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A Lifecourse Approach to Health Development: Implications for the Maternal and Child Health Research Agenda

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Abstract Lifecourse-informed models of health fundamentally challenge simple biomedical models, introducing new ways of thinking about how diseases develop. This paper considers the broad implications of lifecourse theory for the maternal and child health (MCH) research agenda. The Lifecourse Health Development model provides an organizing framework for a synthesis of the existing literature on lifecourse health and identification of gaps in knowledge. Priority areas identified for MCH research in order to close these knowledge gaps include: epigenetic mechanisms and their potential mutability; peri-conception as a critical and sensitive period for environmental exposures; maternal health prior to pregnancy; the role of the placenta as an important regulator of the intra-uterine environment; and ways to strengthen early mother–child interactions. Addressing knowledge gaps will require an emphasis on longitudinal rather than cross-sectional studies, long-term (lifetime) rather than short-term perspectives, datasets that include socio-demographic, biologic and genetic data on the same subjects rather than discipline-specific studies, measurement and study of positive health as well as disease states, and study of multi-rather than single generational cohorts. Adoption of a lifecourse-informed MCH research agenda requires a shift in focus from single cause-single disease epidemiologic inquiry to one that addresses multiple causes and outcomes. Investigators need additional training in effective interdisciplinary collaboration, advanced research methodology and higher-level statistical modeling. Advancing a life course health development research agenda in MCH will be foundational to the nation's long-term health.

Keywords Lifecourse · Health development · Maternal and child health

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Introduction

Foundations of Lifecourse Theory

Lifecourse theory has its origins not in health, but in sociology and developmental psychology. Pioneering studies of the lives of Polish peasants (1918–1920) led to calls for longitudinal approaches to the study of life history [1]. As early as the 1930s, German and British physicians found powerful evidence for the lifelong impact of health during childhood, concluding "data behaved as though the expectation of life was determined by the conditions which existed during the child's early years" [2]. They also discovered that infant mortality rates were directly dependent on the health of the mother, only falling when the vitality of women of childbearing age improved. These important findings went unheeded for decades [1, 3], until the early 1980s when health researchers began to examine and

elucidate the relationship between early life experiences and later health outcomes.

Renewed interest in a lifecourse perspective on health resulted from the groundbreaking work of British epidemiologist Dr. David Barker on the fetal origins of adult diseases. Starting with analysis of midwifery records from the county of Hertfordshire dating back to the 1920s, Barker demonstrated associations between birth weight, early weight gain and the prevalence of adult chronic illness [4–7], relationships that were confirmed in other cohort studies, principally those from Europe, New Zealand and Scandinavia [8, 9]. Meta-analysis confirmed an inverse relationship between birth weight and adult all-cause mortality [10]. Over the past two decades, an explosion of studies has connected prenatal and early life exposures with later health outcomes [11–13].

Lifecourse-informed models of health introduce a new way of thinking about how health and disease develop across the life span, fundamentally challenging existing simple biomedical, and more recent multiple risk factor models. Notions about the early origins of lifelong health have helped to frame the WHO report on Social Inequalities in Health, and several recent landmark policy reports in the U.K. [14–17]. Yet to date, the lack of U.S.-based longitudinal data, and minimal awareness of how a lifecourse approach can inform a more strategic interpretation of epidemiologic data, have limited the use of these insights to inform U.S. programs and policies. In recent years, however, the federal Maternal and Child Health Bureau (MCHB), the National Institutes of Health, and other state and federal agencies and organizations have begun to consider the implications of lifecourse theory for health research, policy and practice. For example, a lifecourse orientation to health development has been incorporated into several recent Institute of Medicine (IOM) reports [18, 19], used to frame Healthy People 2020 in a way that is different from its 2010 predecessor, and has served as the basis of new strategic plan for MCHB.

Lifecourse Health Development (LCHD) Model

Growing interest in lifecourse theory as a guiding framework for health research, policy and practice led to a search for ways to tie together research from divergent fields including chronic disease epidemiology, developmental biology, developmental epigenetics, neurodevelopment, human development, and social demography into a cohesive conceptual model of health [20–27]. One such synthesis is the Life Course Health Development (LCHD) model, proposed by Halfon et al. [28]. The model posits that health is an emergent capacity of human beings that dynamically develops over time, in response to multiple nested, and ever changing genetic, biological, behavioral, social and economic contexts. Risk and protective factors influence the development of biobehavioral regulatory systems during critical and sensitive periods of development. Health at individual and population levels is also influenced by timing and sequence of biological, cultural and historic events and experiences. The LCHD model has informed the theoretical approach to children's health measurement proposed in the IOM's report Children's Health, Nation's Wealth [29], and the National Children's Study. The model suggests multiple potential avenues for optimizing health development, and indicates that the goal of health practice and policy is to go beyond the avoidance of disease to the promotion of positive health at all stages of life.

Lifecourse Health Development and the Maternal and Child Health Research Agenda

National experts have already considered the implications of lifecourse models for MCH policy and practice [27]. In this paper, we consider the implications of the LCHD model for the MCH research agenda. This brief analysis is not intended as an exhaustive review of the vast and growing literature in the field, but rather offers a brief overview intended to stimulate thinking, and point readers in the direction of the kinds of research activity that the LCHD model suggests are needed. This paper also focuses on the implications of the LCHD model for basic and clinical research, only briefly addressing the implications for translation of research findings into practice and policy.

