD and population health sciences will require collaboration with developmental biologists, geneticists and epigeneticists. Furthermore, because numerous epigenetic pathways that translate early experiences (for example early nutritional deficiencies) into adult health outcomes (for example dysregulated glucose metabolism) involve the early establishment and/or subversion of the microbiome, an important part of the research agenda will involve microbiology and epigenetics. Last but not least, DOHaD is emerging as a body of theory that offers ample room to understand determinants of illness and disability in an evolutionary context and could provide population health sciences a bridge to evolutionary biology.

In summary, integration of DOHaD and population health promises a rich multidisciplinary ground, could elucidate mechanisms for delayed effects, improve knowledge of the evolution of human health and illness and of the conditions that give rise to and precipitate the fall of epidemiological regimes, and could lead to far-reaching health policy implications. For all this to happen, a renewed population health research agenda must be formulated now. In particular, three weakness areas must be addressed.

First, there is no systematic work on the formulation of formal demographic models to translate the implications of DOHaD theories into consequences for patterns of morbidity and mortality in human populations. To our knowledge there is only one direct, albeit limited contribution in this area [73, 77, 82]. **Second**, empirical testing of hypotheses in human populations lags behind advances in other area as most advances have been made using animal studies. Testing DOHaD conjectures in human populations has proven difficult since the data required (longitudinal studies of multiple cohorts experiencing contrasting conditions) are rare. Verification of the epigenetic mechanisms is an even harder task because it calls for longitudinal evidence about epigenetic signatures in multiple tissues of the body. **Third**, short and medium run implications of delayed effects for human health and mortality of DOHaD mechanisms have not been systematically investigated.

The overarching goal of this project is to addresses these three areas of research and contribute to the development of new theories of mortality and morbidity informed by DOHaD. This is an admittedly ambitious goal and its attainment requires activities with limited precedent and riskier than average.

2 IMPACT

The project's potential payoffs are significant for it will break new ground in three main areas:

[1] DOHaD encompasses a multiplicity of variants and is not a single theoretical corpus. Throughout, and unless strictly necessary, we use the acronym DOHaD to refer to all its variants. This shortcut saves space and maintains consistency with current usage.

Theory: based on empirical research supporting the existence of epigenetic imprints of early exposures and their adult manifestation, we will formulate new hypotheses about the genesis of selected modern adult conditions and, in particular, formalize predicted relations between early conditions, obesity, T2D and their consequences for adult health, disability and mortality. To the extent permitted by our findings, we will reformulate theories of human morbidity, disability, mortality and aging linking birth cohorts' early conditions and to their adult health, disability and mortality. The new formulations will integrate results of research in developmental biology, microbiome, and epigenetics and should contribute to the establishment of more solid bridges linking population health and evolutionary biology.

Demographic formal models: we will formulate two new formal models to assess the implications of delayed effects on human morbidity, disability and mortality. The first is an aggregate macro model that seeks to *identify at the population level age patterns and magnitude of effects of early exposures and adult health, disability and mortality predicted by DOHaD.* The second is an integrated microsimulation model, ECHOsim, designed to *formalize the dynamic of selected epigenetic changes implied by early exposures at the individual level, verify DOHaD predictions with observed representative national data, and identify the most relevant mediating pathways*. The model will be specialized to two conditions known to be outcomes of early developmental conditions, namely, obesity and T2D; these conditions are a major source of ill-health, disability and excess mortality in most modern human populations;

Empirics: for the first time we will empirically assess the implications of DOHaD relations for patterns of obesity, T2D , disability and excess mortality in very diverse populations with contrasting demographic, social and economic histories.

3 AIMS AND COMPONENTS OF THE PROJECT

The project consists of **three components**, each associated with tightly interwoven aims addressing the three weaknesses identified before, well-defined outcomes and deliverables, and activities set forth in Work Packages 1-3.

3.1 Component and Aim 1

Aim 1 addresses the first area of weakness identified before. It consists of developing a formal demographic model that represents the main pathways through which early conditions manifest themselves as adult chronic illness and mortality. The model generates predictions about adult health and mortality patterns in human populations that are vulnerable to the expression of adverse early conditions. We will then undertake *soft tests* of predictions from DOHaD theories, of which the best known variant is "Barker's hypothesis" [7, 10][2]. We will use two very long trends of period and cohort mortality data available in the Human Mortality Database (http://www.mortality.org/) and the Latin American Mortality database (http://www.ssc.wisc.edu/cdha/latinmortality/). We will estimate a broad spectrum of mortality statistics to characterize child, adult, and old age mortality trajectories during the secular mortality decline, around 1780-2010 in Western-Southern and Northern Europe and North America (NAWE), on one hand, and during the period 1850-2015 in Latin American and Caribbean (LAC) on the other). We will then empirically estimate parameters of observed period and cohort mortality patterns and proceed with statistical tests of the model's predictions. These *soft tests* supply necessary but not sufficient evidence to falsify DOHaD propositions. Implementation of *strong tests* is tackled in component and Aim 2.

Outcomes of component 1: we expect two outcomes. ***First****, formulation of a formal demographic model of DOHaD that will enrich current mortality models accounting for the impact of conditions over individuals' life course. Model development follows the blueprint established in other areas to formalize life history theory, disposable soma theory, pleiotropic effects, and life cycle human health-capital formation. The* ***second*** *outcome is the completion of empirical tests of DOHaD hypotheses to generalize standard theories of adult morbidity, disability and mortality, and human aging.*

3.2 Component and Aim 2

Aim 2 targets the second area of weakness identified before. To increase the strength of empirical tests of DOHaD we will formulate a microsimulation model (ECHOsim) to assess effects of early conditions on two major health conditions that, with some quickly disappearing exceptions, afflict all modern human populations, namely, obesity, T2D, and mortality[3]. ECHOsim will link early conditions to adult experiences via *onset*, *trajectory* and *intergenerational* parameters. It will simulate individuals' trajectories over the life course as they encounter multiple risks correlated with their own and their ancestors' early experiences. ECHOsim will be a tool to enables to handle population heterogeneity and to explicitly account for the role of chance, a large component of the establishment (or erasure) of epigenetic marks.

As the formal demographic model in component 1 does, ECHOsim will generate aggregate, e.g.

[2] Although it is admittedly a rather clumsy terminological strategy, we will use the expression "Barker hypotheses" to refer to both the "thrifty phenotype"[9] conjecture and those associated with 'fetal programming' [59]

[3] In what follows when we will use the acronym T2D to refer to Type 2 Diabetes *and* associated comorbidities.

population level, outcomes (age specific prevalence of obesity, T2D, etc...). But, unlike the formal demographic model, ECHOsim accounts for the role of epigenetic changes and associated randomness, population heterogeneity and intergenerational relations. ECHOsim emulates mechanisms that connect early conditions and adult delayed effects that are manifested in *aggregate trends* of incidence of obesity, T2D, adult disability and mortality. ECHOsim generates aggregate trends of obesity, T2D, disability and excess mortality. Expected trends from ECHOsim can then be compared with observed trends from national health surveys covering the period 1990-2015. This will constitute the core of the *strong test* of DOHaD.

