# Report on various life course models for the effects of early-life exposures on later cardio-metabolic risk factors and disease

Work package 4 - Task 4.2 - Deliverable 4.3

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# 1. Introduction

The aim of WP4 is to examine the associations of early-life stressors during preconception, pregnancy, infancy and early childhood with cardiovascular and metabolic outcomes during fetal life, childhood, adolescence and adulthood. The objective of task 4.2 is to identify early-life stressors related to cardio-vascular and cardio-metabolic outcomes across the life-course, including whether associations vary with age. This related deliverable (D4.3) is to report on various life course models for the effects of early-life exposures on later cardio-metabolic risk factors and disease. It complements D4.2 submitted in July 2021, which reported on the applied research of early-life exposures with subsequent offspring outcomes.

# 2. Work performed

### 2.1. Literature Review

In collaboration with WP7 we conducted a systematic review of difference life course models with the aim of (a) making all relevant published papers widely available to the LC partners via the searchable methodological literature database developed as part of WP7 and reported on in D7.1 in December 2020. We identified and (b) identifying any gaps in this literature that would benefit from more methodological research.
The search identified the following key papers that have been placed on the LC literature database

1. Zhu Y, Simpkin AJ, Suderman MJ, Lussier AA, Walton E, Dunn EC, Smith ADAC. A Structured Approach to Evaluating Life-Course Hypotheses: Moving Beyond Analyses of Exposed Versus Unexposed in the -Omics Context. *American Journal of Epidemiology* 2021; 190:1101-1112.
2. Howe LD, Smith AD, Macdonald-Wallis C, Anderson EL, Galobardes B, Lawlor DA, Ben-Shlomo Y, Hardy R, Cooper R, Tilling K, Fraser A. Relationship between mediation/interaction analysis and the structured life course approach. *International Journal of Epidemiology* 2016;45:1280-1294.
3. Hardy R, Tilling K. Commentary: The use and misuse of life course models. *International Journal of Epidemiology* 2016; 45: 1003-1005.
4. De Stavola BL, Daniel RM. Commentary: Incorporating concepts and methods from causal inference into life course epidemiology. *International Journal of Epidemiology* 2016; 45: 1006-1010.
5. Smith ADAC, Hardy R, Heron J, Joinson CJ, Lawlor DA, Macdonald-Wallis C, Tilling K. A structured approach to hypotheses involving continuous exposures over the life course. *International Journal of Epidemiology* 2016; 45: 1271-1279.
6. Smith ADAC, Heron J, Mishra G, Gilthorpe MS, Ben-Shlomo Y, Tilling K. Model Selection of the Effect of Binary Exposures over the Life Course. E*pidemiology* 2015; 26: 719-726.
7. Hardy R, Lawlor DA, Kuh D. A life course approach to cardiovascular aging. *Future Cardiology* 2015; 11: 101-113.
8. Mishra G, Nitsch D, Black S, De SB, Kuh D, Hardy R. A structured approach to modelling the effects of binary exposure variables over the life course. *International Journal of Epidemiology* 2009;38:528-37.
9. De Stavola BL, Nitsch D, Dos SSI, et al. Statistical issues in life course epidemiology. *American Journal of Epidemiology* 2006;163:84-96

