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Report on the effects of early-life stressors on mental health and psychopathology life course trajectories

LifeCycle report D6.2

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List of Abbreviations

ADHD: Attention deficit hyperactivity disorder

ALSPAC G2: Avon Longitudinal Study of Parents And Children - Generation 2

ALSPAC: Avon Longitudinal Study of Parents And Children

BiB: Born In Bradford Study

CBCL: Child Behaviour Checklist

CHOP: Childhood Obesity Programme study

DNBC: Danish National Birth Cohort

EDEN: Étude des Déterminants pré et postnatals du développement et de la santé de l'Enfant

ELFE: Étude Longitudinale Française depuis l'Enfance

GECKO: Groningen Expertise Centrum voor Kinderen met Obesitas

HBCS: Helsinki Birth Cohort Study

INMA: INfancia y Medio Ambiente Project

MoBa: Norwegian Mother, Father and Child Cohort Study

NFBC1966/1986: Northern Finland Birth Cohort studies

NINFEA: Nascita e INFanzia, gli Effetti dell'Ambiente

Rhea: Mother Child Cohort in Crete

SDQ: Strengths and Difficulties Questionnaire

SWS: Southampton Women's Survey

WP: Work package

Executive summary

The aim of task 6.2 is to identify early-life stressors related to mental health development, and build longitudinal models between important lifestyle and environmental factors and child mental health outcomes during the life-course. Mental health longitudinal modeling was previously applied in task 6.1 after harmonization of the main behavioral domains. We have applied these longitudinal models to social inequalities, breastfeeding duration and sleep duration. The findings indicated higher trajectories of mental health problems (more externalizing and internalizing symptoms) among children from more socially vulnerable families. However, more breastfeeding and more child sleep duration seems to be protective and reduce these mental health trajectories to lower symptom scores. The findings indicate persistent changes in mental health trajectories related to specific environmental factors. The external validity of such findings is enhanced by finding comparable results across several European and Australian birth cohorts. Future research should follow similar analytical methods and create further international synergies and extend harmonized mental health data sets, in order to assess mental health trajectories in human populations.

1. Background and task description

The aim of this task is to identify early-life stressors related to psychological development, mental health and risk factors for psychiatric diseases at various ages across the life course. The purpose of task 6.2 is to build longitudinal models between important lifestyle and environmental factors and child mental health outcomes during the life-course.

Most of the recent scientific literature is based on mental health outcomes measured at a single time point (1). These studies are not able to analyze the complete picture of the human mental health development based on several assessments across the life-course. Modelling mental health trajectories enables health sciences to increase the understanding of the relationship between the environment and mental health development. Understanding how a specific factor alters the mental health trajectory across several time points is more meaningful from a neurodevelopment perspective for human populations than only one specific time point where the participant may recover later in life. This task enables us to go one step further and analyze mental health trajectories in several European regions, which is also important in order to gain external validity of the potential findings, since they are not only based in one specific geographic area (2).

Specifically, this task combines a selection of outputs obtained in three work packages in the LifeCycle project: WP3 (early-life stressors), however, it is important to note that the term ‘stressor’ does not necessarily mean that all the early-life factors are adverse factors, as there are also factors that may improve mental health and these are as important to study as the adverse factors; WP7 (statistical approaches for causal inference and life course trajectory analyses); and Task 6.1 (life course trajectories of mental development and mental health). The objective is to obtain insights into age windows in early life during which interventions could have the greatest impact on improving mental health. The mental health harmonization process is finished and initial trajectory modeling has been completed with successful results in task 6.1 (see Task 6.1 report). Mental health trajectories can be analyzed beyond a specific instrument (i.e., CBCL) and advances in the use of mental health domains, such as internalizing problems, externalizing problems, ADHD symptoms, and autism symptoms can be applied in different cohorts across Europe, in this case involving 19 cohorts in the LifeCycle project. Regarding the methods, we applied splines and/or mixed-effects models, individual participant data meta-analysis, and pooled analyses. To address the objective of this task, we compared the exposure effect at a specific time point on outcomes, and we study risk and resilience factors that change the trajectory.

The environmental-lifestyle factors selected for this task 6.2 were socioeconomic position, child breastfeeding duration and child sleep duration. They are well known mental health determinants (1,3,4) and may be also associated with mental health trajectories. In the next sections we describe the specific research work done on each of these important risk factors.

2. Social inequalities and mental health trajectories (Tim Cadman et al.)

Whilst it is well-established that children born into lower socioeconomic position (SEP) generally have worse mental health outcomes, most research has studied associations between SEP measured at one timepoint and mental health measured at a single future timepoint ("prospective studies"). Longitudinal designs (which model repeat measurements of mental health) are important to establish the age at which inequalities emerge and the course that they take (1,5). Identifying which outcomes show the most persistent inequalities, the ages at which inequalities emerge and the patterns of change over time can provide targets for policy and intervention.

