PART 2.

MECHANISMS AND CONTEXT UNDERLYING SOCIAL INEQUALITIES IN CANCER

CHAPTER 13.

Life-course approach: from socioeconomic determinants to biological embodiment

Michelle Kelly-Irving and Paolo Vineis

Introduction

People with a more disadvantaged socioeconomic position (SEP) have higher rates of mortality at a given age; in other words, they die younger (Gallo et al., 2012). They are also more likely to suffer from worse health, diseases, and disabilities across the life-course, especially in older age. Mechanisms through which SEP may influence health include behaviours (e.g. smoking, unhealthy diets, sedentary lifestyles), availability of and access to health-care services, and chemical and physical exposures (e.g. occupational exposures, pollution). There is increasing evidence that chronic psychosocial stress may exert long-term effects through physiological wear and tear (meaning that a depletion of biological resources in response to the environment occurs over time; Seeman et al., 1997), involving inflammatory responses, reduced immune function, and biological age acceleration.

The socioeconomic gradient in health outcomes has been referred to as a social fact, given its ubiquitous nature, its persistence across a variety of pathological processes, and the fact that its pattern is replicated with new emerging diseases (Hertzman, 2012). The potential impact of SEP on many pathological processes means that it is considered one of the main determinants of life expectancy and health, occurring upstream of typically identified risk factors such as smoking and sedentary lifestyles (the terms upstream and downstream are frequently used in epidemiology, although their use has been criticized; Krieger, 2008). The multilayered social environment within which humans exist and live ultimately affects the cells, organs, and biological systems. This concept, known as embodiment, was initially developed by Krieger (2005) and occurs as a dynamic set of social and biological processes and interactions between individuals within a population and their environments over time (Kelly-Irving and Delpierre, 2018). The pervasive nature of the social structures that make up the outer layer of our environments means that an embodiment dynamic occurs differentially across the strata of SEP. Despite this, SEP remains neglected as a public health imperative and is

not clearly identified as a risk factor in public policies.

The life-course approach to health is a conceptual framework that merges social science and epidemiological methods (Kelly-Irving et al., 2015). It originated in the social sciences, where there was a primary interest in assessing the "social organisation of an individual's passage through life" (Backett and Davison, 1995). In this framework, susceptibility to disease is an inevitable interaction between social and biological phenomena. Therefore, using a life-course approach encapsulates not only the objective measurement of ill health and deprivation but also the subjective ideas about the experience of illness or poor social circumstances. It defines the dichotomy whereby individuals actively determine the trajectory of their life-course but are passively subjected to external insults (Giele and Elder, 1998). The term life-course implies the fluid and continuous movement of individuals and populations through time. Time is also an essential component in the development of chronic diseases, which have long induction and latency periods.

The life-course approach to epidemiology broadens the scope and offers a theoretical backdrop to what is largely a methodological discipline, by looking at human disease and well-being holistically. It is based on "social and biological pathways" and "social and biological chains of risk" (Kuh et al. 1997). These concepts were developed in the book *A Life Course Approach to Chronic Disease Epidemiology* (Kuh and Ben-Shlomo, 1997), which helped to establish life-course epidemiology as a bona fide theoretical and methodological approach. The timing of exposures, in other words the stage along the life-course at which an exposure occurs, can be important in understanding its later effects (Lynch and Smith, 2005) and especially pertinent to the study of chronic diseases such as cancers (Kelly-Irving and Delpierre, 2018). Poor socioeconomic circumstances during childhood are particularly important in determining, for example, a higher risk of stomach cancer through exposure to *Helicobacter pylori* infection (Malaty and Graham, 1994).

The aim of this chapter is to summarize research on social to biological processes that occur over the life-course, with an emphasis on processes involved in social inequalities in cancer, using a multidisciplinary approach that integrates information on SEP, environmental exposures, and risk factors with biological measurements (Vineis et al., 2016). Identification of the biological basis of the social determinants from a life-course perspective is demonstrated with examples from the literature, focusing on results from the Lifepath project (https://www.lifepathproject.eu/).