The LCHD model incorporates five key components, each of which helps to explain the link between early life events and experiences and future health and disease. These components are:

(i) The importance of biological embedding
(ii) The role and developmental influences of risk and protective factors
(iii) The health significance of extended developmental time frames
(iv) Multiple determinants of health outcomes
(v) The representation of health development as functional trajectories

For this analysis, we briefly discuss the background literature on each component, emphasizing "sentinel studies" and reviews. We identify knowledge gaps, then make a series of broad suggestions about the kinds of research that are needed to close these gaps for each component, and the steps needed to create an MCH research infrastructure that will allow such studies to flourish. This paper serves also as a first step towards the development of a more detailed MCH research agenda currently under development in the MCHB-funded Lifecourse Research Network (LCRN). The framework we begin to outline here will help guide development

of over twenty detailed studies of research needs on topics across multiple aspects of maternal and child health.

Research Gaps in Key Components of the LCHD Model

(i) *The Importance of Biological Embedding*

The concept of biological embedding is of fundamental importance to the understanding of LCHD theory. Biological embedding refers to the process by which experiences early in life quite literally get "under the skin," altering neural, endocrine, and immunologic systems and even genetic expression, affecting the course of human development [30]. Although biologic, neurologic, epigenetic and physiologic mechanisms are all understood to play a role in biological embedding, little is known about which mechanisms are most important and their degrees of reversibility, or whether certain key factors act as "triggers," setting in motion a "cascade" of future reactions. In this section, we consider several key mechanisms with potential roles in embedding. These mechanisms include:

(a) The role of candidate systems
(b) Epigenetics
(c) Learned behaviors
(d) Genetic imprinting and intergenerational effects
(e) Fetal adaptive responses

(a) Candidate Systems

Scientists investigating mechanisms that could underlie embedding have turned their attention to those systems that appear to have the most potential to act as "transducers" between the social environment and aspects of human biology that could affect health developmental processes. Multiple studies have identified various forms of excessive "stress" as early risks for future health development, leading researchers to focus on candidate systems that would be biologically plausible as "stress transducers," including:

(a) The hypothalamic-pituitary axis (HPA) and its accompanying secretion of cortisol
(b) The autonomic nervous system (ANS), together with epinephrine and norepinephrine
(c) Development of memory and executive function in the prefrontal cortex
(d) Systems of social affiliation involving the amygdala and locus coeruleus with higher order cerebral connections mediated by serotonin and other hormones

The best documented of these is the HPA. Rat pups removed from their mothers for brief periods during a narrow window of days early in life have been shown to develop permanent changes in their HPA over the rest of the lifecourse. These separated rats show higher basal cortisol levels and a blunted response to stress. Further, they show greater memory loss and cognitive deterioration by age 2 years (equivalent to old age in humans) than rats that were not separated as pups [30]. Recent research is also beginning to examine neural correlates of deprivation and the effects of adversity on human brain architecture and function [31]. The quality of early maternal-child attachment is known to affect HPA function and behavioral response to stress, while social class differences in basal cortisol levels have been demonstrated in primary and secondary school-aged children in the U.S. [32, 33].

(b) Epigenetics

Early models of health viewed genetic factors as "fixed" at birth and essentially unchangeable, while environmental factors influenced a person's health in ways that were quite separate from the genome. In fact, we now know that environmental factors can alter gene expression through mechanisms other than changes in the underlying DNA sequence. These functional modifications to the genome, referred to as "epigenetics," may result from DNA methylation, histone protein modification and other mechanisms [34, 35]. In the rat pup experiments noted above handling and maternal grooming affected methylation of a region of DNA that regulates both HPA and higher-order executive brain function. Further experiments demonstrated that changes in early nurturing behaviors were transmitted intergenerationally, so that pups that were handled less often by their mothers were, in turn, less attentive to their own offspring [36, 37].

Although findings from these animal studies cannot be assumed to generalize to humans, they do raise cogent research questions about the importance of critical or sensitive periods during cognitive and neurological development [38]. Sensitive periods have been hypothesized for numerous aspects of child development, but we currently lack knowledge about when and for how long these periods of heightened sensitivity and responsiveness may last, and at what point effects may, if ever, become irreversible. Human studies are beginning to explore whether well-established risks—such as the experience of social adversity during early childhood—operate through similar epigenetic mechanisms. Early results indicate that adult blood methylation profiles have stronger associations with childhood than adult socio-economic position, suggesting that early environmental influences may influence the emergence of well-defined and long-lasting epigenetic patterns [39].

Several studies have indicated a relationship between birth weight and the development of neuropsychiatric disorders [40]. Recently, there has been increasing interest in how DNA methylation in specific genome regions of the human placenta—which seems to serve as a master regulator of the

intrauterine environment—could affect neurobehavioral outcomes [37, 41]. For example, study of 186 placentas from healthy newborn infants showed an association between methylation of the glucocorticoid receptor gene (NR3C1) promoter, infant quality of movement and infant attention [42]. There is still much to be learned about the relationships between maternal diet and supplementation, epigenetically-altered genes, development and disease [43].

These studies are just beginning to uncover the potential for complex epigenetic effects, and they raise important questions about whether epigenetic modifications can be reversed, and whether identifiable epigenetic markers in childhood predate later adult disease, and could be used as biomarkers for preemptive targeted risk reduction strategies.

(c) Learned Behaviors

Young children are keen observers of their parents' behaviors. Some experts believe that even learned behaviors such as eating patterns and physical activity levels must be in some way biologically influenced, and that this partially explains why these behaviors are so resistant to change later in life [44]. For example, childhood exposure to violence is a major risk factor for later intimate partner violence, suggesting that social learning is a major contributor. Recent animal studies have shown that male rats exposed to non-social stressors in their youth showed increased aggression towards females. Offspring of the male rats also showed increased aggression to females even in the absence of any direct exposure to violence, suggesting that biological factors may be playing an important role in the transgenerational transmission of violent behaviors [45]. Research into how behaviors are learned, whether epigenetic or other biological programming mechanisms are involved, and whether they are mutable across generations is another priority.