For mental health outcomes, longitudinal designs are sparse and findings inconsistent. Whilst studies have reported higher levels of behavioral and hyperactive/inattentive symptoms in lower SEP children as young as three (6,7), to the best of our knowledge only one study has modelled how these differences develop over time (1), finding that they remain stable between ages 7 to 11. There is some evidence that inequalities in anxiety and depressive symptoms may be narrower (8,9), but again there is limited research on how these differences develop over time.

The aim is to use DataSHIELD to social model inequalities in mental health across childhood. Our specific objectives are (i) to identify the age at which inequalities emerge, (ii) to describe the change in inequalities over time and (iii) to compare inequalities between outcomes.

LifeCycle cohorts were eligible if they had at least one mental health outcome measured at a minimum of two time points. Four cohorts were included: ALSPAC, CHOP, MoBa & Raine. The two mental health outcomes chosen were child externalizing and internalizing symptoms, harmonized as percentile scores. Harmonized maternal education at birth (based on ISCED-07 criteria) was used as an indicator of SEP. Maternal education was available in all cohorts and captures both material and non-material aspects of SEP (10).

To model trajectories of symptoms, we used multilevel growth-curve models which account for the dependency between observations from the same individual at different time points. To allow for potential non-linearity in trajectories we used fractional polynomial transformations of the age term (11). Inequalities were described using the Slope Index of Inequality (SII), an indicator of the absolute difference in outcome between the hypothetical lowest and highest levels of a socioeconomic exposure (12). To derive the SII, maternal education was first transformed to a rank variable where 0 = highest education and 1 = lowest. We include maternal education and interactions between maternal education and the polynomial age terms as fixed effects. The full model is provided below:

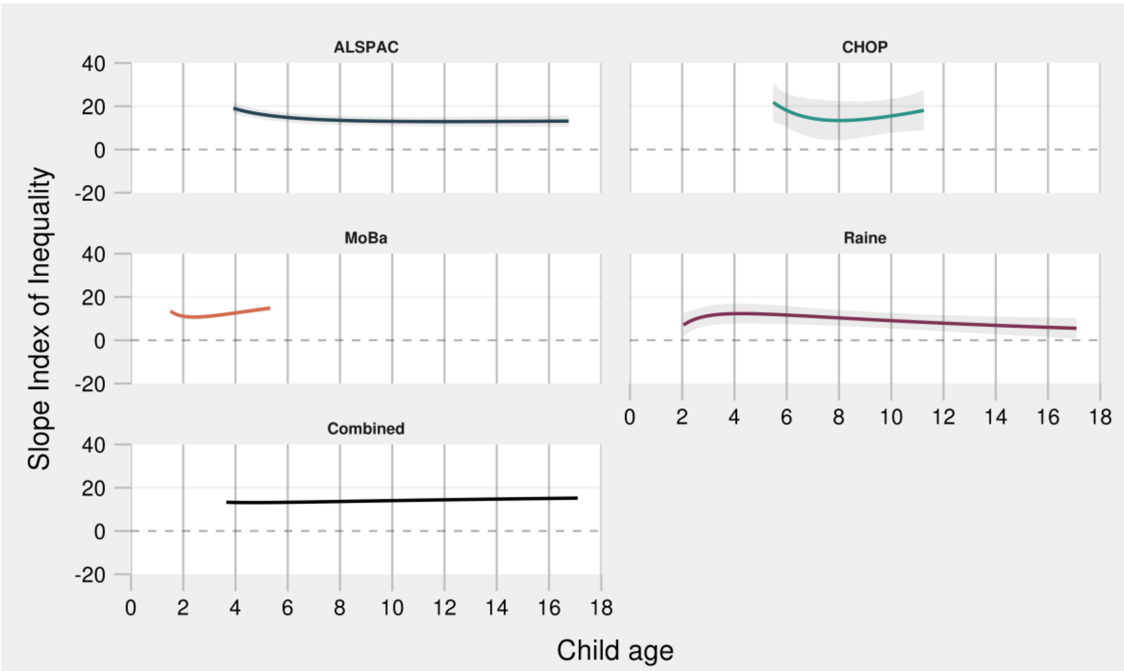
$$Y_{ij} = (\beta 0 + \mu_{0j}) + (\beta 1)(MatEd_j) + (\beta 2 + \mu_{2j})(age_{ij})^{p1} + (\beta 3 + \mu_{3j})(age_{ij})^{p2} + (\beta 4)(MatEd_j)(age_{ij})^{p1} + (\beta 5)(MatEd_j)(age_{ij})^{p2} + (\beta 6)(sex) + e_{ij}$$

Where Y is the mental health outcome for person j at time i, age is the age in years at measurement, MatEd is rank score for maternal education, $\beta 0$ = average value of outcome at age 0, $\beta 1$ = average change in outcome between hypothetical case of 100% of sample having lowest level of maternal education vs 0% (SII), $\beta 2$ & $\beta 3$ = average change in outcome per year age (transformed to the power of p1 and p2, which represent the powers providing best model fit described below), $\beta 4$ & $\beta 5$ = average change in SII per year age (age transformed as described), $\beta 6$ = difference in mental health between boys and girls at age 0, μ = random effect and e = residual.

