Simulating interventions on adolescent behaviours and adverse family environments to mitigate socioeconomic inequalities in accelerated ageing: a Finnish cohort study

Jackisch J, Lehtimäki T, Kähönen M, Raitakari OT, Carmeli C

Introduction

Parental socioeconomic position during childhood or adolescence is associated with mortality and morbidity throughout the life course – this 'long arm of childhood' is a persistent empirical finding and such inequalities might increase over time (Galobardes, Lynch, and Smith 2004; Hayward and Gorman 2004; Martikainen et al. 2020). One of the major proximal biological processes of social-to-biological transitions, next to inflammatory markers, allostatic load and metabolomics, is the epigenetic acceleration of ageing, which can be measured via epigenetic clocks (Duan et al. 2022; Fiorito et al. 2022; Vineis et al. 2020). As a measure of biological ageing, modern epigenetic clocks have been derived from machine learning approaches that combine tens to thousands of DNA methylation sites to predict different age-related measures, such as phenotypic biomarkers, chronic diseases, mortality, or the pace of ageing. Such second generation epigenetic clocks are strongly predictive of many diseases and mortality (Belsky et al. 2022; Hillary et al. 2020; Levine et al. 2018; Lu et al. 2019).

Accelerated epigenetic clocks have been linked to a number of factors in early life such as parental socioeconomic position, health-risk behaviours and adverse family environments (Oblak et al. 2021). Individual behaviours like smoking and alcohol use likely mediate the association between parental socioeconomic inequalities and age acceleration (McCrory et al. 2022). Moreover, parenting and other adverse familial factors, such as parental separation and household dysfunction (parental mental illness, alcohol misuse, placing a child in out-of-home care), might explain parental inequalities in epigenetic ageing (Conger, Conger, and Martin 2010; Jocson and McLoyd 2015; Mrug et al. 2023). Yet it remains unclear whether intervening on intermediate behavioural or family factors could mitigate potential socioeconomic inequalities in accelerated ageing. Such intermediate factors that are in principle modifiable are important to identify as they could be targets for intervention.

This study aims to examine socioeconomic inequalities in accelerated epigenetic ageing by simulating a population intervention where those from low parental socioeconomic position are assigned the same levels of familial social factors and adolescent alcohol use and smoking as those from higher parental socioeconomic positions. Based on data from the Young Finns cohort Study (n=3,569), we will estimate parental socioeconomic inequalities in midlife using second generation epigenetic clocks and a *g*-method-based decomposition technique to show how much inequality could be mitigated by each of those factors. Increased knowledge about the inequalities reduction of hypothetically intervening on these familial social or individual behavioural factors can inform policy and prevention efforts. Policies that aim at mitigating health inequalities are key for sustainable populations.

Theoretical background

Social inequalities, especially in chronic diseases, have complex causes. Understanding the processes underlying their generation requires multi-disciplinary approaches (Ben-Shlomo, Cooper, and Kuh 2016; Eikemo and Øversveen 2019). The life course approach is such a multi-disciplinary approach that can help increase understanding by highlighting the importance of early life roots of inequalities (Hertzman and Boyce 2010; Kuh, Ben Shlomo, and Ezra 2004). In childhood and adolescence, parental socioeconomic position is a key determinant of child's health and associated inequalities can be observed throughout adulthood and until death (Galobardes et al. 2004; Galobardes, Lynch, and Smith 2008; Stringhini et al. 2017). The life course approach has also helped to bridge biological and social research to better understand how the social environments can become embodied (Blane, Kelly-irving, and Bartley 2013; Hertzman and Boyce 2010; Krieger 2005).

