

# Cohort description: Measures of early-life behaviour and later psychopathology in the LifeCycle Project - EU Child Cohort Network

Johanna L. Nader, Mònica López-Vicente, Jordi Julvez, Monica Guxens, Tim Cadman, Ahmed Elhakeem, Marjo-Riitta Järvelin, Nina Rautio, Jouko Miettunen, Hanan El Marroun, et al.

# ▶ To cite this version:

Johanna L. Nader, Mònica López-Vicente, Jordi Julvez, Monica Guxens, Tim Cadman, et al.. Cohort description: Measures of early-life behaviour and later psychopathology in the LifeCycle Project - EU Child Cohort Network. Journal of Epidemiology, In press, 33 (6), pp.321-331. 10.2188/jea.JE20210241. hal-03522806

# HAL Id: hal-03522806 https://hal.sorbonne-universite.fr/hal-03522806

Submitted on 12 Jan2022

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Received May 14, 2021; accepted September 15, 2021; released online November 13, 2021

# 1 Study profile

2	Cohort description: Measures of early-life behaviour and later psychopathology
3	in the LifeCycle Project - EU Child Cohort Network
4	
5	Authors and Affiliations
6	Johanna L. Nader <sup>1*</sup> , Mònica López-Vicente <sup>2,3</sup> , Jordi Julvez <sup>4,2</sup> , Monica Guxens <sup>2,3</sup> , Tim Cadman <sup>5</sup> ,
7	Ahmed Elhakeem <sup>5</sup> , Marjo-Riitta Järvelin <sup>6</sup> , Nina Rautio <sup>6</sup> , Jouko Miettunen <sup>6,7</sup> , Hanan El Marroun <sup>3,8,9</sup> ,
8	Maria Melchior <sup>10</sup> , Barbara Heude <sup>11</sup> , Marie-Aline Charles <sup>11,12</sup> , Tiffany C. Yang <sup>13</sup> , Rosemary R. C.
9	McEachan <sup>13</sup> , John Wright <sup>13</sup> , Kinga Polanska <sup>14</sup> , Jennie Carson <sup>15</sup> , Ashleigh Lin <sup>15</sup> , Sebastian Rauschert <sup>15</sup> ,
10	Rae-Chi Huang <sup>15</sup> , Maja Popovic <sup>16</sup> , Lorenzo Richiardi <sup>16</sup> , Eva Corpeleijn <sup>17</sup> , Marloes Cardol <sup>17</sup> , Tuija M.
11	Mikkola <sup>18,19</sup> , Johan G. Eriksson <sup>18,20,21,22,23</sup> , Theodosia Salika <sup>24</sup> , Hazel Inskip <sup>24,25</sup> , Johan Lerbech
12	Vinther <sup>26</sup> , Katrine Strandberg-Larsen <sup>26</sup> , Kathrin Gürlich <sup>27</sup> , Veit Grote <sup>27</sup> , Berthold Koletzko <sup>27</sup> , Marina
13	Vafeiadi <sup>28</sup> , Jordi Sunyer <sup>2</sup> , Vincent W. V. Jaddoe <sup>8,9</sup> , Jennifer R. Harris <sup>29</sup> for the LifeCycle Project
14	Group.
15	
16	<sup>1</sup> Department of Genetics and Bioinformatics, Division of Health Data and Digitalisation, Norwegian Institute of Public Health, Oslo, Norway
17	<sup>2</sup> ISGlobal, Instituto de Salud Global de Barcelona, Barcelona, Spain
18	<sup>3</sup> Department of Child and Adolescent Psychiatry, University Medical Center Rotterdam, Erasmus MC
19	<sup>4</sup> Institut d'Investigació Sanitària Pere Virgili, Hospital Universitari Sant Joan de Reus, 43204 Reus, Spain
20	<sup>5</sup> MRC Integrative Epidemiology Unit at University of Bristol, Population Health Sciences, Bristol Medical School, Bristol, UK
21	<sup>6</sup> Center for Life Course Health Research, University of Oulu, Oulu, Finland
22	<sup>7</sup> Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland
23	<sup>8</sup> Department of Pediatrics, University Medical Center Rotterdam, Erasmus MC
24	<sup>9</sup> The Generation R Study Group, Erasmus MC, Rotterdam, CA, The Netherlands
25	<sup>10</sup> Sorbonne Université, INSERM, Institut Pierre Louis d'Épidémiologie et de Santé Publique, IPLESP, 75012, Paris, France
26	<sup>11</sup> Université de Paris, Centre for Research in Epidemiology and Statistics (CRESS), INSERM, INRAE, Paris, France
27	<sup>12</sup> Unité mixte Inserm-Ined-EFS Elfe, INED, Paris, France
28	<sup>13</sup> Bradford Institute for Health Research, Bradford Teaching Hospitals NHS Foundation Trust, Bradford, UK
29	<sup>14</sup> Department of Hygiene and Epidemiology, Medical University of Lodz, Lodz, Poland
30	<sup>15</sup> Telethon Kids Institute, University of Western Australia, Australia
31	<sup>16</sup> Cancer Epidemiology Unit, Department of Medical Sciences, University of Turin and CPO Piemonte, Turin, Italy