Construction of health inequalities from early life

Obesity is a risk factor for several types of cancer, including cancer of the stomach, endometrium, colon, breast, pancreas, and liver (Lauby-Secretan et al., 2016). Children with lower SEP literally carry a heavier burden of disease from earlier in the life-course, at least in high-income countries. They accrete fat mass at a faster rate and are more likely to be overweight or obese at any age, to change from not being overweight to being overweight or obese, and to maintain a status of overweight or obesity over time (McCrory et al., 2017). These patterns are difficult to change once entrenched. Overweight and obesity have been shown to have a social pattern from early childhood, with more disadvantaged children having a higher body mass index (BMI) from the age of about 3 years. However, little is known about whether social differentials vary after adipose rebound and into adolescence, and whether these trajectories differ by national context. In a large European study (McCrory et al., 2017), the child BMI growth trajectory was greater for children with mothers with a lower education level. Overall, SEP was strongly implicated in the etiology of childhood obesity. In a previous analysis, it was observed that the BMI of parent and child are linked from age 3 years and remain so throughout the early childhood years (Fantin et al., 2016). The association between the overall social environment and a child's BMI becomes significant and increasingly important over the life-course; adjusting for the BMI of parents only partly reduces this link. This suggests that the observed rise in the BMI of children during the past decades in most populations is reversible.

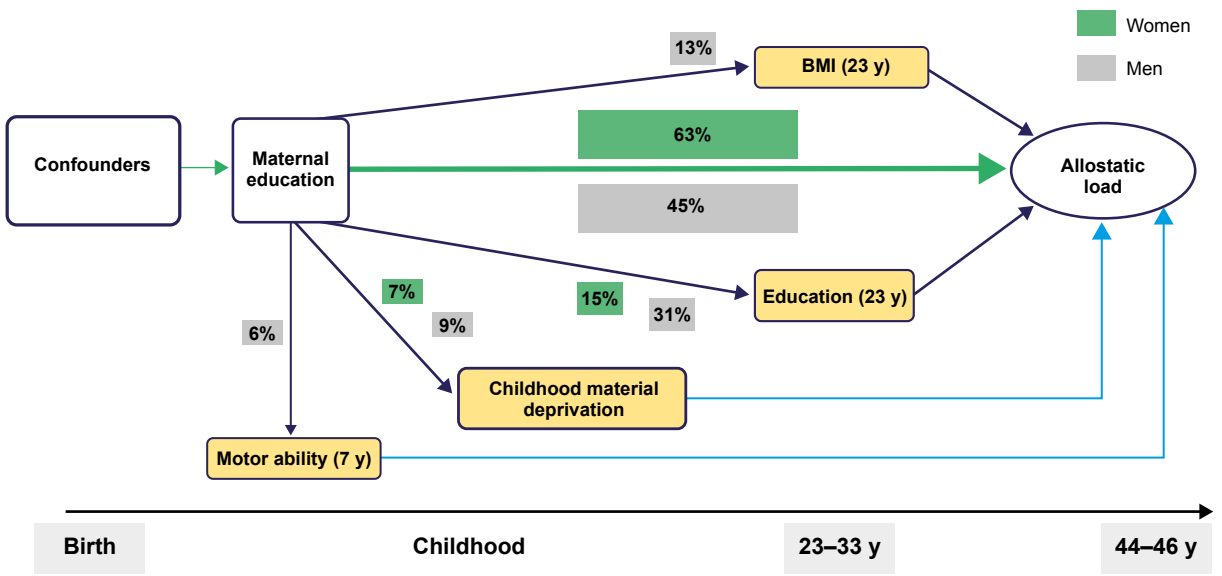
The relationship between higher BMI and risk of cancer is now well documented (Lauby-Secretan et al., 2016; Kyrgiou et al., 2017). Important and still unmeasured biological processes may result from an accumulation of fatty tissue in childhood. A close relationship exists between nutrient excess and dysregulation in the cellular and molecular mediators of immunity and inflammation. So-called lipid spillover from fat promotes metabolic disease by fostering ectopic lipid deposits. Because an estimated excess of 20–30 million macrophages accumulate with each kilogram of excess fat in a human, one could argue that increased adipose tissue mass is a state of increased inflammatory mass (Lumeng

and Saltiel, 2011). This evidence suggests that the etiological backdrop to an association with incidence of cancer begins in early life and may operate through inflammatory and immune system dysregulation.