DNA methylation is considered one of the hallmarks of ageing and a key mechanism by which the environment can modulate gene expression. Hence, epigenetic clocks could explain how social environments early in life can become embodied and might therefore be a salient outcome to study. Yet, how low parental socioeconomic position translates into inequalities in epigenetic clocks is not fully understood and knowledge how to potentially mitigate the social inequalities thus remains limited. While empirical evidence points to a mediating role of health-risk behaviours and own socioeconomic position, other social factors in the family are less well understood. According to the family stress model, low socioeconomic position can lead to parental stress, which is associated with interparental relationship problems and worse family functioning (Masarik and Conger 2017). Based on this theory, we hypothesize that the increased exposure to parental separation, household dysfunction (parental mental illness, alcohol misuse, child's out-of-home care placement), and disrupted parenting (i.e. hash parenting) may be important intermediary factors influencing biological ageing in addition to adolescent health-risk behaviours. Importantly, in as much as these factors are increased by socioeconomic disadvantage, this means that if we could mitigate parental socioeconomic stress, some events indicative poor family functioning and adolescent risk behaviours could be prevented (Pitkänen et al. 2021). Even in the most extreme cases of family crises, some prevention programmes are available that help prevent, i.e., a child from being placed in out-of-home care (Bezeczky et al. 2020).

Methods

Data and sample

Our target population consists of adolescents and adults from high-income European countries. The study population draws on prospective cohort data from the Young Finns Study (YFS). The YFS is an ongoing multicentre prospective cohort study designed to assess risk factors underlying cardiovascular diseases. In 1980, 3,596 individuals ages 3, 6, 9, 12, 15, and 18 were recruited, corresponding to a 83.2% response rate from a random sample of the Finnish population. Follow-up measurements were collected in 1983, 1986, 1989, 1992, 2001, 2007, 2011 and 2018.

Conceptual framework and variables

Our causal framework relies on first explicitly stating the assumed causal relationships in a directed acyclic graph (DAG; for a generalized conceptual framework, see Figure 1). For each of the relationships, we will build a detailed DAG, from which we identify the minimally sufficient adjustment set of confounding factors.

Parental socioeconomic position was measured through parental occupation (dichotomized into manual and non-manual) and household income (dichotomized into low income for those in the lowest income category during adolescence).

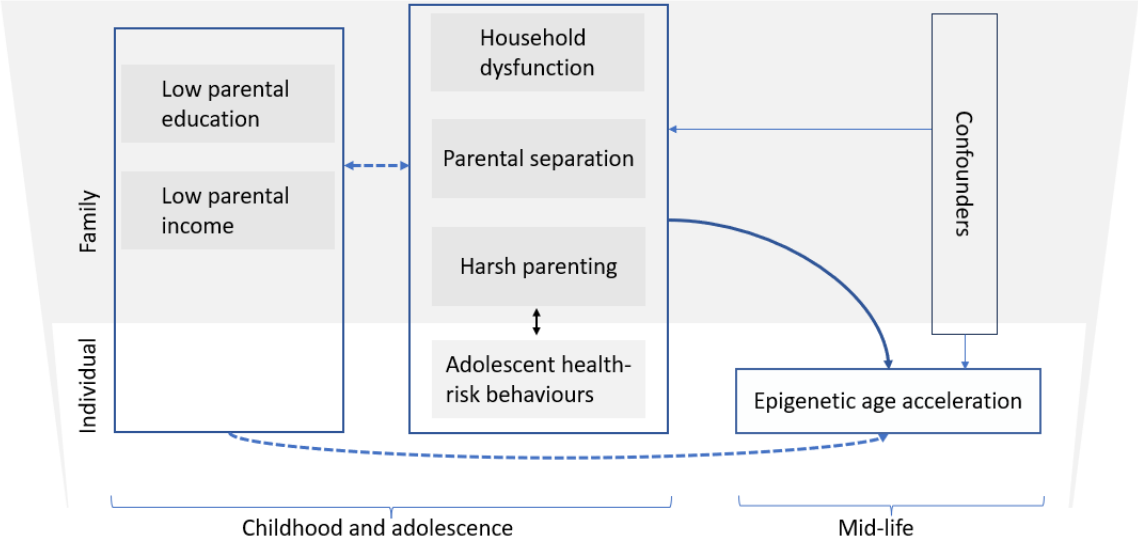

Figure 1. Conceptual model at the basis of our assumed causal directed acyclic graphs. Solid lines represent causal effects, dashed lines represent associations.