In order to meta-analyze trajectories from multiple cohorts, it was necessary to find one pair of polynomial terms for each mental health outcome which adequately fit in all cohorts. We therefore tested multiple combinations of polynomials and chose the models which on average had the best fit in all cohorts (based on negative log-likelihood statistic).

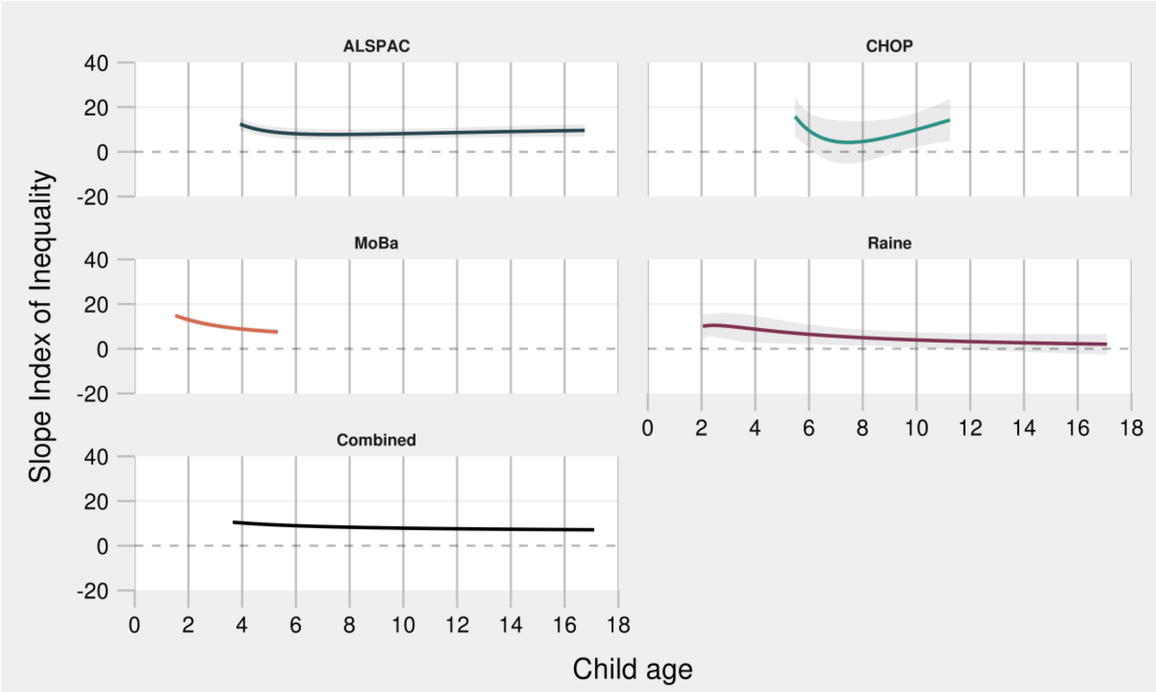
Results presented here were undertaken on 4 cohorts with up to 84,228 participants depending on the outcome. The best-fitting model for externalizing model contained age transformations of ^-1 and ^-0.5, whilst for internalizing the best fitting model contained age transformations of ^-2 & ^-1. Figure 1 shows trajectories of inequality in externalizing symptoms. The value on the y-axis indicates the difference in externalizing symptoms between the highest and lowest values of maternal education, with values above 0 showing that children born to mothers of lower education have greater symptoms. We found that for all cohorts, children of lower socioeconomic position had higher externalizing symptoms at the first measurement occasion. The earliest age at which inequalities were present was age 2 (MoBa). The meta-analyzed trajectory (bottom-left) showed that this gap remained relatively constant across childhood.

Figure 1: Social inequalities in trajectories of externalizing symptoms



We found a similar pattern of results for internalizing symptoms, with social inequalities again present from the earliest measurement point (Figure 2). In contrast to externalizing, we found evidence that this gap slightly narrowed over time. However, it did not disappear, and at age 16 the predicted level of internalizing symptoms was still higher for children born to mothers with lower education.

Figure 2: Social inequalities in trajectories of internalizing symptoms



These preliminary results show that DataSHIELD can be used to conduct trajectory modelling and that findings can be meta-analyzed across cohorts. Using the rich data from the EUCCN, this is first study to model inequalities in mental health symptoms across the whole of childhood. We build on previous findings by showing that for both externalizing and internalizing, inequalities are present from as early as age two, and that this early disadvantage persists across childhood. The effect of SEP appeared greatest for externalizing compared to internalizing. This has important implications, as externalizing is generally associated with poorer later-life outcomes than internalizing, especially in terms of education (13). This study shows the need for policy intervention to reduce mental health inequalities and ensure all children have the best start to life.