(d) Genetic Imprinting and Intergenerational Effects

The extent to which environmentally-induced biological changes can be transmitted to future generations is unclear. Epigenetic patterns acquired during development are generally stable in somatic cells through adult life [46]. However, these patterns must be reset in germ cells, and in early embryos, to achieve developmental pluripotency. This process involves two "waves" of demethylation that are completed in the peri-conceptional period. Genes subject to imprinting, where only one parental copy is expressed after fertilization appear to be marked epigenetically in the germ line, and escape the first but not the second wave of demethylation. For example, both Prader Willi Syndrome (PWS) and Angelman Syndrome (AS) result from small deletions in the imprinted region of chromosome 15. PWS requires paternal transmission of the deletion, while AS requires maternal transmission. Intriguingly, these deletions lead to altered methylation and expression patterns of many imprinted genes in the region, even when separated by several megabases, a phenomenon known as epigenotype spreading. There is growing evidence that the severity of other conditions such as autism, epilepsy, schizophrenia and bipolar disorder varies depending on which parent transmits the disease susceptibility, although no specific imprinted genes have yet been implicated in these diseases. The developmental dynamics of epigenetic deprogramming and reprogramming events, their susceptibility to environmental exposures, and their implications for health through the lifecourse are poorly understood [47, 48].

(e) Fetal Adaptive Responses

Long-term risk of disease may be initially induced through fetal, or infant, adaptive responses to cues from the mother about her health or physical state [12]. A nutrition-poor intrauterine environment leads to compromised fetal growth, during which metabolic and hormonal systems are "set" to make best use of scarce nutritional resources (the "thrifty phenotype" hypothesis) [49]. After birth, when the environment becomes nutrition-rich, the "mis-match" between the predicted (nutrition-scarce) and actual (nutrition-rich) environment results in greater risk of metabolic syndrome and overweight and obesity later in life. Infants with "thrifty phenotypes" that subsequently exhibit rapid childhood growth seem to be at particular risk of poor health outcomes [50–52], including obesity, metabolic syndrome and diabetes. We currently lack knowledge of ways to prevent such adverse fetal programming, or how to preempt or manage the effects once they have occurred.

Maternal and Child Health Research Implications

Given the current state of knowledge of the mechanisms underlying biological embedding, the following are identified as priority areas for maternal and child health research:

- Animal and human studies at genetic, metabolic, and cellular levels to identify the most important mechanisms for biological embedding and fetal programming, and their potential mutability
- Peri-conception as an important critical or sensitive period
- Ways to optimize maternal health prior to pregnancy, potentially involving nutritional, social or pharmacological interventions
- The role of the placenta as an important regulator of the intrauterine environment and transmitter of important ecological information from mother to fetus

- Ways to strengthen early mother–child interactions, and the impact of social environments and policies conducive to such interactions
- The sensitivity of epigenetic changes to environmental manipulation or to pharmacotherapy, and timing as a critical element in understanding the relationship between environmental exposures, biological embedding and long-term effects

(ii) *The Role of Risk and Protective Factors*

Most existing studies of disease causation focus on single or small groups of risk factors operating close to the time of diagnosis. Yet multiple risk and protective factors appear to operate throughout the lifecourse, continually shifting health trajectories in positive and negative directions. The LCHD model considers the effects of:

(a) Multiple versus single risks
(b) Latent, cumulative and pathways effects of risk and protective factors
(c) Gene × environment interactions

(a) Multiple versus single Risks

While there is a tendency to simplify and reduce complicated causal pathways to "single cause-single disease" models, in fact development of health and disease is much more complex. The most prevalent chronic diseases of adult life—including hypertension, diabetes, heart disease, obesity and depression—appear to result from the combined effects of multiple risks, many of which are not specific to any one condition [30]. The LCHD model suggests that both health and human development represent the balance of gain and loss, growth and deterioration resulting from the interplay of positive and negative influences [23]. Multiple risk and protective factors continue to operate throughout the lifecourse, either attenuating or exacerbating the influence of earlier risks. These risks—which may be genetic, epigenetic, biological, physical, economic and/or social—seldom appear in isolation, but frequently cluster. For example, poorer families are more likely to reside in unsafe neighborhoods, have poorer diets and less opportunity for physical exercise.

(b) Latent, Cumulative and Pathways Effects

The influence of individual risk factors on health and development is far from linear. Some factors have *latent* effects in which an exposure at one point in the lifecourse influences an outcome years or decades later, regardless of intervening events [30]. Certain factors have *cumulative* effects whereby multiple exposures combine to influence outcomes, while other factors set in train *pathways* such that an experience at one stage of the lifecourse increases the probability of other experiences that then influence outcomes [21]. For example, high-quality education early in life increases the probability of obtaining a more intellectually stimulating job in mid-life, which may then independently reduce the risk of later-life cognitive decline [53]. Certain risks appear to have "dose effects" that are not necessarily linear. For example, over-protective early childhood environments with a relative "absence" of stress may predispose to less adaptive HPA responses, while high levels of early stress also result in less adaptive responses. An "ideal" level of stress exposure may lying somewhere in the trough of a *U-shaped curve*.