Outcomes of component 2: we expect four outcomes. ***First****, ECHOsim will trace individual life course influences of different regimes of early conditions on the incidence of obesity, T2D, disability and excess mortality and will include an intergenerational dimension.* ***Second****, the first module of ECHOsim will describe the nature and effects of early influences and the role played by maternal and grand-maternal environments. This requires collection of extant information and meta-analysis to retrieve onset parameters that drive the first module. This data collection will result in a new public database with empirical estimates of effects of early conditions retrieved from both human and animal studies.* ***Third*** *the second module of ECHOsim is based on a multistate hazard model that represents the progression of obesity, T2D and sequelae. This constitutes a contribution to population health sciences as the majority of the work in this area relies on simple death processes dependent on highly questionable assumptions. Furthermore, estimation of the multistate model will offer a unique opportunity for comparative studies of the dynamics of obesity and T2D in very diverse populations.* ***Fourth****, the model will include a novel intergenerational component to assess the influence of conditions experienced in one generation on those experienced by subsequent generations.*

3.3 Component and Aim 3

Aim 3 of the project focuses on the third weakness identified before and consists of computing demographic projections and forecasts of prevalence of obesity, T2D, disability and mortality over the next 50 years. These forecasts will reveal the duration and severity of impacts of early conditions experienced by successive birth cohorts and will be informative for those interested in policy interventions. The forecasts will combine standard multistate demographic projections with aggregate results from ECHOsim and will be based on information from multi-year national health surveys in six countries and in Andalusia (Spain) a region with one of the highest prevalence of obesity and T2D in Western Europe

Outcomes of component 3 : *the central outcome will be the forecast of obesity and T2D, disability and mortality) 50 years into the future. Because these forecasts are based on past trends in child obesity and assumptions regarding delayed effects of early obesity, they are a natural tool to evaluate hypothetical health interventions that prevent obesity early in life or reduce the burden of diseases at adult ages.*

4 CONTRIBUTIONS AND INNOVATIONS

The value of this project is rooted in its potential contributions to theories of health, mortality and aging in modern human populations, to formal modeling and empirical testing, and to the design of policy interventions to improve future health and disability among older adults.

4.1 Contributions to theory

The uniqueness of morbidity and mortality experiences of LI and MI countries poses severe challenges to standard theories successfully deployed in the context of classic 'Western' demographic dynamics. Simultaneously, progress in DOHaD offers many insights and findings that can enrich standard theories.

4.1.1 Why is DOHaD relevant for theories of morbidity, mortality and aging?

Over the last ten years or so there have been important advances in research on human morbidity, mortality, and aging. We argue that these advances could be multiplied several fold by fostering progress in two areas. **First**, there is little if any dialogue between research in population health and mortality, on one hand, and research on DOHaD, on the other. So far the bulk of empirical work on DOHaD has been carried out using animal models or small scale clinical studies. Verification of DOHaD theories in population health sciences is limited as empirical testing with human populations has been confined to the study populations from genealogical records [8, 28, 66], to a handful of small cohorts in highly selected populations from LI countries [3, 61–63] and, finally, to one comparative study with limited information on adult mortality in LI to MI countries [64]. The consequence of this is that most advances on the study of morbidity, mortality and aging do not integrate findings from DOHaD at all. **Second**, most if not all recent progress in our understanding of human morbidity, mortality, and aging has been based on highly selected human mortality experiences. There is precious little research on oldest old mortality or on patterns of compression of morbidity and mortality in LI to MI countries. Intense research on a small sample of human mortality experience is possible due to the availability of a harmonized data base on mortality, the HMD. The HMD provides information for understanding past, current and future trends of mortality and longevity [68, 107], for country-specific and cross-country comparative analyses on older age mortality [25, 101], for comparing

population health and mortality across countries [25, 108], for formulating and testing formal models of mortality [105], and for verifying theories about cohort relations, e.g. link between early and late life mortality [18, 24, 32, 52, 109]. For all its virtues, HMD has an important limitation: the majority of countries included in it reflect the post 1800 "Western" experience of Western, Northern, Southern and parts of Eastern Europe and North America (NAWE). If the secular mortality decline in the excluded areas were a lagged expression of the experience already represented in the database, this limitation would only amount to defective coverage, albeit a significant one since more than three quarters of the human population belongs to LI and MI countries. But this is not the case for there are sharp contrasts between these countries' past epidemiological and mortality regimes and those included in HMD. To the extent that these contrasts are significant for the variability of patterns morbidity, disability and mortality that we encounter now or we will encounter in the future, our theories and models should account for them and their consequences. If this is not done, these theories and models will be incomplete, will produce misguided inferences, and support inappropriate interventions.

It has been abundantly documented that LI and MI countries underwent very distinct and unique epidemiological transitions [5, 71, 79, 81, 87, 94]: the timing, the pace and the precipitating factors are quite singular [35, 36, 84, 86, 87, 38]. These unique features prime LI and MI countries to manifest with special force the consequences of adverse early conditions and may influence patterns of conditions (e.g. obesity), chronic illnesses (e.g. T2D and comorbidities) and disability in LI to MI countries [38]. If so, theories about human patterns of morbidity, mortality and aging will require updating to consider explicitly key elements of DOHaD theories. For all these reasons it is essential that we take seriously the challenge of distinguishing human mortality experiences that are qualitatively different. There is important value-added in the analyses we propose here precisely because the nature of some of the data we will use reflect epidemiological experiences that are peculiar, different and strengthen the role that early conditions play in shaping adult health and mortality. In doing so they also constrain pathways toward future gains in survival at older ages. Thus, the integration we propose in this project will not only fine-tune current theories with advances in DOHaD but will also make possible their extension to a much larger swath of human experiences.

The lesson from this is that to increase the power of theories of human morbidity, disability, mortality and aging we should widen the lens and include as many human experiences as possible. **Comparative analysis is not an option but a must**. An important characteristic of this project is that it is comparative in nature and will fully exploit contrasts between radically different health and epidemiological regimes. Contrasts between LI, MI and HI population experiences will strengthen our inferences about how birth cohorts' early circumstances exert durable influence on their future morbidity, disability and mortality trajectories.

4.1.2 Impact on three study areas in health, mortality and aging

We have show elsewhere that formalization of DOHaD [77] leads to predictions that are at odds with and undermine mainstream interpretations of mortality changes and patterns and cast doubts on hypotheses verification using conventional statistics. These preliminary findings-all of which require confirmation-suggest that integration of DOHaD into theories of morbidity, mortality and aging could have important influences on population health studies. Three areas of studies can be affected.

Trajectories of human longevity: Expectations of persistent short to medium increases in life expectancy may be applicable only to the class of mortality decline experienced by Western Europe and North America. We conjecture that populations that underwent very rapid mortality declines initially driven by medical innovations and technology, must contend with strong resistance to continued gains in survival originating in the inflow into older ages of survivors of birth cohorts scarred by adverse early childhood.

