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Article

Why is parental lifespan linked to children's chances of reaching a high age? A transgenerational hypothesis

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ABSTRACT

Purpose: Transgenerational determinants of longevity are poorly understood. We used data from four linked generations (G0, G1, G2 and G3) of the Uppsala Birth Cohort Multigeneration Study to address this issue.

Methods: Mortality in G1 (N = 9565) was followed from 1961–2015 and analysed in relation to tertiles of their parents' (G0) age-at-death using Cox regression. Parental social class and marital status were adjusted for in the analyses, as was G1's birth order and adult social class. For an almost entirely deceased segment of G1 (n = 1149), born 1915–1917, we compared exact age-at-death with G0 parents' age-at-death. Finally, we explored 'resilience' as a potentially important mechanism for intergenerational transmission of longevity, using conscript information from psychological interviews of G2 and G3 men.

Results: G0 men's and women's ages-at-death were independently associated with G1 midlife and old age mortality. This association was robust and minimally reduced when G0 and G1 social class were adjusted for. We observed an increased lifespan in all social groups. Median difference in age-at-death for sons compared to fathers was + 3.9 years, and + 6.9 years for daughters compared to mothers.

Parents' and maternal grandmother's longevity were associated with resilience in subsequent generations. Resilience scores of G2 men were also associated with those of their G3 sons and with their own mortality in midlife.

Conclusions: The chance of reaching a high age is transmitted from parents to children in a modest, but robust way. Longevity inheritance is paralleled by the inheritance of individual resilience. Individual resilience, we propose, develops in the first part of life as a response to adversity and early experience in general. This gives rise to a transgenerational pathway, distinct from social class trajectories. A theory of longevity inheritance should bring together previous thinking around general susceptibility, frailty and resilience with new insights from epigenetics and social epidemiology.

1. Introduction

Mortality, life expectancy and age-at-death are all strongly socially structured. Despite economic growth, welfare state provisions, modern medicine and a fundamental change in disease panorama, we find a negative social gradient in mortality generation after generation. We know from sociological studies that "the long shadow of the past" influences occupational and educational careers in successive generations, creating continuity in social (dis)advantage across generations. Because education, occupation and income all predict health and survival we should also expect such characteristics in the parental generation to predict the next generation's health prospects, resulting in "inheritance of longevity". It is possible, however, that this influence from previous generations is considerably broader than that working through the children's own education, occupation and income. Variation in mortality risk within social groups is great. To understand "inheritance of longevity" we need a conceptual framework that also identifies those within-class influences.

Already in 1934 Kermack, McKendrick, and McKinlay (2001, reprinted) suggested that the first 15 years of life could determine your mortality risk during the entire lifecourse. Similarly, the so-called DOHaD (Developmental Origins of Health and Disease) theory suggests that early life experiences is an important determinant of adult health and disease (Gluckman, Hanson, Cooper, & Thornburg, 2008). DOHaD theory has focused on specific aetiologies and influences, such as that of foetal growth restriction on blood pressure and circulatory disease.

Another, earlier school of thinking, represented by epidemiologists Cassel (1974) and Syme and Berkman (1976) argued for more general disease-causing mechanisms. Demographers Vaupel, Manton, and Stallard (1979) noted the considerable individual

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heterogeneity in mortality risk. Concepts like *frailty* (Sternberg, Schwartz, Karunananthan, Bergman, & Clarfield, 2011; Vaupel et al., 1979), *general susceptibility* (Cassel, 1976; Syme and Berkman, 1976) or *differential vulnerability* (Nordahl et al., 2014) refer to individual differences in the ability to survive hardship. Cassel's (1976) concept of *host resistance* forebodes the recent psychological discourse on *resilience,* defined as the capacity of a human being to "bounce back" in the face of adversity (Rutter, 2006; Windle, 2011). *Weathering* (Simons et al., 2016) and *scarring* (Heckman and Borjas, 1980; Stewart, 2001), are other related, but not identical, terms widely used in the economic literature to describe long-term change of individual characteristics in response to adversity.

Demographic concepts like frailty, epidemiological ones like general susceptibility and psychological ones like resilience all refer to the same real-life-phenomenon: a general rather than specific vulnerability to disease. Cassel (1976) and Syme and Berkman (1976) stressed its social roots, while Vaupel et al. (1979) perhaps assumed it to have a more genetic basis. Resilience, in turn, may be related to both views (Rutter, 2006). It could be thought of as the opposite extreme to susceptibility/frailty on the same underlying dimension. In this study, we argue that resilience is acquired early and maintained throughout life. Resilience should therefore influence the ability to survive up to a high age and be linked to longevity, as a number of studies indeed suggest (Charney, 2004; Shen and Zeng, 2010; Zeng and Shen, 2010).