If not mentioned otherwise, individual behavioural and familial social factors are assessed at baseline in a survey in 1980 or 1989 corresponding to the time point when respondents were adolescents (ages 12, 15 or 18). On the individual level, alcohol use and smoking are measured in self-reported questionnaires. For the familial social factors, a score indicating harsh to supportive parenting is created from the parental relationship questionnaire assessed at baseline in 1980. Parental separation is derived from any reports of a separation (1980 or 1989), or a parent missing from the family (assessed in 1980, 1983 and 1986). Household dysfunction is created as a dummy variable, indicating any or several of the following experiences: frequent parental alcohol intoxication (if either parent was intoxicated more than once per month on average), parental self-reported mental illness, out-of-home care/living outside parental care or having a guardian different from the parents (assessed in 1980 and 1986).

Regarding the outcome, different epigenetic clocks were calculated using the modern PhenoAge, GrimAge, DunedinPACE clocks. DNA methylation data came from blood samples drawn in 2018 when participants were between 40-55 years. We will account for sex, age at baseline survey, sibship size, parental age at birth, parental education, and neighbourhood deprivation as potential

confounders. In the outcome models, we will additionally adjust for adverse birth outcomes, childhood health and other adverse childhood experiences.

Statistical analysis

We will perform the *g*-computation based decomposition—described in detail in Sudharsan & Bijlsma (2021)—through equalizing intermediate factors marginally across the socioeconomic groups. This approach relies on advances situating decomposition analysis in a counterfactual framework (Jackson and VanderWeele 2018; Vanderweele and Robinson 2014). Such decomposition analysis has the aim to identify factors that contribute to inequalities between groups. We will impute the levels of each explanatory factor separately and for behavioural and social factors combined. Compared to causal mediation analysis, decomposition requires fewer assumptions, which is an advantage in the context of social inequalities research that is prone to intermediate confounding (Park, Kang, and Lee 2023).

Anticipated significance and expected results

The results of this study can help to inform strategies on how to mitigate inequalities in epigenetic ageing following low parental socioeconomic position. Questions of potentially modifiable intermediary factors are key for identifying policy targets for mitigating inequalities. We expect the evidence produced by this study to inform prevention efforts that might have the potential to break chains of early disadvantage. From prior research, some socioeconomic inequalities in epigenetic ageing would be expected. We abstain however from speculating about the contributions of explanatory factors as there is a lack of comparable research. Between now and the EPC 2024, we expect to have full results.

Funding: This study was supported by the Swiss National Science Foundation (grant nr. 208205).

References

Belsky, D. W., A. Caspi, D. L. Corcoran, K. Sugden, R. Poulton, L. Arseneault, A. Baccarelli, K. Chamarti, X. Gao, E. Hannon, H. L. Harrington, R. Houts, M. Kothari, D. Kwon, J. Mill, J. Schwartz, P. Vokonas, C. Wang, B. Williams, and T. E. Moffitt. 2022. "DunedinPACE, A DNA Methylation Biomarker of the Pace of Aging." *ELife* 11. doi: 10.7554/ELIFE.73420.

Ben-Shlomo, Yoav, Rachel Cooper, and Diana Kuh. 2016. "The Last Two Decades of Life Course Epidemiology, and Its Relevance for Research on Ageing." *International Journal of Epidemiology* 45(4):973–88. doi: 10.1093/IJE/DYW096.

Bezeczky, Zoe, Asmaa El-Banna, Stavros Petrou, Alison Kemp, Jonathan Scourfield, Donald Forrester, and Ulugbek B. Nurmatov. 2020. "Intensive Family Preservation Services to Prevent Out-of-Home Placement of Children: A Systematic Review and Meta-Analysis." *Child Abuse & Neglect* 102(January):104394. doi: 10.1016/j.chiabu.2020.104394.