An important contingent of researchers identifies evidence suggesting that there are no visible or detectable obstacles toward continued gains in survival at adult ages either. A scenario with continued decline of 1 percent per year in adult mortality rates prevailing since 1960 is not considered a fantasy [53, 54, 96, 98, 99] (but see also [106]). The standard exclusion to this rule is the complex but somewhat deviant dynamics of mortality in the former Soviet Republics [22, 92]. Importantly, none of the evidence that supports this claim includes mortality from LI and MI countries that constitute more than 86 percent of the earth population.

We conjecture that the expectation of business as usual–short to medium run continued survival gains and increases in life expectancy– may be applicable only to the class of mortality decline experienced by Western Europe and North America. Countries that went through a very rapid mortality decline initially driven by medical innovations and technology must contend with strong resistance originating in the inflow into older ages of survivors of birth cohorts scarred by early childhood experiences. Elsewhere we showed that this mechanism could generate foregone gains in life expectancy at age 60 of about 10 to 15 percent of

current values in LAC [83]. These estimates are preliminary but, if confirmed, they imply that future mortality declines in these regions will be partially at the mercy of cohort-specific circumstances[4].

We hasten to emphasize that the potential for stalls and regressions in human gains in survival or of the warped dynamic of patterns of mortality at older ages is unrelated to the length of human lifespan. Lifespan could be infinite and the short and medium run disruptions generated by mortality patterns that are responsive to early conditions would apply all the same.

Dynamics of senescence and aging: An important stream of research regarding old age mortality and senescence theorizes about trends of old age mortality deceleration [51, 99] and shifting age mortality patterns [19, 50]. **First**, it has been predicted that the age-related increase of the rate of mortality risk (rate of aging) should be constant across individuals and over time [31, 99]. This is a controversial issue. Theories and empirical evidence from animal studies suggest that human mortality rates may decelerate at very old ages and even cease to increase altogether [34, 40, 93b, 97, 104]. Evidence from HMD indicates that in modern life tables the onset of mortality deceleration is being delayed to older ages in recent times [17]. However, this work is entirely based on the experience of HI countries and very little of it, if any, refers to mortality in other populations. In preliminary work we demonstrate that one (of many) implications of DOHaD hypotheses is that the slope of adult mortality rates and the rate of mortality change at older ages can remain steady, increase or decrease irrespective of background mortality trends [73, 77]. If some of the biological underpinnings of DOHaD theories are correct (including epigenetic pathways), the rate of human aging and other indicators of old age mortality patterns can experience deviant dynamics that strongly depend on mortality conditions experienced in the remote past (see Research Strategy below). **Second**, standard mortality theories predict that declining child mortality in a cohort translate into and reinforce subsequent mortality decline at older ages [31, 33]. There is some, albeit not strong, empirical evidence corroborating this prediction in the case of Swedish mortality history [33][5]. Findings based on a simple formalization of DOHaD hypotheses suggest that such inferences may not be applicable at all in LI and MI populations. More importantly, our work casts doubts on the validity of interpretations of standard metrics routinely used to assess the importance cohort determinants. Thus, the within-cohort correlation between mortality rates across distant stages of the life course used to assess the importance of cohort conditions, is misleading under delayed effects [73, 77].

Compression/expansion of morbidity, disability and mortality: The controversy over whether aging among modern humans occurs against a backdrop of expanding or compressing morbidity and mortality has not yet had a convincing resolution [39, 60]. Yet, with some exceptions, the bulk of the evidence for or against key conjectures comes from epidemiological regimes and past mortality history experienced in high income countries. Tellingly, the compression/expansion controversy completely ignores the possibility that delayed effects could play an important role even though the existence of adult delayed effects must necessarily influence the incidence of chronic diseases, disabilities and excess mortality associated with, for example, obesity and T2D, both scourges in most modern human populations and drivers of morbidity and disability expansion at older ages. But T2D not only increases the risk of comorbidities (CVD, strokes, kidney failure) and excess adult mortality but also augments the severity and duration of associated disability. Thus, whether or not morbidity and disability, on one hand, and mortality patterns, on the other, are becoming more (or less) rectangular in shape depends crucially on whether or not (and to what an extent) early conditions regulate the incidence of chronic illnesses and associated disability and excess mortality. Improvements in survival among the chronically ill and the disabled will necessarily increase the fraction of years of life that the elderly spend in chronic illness or disability (expansion) whereas postponing the onset of both chronic illness and disability (shifting the corresponding incidence functions) will do the opposite (compression). Shouldn't it be obvious that theorizing about relevant DOHaD mechanisms must have centrality in the expansion/compression controversy in populations suspected to be influenced by a regime of delayed effects? Shouldn't these considerations also be a part of forecasts of future prevalence of chronic illness, disability and health costs?

A potentially powerful impact on theory: Our preliminary formalization of DOHaD leads to predictions that are at odds and undermine a great deal of standard mortality research, cast doubt on routine interpretations of observed phenomena, and invalidate hypotheses testing based on them. If those predictions hold then (a) researchers routinely misinterpret time trends of adult life expectancy; (b)researchers may

[4] In addition to this, other cohort factors may become strong determinants of future trends, e.g. the influence of past smoking and changes in early onset of obesity [78, 80]

[5] But see [6] for another view.

misinterpret observed time trends of the rate of senescence since a regime of delayed effects induces trends in the rate of senescence when there is none; (c) commonly observed within cohort correlations of mortality at older and younger ages may be off the mark and misleadingly suggest attenuation of the association when there is none; (d) when delayed effects are strong and sustained, regression estimates of the within cohort adult mortality slope on measure of the cohort's child mortality are misleading and cannot be interpreted [18]; (e) time trends and comparisons of measures of morbidity and disability compression will be misleading if researchers do not control for the prevalent regime of delayed effects.

4.2. Contributions to and innovations in formal demography and population models

The demographic formal model and ECHOsim are novel attempts to translate DOHaD hypotheses into testable propositions. The demographic formal model has limited scope whereas ECHOsim is broader. When jointly used they are useful for hypotheses testing and both are contributions to formal demography.

4.2.1. Generalized frailty model

The mathematical model that we will formulate in component 1 generalizes the standard frailty mortality model, incorporates variants of theories relating mortality across the life cycle, including Barker and related DOHaD hypotheses, and leads to testable predictions. To our knowledge ours [77] is the first attempt to formalize hypotheses derived from DOHaD (but see [27]). Extant models are suitable to represent relations similar to those implied in DOHaD but are rooted in different theories of adult health and mortality [23, 102–104]. Thus, there are a number of formal models that generalize standard frailty models but have no connection to DOHaD theories [100]. The model proposed here includes properties similar to those for pleiotropic effects with generalized frailty but is tailored to capture DOHaD main theorems. Interestingly, if used to model time varying frailty[1, 2], the model is applicable to events other than mortality.