(c) Gene × Environment Interactions

Because effects are not simply additive, studies examining genetic risk alone or environmental risk alone are incomplete. Gene-by-environment interactions are increasingly understood to have potentially powerful effects on health trajectories [30]. For example, the Dunedin birth cohort study demonstrated that a genetic polymorphism leading to low monoamine oxidase activity (MAOA), when associated with severe maltreatment in childhood, led to antisocial outcomes in 85 % of males, yet had virtually no contribution to anti-social behavior in the absence of childhood maltreatment [54]. Similarly, a variant in the serotonin receptor gene was associated with high depressive symptoms in individuals living in remote rural areas, but low depressive symptoms in urban areas [55]. It is likely that other risks have similar complex interaction patterns that are only beginning to be investigated.

Maternal and Child Health Research Implications

This emerging, more complex picture of risk and protective factors has implications for the MCH research agenda:

- Studies designed to identify single causes of single disease outcomes are ill-equipped to investigate multiple cause-multiple outcome paradigms.
- Many of the exposures of interest are not unusual, sentinel events, but variants of everyday environmental factors (e.g., social hierarchy, family income, diet, social supports). Larger-scale population-based studies with more sophisticated statistical analysis techniques will be needed to demonstrate effects.
- Studies that include detailed data on genetic, epigenetic, social and environmental risks, and on a range of health outcomes, will best address relationships between patterns of risk and disease states.

(iii) *The developmental significance of extended time frames*

Most MCH research to date has been conducted over relatively short time frames, with imprecise measurement

of timing of exposures to social and other risks in relation to the emergence of disease. In this section we consider:

(a) The prolonged time frames influencing developmental and evolutionary history
(b) The elongated time frames throughout which childhood antecedents influence patterns of adult health and disease
(c) The relationships and interactions between culturally and biologically defined developmental time scales

(a) Prolonged Timeframes of Developmental and Evolutionary History

A lifecourse approach to the study of health development addresses the sequence of events across an entire lifetime, and even beyond. Lifecourse models acknowledge the importance of intergenerational factors for health development. In addition, each individual's biology is understood to be the consequence of both a developmental history that begins at conception, and an evolutionary history stretching back hundreds of thousands of years [43]. Offspring biology appears to be responsive to experiences encoded in maternal biology and her epigenome, with information signaled from mother to child through transfer of nutrients and hormones across the placenta and via breast milk. Evolutionary influences dictate that transient fluctuations in early experience have greater impact in small, short-lived species than in large long-lived species like humans. This arrangement tends to buffer infants from the effects of early life stress, but also implies that humans need long-term interventions to change outcomes [34].

Some of the body's developmental processes occur over very long time frames. The first meiotic division in the egg that, on fertilization, will form a zygote begins when the mother is still a fetus in her own mother's womb. Consequently, environmental exposures during grandmother's pregnancy with mother could, in theory, impact this little-studied phase of development. The first meiotic division is completed just prior to ovulation, which could be up to 50 years after commencement [56].

Developmental plasticity—the ability of the genotype to produce different phenotypes in response to different environments—lies at the heart of evolutionary adaptation [35, 57] The 'adaptive fetal responses' referenced earlier likely represent evolutionary adaptations designed to maximize the chance of fetal survival, at least through to the time of reproduction. Lifecourse influences on health are best understood when viewed through the prolonged time frame of an evolutionary lens [58, 59].

(b) Childhood Antecedents of Adult Diseases

Inherent in the LCHD model is an understanding that early life experiences affect functional outcomes decades later, in mid-life and old age [11, 13]. In the intervening years, there may or may not be outward signs of predisposition to disease. For example, it is uncertain whether children who will develop cardiovascular disease in mid-life can be readily identified either though clinical evaluations of factors such as blood pressure and cardiovascular reactivity, or biomarkers such as cholesterol and C-reactive protein [60]. Recently, there has been increasing interest in the concept of endophenotypes, measureable components that occur along the pathway between the distal genotype and a clinically apparent disease state. Much of the work on endophenotypes has taken place in neuropsychiatry [61]. For example, children and adolescents at risk of future bipolar disorder have been shown to have early facial emotion labeling deficits compared with controls [62]. Identification of endophenotypes holds promise for targeted preventive interventions for children that may be on the pathway to a poor health outcome, but many questions remain about their mutability.

(c) Interactions Among Developmental Time Scales

Throughout the lifecourse, biological, psychological, cognitive and social development occurs on different time scales, with their own developmentally-significant transitions and turning points [23, 34, 44]. The "biological clock" determines the timing of puberty in males and females and of menopause in women, yet appears sensitive to social, cultural and nutritional changes, as evidenced by reductions in the age at menarche by up to 4 years over the past 150 years [63].

Different time scales interact with each other over the lifespan, at times in harmony and at times in discordant ways that may produce stress. For example, the biological age of puberty is falling at the same time that the functional period of adolescence and dependence on family support is lengthening [64]. Almost 1 in 10 births take place to women below the age of 20 years, during what is now regarded as the period of prolonged adolescence. Interactions between these variously-defined time epochs have not been well studied. Timing of working life (the workspan) in relation to the duration of parenting and biological reproductive ability is likely to impact the health of mothers and children in ways that have been insufficiently examined.

Maternal and Child Health Research Implications

- Longitudinal studies commencing prior to conception and extending throughout the lifespan offer the best design for investigation of risk-outcome associations over an extended timeframe.
- Further analysis of historic cohort data from a lifecourse perspective could provide useful information on

evolutionarily-driven developmental trends across generations, and their environmental contributors.
- Studies of the health of mothers and children should include data on past generations, including biological data wherever possible.
- A better definition of culturally-defined developmental time scales including the workspan and parenting years, and study of their relationship to biological time frames, could add significantly to our understanding of the health development of mothers and children in contemporary culture.