Blane, David, Michelle Kelly-irving, and Melanie Bartley. 2013. "Social-Biological Transitions: How Does the Social Become Biological?" *Longitudinal and Life Course Studies* 4(2):136–46. doi: 10.14301/llcs.v4i2.236.

Conger, Rand D., Katherine J. Conger, and Monica J. Martin. 2010. “Socioeconomic Status, Family Processes,and Individual Development.” *Journal of Marriage and Family* 72(3):685–704. doi: 10.1111/J.1741-3737.2010.00725.X.

Duan, Ran, Qiaoyu Fu, Yu Sun, and Qingfeng Li. 2022. “Epigenetic Clock: A Promising Biomarker and Practical Tool in Aging.” *Ageing Research Reviews* 81. doi: 10.1016/J.ARR.2022.101743.

Eikemo, Terje A., and Emil Øversveen. 2019. “Social Inequalities in Health: Challenges, Knowledge Gaps, Key Debates and the Need for New Data.” *Scandinavian Journal of Public Health* 47(6):593–97. doi: 10.1177/1403494819866416.

Fiorito, Giovanni, Sara Pedron, Carolina Ochoa-Rosales, Cathal Mccrory, Silvia Polidoro, Yan Zhang, Pierre Antoine Dugu, Scott Ratliff, Wei N. Zhao, Gareth J. Mckay, Giuseppe Costa, Maria Giuliana Solinas, Kathleen Mullan Harris, Rosario Tumino, Sara Grioni, Fulvio Ricceri, Salvatore Panico, Hermann Brenner, Lars Schwettmann, Melanie Waldenberger, Pamela R. Matias-Garcia, Annette Peters, Allison Hodge, Graham G. Giles, Lauren L. Schmitz, Morgan Levine, Jennifer A. Smith, Yongmei Liu, Frank Kee, Ian S. Young, Bernadette Mcguinness, Amy Jayne Mcknight, Joyce Van Meurs, Trudy Voortman, Rose A. Kenny, Paolo Vineis, and Cristian Carmeli. 2022. “The Role of Epigenetic Clocks in Explaining Educational Inequalities in Mortality: A Multicohort Study and Meta-Analysis.” *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 77(9):1750. doi: 10.1093/GERONA/GLAC041.

Galobardes, Bruna, J. W. Lynch, and G. D. Smith. 2008. “Is the Association between Childhood Socioeconomic Circumstances and Cause-Specific Mortality Established? Update of a Systematic Review.” *Journal of Epidemiology & Community Health* 62(5):387–90. doi: 10.1136/jech.2007.065508.

Galobardes, Bruna, John W. Lynch, and George Davey Smith. 2004. “Childhood Socioeconomic Circumstances and Cause-Specific Mortality in Adulthood: Systematic Review and Interpretation.” *Epidemiologic Reviews* 26(1):7–21. doi: 10.1093/epirev/mxh008.

Hayward, Mark D., and Bridget K. Gorman. 2004. “The Long Arm of Childhood: The Influence of Early-Life Social Conditions on Men’s Mortality.” *Demography* 41(1):87–107. doi: 10.1353/dem.2004.0005.

Hertzman, Clyde, and Thomas Boyce. 2010. “How Experience Gets Under the Skin to Create Gradients in Developmental Health.” *Annual Review of Public Health* 31(1):329–47. doi: 10.1146/annurev.publhealth.012809.103538.

Hillary, Robert F., Anna J. Stevenson, Daniel L. McCartney, Archie Campbell, Rosie M. Walker, David M. Howard, Craig W. Ritchie, Steve Horvath, Caroline Hayward, Andrew M. McIntosh, David J. Porteous, Ian J. Deary, Kathryn L. Evans, and Riccardo E. Marioni. 2020. “Epigenetic Measures of Ageing Predict the Prevalence and Incidence of Leading Causes of Death and Disease Burden.” *Clinical Epigenetics* 12(1). doi: 10.1186/s13148-020-00905-6.