3. Infant breastfeeding practices and externalizing behavior in preschool children (Johana L. Nader et al.)

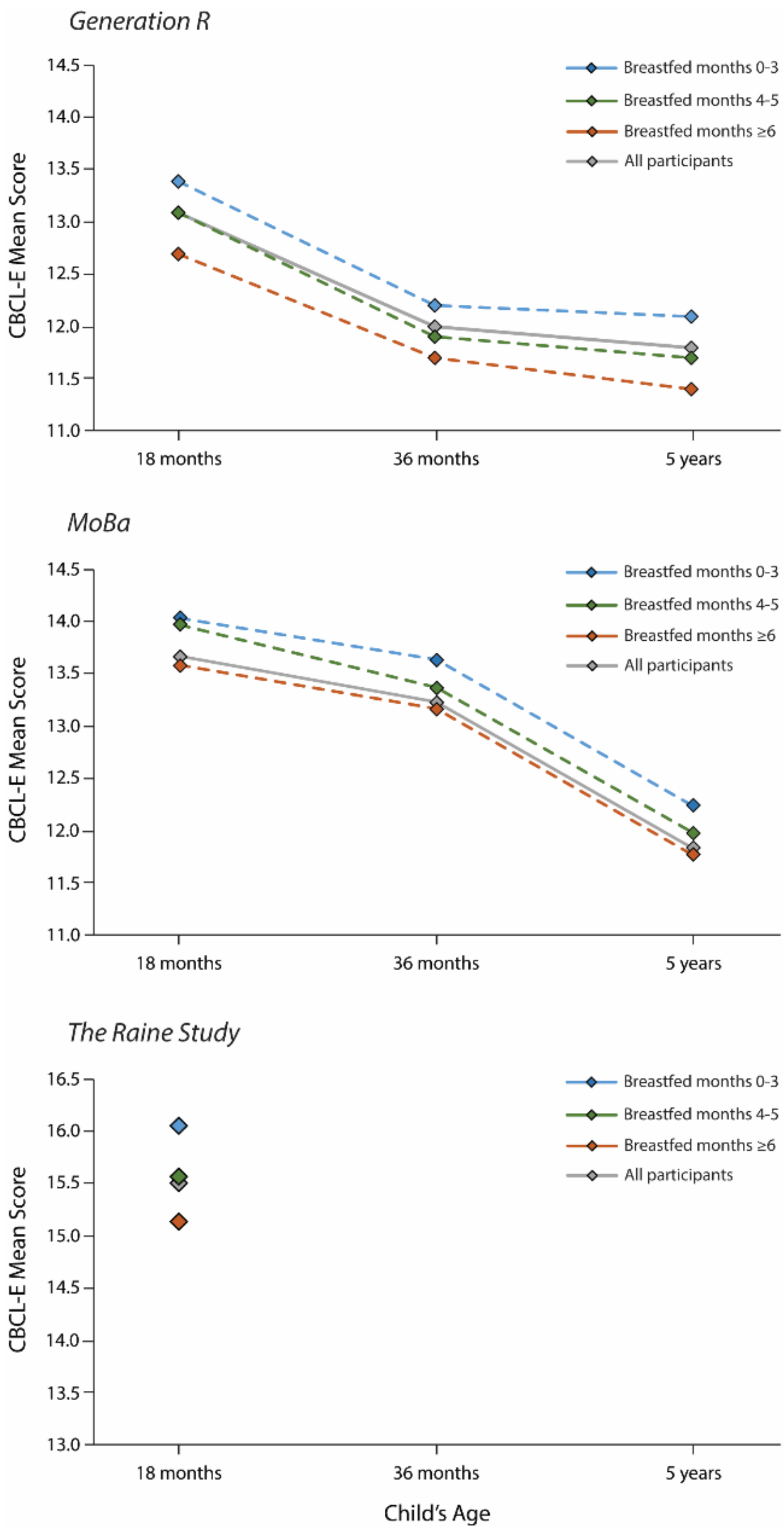
Infant breastfeeding practices directly following birth have long been the focus of research on lifetime health (14). More recently, the relationship between breastfeeding and adverse childhood behavior have come into focus, and associations between shorter breastfeeding duration and increased risk for behavioral problems in childhood have been reported (15-18). These findings point towards an interesting potential link, but the reliability and wider representability of these associations can be improved by extending relevant analyses to larger sample sizes and more diverse populations, and by analyzing the mental health outcomes in several time points.

The current study comprises overlapping data on early infant feeding practices and subsequent externalizing behavior in preschoolers from The Generation R Study (Generation R), The Norwegian Mother, Father and Child Cohort Study (MoBa) and The Western Australian Pregnancy Cohort Study (The Raine Study). Developmental trajectories describe how externalizing behavior progresses across age, and how these differ by infant feeding practices and maternal socioeconomic and lifestyle traits. Finally, we explore and discuss the potential association certain infant feeding practices may have with increasing the risk for adverse early childhood behavior.

Multivariate logistic regression models were constructed and performed to assess potential associations between duration of any breastfeeding or timing of solid food introduction, and externalizing behavioral problems in children aged 18 months, 36 months, and 5 years. The regression models were adjusted for by child’s sex, maternal education, maternal pre-pregnancy smoking, whether the pregnancy was planned, parity, and a history of any psychological disorder prior to the index pregnancy.