Beyond examining physiological dysregulation within one system, researchers have also been interested in examining how early-life social conditions may be involved in overall physiological wear and tear across systems. A composite measure of biological health has been developed called allostatic load (Seeman et al. 1997); originally defined as a score based on selected biomarkers, allostatic load measures the lifelong physiological wear and tear (originally mainly related to stress response). Research has demonstrated that socioeconomic adversity, in particular in early life, leads to a higher allostatic load (i.e. higher lifelong stimulation of several key physiological systems), which in turn is related to increased risks of health outcomes and unhealthy ageing. Barboza Solís et al. (2016) carried out a study in a large British birth cohort to examine the relationship between low SEP at birth (identified by either the mother's low education level or the father's manual occupation) and a higher allostatic load in midlife (age ~45 years). By conducting path analyses (Fig. 13.1), it was discovered that the pathways between maternal education level and paternal occupation and allostatic load were largely the same. They operated through childhood material deprivation level, educational attainment in adulthood, and adult BMI in both men and women. Such physiological wear and tear is only one process among other interrelated processes, such as cellular senescence and functional decline, involved in accelerated biological ageing (Delpierre et al., 2016).

Another set of important social to biological mechanisms involving the immune system may be set up in childhood. A study by Gares et al. (2017) showed that children from more disadvantaged social backgrounds are more likely than advantaged children to be infected by a ubiquitous herpesvirus, Epstein–Barr virus (EBV), by the age of 3 years, because of the material conditions to which they were exposed. EBV is involved in certain types of cancers (including nasopharyngeal carcinoma, Burkitt lymphoma, Hodgkin lymphoma, and post-transplant lymphoproliferative disorder). The main interest of this finding is that early acquisition of pathogens affects the maturation of the immune system, in turn affecting its function either positively or negatively. EBV is largely benign, but a social pattern was observed in the timing of exposure and acquisition, which means that immune maturation and function may be modified by these material and social conditions in the early-life environment. Understanding the development and determinants of immune function may be important in explaining why some social groups are more susceptible to certain cancers, because tumour development is determined partly by immune surveillance (Kelly-Irving et al., 2017).

Fig. 13.1. Relationship between maternal educational attainment at birth and allostatic load at age 45 years in the 1958 British birth cohort, highlighting the percentage of the association explained by different pathways. BMI, body mass index. Source: reprinted from Barboza Solís et al. (2016), copyright 2016, with permission from Elsevier.

