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Introduction

Pathways to Health and Well-being

Adverse early-life conditions have lasting effects on old-age health and mortality (Almond, 2006; Barker 1992, 1994; Mazumder et al., 2010; Roseboom et al., 2006). Some have even considered reductions in early life disease exposure to be a primary driver of historical mortality declines (Finch and Crimmins, 2004). Consequently, understanding the mechanisms through which early and later life are linked is important for the development of strategies for population health and successful ageing.

Prior research shows that exposure to disease (Bengtsson and Lindström 2000, 2003; Crimmins and Finch 2006), nutritional deprivation (Barker, 1994), or adverse socioeconomic conditions (Hayward and Gorman, 2004; Smith, 1997) early in life, possibly as early as in the fetal stage but also in early childhood, are linked to worsened adult health. Evidence from natural or quasi-natural experiments suggests that the association between these and other adverse early-life conditions and later health may be causal. Although numerous pathways have been postulated, including those relating to fetal under-nutrition, dysregulation of the immune function, and compromised socioeconomic attainment (Barker 1994; Costa, 2000; Gluckman et al., 2008; Schulz, 2010), the mechanisms remain largely unclear.

The aim of this Special Issue is to analyse the pathways through which early-life experiences are related to later-life health, and whether the associations are mediated, moderated, or buffered by intermediate characteristics such as own socioeconomic attainment at young adult ages. We have included 13 papers that cover key early-life exposures and take advantage of two complementary conceptual frameworks for understanding the mechanisms.

1. Important early-life exposures

Earlier research has identified three chief factors that may be particularly important for health in later life: nutritional deprivation, exposure to disease, and socioeconomic adversity. First, inadequate nutrition *in utero* may result in physiological and metabolic restrictions that increase the risk of cardiovascular disease mortality in later life (Barker, 2006; Cameron and Demerath, 2002). Prenatal nutritional deprivation has also been connected to higher prevalence of death due to infectious diseases in adolescence in a series of contemporary African studies (McDade et al., 2001; Moore et al., 1999, 1997), while Fogel (2004), Costa and Lahey (2005), and Floud et al. (2011) attribute much of the secular decline in old-age mortality to improved early-life nutrition. The basic idea is that malnourished children do not develop cells and organs, such as the artery system, as they should and are therefore more likely to develop diabetes, cancer, cardiovascular disease, metabolic disorders, and so on later in life.

Second, exposure to infectious disease early in life may cause damage that influences adult health and mortality. One possible mechanism is inflammation caused by infections, such as whooping cough, which damages the artery system and can lead to chronic disease in later life (Bengtsson and Lindström, 2003; Quaranta, 2013). Two English studies demonstrated that exposure to airborne infectious diseases at a young age is associated with cough, phlegm, and impaired ventilatory function later in life (Barker et al., 1991; Shaheen et al., 1994). In 18th–19th century Sweden, an analysis based on longitudinal individual level data showed that individuals born during smallpox and whooping cough epidemics had an increased risk of death after age 50 (Bengtsson and Lindström, 2003). Almond and Mazumder (2005) found that *in utero* exposure to the 1918 pandemic was associated with decreased self-reported health of adults over age 50. Exposure to the 1918 Pandemic in late stages of fetal development also appears to influence educational and job-market outcomes as well as cardiovascular disease prevalence and mortality (Almond, 2006; Mazumder et al., 2010; Myrskylä et al., 2013). These studies are consistent with the hypothesis that reductions in exposure to infectious diseases made a major contribution to the historical decline in old-age mortality (Crimmins and Finch, 2006; Finch and Crimmins, 2004).

Third, early-life family characteristics and socioeconomic conditions (SES) are important predictors of later health. Many studies have documented strong associations between childhood SES, measured by parental occupation, education, housing characteristics or family income, and various adult health outcomes and mortality (Hayward and Gorman, 2004; Preston et al., 1998; Strand and Kunst, 2007). Analyses exploiting exogenous macro variation in socioeconomic conditions, typically fluctuations in per capita gross domestic product, have obtained results that are consistent with those that consider socioeconomic conditions at an individual level. For example, van den Berg and colleagues show that being born in a recession, compared to being born in a period of economic growth, increases all-cause, and in particular cardiovascular disease, mortality (van den Berg et al., 2006; van den Berg et al., 2009).

Many of the aforementioned studies pay particular attention to identifying a causal association between early-life conditions and later-life health. According to Ben-Shlomo and Kuh (2002), however, the aim of life course epidemiology goes beyond correlating intrauterine and childhood circumstances to later health and should build models that test for causal mechanisms and pathways linking later-life health with exposures across the whole life course.

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2. Pathways and mechanisms

The fundamental questions regarding the link between early and later life health are whether the mechanism is direct or indirect, and if indirect, whether the pathway runs through modifiable factors which could be influenced by policy. The conceptual frameworks by Preston et al. (1998) and Ben-Shlomo and Kuh (2002) are useful for understanding these processes.

Preston et al. (1998) discuss the difference between individual and population level associations, and set up a framework that allows for distinguishing between direct physiological and indirect associational pathways by presenting a typology of four mechanisms that may relate early-life conditions to adult and old-age health. These mechanisms are (1) scarring, which is positive and direct or physiological, (2) acquired immunity, which is inverse and direct or physiological, (3) correlated environments, which is positive and indirect or associational, and (4) selection, which is inverse and indirect or compositional.