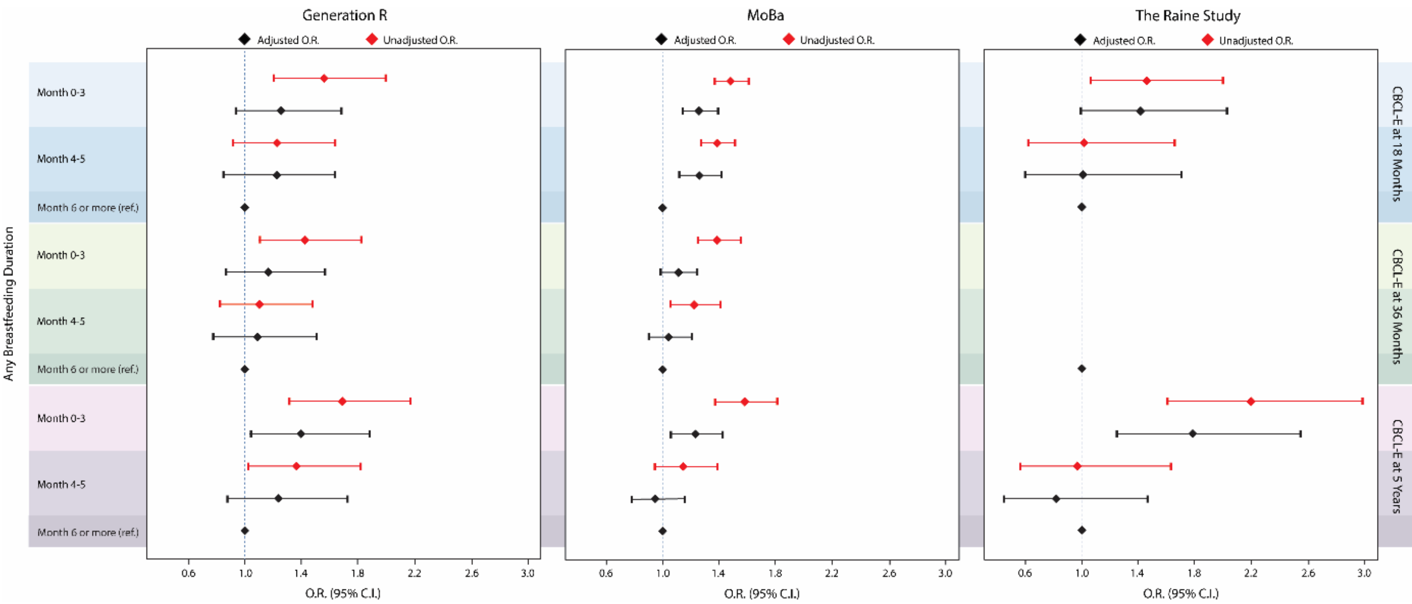
Longitudinal trajectories across these three ages could only be compared directly between Generation R and MoBa, and these revealed somewhat divergent patterns in how mean externalizing scores change for child participants over time, but illustrate an overall decrease in externalizing behavior between 18 months and 5 years of age (Figure 3).

Figure 3. Mean CBCL-Externalizing scores across age by breastfeeding duration in three pregnancy cohort studies (Generation R, MoBa, The Raine Study)



The results for crude and adjusted multivariate analyses revealed that a shorter breastfeeding duration increased the odds for adverse externalizing scores at 5 years of age in all three of the included cohort studies (Figure 4).

Figure 4. Crude and adjusted odds ratios for adverse CBCL externalizing scores (>90th percentile) at 18 months, 36 months, and 5 years of age by maternal breastfeeding duration (adjusted for by child's sex, maternal education, maternal pre-pregnancy smoking, whether the pregnancy was planned, parity, and maternal history of psychological problems before pregnancy)



In this study, shorter duration of breastfeeding was found to significantly increase the risk for adverse externalizing behavior in children aged 5 years in all three of the pregnancy and child cohort studies. Furthermore, findings from the MoBa cohort reveal that shorter breastfeeding also increased the risk of externalizing morbidity at 18 and 36 months as well.

4. Association between preschool sleep and behavior and cognition (Kathrin Guerlich et al.)

Sleep is important for children's healthy development. There is increasing evidence that sleep difficulties and short sleep duration are associated with more behavioral problems and cognitive difficulties in school-aged children (19-21). However, for younger children of preschool age the association is less clear as there is a paucity of studies. Two systematic reviews on sleep and its relation to behavior and cognition concluded that a higher quantity of sleep was associated with better behavioral outcomes and reported mixed evidence for cognitive development (22,23). Mainly cross-sectional designs, inappropriate adjustments for covariates and a small number of publications limited the validity of results. The aim of this study was to investigate the associations between sleep duration in preschool years with later internalizing and externalizing problems and/or cognitive performance (verbal and non-verbal intelligence) at 4 to 6 years of age.