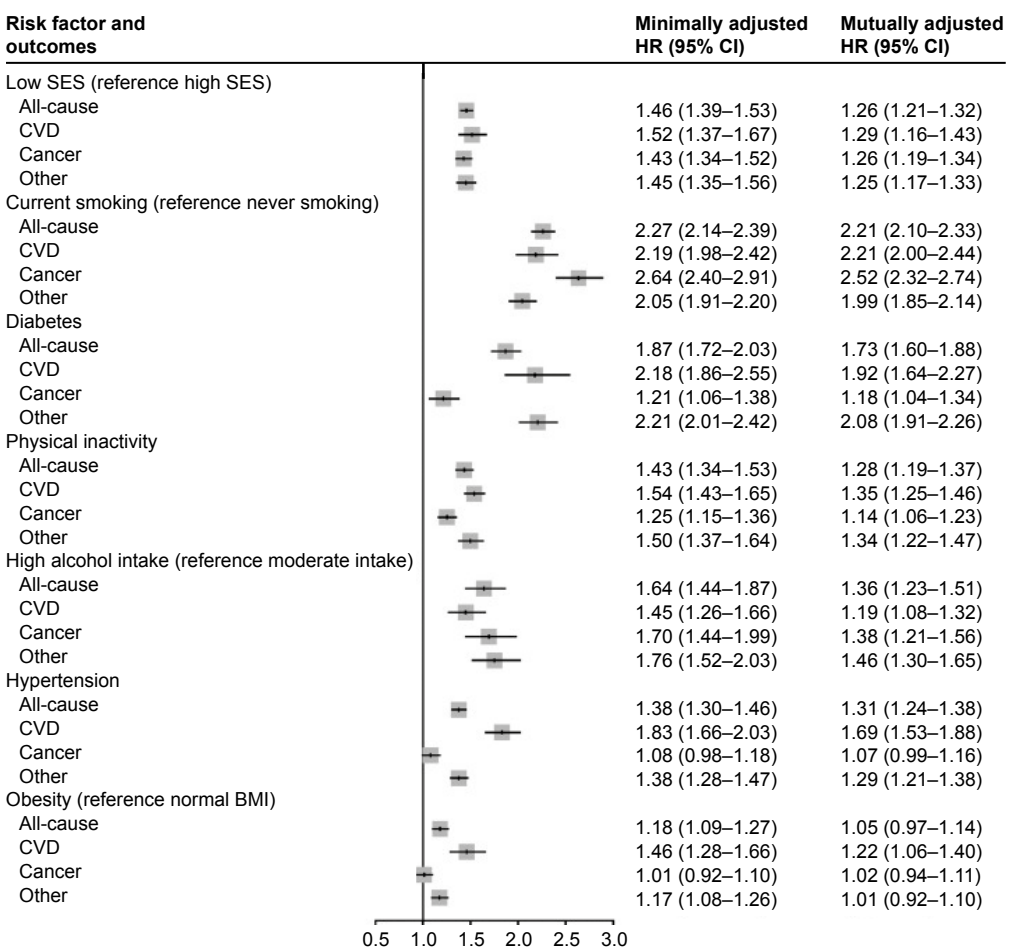


SEP as a risk factor for noncommunicable diseases in adults

There is evidence that SEP is associated with the risk of noncommunicable diseases (NCDs), including cancer. A large multicohort study and meta-analysis was carried out with individual-level data from 48 independent prospective cohort studies. Information about SEP (indexed by occupation), risk factors (high alcohol intake, physical inactivity, current smoking, hypertension, diabetes, and obesity), and mortality for a total population of 1 751 479 (54% women) from seven high-income countries was used.

Participants with low SEP had greater mortality compared with those with high SEP, and this association weakened but remained significant in mutually adjusted models that included the risk factors (Fig. 13.2). The population attributable fraction was highest for smoking, followed by physical inactivity and SEP. Low SEP was associated with a 2.1-year reduction in life expectancy between the ages of 40 years and 85 years; considering the risk factors individually, the corresponding years of life lost were 0.5 years for high alcohol intake, 0.7 years for obesity, 3.9 years for diabetes, 1.6 years for hypertension, 2.4 years for physical inactivity, and 4.8 years for current smoking (Stringhini et al., 2017). For cancer, the hazard ratio associated with low SEP (after adjustment for risk factors) was 1.26 (95% confidence interval [CI], 1.19–1.34), which is comparable with that for other NCDs. This work underlines the importance of considering social circumstances as important determinants of mortality and accelerated ageing in their own right.

Fig. 13.2. Pooled hazard ratios of socioeconomic position (SEP) and 25 × 25 (an initiative to cut mortality due to noncommunicable diseases by 25% by 2025) risk factors for all-cause mortality and cause-specific mortality. The minimally adjusted models were only adjusted for sex, age, and race or ethnicity; in the mutually adjusted models, SEP and the 25 × 25 risk factors are mutually adjusted. BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio. Source: Stringhini et al. (2017) © 2017 Stringhini et al. Published by Elsevier Ltd.



Social and biological mechanisms: pathways towards health inequalities

In a study that used data from the European Prospective Investigation into Cancer and Nutrition (EPIC) Italy cohort, retrospective information was collected about participants' childhood SEP, their highest educational attainment, and their adult occupation (Castagné et al., 2016). The aim was to examine whether SEP over the life-course affected the inflammatory system in adulthood. Early-life manual occupation was linked with a higher inflammatory score (β = 0.29; P = 0.002). When basal inflammation is chronically elevated, it is linked with metabolic and cardiovascular pathologies and cancer. Inflammation is one of the so-called enabling events associated with the hallmarks of cancer described by Hanahan and Weinberg (2011).

In addition to attempts to understand the relationships between social factors and biological factors, the association between these biological factors and subsequent health outcomes has been investigated. For example, a positive association was established between overall physiological wear and tear at the age of 45 years and mortality before the age of 55 years. This relationship was stronger than the association between any individual biomarker and mortality (Castagné et al., 2018).

Another analysis focused more specifically on how the educational attainment of individuals is related to an epigenetic mechanism, DNA methylation, which is used to represent overall biological ageing (Fiorito et al., 2017). Compared with those with high SEP, having low SEP was associated with greater accelerated ageing (β = 0.99 years; 95% CI, 0.39–1.59; P = 0.002). The results suggested that individuals with a lower education level experienced a higher rate of biological ageing than those with a higher education level, even after controlling for several behavioural factors. Individuals who experienced life-course SEP improvement had intermediate levels of accelerated ageing compared with those with low or high SEP, suggesting a possible reversibility of the effect and supporting the relative importance of the early-life social environment. In a related study, the same age-acceleration DNA-based indicator was able to predict cancer mortality during follow-up (Dugué et al., 2018). Overall, these studies provide evidence for the existence of social to biological processes that go beyond behavioural factors. Socioeconomic adversity may be associated with accelerated epigenetic ageing, implicating biomolecular mechanisms that link SEP to age-related diseases and longevity.