4.2.2. Microsimulation model (ECHOsim)

In component 2 of the project we will formulate a new microsimulation model to link influences of early conditions to adult experiences. ECHOsim contains three modules and combines three suites of parameters. The first suite, *onset parameters*, is the basis for the first module and consists of estimates of effects of selected early conditions (maternal obesity, gestational diabetes, maternal nutrition, quantity/type of breast- feeding, early child nutrition, early illnesses) on child and adult obesity and metabolic disorders, principally T2D. These parameters will encapsulate information on epigenetic mechanisms that are known to operate. The second suite, *trajectory parameters* is the basis for the ECHOsim's second module and consists of estimates of a multistate model for failure times associated with obesity, T2D, disability and mortality. These parameters control individual transitions from (to) obesity, T2D, disability and mortality. Finally, the third suite, *intergenerational parameters* drives the third module that converts ECHOsim into a tool for assessing the influence of maternal on offspring early experiences. This will be useful to evaluate the impact of adverse conditions in a generation of origin $F0$ on subsequent generations F_j , $j > 0$. This extension provides us with a platform to test conjectures from the Predictive Adaptive Response (PAR) [15, 46, 48] and the phenotypic inertia (PI) [56], two variants of DOHaD. To our knowledge no such model has been proposed to emulate effects of early conditions in populations where exposure straddles multiple generations. It is in this sense that component 2 of the project is dedicated to implement *strong* tests of DOHaD conjectures. ECHOsim is a tool to follow lifecourse trajectories of individuals who are (are not) exposed to adverse early conditions and, in particular, to track their experiences of obesity and metabolic disorders (T2D), the two better understood outcomes of adverse early conditions.

4.3. Contributions to and innovations in statistical inference using population data

The three components require statistical applications that have not been previously used in population studies. This include: generalized bootstrap (GB), Bayesian Model Averaging (BMA), and Approximate Bayesian Calculations(ABC). All three components of the project will make extensive use of new approaches to statistical inference to account for uncertainty of population parameters and models.

Testing mortality theories with West European and North American data is relatively unproblematic. While precision issues should not be dismissed [87-89], none of them are known to seriously threat the validity of very general inferences. In contrast, analyses of mortality patterns in LI to MI populations are marred by accuracy problems. Even in a benign scenario it is not rare to have 'undecidable estimates', that is, multiple estimates for a single population parameter (e.g. life expectancy at birth for a country-year) that are equally defensible. With one exception [90] this problem has not been dealt with, as population experts routinely select *a priori* a single estimate to work with (and usually with no convincing justifications). For many of the analyses that will be carried out in this project we can do much better than this. We propose to apply a new procedure that includes multiple estimates of mortality and associated accuracy scores. These scores are then taken into account in conventional statistical estimation (GLS, HLM etc…) to compute estimates of relations of interest with uncertainty. The procedure has already been applied with success to data in LAMBdA [72]

The three components of the project rely on estimation of relations between well-defined variables. These relations are formalized using not one but several plausible models. Standard practice is to choose *ex ante* one among the various models and produce inferences accordingly. We will depart from this standard practice by accounting for model uncertainty using two alternative strategies, namely, BMA and GB. Neither has ever been used in standard analysis of mortality and health statistics. We successfully demonstrated the use of GB in an application to the analysis of historical mortality determinants in Latin America [72]

Finally, the empirical testing of ECHOsim involves comparisons between predicted and observed time trends of prevalence of conditions and excess mortality. The simulation model is run multiple times and each time we draw parameters from a prior distribution to compute predicted outcomes. Up until recently the only Bayesian technique available to assess how satisfactory is the fit of predicted and observed outcomes was Markov Chain Montecarlo Method (MCMC). But implementation of MCMC requires the computation of an exact likelihood function and for ECHOsim we will only be able to produce an approximation. This can be handled via ABC, a procedure used quite extensively in biology and evolutionary biology models. To our knowledge this is the first time that ABC will be applied to solve a problem in population health.

4.4 Contributions to forecasts and evaluation of policy interventions

Component 3 contributes to the assessment of short, medium and long run consequences of alternative regimes of early conditions and adult delayed effects expected by multiple variants of DOHaD. The assessment will be carried out using two different approaches. The first is a standard multistate demographic projection using to compute future prevalence of obesity, T2D disability and mortality. The second approach is new. It will utilize ECHOsim to account for (i) relations between outcomes (obesity and T2D; T2D and comorbidities; T2D, disability and mortality) estimated as part of component II and (ii) multigenerational relations. Unlike the use of standard demographic projections, this strategy explicitly considers the correlation between health outcomes across generations and, in particular, the correlation between maternal and offspring obesity as well as between early child hood obesity and adult obesity. The key application of this approach will be to assess outcomes of alternative interventions strategies geared toward modification of effects of exposures to early conditions, behavioral modifications, and technology.

Section b. Methodology

5 RESEARCH STRATEGIES

In what follows we describe approaches for each of the three components of the project. The narrative contains a description of (a) models and methods, (b) data sources, and (c) data analysis.

5.1 Formal model of DOHaD and testing of predictions (AIM 1 and component 1)

In this component we will develop a formal demographic model for relations conjectured by DOHaD theories, derive predictions and carry out empirical tests using two large human mortality databases.

5.1.1 Models

The model we propose is member of a class of models developed to understand human senescence and its relation to environmental, genetic, and epigenetic factors [29, 30]. Although these models emerged independently, they are tightly interwoven with theories about the biology of growth and development, life history theory, life cycle investments in soma and reproduction and life cycle models of human capital, all of which pose relations between health status over distant stages of the life cycle. Some explicitly integrate the role of random change (mutations) and environments (epigenetic changes) early in life and their effects on the rate of aging [93a, 102, 103]. A central feature of these models is the relation between cohorts' early experiences and their health and mortality impacts at older ages [11, 33]. There are multiple variants of these theories and all have distinct, contrasting predictions [15, 46].

Conceptual foundation: to simplify description we assume that all mechanisms invoked by DOHaD theories have identical delayed effects characterized by organ damage or abnormal immune/metabolic response triggered by adverse early experiences, long latency periods, and delayed illness and mortality manifestations in late adulthood. Effects can be amplified as a consequence of mismatches between embryonic or *in utero* adaptations and subsequent environmental exposures during early life and even response and stimulus is short (less than a generation) and "phenotypic inertia" (PI) if the lag is longer. This is thought to be an adaptation that endows mammals with an evolutionary advantage. However, under rapidly changing environmental conditions, it could backfire and increase lifelong risks of adult chronic illnesses [45, 56] To abbreviate we use the terms 'Barker frailty' to refer to any of the DOHaD mechanisms referred to above, alone or in combination with others, and 'Barker effect' to refer to delayed effects on adult mortality[6].

[6] We use "Barker" frailty and "Barker effects" as shortcuts to refer to the exposure to early adverse conditions and its adult effects respectively. As is the case with the use of "Barker hypotheses", the shortcut is necessary albeit rather clumsy.

Formal representation: The formal model we propose is an extension of the standard frailty model in demographic analysis [31, 32]. Adult mortality patterns in populations with Barker frailty are equivalent to adult mortality patterns in populations with a class of time-varying frailty and/or age dependent frailty. The formal model requires the specification of four sets of parameters. The first set controls the patterns of mortality decline of a sequence of birth cohorts. The second set includes regulate the threshold age Y –a quantity that is potentially variable depending on the mechanisms producing delayed effects –above which Barker effects are expressed. The third set includes parameters for the distribution of a random trait that represents susceptibility to Barker frailty among members of a birth cohort. The fourth set consists parameters to capture excess mortality risks due to delayed effects. In its current version the model produces five predictions for population with the potential to express delayed effects. We show elsewhere [73, 77] that these predictions *are inconsistent with standard mortality theories.* Further developments of the model will surely uncover additional inconsistencies thus highlighting the need to revamp conventional or standard theories in light of DOHaD hypotheses.