(iv) *Multiple determinants of health outcomes*

The LCHD model acknowledges that most health outcomes are the result of multiple determinants from different domains. Once dismissed as "confounders" in biologically-driven studies of disease causation, social risks are now understood to play important roles in the development of health and disease across all populations studied. Here we consider:

(a) The importance of social risks
(b) Interactions among multiple determinants of health

(a) Social Risks

Researchers have demonstrated social gradients for almost all diseases in both the developed and developing worlds [65]. As one moves from the most to the least privileged groups in society, health and developmental outcomes—including those in the physical, cognitive and social-emotional domains—decline gradually without a critical threshold [30]. There is overwhelming evidence that social circumstances early in life influence multiple lifelong health outcomes, including cardiovascular disease, obesity, diabetes, disability and all-cause mortality even after controlling for social position in adult life. Social partitioning is not confined to socio-economic status, usually measured as family income or educational level, but includes other forms of social and classroom hierarchies, neighborhood and family dynamics, and workplace and other dominance hierarchies. Even preschoolers have been demonstrated to display different responses to stress based on position in class hierarchy [30].

From a policy perspective, a profound and provocative question is whether eliminating social disparities would improve population health. Available evidence suggests that policies aimed at "flattening the gradient upward" (i.e., minimizing relative poverty and more evenly distributing the resources that are associated with more optimal health and developmental trajectories) could be a more efficient strategy for improving population health than efforts to improve outcomes among high-risk populations without addressing income inequality [66, 67]. Experts have also suggested that interventions aimed at supporting early child development may be key to reducing health and social inequalities in society, [68] but the optimal content for such interventions remains uncertain.

(b) Interaction of Multiple Determinants of Health

Social risks interact with environmental, psychological, genetic and biological systems to influence health and developmental outcomes in complex, multidimensional ways. Designing and conducting research to disentangle the influences of these multiple dimensions of risk, determine which are most important, and identify ways of intervening to promote protective determinants while reducing risks represents an immense challenge.

Maternal and Child Health Research Implications

- Studies that help us to identify and disrupt the mechanisms by which early life exposure to social risks affect adult function and position in the social hierarchy have the potential to break intergenerational cycles of social disadvantage. In general, these studies will require detailed measures of objective and subjective social risks across generations, together with detailed genetic, epigenetic and physiologic measures from candidate biological pathways over time. Statistical models will need to account for relationships among variables that are non-linear, dynamic and transactional. Results from such studies could lead directly to effective interventions. For example, if young children from socially disadvantaged backgrounds with high basal cortisol levels and reduced cortisol variability are shown to be at increased risk of lifetime anxiety disorders, they could be targeted for early cognitive re-programming of perceived stressors. Interventions that effectively reframe unavoidable social stressors as opportunities for adaptive responses, coupled with education on how to mount such responses, could have lifelong health benefits. Similarly, mothers who themselves experienced abuse or neglect in their early childhoods are known to be at increased risk for repeating less nurturing interactions with their own infants. Identification of effective interventions to improve the quality of early mother-infant interactions would have the potential to disrupt intergenerational cycles of neglect.
- New forms of interdisciplinary investigation (e.g., involving both economists and health researchers) are needed to evaluate the impact of existing or suggested social policies either through collection of population data or computer simulation modeling, similar to work that has been conducted to predict the health and costs of care for the elderly in the "Future Elderly Model"

[69]. For example, proposed policy for the provision of a universal preschool experience could have health and developmental benefits such as cognitive stimulation, and planned early learning experiences, but also carries risk of increased mother–child separation. Long-term follow-up coupled with broad cost-benefit analysis is needed to determine effects on health, educational achievement and occupational outcomes, and to evaluate the true economic and social impact of this policy.

(v) *The representation of health development as functional trajectories*

In the LCHD model, health development trajectories can be constructed for individuals or for populations, examined for important transitions and turning points, and used to depict how patterns of development of health and illness emerge. Here we consider what is known about

(a) Health trajectories
(b) Transitions and turning points
(c) Positive health development

(a) Health Development Trajectories

Changes in functional status over time are best represented as trajectories of development. Trajectories represent the end results of evolutionary and intergenerational influences, early biological embedding, and multiple risk and protective factors operating through latent, cumulative and pathways mechanisms, and multiple determinants of health operating over time. Plotting health change and functional trajectories requires that at least two, but preferably more, valid measures of health status are known at defined times in the lifecourse. The influence or pressure of risk factors tends to lower trajectories, while protective factors help to raise them [23]. Trajectories can be used to illustrate changes in general health over time (e.g., self-reported health status), or in specific dimensions of health such as lung function, hearing ability, BMI, and cognitive function. They represent the rate of change of health per unit time, usually age. Measures of change in function over time may prove a very useful supplement to measurement of disease onset, as clinical diagnoses may occur at the "tail end" of pathological processes set in train many years earlier [53].

Statistical methodologies for investigating health trajectories across time have made great strides in recent years, particularly with the development of flexible latent growth curve and growth mixture models. Nonetheless, a wide variety of methodological challenges complicate applications, and there are few health conditions or measures that have been studied over time in a population from birth to older age. Most condition-specific trajectories cover only a portion of the lifespan, or represent a combination of data from different studies. As trajectories are dependent on data acquired at different time points, they are sensitive to the effects of missing data. Given the longer timeframe for data collection, the attrition of subjects—particularly those who are lower income and/or less healthy—reduces the accuracy and generalizability of findings.