Translating research findings for policy action

Research focused on understanding life-course mechanisms must be translated into meaningful findings for potential policy use, either as interventional research or as policy recommendations. Results so far emphasize the need for primary prevention within the childhood and adolescent environment to slow the trend towards higher BMI and the consequent propensity towards a pro-inflammatory state. Primary prevention involves acting upon social material as well as psychosocial factors. However, mitigating the consequences of adverse social trajectories in adulthood to encourage behaviour change, and limiting the consequences of occupational hazards, is also likely to affect biological predispositions to chronic diseases at their roots.

Social environments may act on biology through the action of exogenous exposures that encompass chemical and physical exposures (air pollution, pesticides, viral exposures, occupational exposures) or behavioural exposures (tobacco, alcohol, food, etc.). In addition to these material agents, social relationships (e.g. isolation) or life stress events (e.g. adverse childhood experiences [ACEs]) can lead to unhealthy ageing. In this case perception and interpretation are involved, together with internal molecules from the body, mainly linked to stress–perception and stress–response systems.

In our research, we consider primary prevention in terms of the common root of the most prevalent chronic diseases, including cancers, linked with accelerated ageing. There is much evidence for interrelations between obesity, diabetes, cardiovascular diseases, cognitive decline, and cancer (Giovannucci et al., 2010; Fatke et al., 2013; Tolppanen et al., 2013; Vagelatos and Eslick, 2013). Researchers have even proposed a human disease network based on the molecular relationships between phenotypes (Goh et al., 2007; Barabási et al., 2011). In parallel, socioeconomic and psychosocial factors such as ACEs have been identified as important upstream exposures for many of these chronic conditions and their risk factors (see Krieger, 2008 for limitations of the concepts of upstream and downstream). ACEs have been associated with ischaemic heart disease (Dong et al., 2004), obesity (Thomas et al., 2008), perceived health (Dube et al., 2010), self-reported cancer (Kelly-Irving et al., 2013a), psychopathology (Clark et al., 2010), inflammation (Danese et al., 2009),

mortality (Felitti et al., 1998; Kelly-Irving et al., 2013b), health behaviours (Anda et al., 2002; Dube et al., 2002, 2003), and allostatic load (Barboza-Solís et al., 2015) (for a review see also Hughes et al., 2017). Policies targeting socioeconomic and psychosocial factors in childhood may be an effective method of improving the lives of children in the present, and preventing the onset of chronic conditions such as cancer in the future. Such an outcome-wide approach to epidemiology can facilitate the translation into public health policy (VanderWeele, 2017), and can be carried out in parallel with mechanism-focused approaches.

Conclusions

To reduce the impact of socioeconomic inequalities on health, building a dialogue between researchers, policy-makers, and other stakeholders is key. Life-course evidence of the social to biological embodiment highlights the need for investment in early life to prevent the onset of NCDs, including cancer, in later life.

Acknowledgements

This research was supported by the Lifepath grant to Paolo Vineis (European Commission H2020 grant no. 633 666). The authors acknowledge contributions from all the Lifepath members, particularly from Thierry Lang, Richard Layte, Cyrille Delpierre, Angela Donkin, and Mauricio Avendano.

Key points

- This chapter summarizes life-course approaches to assess socioeconomic inequalities in cancer, providing results from the Lifepath project that are relevant to cancer.
- The life-course approach to health is a conceptual framework where the primary interest is in assessing the "social organisation of an individual's passage through life".
- Social determinants of risk factors associated with cancer begin in early life and persist across the life-course.
- The pathways between social determinants and health outcomes operate as a dynamic set of social and biological processes and interactions between individuals within a population and their environments over time.
- A multidisciplinary approach is needed, integrating information on socioeconomic position, environmental exposures, and risk factors with biological measurements.
- The evidence on social determinants of disease, including cancer, needs to be translated for use by policy-makers.