For the analyses, we used data from the EU Child Cohort Network. A cohort was eligible if it had harmonized data on sleep duration in preschool age and at least one behavior or cognition outcome measured from age 4 to 6 years. Five European cohorts participated: ALSPAC (United Kingdom), EDEN (France), ELFE (France), INMA (Spain) and SWS (United Kingdom). Preschool sleep was harmonized as the child's total sleep duration in hours per day reported by parents at around 3 to 4 years of age. Internalizing and externalizing behavior were measured with the Strengths and Difficulties Questionnaire and harmonized as percentile scores. Language and non-verbal intelligence were assessed by the Wechsler Preschool and Primary Scale of Intelligence or with the McCarthy Scales of Children's Abilities depending on the cohort and harmonized as standardized scores. We applied two-stage IPD meta-analysis, adjusted for multiple covariates (socio-demographic, pregnancy and household characteristics), to test the association between sleep duration during preschool age and later behavior and/or cognition from ages 4 to 6 years. All analyses were performed using DataSHIELD.

Mean sleep duration differed between country of cohort, with children from France showing a longer sleep duration than children from the UK or Spain. Around 14.330 children (3 cohorts) were included in the analysis of sleep duration and behavioral outcomes. 51.6% were boys. Mean age at sleep duration measurement was 3.5 years (SD: 0.2) and at behavior measurement 5.1 years (SD: 0.8). One hour of additional sleep duration during preschool age was associated with reduced internalizing and externalizing behavior percentile scores at 4 to 6 years of age after adjustment (Figure 5 and 6). Around 3.310 children were included in the analysis of sleep duration and language (4 cohorts), and sleep duration and non-verbal intelligence (4 cohorts), respectively. 53.3% were boys. Mean age at sleep duration measurement was 3.7 years (SD: 0.6) and at language or non-verbal intelligence measurement 4.9 years (SD: 0.7). No association was observed between sleep duration at preschool age and language or non-verbal intelligence at 4 to 6 years (Figure 7 and 8).

Figure 5: Total sleep duration at age 3-4 years and internalizing percentile score at 4-6 years – adjusted model

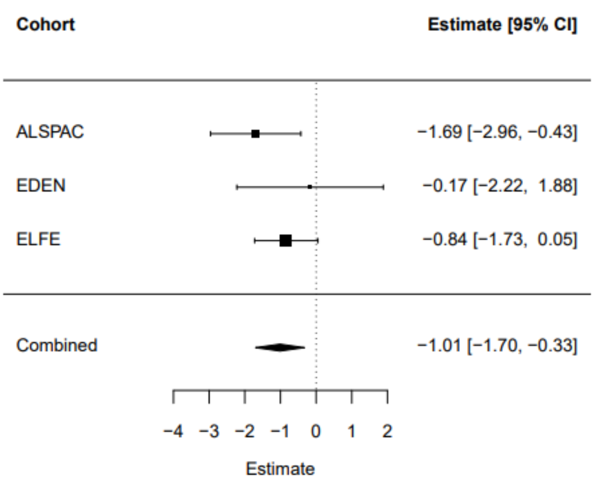


Figure 6: Total sleep duration at age 3-4 years and externalizing percentile score at 4-6 years – adjusted model

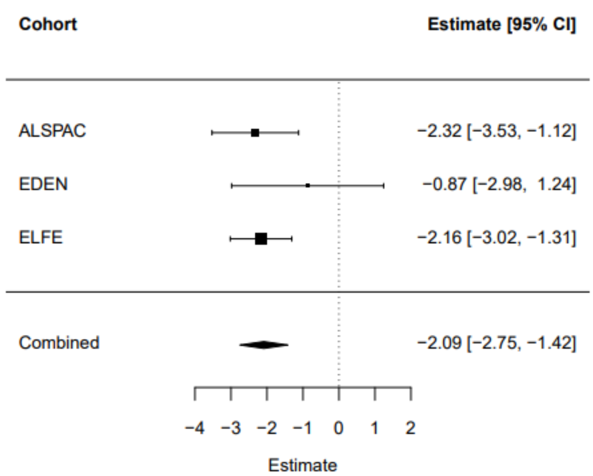


Figure 7: Total sleep duration at age 3-4 years and language standardized score at 4-6 years – adjusted model