Jackson, John W., and Tyler J. VanderWeele. 2018. “Decomposition Analysis to Identify Intervention Targets for Reducing Disparities.” *Epidemiology* 29(6):825–35. doi: 10.1097/EDE.0000000000000901.

Jocson, Rosanne M., and Vonnie C. McLoyd. 2015. “Neighborhood and Housing Disorder, Parenting, and Youth Adjustment in Low-Income Urban Families.” *American Journal of Community Psychology* 55(3–4):304–13. doi: 10.1007/S10464-015-9710-6.

Krieger, Nancy. 2005. “Embodiment: A Conceptual Glossary for Epidemiology.” *Journal of Epidemiology and Community Health* 59(5):350–55. doi: 10.1136/jech.2004.024562.

Kuh, Diana, Yoav Ben Shlomo, and Susser Ezra, eds. 2004. *A Life Course Approach to Chronic Disease Epidemiology*. Oxford University Press.

Levine, Morgan E., Ake T. Lu, Austin Quach, Brian H. Chen, Themistocles L. Assimes, Stefania Bandinelli, Lifang Hou, Andrea A. Baccarelli, James D. Stewart, Yun Li, Eric A. Whitsel, James G. Wilson, Alex P. Reiner, Abraham Aviv, Kurt Lohman, Yongmei Liu, Luigi Ferrucci, and Steve Horvath. 2018. "An Epigenetic Biomarker of Aging for Lifespan and Healthspan." *AGING* 10(4).

Lu, Ake T., Austin Quach, James G. Wilson, Alex P. Reiner, Abraham Aviv, Kenneth Raj, Lifang Hou, Andrea A. Baccarelli, Yun Li, James D. Stewart, Eric A. Whitsel, Themistocles L. Assimes, Luigi Ferrucci, and Steve Horvath. 2019. "DNA Methylation GrimAge Strongly Predicts Lifespan and Healthspan." *Aging (Albany NY)* 11(2):303. doi: 10.18632/AGING.101684.

Martikainen, Pekka, Irma T. Elo, Lasse Tarkiainen, Janne Mikkonen, Mikko Myrskylä, and Heta Moustgaard. 2020. "The Changing Contribution of Childhood Social Characteristics to Mortality: A Comparison of Finnish Cohorts Born in 1936-50 and 1961-75." *International Journal of Epidemiology* 49(3):896–907. doi: 10.1093/ije/dyaa041.

Masarik, April S., and Rand D. Conger. 2017. "Stress and Child Development: A Review of the Family Stress Model." *Current Opinion in Psychology* 13:85–90. doi: 10.1016/J.COPSYC.2016.05.008.

McCrory, Cathal, Giovanni Fiorito, Aisling M. O'Halloran, Silvia Polidoro, Paolo Vineis, and Rose Anne Kenny. 2022. "Early Life Adversity and Age Acceleration at Mid-Life and Older Ages Indexed Using the next-Generation GrimAge and Pace of Aging Epigenetic Clocks." *Psychoneuroendocrinology* 137. doi: 10.1016/j.psyneuen.2021.105643.

Mrug, Sylvie, Malcolm Barker-Kamps, Marlon Goering, Amit Patki, and Hemant K. Tiwari. 2023. "Neighborhood Disadvantage and Parenting in Early Adolescence Predict Epigenetic Aging and Mortality Risk in Adulthood." *Journal of Youth and Adolescence* 1–15. doi: 10.1007/S10964-023-01863-X/FIGURES/2.

Oblak, Lara, Jeroen van der Zaag, Albert T. Higgins-Chen, Morgan E. Levine, and Marco P. Boks. 2021. "A Systematic Review of Biological, Social and Environmental Factors Associated with Epigenetic Clock Acceleration." *Ageing Research Reviews* 69. doi: 10.1016/j.arr.2021.101348.