Extensions and development: To accommodate differences between the various mechanisms of delayed effects we will introduce modify parameters that regulate (a) the critical age Y , (b) the magnitude of the excess adult mortality, R, and (c) the age pattern of damage accumulation, e.g. R's age pattern. Information about Y will be retrieved from estimates of the incidence curve of chronic illnesses more strongly associated with adverse early conditions (T2D, CVD, COPD). The cumulative distribution of the age of incidence can then be used to identify key age thresholds beyond which the rate of incidence of the illness begins to accelerate. Estimates of mortality excesses, R, will be obtained from panels of adults that follow those who contract the target illness (HRS, ELSA, SHARE-SPAIN, MHAS, CRELES, PREHCO). Survival models will be estimated o ascertain excess mortality attributable to these illnesses. In addition, we will complement these estimates with those drawn directly from the same survey that enable us to compute effects of adverse conditions on excess adult mortality (e.g. without information on chronic illnesses). Finally, to obtain estimates of age patterns of R we will proceed with standard estimation of alternative age patterns of excess mortality (total and by target chronic illness) following the hazard version of a two-parameter logit model that enables modification of levels as well as of rotations around a standard [20].

5.1.2 Data sources

We require two types of data. First, the model must be calibrated and tested via numerical simulation. Second, the predictions must tested in log historical series of period and cohort life tables representing both the "Western" mortality decline experience and that of LI and MI countries.

Numerical simulations: We use a macrosimulation model for cohort mortality that depends on parameters estimated from empirical data [31, 32]. Estimates of critical ages, Y , will be derived from functions fitted to T2D and CVD incidence in national health surveys. Alternative critical ages will be defined using centiles of the estimated distribution functions. Excess mortality rates or Barker effects, R will be obtained from survey of elderly with information on experience of adverse early conditions and own morbidity and mortality. Finally, parameters and shape of the distribution of Barker frailty will be retrieved from empirical (joint) distribution of birthweight and length of gestation of recent (last twenty years) births. We use numerical simulations to verify the behavior of mortality patterns implied by the more general model and to calibrate parameters so that the outcomes of the model are approximately consistent with observed patterns of human mortality in LI and MI countries.

HMD and LAM$_d$A: HMD (website) is well known and highly utilized mortality data base that includes mostly countries of North America and Europe. LAMBdA is a much younger database and contains nearly 500 life tables for 19 countries of the Latin American and Caribbean (LAC) spanning the period 1850-2015. Unlike HMD, LAMBdA's life tables are adjusted for coverage and age misreporting and, particularly for the period 1930, include multiple estimates with associated measures of uncertainty. *The simultaneous utilization of both databases is crucial for testing hypotheses about DOHaD* This is because relations we would expect to observe in LAMBda life tables should NOT be verified in all life tables for HMD populations as the role of delayed effects in them *must* be highly variable: it may be minuscule in some, attenuated in others and comparable to those in LAC in yet others. This expectation leads to a series of strong "placebo" tests that will enable us to identify models and parameters (See illustrations 1 and 2 below).

5.1.3 Data analysis

Due to space restrictions we can only describe a few examples of data analysis we will pursue to test model predictions. We also identify the key inferential strategies we propose to use.

Illustration 1: Consider the following test of the more general hypothesis that Barker effects should be larger in countries whose mortality decline is more a result of reductions in infectious and parasitic diseases than to improvements in standards of living. We first estimate the relation between cohorts' Gompertz slopes and cohorts' child mortality using selected data from NAWE only. We then use the estimated relation to

predict Gompertz slopes in cohorts of LAC given their known levels of child mortality *if the relation in NAWE applies in LAC*. The model predicts that the expected slopes should be significantly higher than the observed ones. Moreover, we expect that there should be a positive relation between the absolute value of the difference between observed and expected slopes and the fraction of mortality decline due to advances in medical technology to control infectious and parasitic diseases.

Illustration 2: Consider estimates of rates of decline of mortality in adult age groups. The first derivatives of these rates should be positive for cohorts born before the onset of mortality decline and should become negative thereafter. One can then compute the contribution to the change in the sign of the derivative associated with two key causes of death: CVD and T2D. If the prediction from DOHaD is correct one will find that the bulk of the change is attributable to these two chronic conditions. In addition, in countries that experienced mortality declines more strongly dominated by advances of medicine to treat and prevent infectious and parasitic diseases we should find that the role played by these two chronic conditions in the shifting curvature of the mortality trajectory is more important than in countries where the mortality decline was a function of improvements in standards of living. In contrast, we should find no relations in the "Western" experienced in countries in HMD.

Inferential strategies: The program for hypotheses testing outlined above rests on what we consider two a massive assumptions: that there is no uncertainty in the estimates of mortality and that there is no uncertainty in the models posed to retrieve parameters of interest. We deal with each of this in turn.

*1. Uncertainty of estimates***:** while it may not be a serious concern in the case of some countries in HMD, it should be for a subset of HMD countries, and must be for but a handful of countries included in LAMBdA. With recent exceptions [4, 41, 88–91] the bulk of standard demographic analysis in LI and MI countries assumes that a single parameter estimate is sufficient to engage in general inferences. In most cases, however, there are multiple equally defensible estimates of the same population parameter. Thus, different methods to adjust for completeness of death registration and age misreporting used in LAMBdA depend on plausible assumptions but rarely yield identical values for functions of a life table. To account for this uncertainty we formulate reproducible algorithms to compute 'expected' values of model parameters and associated 'dispersion'. This is done via GB that provides an easy-to-apply and accurate measure of uncertainty of model parameters when these are estimated with indicators subject to measurement uncertainty. [26]

2. Uncertainty of models: The strategy above only handles uncertainty in measurement. What about uncertainty of models? For example, what about if the within cohort relation between child mortality and the rate of senescence is non-linear? To handle model uncertainty we propose to combine the bootstrap for uncertain estimates with a "bagging" technique formulated by Efron and others [26]. When only a single estimate of mortality parameters (slope and child mortality) is available, the bagging technique reduces to a bootstrap performed once for each model to obtain the desired parameter. When, as is our case, one has multiple estimates of the key indicators (mortality estimates) we apply the bagging technique once for each model but drawing bootstrapped mortality estimates with the probabilities defined before. This blended strategy turns out to be a bootstrap of the bootstrap and the final result will be model estimates that account for both measurement and model uncertainty. An illustration of the successful application of this technique is in [72]]. An alternative to the above frequentist approach we will pursue is application of BMA [37, 49] jointly with the bootstrap for mortality estimates. One can choose alternative priors for the models and compute an estimate of the desired parameter that will account only for model uncertainty. Repeating the procedure for each bootstrap will result in an estimate and associated standard errors that account for parameter and model uncertainty. The disadvantage of this approach is the requirement to choose priors for the model instead of scrutinizing the best-fitting one as in GB.