An example of the direct and physiological scarring is the effect of low birth weight and growth retardation in childhood on cardiovascular diseases and diabetes later in life (Barker, 1992). A direct, but inverse, physiological effect may arise through acquired immunity. For example, exposure to infectious diseases early in life may give protection against similar diseases in older age (Willführ and Myrskylä, 2014). Among the indirect mechanisms, the "correlated environments" refers to a process in which those who are born into (dis)advantaged socioeconomic circumstances retain some of those (dis)advantages throughout life (Mare, 1990). Another indirect mechanism linking early-life conditions to later-life health is selection, in which only the more robust individuals survive to older ages. Such a population level process may result in an inverse association between adverse early-life conditions and later mortality, or attenuate the otherwise positive association (Gagnon and Bohnert, 2012). Studies that have followed cohorts from birth have found that selection might be dominant in childhood, while the opposite holds true later in life, resulting in mortality crossover between the exposed and unexposed cohorts (Quaranta, 2013; Myrskylä, 2010).

A second framework which distinguishes between critical and non-critical exposure periods as well as between different kinds of risk accumulation processes was developed by Ben-Shlomo and Kuh (2002). By critical periods, they mean that exposure must take place during a specific age window in order to have a lasting effect. An example of the critical period model is the fetal origins of adult disease hypothesis (Barker, 1992). Examples of a postnatal critical period model are the studies focusing on inflammation in the first years of life (Bengtsson and Lindström, 2003; Finch and Crimmins, 2004).

The Preston et al. (1998) and Ben-Shlomo and Kuh (2002) frameworks are overlapping and complementary. In the Ben-Shlomo and Kuh framework, an exposure during a critical period that has a direct effect corresponds to scarring in the Preston et al. model. The Ben-Shlomo and Kuh framework extends beyond the Preston et al. framework through the consideration of later-life modifiers and different kinds of accumulation of risks. These are critical for understanding the pathways linking early and later-life health. For example, a scarring effect that is direct and physiological could potentially be modified by the later-life environment. An example is the impact of adverse early-life conditions on cardiovascular disease mortality in adulthood that may be mitigated or even eliminated by medical treatment. Within the accumulation of risks framework, which corresponds closely to the Preston et al. correlated environments pathway, Ben-Shlomo and Kuh consider both correlated and independent risks. An important special case of correlated risks is the "chains of risk" model with a "trigger effect". This model postulates that the initial exposure leads to a sequence of linked exposures in which only the final link in the chain has a marked effect on disease risk. An example of such a process is the effect of adverse early-life socioeconomic conditions, which may be related to adult mortality mostly through a chain that connects the early-life circumstances to the trigger factor adult socioeconomic status.

3. The Berkeley seminar

To explore the pathways through which early-life conditions influence later health, we organized an international meeting entitled "Pathways to Health: How intermediary life events and conditions mediate or modify the early-life effects" in May 1–2, 2012, at the University of California, Berkeley. The meeting, jointly organized by the International Union for the Scientific Study of Population (IUSSP), the Berkeley Population Center, and the Institute for the Study of Societal Issues at Berkeley, brought together a multi-disciplinary group of investigators with interests in demography, epidemiology, and public health. This Special Issue includes nine of the 13 seminar papers. In addition, we have included four other papers that were submitted to this Special Issue of which two were presented at the "Pathways to Health" sessions that we organized at the 27th IUSSP International Population Conference in Busan, Korea, in 2013. This introduction summarizes the key themes of the 13 papers and highlights their common elements.

Most papers that are included in this Special Issue use high-quality individual-level micro data that incorporate either a longitudinal follow-up from early life to old age, or use macro-level characteristics of the early-life conditions as instruments for the early-life conditions. Several papers use analytical designs which allow conditional causal inference regarding the effect of the early-life exposure. For example, the paper by Fritze et al. (2014) uses the prevailing phase of the business cycle as an instrument for early-life socioeconomic conditions; Quaranta (2014) analyses how exogenous measures of early-life disease exposure are associated with later mortality; Ekamper et al. (2014) focus on the long-term impact of prenatal famine exposure; and Lee (2014) analyses the impact of maternal psychological stress arising from civil unrest. Each of these papers first establishes the effects and then proceeds to analyse the pathway through which the effect runs. Other papers included in this Special Issue use extensive controls for early-life characteristics to reduce the risk of unobserved confounding.

The papers provide evidence for both direct and indirect mechanisms. For example, Elo et al. (2014) analyse Finnish cohorts born in 1936–1950 and find significant associations between early-life social and family conditions and all-cause mortality and cause-specific mortality. These associations were mostly mediated through adult educational attainment and occupation, suggesting that the indirect effects of childhood conditions were more important than their direct effects. Shen and Zeng (2014) analyse data from the 2008–2009 and 2011–2012 waves of the Chinese Longitudinal Healthy Longevity Survey and apply structural equation modelling to test whether childhood conditions affect late-life survival and health directly or indirectly through their influence on socioeconomic conditions in adulthood. They find that advantageous childhood conditions may improve socioeconomic status in adulthood, and thus indirectly promote longevity at advanced ages. Myrskylä et al. (2014) analyse the mechanism through which advanced maternal and paternal ages at birth are associated with later-life mortality. They find evidence for a process that is more indirect rather than direct and biological: children that are born to old parents tend to lose their parents at a relatively young age, and parental loss explains most of the association between parental age and mortality. These results indicate that the mechanism