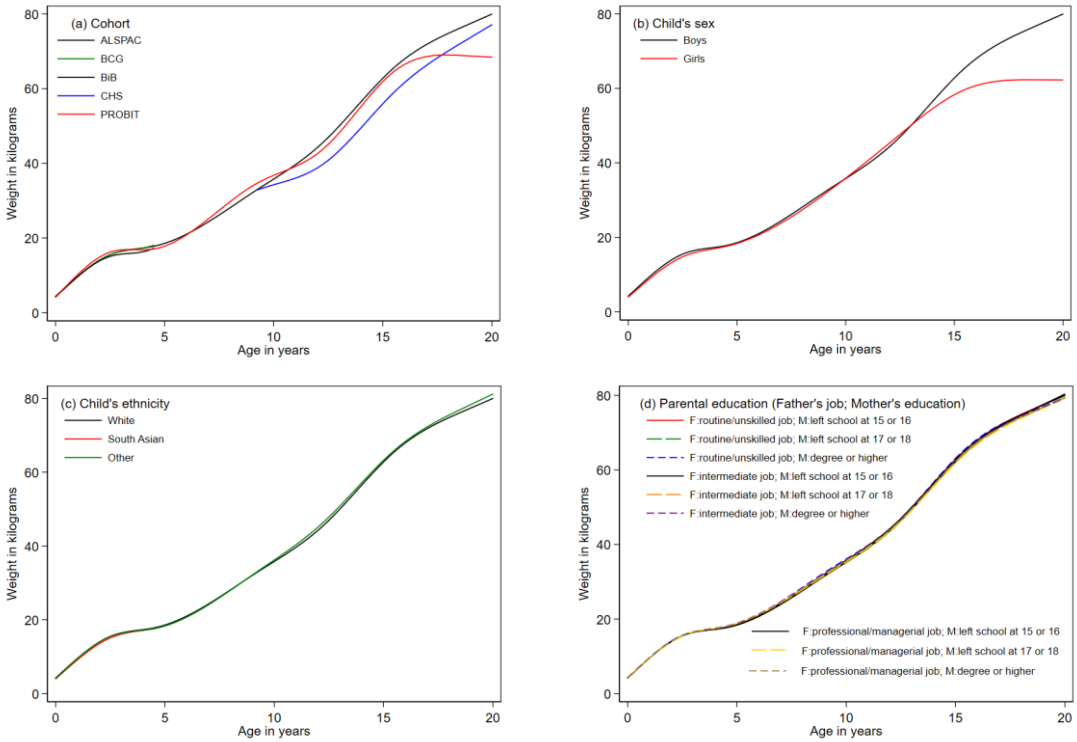
## 2.2. Summary of published research

From the literature review (see above) we identified a key gap, which was the absence of modelling strategies for repeat outcomes that could join individual participant data from across several cohorts in order to extend the life course period covered. This is important as no single study has repeat data from infancy through to late adulthood. Research undertaken to address this issue was published:

**Abstract**: Longitudinal data are necessary to reveal changes within the same individual as they age. However, rarely will a single cohort capture data throughout the lifespan. We describe in detail the steps needed to develop life-course trajectories from cohorts that cover different and overlapping periods of life. Such independent studies are likely from heterogenous populations which raises several challenges including: data harmonisation (deriving new harmonised variables from differently measured variables by identifying common elements across all studies); systematically missing data (variables not measured are missing for all participants of a cohort); and model selection with differing age ranges and measurement schedules. We illustrate how to overcome these challenges using an example which examines the effects of parental education, sex, and ethnicity on weight trajectories. Data were from five prospective cohorts (Belarus and four UK regions), spanning from birth to early adulthood during differing calendar periods. Key strengths of our approach include modelling trajectories over wide age ranges, sharing of information across studies and direct comparison of the same parts of the life-course in different geographical regions and time periods. We also introduce a novel approach of imputing individual-level covariates of a multilevel model with a nonlinear growth trajectory and interactions.

### Selected results

**Figure 1: Differences by cohort (panel (a)) and associations of sex (b), ethnicity (c) and socioeconomic position (d) with change in weight from birth to age 20**



### 2.3 Summary of on-going work

In ongoing work we are extending previously reported fetal growth trajectories (from repeat ultrasound scans) to continue postnatally, so that we have trajectories of weight from early fetal life to mid-childhood. This will be highly novel research and enable exploration of (a) whether patterns of postnatal growth are in anyway 'fixed' by growth in-utero and (b) the impact of early life exposures such as mothers behaviours (smoking, diet, etc.) and metabolomic profiles on growth from in-utero to postnatal.

## 3. Conclusions

For this deliverable we have completed a literature review and posted relevant papers on a LC searchable literature platform. A gap in that literature was how to join repeat measures from across the life-course in different studies and that method is now being used in WP4 as well as other applied WPs in lifecycle. In on-going work we are combining data to develop trajectories of growth from early uterine life to mid-childhood.