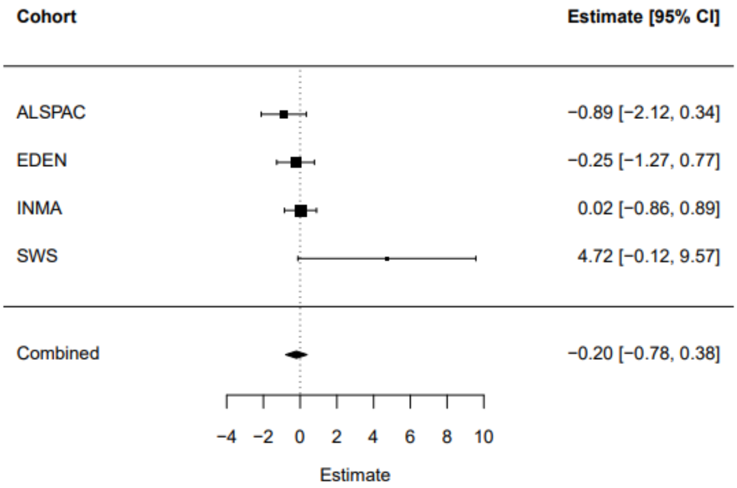
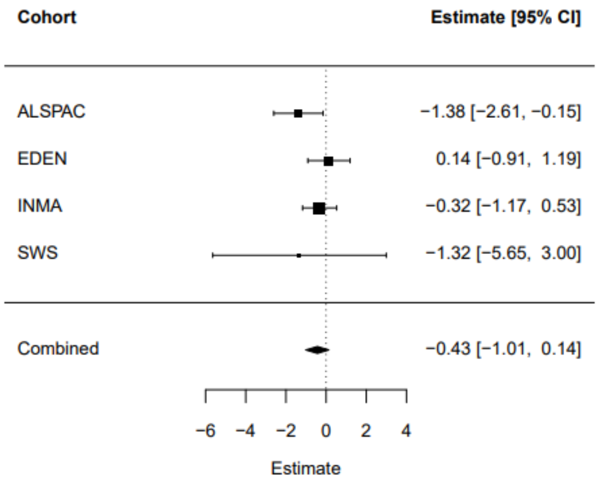


Figure 8: Total sleep duration at age 3-4 years and non-verbal intelligence standardized score at 4-6 years – adjusted model



We showed using data from five large European birth-cohorts, that shorter sleep duration in preschool age was associated with both higher internalizing and externalizing behavior scores from ages 4 to 6 years, while sleep duration was not associated with either language or non-verbal intelligence. Thus, an adequate sleep duration at an early age is important for children's later mental health.

5. Other research papers underway contributing to task 6.2

There is a number of other studies that are aiming to assess how early life stressors are associated with mental health trajectories following similar methods as work presented in this report.

1) **Nature and Child Cognition and Behavior (study under planning)**
Leads: Payam Dadvand, Jordi Julvez, Jordi Sunyer
Cohorts: DNBC, HBC, EDEN, ELFE, CHOP, RHEA, NINFEA, MoBa, REPRO_PL, INMA, Generation R, BiB, ALSPAC, The Raine Study

2) **Sibling effects and pre-maturity**
Leads: Ninha Silva, Eero Kajantie, Sylvain Sebert (UOULU)
Objective: 1) associate the presence of term-born sibling(s) with the health and social risk of the preterm child; and 2) investigate the impact of prematurity on term-born siblings' physical behavioral and social outcomes.

3) **Daycare and emotional and behavioural symptoms**
Leads: Maria Melchior, Barbara Heude, Marie-Aline Charles (INSERM)
Cohorts: EDEN, ELFE

Objective: investigate the relationship between childcare attendance prior to school entry and children's later psychological development.

4) **Maternal smoking score and mental health**

Leads: Justiina Ronkainen, Sylvain Sebert, Rae-Chi Huang, Phillip Melton, Ashleigh Lin (UOULU, UWA)

Objective: associate DNA methylation induced by maternal smoking during pregnancy with later behaviour scores in childhood and adolescence.

5) **Pregnancy lifestyle and child behavior**

Leads: Jordi Julvez, Raquel Garcia, Sílvia Fernández, Jordi Sunyer

Cohorts: ALSPAC, ERASMUS, MoBa, DNBC, The Raine Study, INMA, GECKO, CHOP, SWS, BiB

Objective: associate a maternal lifestyle score during pregnancy with the trajectories of child internalizing and externalizing problems.

6) **Urban exposome during pregnancy and early childhood and child cognitive and motor function**

Leads: Anne-Clair Binter, Monica Guxens (ISGLOBAL)

Cohorts: ALSPAC, EDEN, GenR, INMA, MoBa, NINFEA, BiB, RHEA (+WP3 cohorts: ABCD, GASPII, PICCOLOPIÙ)

Objective: assess whether the urban exposome during pregnancy and early childhood is related to cognitive and motor function in children.

7) **Urban exposome during pregnancy and early childhood and child emotional and behavioral problems**

Leads: Anne-Clair Binter, Monica Guxens (ISGLOBAL)

Cohorts: ALSPAC, EDEN, GenR, INMA, MoBa, NINFEA, BiB, RHEA, ABCD, GASPII, PICCOLOPIÙ

Objective: assess whether the urban exposome during pregnancy and early childhood is related to emotional and behavioural problems in children.

8) **Maternal postnatal depression and childhood temperament: insights from the Norwegian Mother, Father and Child Study (MoBa)**

Leads: Johanna L. Nader (NIPH), Jennifer R. Harris (NIPH)

Cohorts: MoBa

Objective: This study uses data from the Norwegian Mother and Child Cohort Study (MoBa) to examine how maternal postnatal depression 6 months after birth predicts symptoms of activity, shyness and emotionality at three stages of preschool age (18 months, 36 months, and 5 years).

