

Title Lifespan Fluidity and its Biological Limitations in Socio-Economic Health Differences

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Running title: Limitations of Lifespan Fluidity by SES

Caleb E. Finch, PhD; corresponding author

University of Southern California, 3715 McClintock Ave, Los Angeles CA, 90089;

cefinch@usc.edu

Marja K. Jylhä, MD, PhD

Tampere University, Tampere, Finland; marja.jylha@tuni.fi

Key points:

- The strong impacts of socioeconomic status (SES) on health are modified with individual SES transitions between early and adult life ('lifespan fluidity').
- Upward SES mobility increases the odds for longer life and good health, but those with upward mobility usually do not reach the level of those with stable high status.
- The fluidity of lifespans is limited by early age exposures that critically influence organ development, such as maternal smoking and air pollution that can modify DNA methylation and adult brain neurogenesis with potential impact on later life.

Why this matters:

Health in old age is outcome of lifelong exposures and protective factors with strong SES dependence. Crucial childhood exposures may persist into late life. Geriatricians need to consider the whole life-course of health and exposures in the diagnosis and care of their older patients.

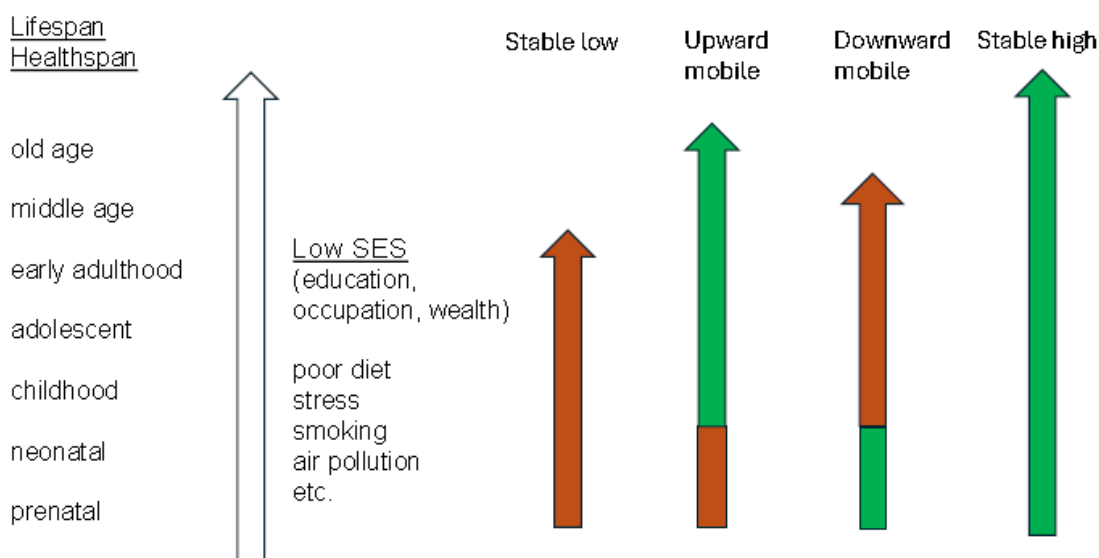
Key words aging, human biology, life course, lifespan, social class

Biological Lifespan Fluidity and its Limitations in Socio-Economic Health Differences

SES gradients of education and income are well established for lifespan and are associated with many diseases of aging, resulting up to 10-15 years difference in lifespan in many countries. Lower income, education, and occupational class impact onset age and rates of cardiovascular disease, obesity, and dementia. In the U.S. Health and Retirement Study (HRS), longitudinal analysis of short-term memory showed faster decline for each 0.4 standard deviation (SD) of less education¹.

While SES has major influences on aging and health in populations, less is known of how individual social mobility impacts healthspan and lifespan, or what are the biological limitations of these impacts. We discuss how transitions from low early SES to higher adult SES may benefit later life, and how early life exposures may limit these benefits. The concept of 'lifespan fluidity' is introduced to describe the impact of these transitions (Figure).

Lifespan and healthspan by social mobility



Healthspan, lifespan, and environmental risk factors vary by socio-economic strata (SES) and are further modified by individual transitions between SES ('lifespan fluidity'). High SES (green) is associated with longer lifespan and healthspan than low SES (red). Individual transitions from low childhood SES to high adult SES improve odds for longer healthspan and lifespan. Conversely, individual transitions from high childhood SES to low adult SES decrease these odds. Underlying this pattern are multiple external risk factors that are more frequent, and protective factors that are less frequent in lower than higher SES. The figure summarizes population studies that used diverse methods and types of data for individual SES transitions between early and adult life.