(b) Transitions and Turning Points

Health development trajectories appear particularly sensitive to biological, psychological, and social transitions and turning points. Life transitions, such as starting preschool, puberty, entering high school, or entering the workforce are periods of rapid change which heighten individual vulnerability by imposing stress on adaptive and regulatory systems. By better understanding the impact of different transitions on adaptive and regulatory functions, it will be possible to respond proactively to anticipated transitions, provide additional supports and protective factors, and smooth the way over developmental "rough spots." Recent attention to the importance of transitions for children with special healthcare needs is a specific example of this more general phenomenon.

(c) Positive Health

Most MCH research studies have focused primarily on investigation of problematic health states and disease. The LCHD model proposes a dynamic, emergent model of health in which the goal is not just the prevention of disease but attaining a positive state of well-being. Lack of achievement of positive health early in life, even in the absence of any diagnosed conditions, might impact later health status. Better definitions of positive health and better measures of health potential and health reserves are needed to address this issue. Detailed study of the pathways leading to positive health could identify important protective factors that could be replicated in health-promoting interventions.

Maternal and Child Health Research Implications

- Longitudinal data are needed to construct functional health development trajectories. Growth models require a minimum of three repeated measures, with more time points needed to examine complicated, non-linear change patterns. Because similar measurement scales are required at different ages/time periods, study designs need careful planning. New measures of children's health and development are needed to adequately capture functional trajectories across time.
- A clear definition of positive health and a sophisticated set of new health measures are needed to adequately assess positive health of mothers as well as children. Ideally, this should include self-report, clinical and

biological measures of health potential, positive states of well-being, and health capacity and functioning.
- New longitudinal health surveys should be designed with an eye toward investigating health change across critical life transitions. As lifecourse researchers continue to develop ways to compensate for missing data and case attrition, and to develop new analytic methods to best represent trajectories mathematically, substantive health researchers must be trained in these newer sophisticated longitudinal modeling techniques.

Maternal and Child Health Research Infrastructure

The previous analysis of knowledge gaps and research priorities has a number of implications for the types of research needed to fill those gaps, and the infrastructure in which MCH research is conducted. (see Fig. 1) Creating an infrastructure that can support the requisite new studies will require

(a) A new synthesis of existing knowledge from a lifecourse perspective
(b) Further development of LCHD theory
(c) Development of empiric research
(d) Translational analysis and research to move new knowledge into practice

These steps are illustrated in Fig. 1, and discussed below.

(a) Knowledge Analysis and Synthesis

Multiple strands of evidence relevant to lifecourse models of health development exist in discipline-specific silos including genetics, child development, social sciences, psychology, health and economics. Interdisciplinary teams of investigators need to work together to analyze evidence from each of these fields from a life course health development perspective, and synthesize the findings to guide future hypothesis formation and model building. The integration of increasingly vast amounts of knowledge represents an immense challenge for MCH research, with the solutions likely involving large warehouse-style computing and sophisticated algorithms [70].

(b) LCHD Theory Development

Summative findings from the knowledge synthesis process can be used to further refine and develop the LCHD model. Ongoing research findings will either confirm or repute aspects of the model, and clarify its underlying mechanisms. In the present system, it is unclear who would perform this ongoing "thought work," or how it would be funded.

(c) Empiric Research

Existing approaches to empiric MCH research contrast sharply with a lifecourse-informed approach (see Table 1). A change in perspective will require a shift in emphasis from cross-sectional to longitudinal study designs, and from studies that address biological, genetic or social contributors to health to studies that address all of these aspects. These studies must be conducted over extended time frames, or use a "domino" approach where successive age cohorts of children are followed for shorter time periods, and the results combined to infer longer-term influences. Similarly, either follow-back or follow-up supplements to existing studies, or the addition of biological measures to self-reported survey measures (or vice versa), all provide relatively inexpensive routes to knowledge acquisition. Synthetic data sets constructed from multiple data sources in order to run simulations across the lifecourse could be used to identify time periods where interventions would have the greatest impact.

(d) Translational Analysis and Research

Although a full analysis of the implications of lifecourse theory for the translational research agenda is beyond the scope of this paper, some general principles can be drawn and more specific research priorities identified. As evidence accrues for the mechanisms underlying biological embedding and health trajectory development, investigators must test their potential mutability and determine implications for clinical practice (see Fig. 1). Promising interventions that demonstrate evidence of more adaptive biological pathway development must undergo further translational research in order to move this new knowledge into practice. The translational research agenda must include: type 1 (T1) studies that test new basic science discoveries for clinical effect and for applicability (e.g. preclinical and clinical studies and Phase 1 trials); T2 studies that test new interventions in human subjects under controlled environments to form the basis for clinical applications and evidence-based guidelines (e.g. Phase 2 and 3 trials); T3 research on the application of new interventions in clinical practice, including health services and clinical outcomes research; and T4 research on the factors or interventions that influence the health of entire populations, including the impact of policies on health and health care utilization, and ways to scale and spread successful interventions. (http://ctsicn.org/) While specific details of the content of these studies will need to be driven by the discovery of the mechanisms underlying health trajectory development, it is clear that all 4 types of study will be needed to determine how best to apply new knowledge to improve the population's health.

Achieving all of these steps within the existing national health research infrastructure will be challenging. NIH separates funding primarily by disease states. Each of its 27 institutes and centers has a specific research agenda, often focused on a single disease or body system. The Eunice K.