5.2 Development of ECHOsim (AIM 2 and component 2)

In this component we implement ECHOsim to build health, disability and mortality trajectories of individuals with heterogeneous early and adult experiences and subject to stochastic events or shocks.

5.2.1 Model

ECHOsim will include three modules: onset, trajectory, and intergenerational. When all three modules are used it will be possible to follow trajectories of individuals and their descendants. When only the first two modules are used ECHOsim will produce trajectories for only one generation (offspring).

Onset module: we will select a limited but well-defined set of early experiences that are conjectured to influence the propensity of individuals to develop conditions that dysregulate their metabolism (particularly sugar metabolism) and derail the stress response by interfering with the HPG axis. The outcomes of interest are three: birthweight, child obesity, and nutritional status early (age 0) and late (ages 1-14) childhood and adolescence. The early experiences we will consider are maternal birth weight, maternal obesity before and during pregnancy, and gestational diabetes. The content of the first module will be a set of parameters

identifying the effect that early conditions have on selected outcomes. Some of these estimates will be the result of our own analysis of original sources whereas others will the result of meta-analyses of human and animal studies that provide sufficient information to identify expected values and standard errors. The final result of the first module is to generate estimates of the following structural equation model.

$$F_k\,(O_k\,(x)) = \Gamma_k\, W_k\,(x - j_k\,) + \Sigma_{j=1,r}\, G_j\,(O_{j-r}\,)\gamma_r + \xi_k \qquad (1)$$

where $O_k\,(x)$ is outcome k evaluated at age x, Γ_k and $W_k\,(x - j)$ are vectors of effects and of lagged covariates (with lags depending on outcome) relevant for outcome k, γr are lagged effects of previous outcomes ($j = 1, ..r$), ξ_k is an error term, and F and G are functions (logistic, log log etc...). Two remarks are necessary. First, in some of the studies that will be sources of estimates of parameters in the expression above reflect effects via epigenetic pathways. We will distinguish these from estimates that reflect gross (total) effects, irrespective of pathway. Second, he set of independent variables for outcomes assessed in infancy, early childhood and adolescence includes events that perturb initial conditions such as episodes of illnesses, breastfeeding discontinuation, dietary constraints, etc...

Trajectory module: this module will be designed to follow individual trajectories across a multistate space. The states will correspond to conditions defining obesity (body mass), T2D and ancillary comorbidities (hypertension, CVD, stroke, kidney and liver disease), disability and mortality. A simplified representation that ignores disability, lumps together conditions other than T2D, and assumes that the remaining dimensions are treated as categorical binary 1/0 variables yields a theoretical space state containing 7 states and a total of 14 relevant transitions. The model can be expressed as a set of structural equations of the following form (to avoid cluttering we omit subscript for individual observations) [75]

$$\mu_{ij}\,(t) = \mu_{0ij}\,(t)\,\exp(\Pi\mathbf{Z(t)} + v_{ij}\,) \qquad (2)$$

where $\mu_{ij}\,(t)$ is the instantaneous transition rate from state i to state j, $\mu 0_{ij}\,(t)$ is a baseline transition rate from i to j, Π and $\mathbf{Z(t)}$ are vectors of coefficients and covariates at time t, respectively and, v_{ij} is an unknown error term. The parameters of a system of structural equations of this type can be estimated from longitudinal multipanel surveys (such as HRS and SHARE) and, with suitable constraints on transition parameters and error terms, via ML methods. Once the parameters are estimated we can compute predicted distribution functions associated with each of the relevant waiting times and all statistics for their moments. Thus, for example, we will estimate the average duration spent as T2D patient or the average duration spend in the healthy obese before contracting T2D. When the multistate model includes disability states, we will be able to compute duration "in disability" (of various) types. These are statistics required for assessing healthy life expectancy and identifying expansion (compression) of morbidity and mortality. Moreover, the same distribution functions will be used to simulate the trajectories of a cohort of arbitrary size and composition beginning at some age Y 50 and with initial conditions for the joint distributions by body mass and health status. If suitably aggregated these trajectories are the inputs for the computation of cohort-specific time trends (e.g. age trajectories) of prevalence rates (obesity, T2D and other conditions) and mortality. Finally, simulation of multiple birth cohorts will result in prevalence and mortality trends over successive cross sections. Because the original model includes estimates of effects of covariates, it will be possible to implement the simulations by subgroups defined, say, by education, wealth, income, gender, etc... Our target model will be general, will include more than one chronic condition other than T2D and at least two states for disability. Thus, the post-estimation simulation will generate statistics associated with comorbidities (related and unrelated to T2D) as well as disability states. The mulstistate model is a *de facto* complex function that translates individual initial health and body mass conditions at some age Y 50 , exogenous characteristics (e.g. education), and recent past health and body mass conditions into a stream of health, disability and mortality outcomes at ages $x > Y$. When these individual streams are aggregated across members of multiple hypothetical cohorts we obtain predicted population trends of prevalence of conditions (e.g. obesity, T2D, disability) and mortality rates older ages.

Intergenerational module: The intergenerational module will include parameters of relations that connect conditions across generations. Thus, for example, it is believed that conditions that lead to birthweight-constrained female offspring induces, among others via epigenetic mechanisms, the risk of low birthweight infants to those female offspring. In this way the DOHaD response is really spread over generations and a sudden change in ecological conditions may not have as large an impact as if the DOHaD responses had no memory. In addition to maternal birthweight, other conditions such as maternal gestational diabetes and maternal obesity could operate similarly and induce changes during gestational and embryonic development that constrain/modify females risk of producing offspring that 'inherit' these characteristics.

Putting it all together in a simple illustration: Because of space restrictions, we will use a highly

stylized illustration. Assume that in the first module we gather information about parameters of the relation between maternal birthweight, maternal gestational diabetes, and maternal obesity, on one hand, and child birth weight and child obesity before attaining age 10[7]. An additional input parameter from the first module is the correlation between obesity in childhood and obesity at adult ages conditional on selected individual traits. Starting with a population of mothers with an arbitrary composition by maternal birthweight, gestational diabetes and maternal obesity (and possibly other individual characteristics) these parameters can be used to compute the expected distribution of offspring by body mass at some arbitrary adult age, say Y. This information is then channeled to the second module to estimate individual trajectories after age Y across the obesity-T2D-disability state space thus generating aggregate trends of incidence and prevalence of selected health and disability conditions. Armed with this information it is then possible to answer questions of the following sort: (i) are the impacts of early conditions (reflected in the effects of maternal birth weight, gestational diabetes and maternal obesity) strong enough to influence the degree of morbidity-disability-mortality compression in the offspring generation at older ages? (ii) what would these impacts be under scenarios with different composition of the maternal population of origin?, (iii) by how much could adult healthy life expectancy during adulthood be increased if health interventions could decouple early childhood and adult obesity? This strategy, however, only accounts for events occurring to the offspring generation. The final step in ECHOsim involves the inclusion of the intergenerational dimension and the third module. To accommodate a mechanism of intergenerational transmission we must introduce (at a minimum) an age-specific pattern of fertility which may or not depend on the obesity status of the females. The application of the fertility functions generates the offspring generation among mothers by initial conditions (of obesity, gestational diabetes and maternal birth- weight). Once the distribution of number of offspring by maternal composition is identified, computations return to the first module to estimate the distribution of offspring by age Y and then to the second module to trace their subsequent trajectories in the obesity-morbidity-disability-mortality state space.