References

Anda RF, Chapman DP, Felitti VJ, Edwards V, Williamson DF, Croft JB, et al. (2002). Adverse childhood experiences and risk of paternity in teen pregnancy. Obstet Gynecol. 100(1):37–45. PMID:12100801

Backett KC, Davison C (1995). Lifecourse and lifestyle: the social and cultural location of health behaviours. Soc Sci Med. 40(5):629–38. https://doi.org/10.1016/0277-9536(95)80007-7 PMID:7747198

Barabási A-L, Gulbahce N, Loscalzo J (2011). Network medicine: a network-based approach to human disease. Nat Rev Genet. 12(1):56–68. https://doi.org/10.1038/nrg2918 PMID:21164525

Barboza Solís C, Fantin R, Castagné R, Lang T, Delpierre C, Kelly-Irving M (2016). Mediating pathways between parental socio-economic position and allostatic load in mid-life: findings from the 1958 British birth cohort. Soc Sci Med. 165:19–27. https://doi.org/10.1016/j.socscimed.2016.07.031 PMID:27485729

Barboza Solís C, Kelly-Irving M, Fantin R, Darnaudéry M, Torrisani J, Lang T, et al. (2015). Adverse childhood experiences and physiological wear-and-tear in midlife: findings from the 1958 British birth cohort. Proc Natl Acad Sci U S A. 112(7):E738–46. https://doi.org/10.1073/pnas.1417325112 PMID:25646470

Castagné R, Delpierre C, Kelly-Irving M, Campanella G, Guida F, Krogh V, Palli D, Panico S, Sacerdote C, Tumino R, Kyrtopoulos S, Hosnijeh FS, Lang T, Vermeulen R, Vineis P, Stringhini S, Chadeau-Hyam M (2016). A life course approach to explore the biological embedding of socioeconomic position and social mobility through circulating inflammatory markers. Sci Rep. 6:25170. https://doi.org/10.1038/srep25170.

Castagné R, Garès V, Karimi M, Chadeau-Hyam M, Vineis P, Delpierre C, et al.; Lifepath Consortium (2018). Allostatic load and subsequent all-cause mortality: which biological markers drive the relationship? Findings from a UK birth cohort. Eur J Epidemiol. 33(5):441–58. https://doi.org/10.1007/s10654-018-0364-1 PMID:29476357

Clark C, Caldwell T, Power C, Stansfeld SA (2010). Does the influence of childhood adversity on psychopathology persist across the lifecourse? A 45-year prospective epidemiologic study. Ann Epidemiol. 20(5):385–94. https://doi.org/10.1016/j.annepidem.2010.02.008 PMID:20382340

Danese A, Moffitt TE, Harrington H, Milne BJ, Polanczyk G, Pariante CM, et al. (2009). Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. Arch Pediatr Adolesc Med. 163(12):1135–43. https://doi.org/10.1001/archpediatrics.2009.214 PMID:19996051

Delpierre C, Barboza-Solis C, Torrisani J, Darnaudery M, Bartley M, Blane D, et al. (2016). Origins of health inequalities: the case for allostatic load. Longitudinal and Life Course Studies. 7(1):25. https://doi.org/10.14301/llcs.v7i1.325

Dong M, Giles WH, Felitti VJ, Dube SR, Williams JE, Chapman DP, et al. (2004). Insights into causal pathways for ischemic heart disease: adverse childhood experiences study. Circulation. 110(13):1761–6. https://doi.org/10.1161/01.CIR.0000143074.54995.7F PMID:15381652

Dube SR, Anda RF, Felitti VJ, Edwards VJ, Croft JB (2002). Adverse childhood experiences and personal alcohol abuse as an adult. Addict Behav. 27(5):713–25. https://doi.org/10.1016/S0306-4603(01)00204-0 PMID:12201379

Dube SR, Cook ML, Edwards VJ (2010). Health-related outcomes of adverse childhood experiences in Texas, 2002. Prev Chronic Dis. 7(3):A52. PMID:20394691

Dube SR, Felitti VJ, Dong M, Chapman DP, Giles WH, Anda RF (2003). Childhood abuse, neglect, and household dysfunction and the risk of illicit drug use: the adverse childhood experiences study. Pediatrics. 111(3):564–72. https://doi.org/10.1542/peds.111.3.564 PMID:12612237