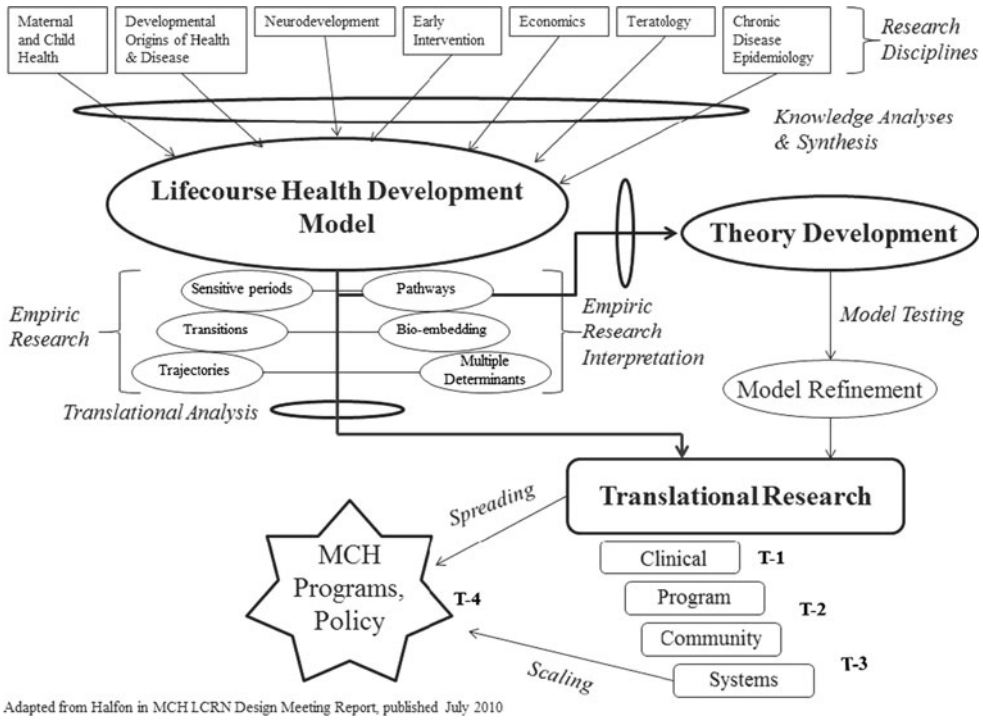

Fig. 1 Implications of a Lifecourse Health Development Approach for the Maternal and Child Health Research Infrastructure. Knowledge synthesis of findings from multiple research streams including maternal and child health, developmental origins of health and disease and chronic disease epidemiology led to the development of the LCHD model. Empiric research to elucidate components of the model will drive further theory development, model testing and model refinement. Application of the LCHD model to practice will require translational research to determine optimal clinical and programmatic responses to this new knowledge, and the best ways to scale and spread successful interventions. MCH research infrastructure must adapt to support each of these types of scientific enquiry

Shriver National Institute of Child Health and Human Development (NICHD) incorporates a research agenda focused on maternal health. Its Center for Research for Mothers and Children serves as the principal source of NIH support for research and research training in MCH (see http://www.nichd.nih.gov/about/org/crmc/). Although a wide range of studies are supported, funding allocation for each is generally limited to a 5-year time frame, precluding ambitious longitudinal studies. In addition, most studies have a traditional single-principal-investigator structure with co-investigators from the same or related fields, and are focused on either biological or genetic or socio-demographic measures but seldom on all dimensions of health. The Clinical Translational Science Award Program, led by the NIH's National Center for Advancing Translational Science (NCATS), supports a national consortium of medical research institutions working to improve the conduct of clinical and translational research. Funding opportunities made available through this program could address LCHD-informed research priorities (http://www.ncats.nih.gov/research/cts/ctsa/ctsa.html).

The Agency for Healthcare Research and Quality (AHRQ) also funds studies of aspects of healthcare delivery relevant to lifecourse, but the budget and hence scale of these efforts is very limited. The MCHB has made a major commitment to lifecourse framing, adopting lifecourse models as a basis for its current strategic plan, and has funded development of resources such as the MCH Lifecourse Toolbox (http://www.citymatch.org/lifecoursetoolbox/). However, its budget to fund MCH research is also very limited.

Results of federally-funded studies are always made available to the public, but are generally published in discipline-specific peer-reviewed journals, rather than "plain language" form. Few clinicians are aware of study findings that offer immediate clinical application, especially outside their own specialty. Policymakers rarely consult the primary literature to guide decision-making on funding allocations and priorities. Although multiple studies demonstrate the impacts of social and economic policies on the population, most are focused on economic, educational and occupational outcomes, with less research available on specific health impacts or, perhaps more importantly, on future health trajectories. For example, studies of the impact of length of maternity leave for women address economic costs and benefits and even short-term health impacts such as breastfeeding rates, but seldom address longer-term potential health impacts such as adolescent mental health. In addition, most programmatic and policy interventions address only one or a narrow range of factors (e.g. family income, or access to health services), whereas

Table 1 Comparison of existing and lifecourse-informed approaches to maternal and child health research

	Existing MCH research	Lifecourse-informed MCH research
Study design	Cross-sectional	Longitudinal
Time frame	Single point in time/ short-term	Long-term
Investigators	Single/related disciplines	Multiple disciplines
Focus	Single exposure- single outcome	Multiple exposures- multiple outcomes
Scope	Socio-demographic or biological or genetic data.	Socio-demographic, biologic and genetic data all collected on same subjects
Subjects	One generation	Multi-generational
Risk factors	Descriptions of associations with health outcomes	Determine mechanisms accounting for association of risk factor with health outcome
Timing	Temporal association between risk factor and outcome	Risk factor may be separated from health outcome by years or even decades. Identification of latent risks, cumulative risks and risk pathways
Critical and sensitive periods	Conception-3 years.	May include preconception, peri-conception. Within the 0–3 sensitive period, may be critical windows for biological embedding of short duration
Investigator training	Basic research methodology and data analysis	Advanced research methodology and higher-level statistical modeling
Outcomes	Disease states, morbidity and mortality	Positive health
Study type	Observational, short-term intervention	Observational, long-term interventional, computer simulations
Health impacts of changes in maternal and child health policy	Descriptive, conjectural	Priority for study
Importance of MCH Research	Specialty area, low national priority	Foundation of nation's health, research priority

LCHD models suggest that multifaceted interventions addressing social and medical risks over prolonged periods may have the greatest chance of success.