- 32 <sup>17</sup>Department of Epidemiology, University Medical Center Groningen, Groningen, The Netherlands
- 33 <sup>18</sup>Folkhälsan Research Center, Helsinki, Finland
- 34 <sup>19</sup>Clinicum, Faculty of Medicine, University of Helsinki, Finland
- 35 <sup>20</sup>Public Health Promotion Unit, National Institute for Health and Welfare, Helsinki, Finland
- 36 <sup>21</sup>Department of General Practice and Primary Health Care, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
- 37 <sup>22</sup>Singapore Institute for Clinical Sciences, Agency for Science, Technology, and Research, Singapore
- 38 <sup>23</sup>Department of Obstetrics & Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore
- 39 <sup>24</sup>Medical Research Council Lifecourse Epidemiology Unit, Southampton General Hospital, University of Southampton, Southampton, UK.
- 40 <sup>25</sup>NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, University of Southampton,
- 41 Southampton, UK.
- 42 <sup>26</sup>Section of Epidemiology, Department of Public Health, University of Copenhagen, Copenhagen, Denmark
- 43 <sup>27</sup>Division of Metabolic and Nutritional Medicine, Department of Pediatrics, Dr. von Hauner Children's Hospital, University Hospital, LMU,
- 44 Munich, Germany
- 45 <sup>28</sup>Department of Social Medicine, Faculty of Medicine, University of Crete, Heraklion, Greece.
- 46 <sup>29</sup>Division of Health Data and Digitalization, Center for Fertility and Health and Department of Genetics and Bioinformatics, The Norwegian
- 47 Institute of Public Health, Oslo, Norway
- 48
- 49 Corresponding author: Dr. Johanna Lucia Nader, Department of Genetics and Bioinformatics, Norwegian Institute of Public
- 50 Health, Sandakerveien 24 C, 0473 Oslo, Norway. E-mail: JohannaLuciaThorbjornsrud.Nader@fhi.no
- 51
- 52 Short Title (Running Title): Early-life behaviour and later psychopathology in LifeCycle
- 53 Number of Tables: 2
- 54 Number of Figures: 5
- 55 Number of Supplementary Files: 3
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## 68 Abstract

Background: The EU LifeCycle Project was launched in 2017 to combine, harmonise, and analyse
data from more than 250,000 participants across Europe and Australia, involving cohorts participating
in the EU-funded LifeCycle Project. The purpose of this cohort description is to provide a detailed
overview over the major measures within mental health domains that are available in 17 European and
Australian cohorts participating in the LifeCycle Project.

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75 Methods: Data on cognitive, behavioural and psychological development has been collected on 76 participants from birth until adulthood through questionnaire and medical data. We developed an 77 inventory of the available data by mapping individual instruments, domain types, and age groups, 78 providing the basis for statistical harmonization across mental health measures.

79

Results: The mental health data in LifeCycle contain longitudinal and cross-sectional data for ages 0-80 18+ years, covering domains across a wide range of behavioural and psychopathology indicators and 81 82 outcomes (including executive function, depression, ADHD and cognition). These data span a unique 83 combination of qualitative data collected through behavioural/cognitive/mental health questionnaires and examination, as well as data from biological samples and indices in the form of brain imaging 84 (MRI, foetal ultrasound) and DNA methylation data. Harmonized variables on a subset of mental 85 86 health domains have been developed, providing statistical equivalence of measures required for 87 longitudinal meta-analyses across instruments and cohorts.

88

89 Conclusion: Mental health data harmonized through the LifeCycle project can be used to study life
90 course trajectories and exposure-outcome models that examine early life risk factors for mental illness
91 and develop predictive markers for later-life disease.