Fluidity of individual lifespans and healthspan is shown by many studies. In the US-HRS at age of 67, the number of functional limitations among upward mobile adults was about half of those with stable low SES (2.05 vs 3.72)². Similarly, in China, upward mobility increased disability-free life expectancy at age 45 by 3 years above those with stable low SES. Conversely, downward mobility from high to low SES decreased disability-free lifespan by 6 years below high-high³. In Denmark, the 8-year odds of death were 2.0 for low-to-high and 3.8 for high-to-low compared to stable high SES⁴. A recent Finnish study shows higher odds (OR 2.41) for downward trajectory in physical functioning for men (average age 71) with declining SES compared to stable high⁵. Similar associations of social mobility with mortality and functioning are shown in many studies irrespective of whether the indicator of SES is education, occupational class, or income. These studies suggest partial reversibility or attenuation of low childhood SES disadvantage, but also negative impact for downward mobility.

SES fluidity of DNA methylation (DNAm) was recently analyzed in the Framingham Heart Study⁶ by the DunedinPACE epigenetic clock that estimates the ‘pace of aging’ from 19 biomarkers together with DNAm from single blood samples⁷. During three Framingham generations, upward mobility for education slowed the ‘pace of aging’ for the next generation⁶. Smoking history attenuated some effects, consistent with the impact of household smoking on childhood DNAm and obesity⁸. Mortality rates varied inversely with parental education (hazard ratio 0.89), in which half the education impact was attributed to ‘pace of aging’. This analysis did not discuss downward education transitions, shown above for population studies without DNAm data.

These limitations of fluidity imply persistence of poor early life SES conditions that may impact arteries and brain prenatally and in early childhood, for example maternal hypercholesterolemia increased coronary fatty streaks⁹. Prenatally, most organs are completely formed except the brain, which continues to add neurons critical for memory in the hippocampus into adulthood. Additionally, the white matter ‘myelinated’ tracts that enable fast connections across the brain continue to mature until age 30. The aorta at birth has fat deposits that are 5-fold larger in hypercholesterolemic mothers⁹. Low SES children incur multiple stresses from poor diet, household smoking, and psychological stress¹⁰. Slower aging assessed by DunedinPace⁷ in a large sample with European ancestry was most strongly associated with higher education, after accounting for smoking and genome-wide association study (GWAS)¹¹. Maternal smoking and high air pollution PM2.5, which are more prevalent in lower SES homes, increase childhood obesity and systolic blood pressure^{12,13}. Parental smoking impacts DNAm of neonatal white blood cells. For example, in the Pregnancy and Childhood Epigenetics (PACE) Consortium, 2,000 DNAm sites of neonates were altered by maternal smoking⁸. One gene with particular significance is the *AHRR* gene that encodes the aryl hydrocarbon receptor repressor for removing cigarette toxins: maternal smoking decreased DNAm in fetal blood *AHRR* by 10%¹⁴. Placental DNAm is impacted in multiple genes^{15,16} by exposure to maternal smoke and to air pollution; the inhaled particles share many chemical toxicities¹⁶. The Finch lab has developed a mouse model for prenatal exposure to air pollution that caused increased adult body mass index (BMI), impaired glucose clearance, and decreased neurogenesis in the hippocampus¹⁷. We anticipate synergies of maternal smoke with air pollutants that may limit fluidity of adult lifespans by SES. For example, adult lung cancer has super-additive synergy with PM2.5 and cigarette packyears¹⁸.

DNAm differences by SES show corresponding messenger RNA differences^{19,20}. Particular gene functions were associated with BMI, smoking, and immunity. Different SES markers were associated with RNA changes in these studies, suggesting multiple SES stress pathways. The putative SES-sensitive genes are regulated in part by shared transcription factors associated with stress responses and with cancer (NFkB, cfos)^{19,20}. Thus, SES-related factors that limit the fluidity of lifespans may become understood as interactions of gene by environment (GxE). Just one longevity-associated gene has been considered for GxE so far: the ApoE4 allele risk factor of dementia that increases brain damage from air pollution¹⁶.

In sum, decades of data on diverse populations show the deep dependance of human biological aging on SES. The evident fluidity of individual aging with transitions in SES and the biological mechanisms that limit this fluidity will provide important missing links for health-SES association. While upward mobility does improve the impact of early low SES, we do not how much early deficits can be modified in adult life. Nor do we know of gender or ethnic differences in fluidity. GxE interactions merit further study, for which GWAS are needed on diverse ethnic populations. New public health approaches are needed to correct consequences from adverse early-life exposures of lower SES.

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