"Inheritance of longevity" has been discussed at length in the literature. Its precise nature is somewhat elusive (Christensen, Johnson, & Vaupel, 2006; Pal and Tyler, 2016; Piraino, Muller, Cilliers, & Fourie, 2014; Vaupel et al., 1998). Gudmundsson et al. (2000), studying the entire Icelandic population, concluded that longevity was inherited within families, in their view probably because of shared genes. Hjelmborg et al. (2006), looking at twin data, concluded that genetic influences on the lifespan were minimal before age 60 and only increase after that age. Kowald and Kirkwood (2016), on the other hand, rejected any idea that mortality in old age is genetically programmed. Consistent with that view, a Swedish study of men born in 1913, found that a number of social and behavioural factors measured at age 50, but not their parents' survival, predicted longevity (Wilhelmsen et al., 2011).

Evolutionary theorists have debated whether there is any evolutionary pressure to promote survival into old age (Williams, 1957). Nevertheless, we observe a steady lifespan extension in modern societies, especially among women, partly based on falling mortality rates across their long post-reproductive period. That children tend to live longer than their parents is likely to be determined both by what experience parents brings to the next generation, and by the improved life circumstances of the children themselves in their childhood and adult life. The importance of genetic factors for longevity, we suggest, may lie in their interaction with other factors, perhaps especially if this interaction takes place at an early age.

2. Theory

We make these theoretical proposals: The ability to survive into old age may be transmitted across generations. This *inheritance* cannot be reduced to the influence of parents' social class or marital status at the time of the birth of the child or to the birth order of the new individual or to shared genes. In all social classes and family types there is considerable individual heterogeneity in the ability to reach a high age. We propose that this heterogeneity to some extent mirrors a person's very early experience, such as her history of coping with challenging and adverse experience early in life. This would constitute a fundamental learning process, engaging the whole individual, mentally and physiologically, including the hypothalamus-pituitary-adrenal (HPA) axis, regulating neuroendocrine stress responses. How the individual handles early experiences, and whether or not she can rely on support from family and friends in this, may be crucial for the differential adaption to adversity. Small initial differences in trajectories between children in similar family circumstances, even between siblings, may be reinforced and greatly magnified during development, along a resilience/susceptibility dimension.

We may think of this process, determining resilience/susceptibility as a (potentially) adaptive "switch", turned on early in life. The switch may involve epigenetic changes across large parts of the genome. If resilience is transmitted across generations, it would contribute to inheritance of longevity, beyond its link to social class. Three intergenerational pathways of resilience transmittance should be considered. Firstly, parental care and understanding how to cope with success and adversity (Meaney, 2001). Secondly, specific "longevity genes", which promote resilience and a long life could be inherited in families (Gudmundsson et al., 2000). More intriguingly, thirdly, is the possibility that resilience may be fixed in the germline epigenome early in life as has been suggested by several researchers (Franklin et al., 2010; Marsland, 2017; Rando, 2016; Sharma, 2017; Vaiserman, 2012).

2.1. Aims of this study

Our theoretical ideas about longevity inheritance, and the role of resilience in this, led to a set of prior hypotheses, which we wanted to test. Thus, we examined length of lifespan and/or survival into old age in two consecutive generations: parents (G0) and their children (G1). In the next two generations, we compared fathers (G2) and sons (G3), with regard to a resilience measure, based on a psychological interview at military conscription at age 18. Finally, we explored the association between resilience and mortality, within and across generations.

We were able to address these questions empirically:

1) Does age-at-death of parents (G0) predict offspring's (G1) mortality risk in midlife and old age?
2) If so, is this because parents (G0) who live longer also tend to promote a more advantageous social class trajectory for their children (G1)?
3) How do parents' (G0) and their children's (G1) lifespans compare?
4) Is resilience a characteristic which

a) predicts later mortality (in G2)?
b) is transmitted across generations (from G2 fathers to G3 sons)?
c) is predicted by longevity in previous family generations (from G0 and G1 men and women to G2 and G3 men)?

3. Methods

3.1. Data material

Four successive generations were linked by combining existing data on a cohort of all 14,193 men and women born alive at Uppsala Academic Hospital in 1915–1929 (Uppsala Birth Cohort Study: UBCoS) with information from Statistic Sweden's Multigeneration Register through their personal identity numbers, to create UBCoS Multigen (Fig. 1). UBCoS individuals who were alive and resident in Sweden in 1947 (when PIN-numbers were introduced in Sweden) constitute generation 1 (G1: N = 12,168) in UBCoS Multigen (Fig. 2). This cohort and its successive generations have been extensively studied and presented previously (de Stavola, Leon, & Koupil, 2011; Fors, Modin, Koupil, & Vågerö, 2012; Juarez, Goodman, & Koupil, 2016; Modin 2002; Modin, Vågerö, Hallqvist, & Koupil, 2008; Modin, Koupil, & Vågerö, 2009).

We have now traced the parents of G1, with full names and birth date, through hospital records and parish registers. Members of this generation (G0: N = 15,706), are now dead; their date-of-death were traced through the Swedish Death Index (6th edition), published by Statistics Sweden and the Swedish Genealogical Society. This includes all recorded deaths in Sweden 1901–2013.

To increase comparability between G0 and G1, parenthood was an