Dugué PA, Bassett JK, Joo JE, Baglietto L, Jung CH, Wong EM, et al. (2018). Association of DNA methylation-based biological age with health risk factors and overall and cause-specific mortality. Am J Epidemiol. 187(3):529–38. https://doi.org/10.1093/aje/kwx291 PMID:29020168

Fantin R, Delpierre C, Dimeglio C, Lamy S, Barboza Solís C, Charles MA, et al. (2016). Disentangling the respective roles of the early environment and parental BMI on BMI change across childhood: a counterfactual analysis using the Millennium Cohort Study. Prev Med. 89:146–53. https://doi.org/10.1016/j.ypmed.2016.05.028 PMID:27240452

Fatke B, Förstl H, Risse A (2013). Diabetes. Risk factor for dementia. Diabetologe (Heidelb). 9(6):475–84. https://doi.org/10.1007/s11428-013-1109-0

Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med. 14(4):245–58. https://doi.org/10.1016/S0749-3797(98)00017-8 PMID:9635069

Fiorito G, Polidoro S, Dugué P-A, Kivimaki M, Ponzi E, Matullo G, et al. (2017). Social adversity and epigenetic aging: a multi-cohort study on socioeconomic differences in peripheral blood DNA methylation. Sci Rep. 7(1):16266. https://doi.org/10.1038/s41598-017-16391-5 PMID:29176660

Gallo V, Mackenbach JP, Ezzati M, Menvielle G, Kunst AE, Rohrmann S, et al. (2012). Social inequalities and mortality in Europe–results from a large multi-national cohort. PLoS One. 7(7):e39013. https://doi.org/10.1371/journal.pone.0039013 PMID:22848347

Gares V, Panico L, Castagne R, Delpierre C, Kelly-Irving M, Consortium L (2017). The role of the early social environment on Epstein Barr virus infection: a prospective observational design using the Millennium Cohort Study. Epidemiol Infect. 145(16):3405–12. https://doi.org/10.1017/S0950268817002515 PMID:29202893

Giele JZ, Elder GH Jr, editors (1998). Methods of life course research: qualitative and quantitative approaches. London, UK: Sage. https://doi.org/10.4135/9781483348919

Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. (2010). Diabetes and cancer: a consensus report. Diabetes Care. 33(7):1674– 85. https://doi.org/10.2337/dc10-0666 PMID:20587728

Goh K-I, Cusick ME, Valle D, Childs B, Vidal M, Barabási A-L (2007). The human disease network. Proc Natl Acad Sci U S A. 104(21):8685–90. https://doi.org/10.1073/pnas.0701361104 PMID:17502601

Hanahan D, Weinberg RA (2011). Hallmarks of cancer: the next generation. Cell. 144(5):646–74. https://doi.org/10.1016/j.cell.2011.02.013 PMID:21376230

Hertzman C (2012). Putting the concept of biological embedding in historical perspective. Proc Natl Acad Sci USA. 109(Suppl 2):17160–7. https://doi.org/10.1073/pnas.1202203109 PMID:23045673

Hughes K, Bellis MA, Hardcastle KA, Sethi D, Butchart A, Mikton C, et al. (2017). The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. Lancet Public Health. 2(8):e356–66. https://doi.org/10.1016/S2468-2667(17)30118-4 PMID:29253477

Kelly-Irving M, Delpierre C (2018). The embodiment dynamic over the life course: a case for examining cancer aetiology. In: Meloni M, Cromby J, Fiztgerald D, editors. The Palgrave handbook of biology and society. London, UK: Palgrave Macmillan; pp. 519–540.

Kelly-Irving M, Delpierre C, Vineis P (2017). Beyond bad luck: induced mutations and hallmarks of cancer. Lancet Oncol. 18(8):999–1000. https://doi.org/10.1016/S1470-2045(17)30520-X PMID:28759371

Kelly-Irving M, Lepage B, Dedieu D, Bartley M, Blane D, Grosclaude P, et al. (2013b). Adverse childhood experiences and premature all-cause mortality. Eur J Epidemiol. 28(9):721–34. https://doi.org/10.1007/s10654-013-9832-9 PMID:23887883

Kelly-Irving M, Lepage B, Dedieu D, Lacey R, Cable N, Bartley M, et al. (2013a). Childhood adversity as a risk for cancer: findings from the 1958 British birth cohort study. BMC Public Health. 13(1):767. https://doi.org/10.1186/1471-2458-13-767 PMID:23957659