In light of this analysis, we make the following broad summary recommendations for consideration.

Summary Recommendations for the Maternal and Child Health Research Agenda

(1) The U.S. should consider investing in large-scale longitudinal, interdisciplinary, nationally-representative population studies starting before conception and continuing through the lifespan. The National Children's Study would need to be funded through the cohort's entire lifecourse to achieve the greatest return on investment.

(2) Training in MCH research must be interdisciplinary, equip researchers to design and conduct studies on multiple determinants of health, and analyze data incorporating appropriate statistical analysis methods.

(3) National cross-sectional studies including the National Survey of Children's Health (NSCH) and the National Survey of Children with Special Healthcare Needs (NS-CSHCN) could identify a random subset of children to be interviewed at successive time waves, adding a longitudinal component. Addition of biological and physiologic measures from the same subset over time could further expand the study. New and ongoing longitudinal data sets such as the Early Childhood Longitudinal Survey (ECLS), the National Longitudinal Survey of Youth (NLSY), and the Panel Study of Income Dynamics (PSID) could all be amended to include better health development measures.

(4) The National Health and Nutritional Examination Surveys (NHANES) could be enhanced by the addition of longitudinal components, or by a focus

on populations at critical and sensitive time periods. Follow-back surveys asking detailed questions about early childhood health and exposures, although reliant on retrospective data, could add a lifecourse perspective to NHANES, while examination of parents and grandparents of a subset of study subjects could add an intergenerational component.

(5) As in Scandinavia, greater use could be made of the large amounts of data routinely collected during clinical care of mothers and children. As hospitals and office-based providers adopt electronic health records, the potential exists to aggregate these data in ways that facilitate research without breaching patient confidentiality. Patients could "opt-in" to have their data used, or large Health Maintenance Organizations could analyze de-identified data on their patient populations.

(6) In addition to the general research gaps noted in this paper, disease-specific research gaps and priorities should also be identified. MCHB has funded the Lifecourse Research Network (LCRN), a virtual collaborative network of over 500 members, to identify knowledge gaps and research priorities in key theme areas including health disparities, mental health, self-regulation, hearing ability, and autism. Researchers from different disciplines, institutions and even countries are working together to continually synthesize findings as new research emerges. The network will build on the work begun in this paper to develop a detailed MCH Lifecourse Research Agenda (see http://www.lcrn.net).

(7) Infrastructure and funding must be developed for studying the short and long-term health impacts of existing and proposed MCH policies. Findings should be summarized and communicated to policymakers.

(8) A national infrastructure and funding must be established for the study of positive health development. This will require a commitment to the definition and measurement of positive health over the lifecourse, and to identification of protective and health-promoting factors.

(9) Pre-conception health should be prioritized for study of determinants of future maternal and child health, and for development and testing of interventions designed to change health trajectories both of mother and child.

(10) Computer simulation models should be trialed for prediction of health trajectories at individual and population level. Individualized genomic medicine is unlikely to achieve its full potential in the absence of accompanying use of social, environmental and biological data to guide individual health promotion from a lifecourse perspective.

Summary

The LCHD model provides an integrative framework for understanding how multiple determinants act over the lifespan to produce defined health trajectories. This brief analysis has suggested some broad implications of lifecourse theory for the MCH research agenda including a focus on longitudinal rather than cross-sectional study design, an interdisciplinary approach to hypothesis formation, model-building and testing, and incorporation of social, environmental, genetic and biological variables into the same studies. Moving forward with this agenda will require a commitment to knowledge synthesis of the existing evidence-base for the LCHD model applied to specific health topics- work that is currently being undertaken by the Lifecourse Research Network (LCRN), further theory development based on the results of these analyses and growth of an empiric research agenda. This agenda will include a focus on:

- The biological and epigenetic mechanisms underlying embedding
- Pre-conception as a time for maternal health optimization prior to pregnancy
- Peri-conception as a critical and sensitive period in development
- Application of higher-level statistical analyses to facilitate study of lifecourse health trajectories

New knowledge must be translated into meaningful forms that both the lay public and policymakers can use to inform changes to policy and practice. Findings from lifecourse studies will have major implications for the design and operation of the health care system, as well as for future research priorities and national policy-setting. The gap between knowledge and practice is vast. For example, despite strong evidence that events in fetal life and health markers such as birth weight have implications for mid-life health risks, there are no routine efforts to document birth weight for patients beyond the childhood years. Ensuring that adult healthcare providers have reliable access to accurate birth weight data will involve significant system change. Standardizing documentation of birth weight and other relevant prenatal and perinatal information into an integrated data system that follows patients as they transition from pediatric to adult care would be a first step. Achieving even this one aim presents formidable challenges for our existing fragmented care system where there is little continuity from year to year, let alone across successive life stages.

Adoption of the LCHD model to guide the MCH research agenda represents a major paradigm shift. Rigorous scientific testing of lifecourse models will be needed to convince skeptics. A lifecourse vision, suitably refined as

evidence accrues, could drive the transformation of the US healthcare system. Increased investments in MCH research, led by integrated funding initiatives through federal agencies including NIH, AHRQ, MCHB and others, coupled with private sector investments, hold promise as a prudent use of national resources. MCH research should no longer be regarded as a specialist area, but as foundational to improving the nation's health.

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