5.2.2 Data sources

ECHOsim's modules draws from data sources described below

Onset module: Two data sources will support this module. First, original and publicly available data collected on human populations with information on life stages of birth cohorts. Examples are the following studies: CEBU, INCAP, MATLAB in LI and MI countries and cohort studies in Sweden, Finland, Holland and Russia. Second, we will collect and organize published studies that focus on a subset of parameters of interest in the first module. These will include studies with human populations (small samples, clinical studies) as well as animal studies with rich information on conditions to which multiple generations are exposed.

Trajectory module: This module will depend closely on two sets of data sources. The first are the multi-wave panel studies of adults belonging to the family of HRS-type panels including HRS(USA),ELSA(UK), SHARE(Spain) , MHAS(Mexico), CRELES(Costa Rica), PREHCO(Puerto Rico)[8].

Only the last two of these are limited by a number of panel less than 4.All others include more than 4 follow-up panels. In all cases these sources provide sufficient information to estimate discrete multistate hazard models of the type described above. The second set of data is the National Health Surveys in USA, UK, Spain, Mexico, Costa Rica and Puerto Rico. These are repeated cross sections starting in 1985 and carried out, on average, every two years. In addition to basic demographic characteristics and individual behaviors (smoking, diet, exercise) these surveys include information on body mass, current chronic illnesses and disability. Because they are cross sections (except for a limited panel in the US) these sources enable us to compute age-gender specific prevalence are not suitable to estimate incidence (unless some assumptions are made). An important addition to the above data sources is the set of Andalusia Health Surveys that will be included to analyze in more depth time trends and factors associated with obesity, T2D, and disability in this region that experiences one of the highest rates of obesity and T2D in Western Europe. **Intergenerational module**: The data sources on which this module relies include the same longitudinal studies identified above, particularly CEBU, INCAP and MATLAB, animal studies with information on multiple generations and ancillary longitudinal studies with information on the correlation between conditions experienced in early childhood and adulthood. For example, the correlation between adolescent and adult obesity can be obtained from British cohorts studies (1947, 1957, 1970) and from the US AddHealth study.

5.2.3 Data analyses

[7] For simplicity we ignore the role of childhood infections, breastfeeding and childhood nutrition.

[8] In addition to Spain we may include if needed for comparative purposes, all or a subset of the other SHARE studies.

The bulk of analyses in the first module consists of standard meta-analysis of published studies and, in addition, conventional statistical empirical estimation via discrete models of extant data sources. The second module is data-analysis intensive. It requires three different analytical strategies.

Multistate hazard model with GB and BMA: Streamlined multistate hazard model can be estimated via standard ML procedures. There are a number of software packages to do so (R-built packages; Continuous Time Models (CTM); dedicated "Stata-DO" files created written by Palloni). However, our goal is to include measurement and model uncertainty. **First**, as proposed in component 1 we will use GB to handle uncertainty in the measurement of the key parameters computed via ECHOsim onset parameters The meta-analysis will produce a range of estimates that can be utilized (in lieu of an *ex ante* chosen estimate) to fully account for estimates' uncertainty. **Second**, BMA will be deployed to estimate parameters when two or more alternative multistate model specifications need to be considered. This will be done via BUGS and/or STATE STAN. Both GB and ABM will dedicated to estimation based *only* on the multi-panel data on adults as tools to select optimal parameters given the observed longitudinal observations.

Approximate Bayesian computation: ECHOsim will be only as useful as is its power of replication of observed data. Thus, a key component of our project is to employ novel tools to establish consistency between ECHOsim and observations. To simplify description we assume we are only interested in replicating trends of T2D. The observables, $Y0$ are retrieved from the National Surveys of Health and could correspond, for example, to T2D age -specific prevalence rates for the total population (or for relevant subgroups). The predicted values Y_p are generated by ECHOsim when a given set of parameters Θ are specified. The predicted values correspond to the distribution of Y given the complete model (all three modules) and the input parameters, $Y_p \sim p(Y|\Theta*)$. Because of the complexity of the model, the exact likelihood function is unknown and traditional MCMC methods cannot be obtained to generate posterior distributions of parameters. A solution to this consists of drawing the parameters from a prior distribution, use these in ECHOsim to generate outcomes, Y_p . In the next stage we construct measures of "distance" to compare observed and predicted values of the age-specific T2D prevalence rates. We then select the parameters produce the best fit and use these to construct the posterior distribution. The complication in our case is that ECHOsim produces multiple outcomes of interest (including prevalence and incidence rates of various health and disability conditions as well as mortality). It is possible that while a set of parameters does well for, for example, predictions of disability, it may be inferior when it comes to predicting T2D. This inconsistency is by itself an important indicator that the model requires fine-tuning (for example by specifying additional transitions or states) [16].

5.3. Forecasts and policy evaluation (AIM 3 and component 3)

The aim of component 3 is to produce demographic projections and forecasts of future trends of obesity and T2D, disability, and excess mortality associated with obesity and T2D. The ultimate purpose is to develop a toolkit that enables users to assess the impact of hypothetical interventions at any point in the trajectories that produce outcomes of interest, e.g. at any point in the life course of individuals. We will use two strategies:

Traditional multistate demographic projection: The simplest tool is a traditional demographic projection based on the results from the multistate model. Once its parameters are estimated we can construct a simplified state space that includes only a few outcomes of interest, for example, body mass and T2D (ignoring disability). We can then use the predicted transition rates to project into the future a population with a known composition by body mass and T2D. This classic demographic projection can be made as complex as one wishes to. For example, we could add multiple disability states or comorbidities associated with T2D. In addition, it is possible to add components to account for uncertainty in the forecasts in the same was as is being done currently by the United Nation with conventional population projections. The value of this tool is rooted in its simplicity and the familiarity researchers may have with its rationale since it is a simple extension of the well-known two state demographic projections into a multistate space.

Unconventional use of ECHOSIM: A more sophisticated type of forecast can be implemented by using ECHOsim to produce individual trajectories into the future from a population with an arbitrary initial composition by conditions. These trajectories can then be aggregated and converted into distributions of population in various states of interest just as the conventional demographic projection does. There are two important differences to note however. **First** the ECHOsim projection is subject to well-defined sources of uncertainty reflected in the standard errors of the estimated parameters that drive the multistate model. Using bootstrapped projections (by drawing from the estimated distribution of each parameter) will naturally lead to stochastic levels of uncertainty of the forecasts. **Second**, ECHOsim can be designed to produce forecasts under a very broad variety of stochastic scenarios, something that it is not possible with demographic projections that can produce outcomes only by altering a handful of dimensions at a time.