9) **Sleep and ASD/ADHD symptoms and diagnoses in children**

Lead: Sabine Plancoulaine (INSERM)

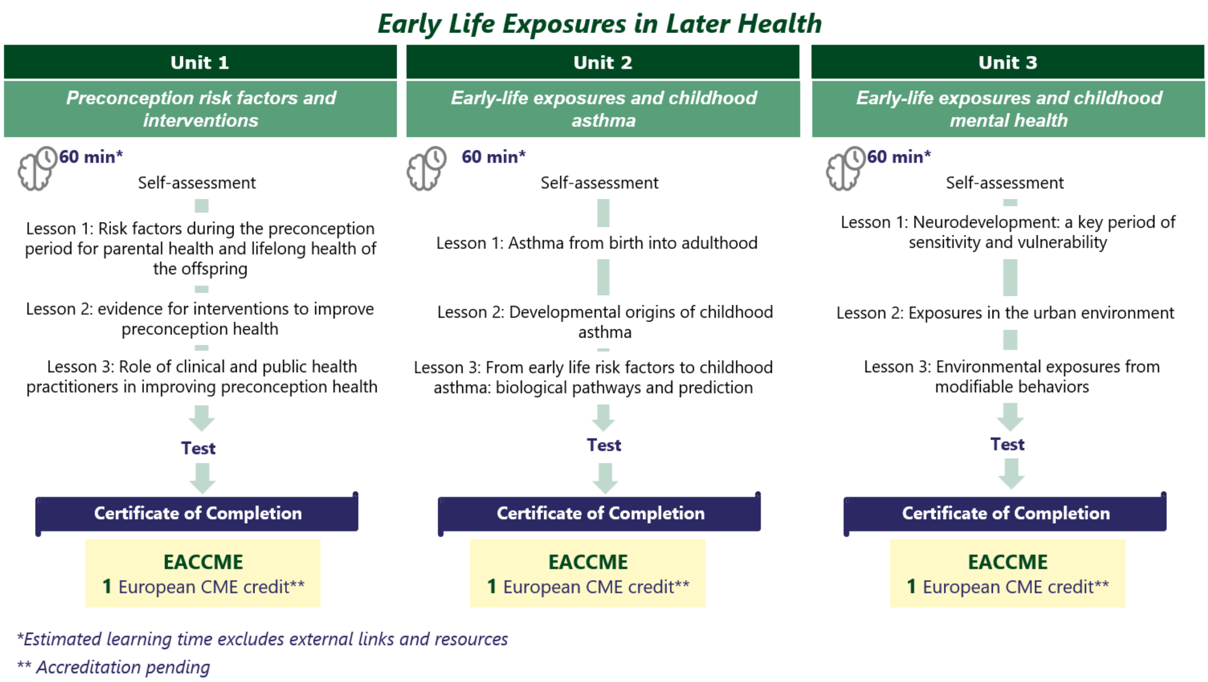
Cohorts: ALSPAC, EDEN, ELFE, INMA, MoBa, RHEA

Objectives: 1) To study the relations between ASD and ADHD symptoms before 3 years of age and sleep duration at age 3 (+/- 6 months); 2) To study the relations between sleep duration at age 3 (+/- 6 months) and ASD and ADHD symptoms and diagnosis at later ages.

6. e-Learning Module: Early Life Exposures in Later Health

An open access e-Learning module will be launched on the ENeA platform (https://enea.med.lmu.de/) in Fall 2021. The module Early Life Exposures in Later Health consolidates the scientific evidence base and status of recommendations of LifeCycle topics and outcomes. This e-learning module is targeted to international allied healthcare professionals and researchers working in the field. WP6 members has contributed to create a specific lesson relating urban exposures and later child mental health, in addition to this, we suggested some recommendations in order to avoid risk factors potentially hazardous to the mental health, and with this, we are aiming to improve mental health development in the general population (Figure 9). By this means, research findings will be transferred into practical applications and effectively disseminated in line with current concepts of using digital information sharing with a broad global outreach.

Figure 9. Early life exposure and later health lessons (Unit 3 from WP6)



7. Conclusions

The task of relating early-life stressors (or environmental-lifestyle factors) with mental health outcomes has shown association patterns that go beyond a specific time point. We observed changes in the mental health trajectories across age. Low maternal education is longitudinally associated with more externalizing and internalizing problems starting at young age and following a similar trajectory during several years of follow up. Similarly, longer breastfeeding and sleep durations were associated with lower trajectories of mental health problems, particularly for externalizing symptoms. The external validity of these findings is enhanced since the LifeCycle project includes harmonized data from several population-based birth cohorts across Europe and Australia. The outcome of this task should be taken as an example for future studies aiming to understand how the environmental factors may be associated with mental health trajectories. It is important to extend the experience and lessons learned in this project, and create more international synergies and scientific collaborations aiming to create larger consortiums of harmonized data. Indeed, these actions should promote the use of mental health repeated measurements based on the main behavioral domains in order to describe mental health trajectories. The understanding of environmental factors influencing mental health trajectories may permit us to look for early-life strategies and public health recommendations in order to improve the mental health of the general population, particularly during development periods of more vulnerability to potential stressors.

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