Kelly-Irving M, Tophoven S, Blane D (2015). Life course research: new opportunities for establishing social and biological plausibility. Int J Public Health. 60(6):629–30. https://doi.org/10.1007/s00038-015-0688-5 PMID:25981211

Krieger N (2005). Embodiment: a conceptual glossary for epidemiology. J Epidemiol Community Health. 59(5):350–5. https://doi.org/10.1136/jech.2004.024562 PMID:15831681

Krieger N (2008). Proximal, distal, and the politics of causation: what's level got to do with it? Am J Public Health. 98(2):221–30. https://doi.org/10.2105/AJPH.2007.111278 PMID:18172144

Kuh D, Ben-Shlomo Y, editors (1997). A life course approach to chronic disease epidemiology. Oxford, UK: Oxford University Press.

Kuh D, Power C, Blane D, Bartley M (1997). Social pathways between childhood and adult health. In: Kuh D, Ben-Shlomo Y, editors. A life course approach to chronic disease epidemiology. Oxford, UK: Oxford University Press.

Kyrgiou M, Kalliala I, Markozannes G, Gunter MJ, Paraskevaidis E, Gabra H, et al. (2017). Adiposity and cancer at major anatomical sites: umbrella review of the literature. BMJ. 356:j477. https://doi.org/10.1136/bmj.j477 PMID:28246088

Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K; International Agency for Research on Cancer Handbook Working Group (2016). Body fatness and cancer – viewpoint of the IARC working group. N Engl J Med. 375(8):794–8. https://doi.org/10.1056/NEJMsr1606602 PMID:27557308

Lumeng CN, Saltiel AR (2011). Inflammatory links between obesity and metabolic disease. J Clin Invest. 121(6):2111–7. https://doi.org/10.1172/JCI57132 PMID:21633179

Lynch J, Smith GD (2005). A life course approach to chronic disease epidemiology. Annu Rev Public Health. 26(1):1–35. https://doi.org/10.1146/annurev.publhealth.26.021304.144505 PMID:15760279

Malaty HM, Graham DY (1994). Importance of childhood socioeconomic status on the current prevalence of *Helicobacter pylori* infection. Gut. 35(6):742–5. https://doi.org/10.1136/gut.35.6.742 PMID:8020796

McCrory C, Leahy S, Ribeiro AI, Fraga S, Barros H, Layte R (2017). Socio-economic variation in child BMI trajectory from infancy to adolescence in three contemporary European child cohorts. J Epidemiol Community Health. 71:A92–92.

Seeman TE, Singer BH, Rowe JW, Horwitz RI, McEwen BS (1997). Price of adaptation – allostatic load and its health consequences. MacArthur studies of successful aging. Arch Intern Med. 157(19):2259–68. https://doi.org/10.1001/archinte.1997.00440400111013 PMID:9343003

Stringhini S, Carmeli C, Jokela M, Avendaño M, Muennig P, Guida F, et al. (2017). Socioeconomic status and the 25 × 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1.7 million men and women. Lancet. 389(10075):1229–37. https://doi.org/10.1016/S0140-6736(16)32380-7 PMID:28159391

Thomas C, Hyppönen E, Power C (2008). Obesity and type 2 diabetes risk in midadult life: the role of childhood adversity. Pediatrics. 121(5):e1240–9. https://doi.org/10.1542/peds.2007-2403 PMID:18450866

Tolppanen AM, Lavikainen P, Solomon A, Kivipelto M, Uusitupa M, Soininen H, et al. (2013). History of medically treated diabetes and risk of Alzheimer disease in a nationwide case-control study. Diabetes Care. 36(7):2015–9. https://doi.org/10.2337/dc12-1287 PMID:23340883

Vagelatos NT, Eslick GD (2013). Type 2 diabetes as a risk factor for Alzheimer's disease: the confounders, interactions, and neuropathology associated with this relationship. Epidemiol Rev. 35(1):152–60. https://doi.org/10.1093/epirev/mxs012 PMID:23314404

VanderWeele TJ (2017). Outcome-wide epidemiology. Epidemiology. 28(3):399–402. https://doi.org/10.1097/EDE.0000000000000641 PMID:28166102

Vineis P, Kelly-Irving M, Rappaport S, Stringhini S (2016). The biological embedding of social differences in ageing trajectories. J Epidemiol Community Health. 70(2):111–3. https://doi.org/10.1136/jech-2015-206089 PMID:26254294