Park, Soojin, Suyeon Kang, and Chioun Lee. 2023. "Choosing an Optimal Method for Causal Decomposition Analysis with Continuous Outcomes: A Review and Simulation Study." *Sociological Methodology* 1–26. doi: 10.1177/00811750231183711.

Pitkänen, Joonas, Maarten J. Bijlsma, Hanna Remes, Mikko Aaltonen, and Pekka Martikainen. 2021. "The Effect of Low Childhood Income on Self-Harm in Young Adulthood: Mediation by Adolescent Mental Health, Behavioural Factors and School Performance." *SSM - Population Health* 13(February). doi: 10.1016/j.ssmph.2021.100756.

Stringhini, Silvia, Cristian Carmeli, Markus Jokela, Mauricio Avendaño, Peter Muennig, Florence Guida, Fulvio Ricceri, Angelo D'Errico, Henrique Barros, Murielle Bochud, Marc Chadeau-Hyam, Françoise Clavel-Chapelon, Giuseppe Costa, Cyrille Delpierre, Silvia Fraga, Marcel Goldberg, Graham G. Giles, Vittorio Krogh, Michelle Kelly-Irving, Richard Layte, Aurélie M. Lasserre, Michael G. Marmot, Martin Preisig, Martin J. Shipley, Peter Vollenweider, Marie Zins, Ichiro Kawachi, Andrew Steptoe, Johan P. Mackenbach, Paolo Vineis, Mika Kivimäki, Harri Alenius, Mauricio Avendano, Luca Carra, Raphaële Castagné, Emilie Courtin, Pierre-Antoine Dugué, Paul Elliott, Valérie Gares, Graham Giles, Dario Greco, Allison Hodge, Michelle Kelly Irving, Piia Karisola, Thierry Lang, Benoit Lepage,

Michael Marmot, Cathal McCrory, Roger Milne, Wilma Nusselder, Salvatore Panico, Dusan Petrovic, Silvia Polidoro, Olli Raitakari, Ana Isabel Ribeiro, Oliver Robinson, Jose Rubio Valverde, Carlotta Sacerdote, Roberto Satolli, Gianluca Severi, and Rosario Tumino. 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." *The Lancet* 389(10075):1229–37. doi: 10.1016/S0140-6736(16)32380-7.

Sudharsanan, Nikkil, and Maarten J. Bijlsma. 2021. "Education Corner Educational Note: Causal Decomposition of Population Health Differences Using Monte Carlo Integration and the g-Formula." *International Epidemiological Association International Journal of Epidemiology* 2098–2107. doi: 10.1093/ije/dyab090.

Vanderweele, Tyler J., and Whitney R. Robinson. 2014. "On Causal Interpretation of Race in Regressions Adjusting for Confounding and Mediating Variables NIH Public Access." *Epidemiology* 25(4):473–84. doi: 10.1097/EDE.0000000000000105.

Vineis, Paolo, Mauricio Avendano-Pabon, Henrique Barros, Mel Bartley, Cristian Carmeli, Luca Carra, Marc Chadeau-Hyam, Giuseppe Costa, Cyrille Delpierre, Angelo D'Errico, Silvia Fraga, Graham Giles, Marcel Goldberg, Michelle Kelly-Irving, Mika Kivimäki, Benoit Lepage, Thierry Lang, Richard Layte, Frances MacGuire, Johan P. Mackenbach, Michael Marmot, Cathal McCrory, Roger L. Milne, Peter Muennig, Wilma Nusselder, Dusan Petrovic, Silvia Polidoro, Fulvio Ricceri, Oliver Robinson, Silvia Stringhini, and Marie Zins. 2020. "Special Report: The Biology of Inequalities in Health: The Lifepath Consortium." *Frontiers in Public Health* 8:118. doi: 10.3389/FPUBH.2020.00118/BIBTEX.