An important feature component 3 is that it opens up the possibility of performing complex

computations about health costs. Indeed, the main outcome of ECHOsim, for example, will be a distribution of the population by individual characteristics and by health and disability states. One can then pair this complex outcome with information on the direct and indirect economic costs of occupancy in states (illness with a well defined chronic diseases and under a medical for a known duration or disabled with a particular type of disability after some age). The success of this component will secure a rather unexpected outcome, namely, the ability to determine the health costs of DOHaD implications for human health, disability, aging and mortality.

6 RESEARCH TEAM

The research team will be composed of the PI, one post-doc researcher, one doctoral student, and two applied scientists (a statistician/computer programmer, and an epigeneticist/developmental biologist). This team will be supported by Dr. Diego Ramiro Fariñas, who is the Head of the Department of Population from IEGD-CCHS (CSIC), the host institution of this project. In addition, we will select a cadre of six to eight national and international experts who will work with the research team and will spend four weeks per year each in residence. The expertise of external advisors in residence in each year will be harmonized with the main task for that year. We propose the following external advisors: Ken Wachter (Statistics/Demography), James Vaupel (Demography); Chris Kuzawa (Anthropology/Ev. Biology), Thom McDade (Biological Anthropology), Shripad Tuljapurkar (Mathematical Demography), Federico Rey (Microbiology); John Denu (Epigenetics), Caleb Finch (Biology). We will organize a **yearly workshop** dedicated to (a) review accomplishments of previous years and plan activities for subsequent years, (b) presentation and discussion of relevant work by prominent researchers in the field. Participants will include (a) members of the research team, (b) in-residence visiting scholars, (c) invited scientists (local and international) and (d) members of national and international health institutions.

7 IMPLEMENTATION

The project is designed in components and each one of them is associated with a work package (WP). The packages identify precisely the following: main research tasks in the component; lead and support teams; deliverables, and risks. The WP are described below.

Work Package Nº	1	Months 1-24
Work Package Title	**Component 1: Demographic Formal Model**	
Leads	PI and post-doctoral researcher	
Support	Statistician/computer programmer, epigeneticist/developmental biologist and doctoral student	
Objectives	Development of formal demographic model; parameterization of key dimensions (frailty of onset, critical ages, chronic illness involved; patterns of excess morbidity and mortality); empirical testing using HMD and LAMBdA; projections.	
Deliverables	Working (calibrated/tested) formal model. Empirical tests	
Risks	Moderate; limited power of model to include all relevant factors. To mitigate we will rely on results from ECHOsim and reformulate the demographic model accordingly	

Work Package Nº	2	Months 6-48
Work Package Title	**Component 2: ECHOsim and multistate hazard model**	
Leads	PI and post-doctoral researcher	
Support	Statistician/computer programmer, epigeneticist/developmental biologist and doctoral student	
Objectives	Meta-analyses to retrieve onset and interg. Parameters; estimation of multistate model (trajectory parameters); formulation/testing of ECHOsim; production of stochastic forecasts and multistate demographic projections; comparative analyses of multistate parameters; ABC analyses of stochastic forecasts	
Deliverables	Large data base from meta-analyses; multistate model parameter estimates; working (calibrated/tested) model; empirical testing of DOHaD hypotheses; comparative analysis	
Risks	High: precision of onset parameters may be low relative to trajectory parameters due to uncertainty about epigenetic effects. To mitigate and to the extent permitted by results we retrieve in meta-analysis we pull estimates of epigenetic and other effects	

Work Package Nº	3	Months 36-60
Work Package Title	**Component 3: Forecasts, projections, assessments of interventions**	
Leads	PI and post-doctoral researcher	
Support	Statistician/computer programmer, epigeneticist/developmental biologist and doctoral student	
Objectives	Produce 50-year forecasts of obesity, T2D, disability and mortality	
Deliverables	Easy to use tools to assess effects of health interventions	
Risks	Moderate to high: uncertainty of forecasts may be large due to uncertainty of onset parameters. To mitigate we can reduce parameter space thereby losing precision by possibly reducing mean squared errors.	

8 DISSEMINATION AND SYNERGIES WITH EC FUNDED PROJECT

Dissemination I: The main venue for the assessment of each year findings and planning of subsequent years activities will be the **yearly workshop** to be held in CSIC headquarters. The workshop will be the main locus for the production of summaries of findings, results, and policy implications. These will be disseminated via traditional academic channels, global and local institutional venues, disseminated via traditional academic channels and institutions, including *CSIC* (hosting institution), the *Spanish National Institute of Statistics (INE)* and the *Andalusian Institute of Statistics and Cartography (IECA),* the two other Spanish institutions that sponsor this project (see letters of support), and specialized public media. Traditional academic channels include seminars and professional meetings in Spain, international seminars and professional meetings, technical reports, and professional journals. We will assign priority to professional meetings in the areas of population health studies, formal demography and statistics, epidemiology, developmental biology, epigenetics, and evolutionary biology. This project is of interest to large scale institutions such as the United Nations, UNFPA, UNICEF and the World Health Organization (including the Pan American Health Organization) and we will ensure that summaries of findings, results and policy implications are disseminated via official channels to these organizations. Finally, we will seek to promote our work through dedicated and specialized public media. The most cost-effective way to do this is to plan a yearly public press release coinciding with the workshop, as well as social media and a website.

Dissemination II: Synergies with EC funded project: LONGPOP is a Marie Skłodowska-Curie Innovative Training Network conducted by IEGD to support a network of population experts that utilize longitudinal databases for demographic analysis. Our project will contribute to this network by offering a yearly workshop on the nature of longitudinal data sets needed for testing of DOHaD hypotheses. The workshop will include training on basic genetics and epigenetics, developmental biology and on mathematical models and statistical estimation advanced in our project. This will promote the use of extant or the design of new data sets targeting the testing of DOHaD hypotheses in a large community of population experts.

9 Steering committee

To secure timely input from experts, we propose a Steering Committee including the same six to eight external advisors who will participate in the planning and organization of activities. The Steering Committee will meet once a year immediately before or after the yearly workshop.

Section c. Resources (including project costs)

JUSTIFICATION OF BUDGET AND TIME COMMITMENT

Principal investigator: Over the 5 year duration the PI plans to spend an average of 100 percent of his total working time on the project. The PI will be involved in all three components and will spearhead the planning and execution of the study. He will be in charge of coordinating the research team, establish professional links to other research teams working on the subject both in Europe and the USA, will represent the team in public venues, professional meetings and seminars, and will be the visible head of the project vis a vis ERC and Spanish Scientific Institutions.

Post-Doctoral and predoctoral trainees: we request support for one doctoral candidate and one postdoctoral fellow. Our preference would be to hire a predoctoral candidate in population health sciences with a strong technical demography background. The post doc will ideally have the profile of an epidemiologist/demographer. Both will be the most important support for the PI and will help him in the day-to-day operations of the project and the coordination of the research work among the various team members including the statistician/programmer and the expert in epigenetics (see below).

Cadre of supporting professionals: we request funds to support the integration to the research team of an expert statistician programmer to support operations associated with programming of simulation models

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