92

93 *Keywords:* Birth and pregnancy cohorts, Child behaviour and mental health, Population
94 epidemiology, Child development, DataSHIELD

#### 96 Background and Purpose

Effects of early life exposures on later life mental health are well known, but more research to 97 98 understand and elucidate the pathways from stressors to outcomes is needed. The LifeCycle Project -EU Child Cohort Network, a Horizon 2020 project, is a pan-European and Australian initiative 99 comprised of 19 pregnancy and birth cohorts, established to study exposure-to-outcome associations 100 and trajectories across the life course (https://lifecycle-project.eu/).<sup>1</sup> In general, studies in LifeCycle 101 102 aim to construct developmental trajectories, develop risk assessment models, measure developmental 103 adaptations and evaluate mediating epigenetic effects to better understand the consequences of early-104 life exposures to stressors for risk factors and diseases in adulthood. The large sample sizes achieved through this consortium facilitate high statistical power needed for increased accuracy of estimates and 105 106 more robust findings.

107

Mental health is one of the main outcomes within the LifeCycle Project.<sup>1</sup> While mortality rates for 108 many non-communicable diseases have steadily declined in some populations over the past few 109 decades, such as coronary heart disease<sup>2,3</sup> and chronic obstructive pulmonary disease,<sup>4</sup> the global 110 burden of mental illness is on the rise.<sup>5</sup> The impact of mental illness on disability and socioeconomic 111 prosperity is increasing around the world, and it is predicted that mental illness will contribute more to 112 disability-adjusted life years (DALYs) than any other category of diseases by the year 2030.<sup>6</sup> An 113 114 understanding of how mental health impacts and mediates disease risk and prognosis for other 115 conditions is also beginning to emerge, with recent meta-analyses revealing significantly higher risks for cardiovascular<sup>7</sup> and metabolic<sup>8</sup> diseases linked to severe mental illness. 116

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This cohort description focuses on the extensive work done to catalogue and harmonise variables
related to cognitive, behavioural, and psychological development within the broader LifeCycle
consortium.<sup>1</sup> It is well-recognised that experiences in early life play an important part in shaping later
mental health<sup>9</sup> and the data within the LifeCycle Project permit analyses of these associations.
LifeCycle includes many pregnancy and birth cohorts that prospectively collected data on offspring
from conception and across different ages of child, adolescent, and adult development. The

availability of data from multiple follow-up assessments is essential for probing questions aboutcausality and linking early life stressors with later life mental health symptoms and outcomes.

126

The mental health studies in LifeCycle aim to investigate epidemiological interrelations between early 127 128 life exposures, behaviour, and cognition, with later mental and physical health. Towards this end we 129 have harmonised measures from 17 LifeCycle cohorts to enable studies that examine how 130 environmental stressors in utero and in early childhood affect, or are associated with, psychological 131 trajectories, behaviours, and mental outcomes throughout childhood, adolescence and adulthood. Additionally, we are examining the nature and degree of mediation of these associations through 132 epigenetic changes and brain development (Figure 1). To our knowledge, the data compiled for these 133 studies within LifeCycle represents the largest ongoing consolidation of childhood behaviour, 134 psychopathology and cognition data to date, encompassing more than 200 multidimensional and 135 multi-informant established mental health measures collected from at least 250,000 participants. 136



137 Figure 1. Available mental health outcomes from prenatal to adulthood in the LifeCycle mental health and cognitive

138 data

140 disorders)

<sup>139 (</sup>ADHD: Attention deficit hyperactivity disorder; ASD: Autism spectrum disorders; CD: cognitive disorders; PD: psychiatric

# 141 Cohorts, participants and follow-up

142 A total of 17 child-parent cohorts based in 13 countries are contributing with mental health data: Avon

- 143 Longitudinal Study of Parents and Children (ALSPAC, United Kingdom), Born in Bradford (BiB,
- 144 United Kingdom), EU Childhood Obesity Programme (CHOP, Germany/Italy/Spain/Poland/Belgium),
- 145 Danish National Birth Cohort (DNBC, Denmark), Etude des Déterminants du développement et de la
- 146 santé de l'Enfant (EDEN, France), Etude Longitudinale Française depuis l'Enfance (ELFE, France),
- 147 Groningen Expert Center for Kids with Obesity Drenthe cohort (GECKO Drenthe cohort, The
- 148 Netherlands), the Generation R Study (Generation R, The Netherlands), Helsinki Birth Cohort Study
- 149 (HBCS, Finland), Infancia y Medio Ambiente (INMA, Spain), The Norwegian Mother, Father and
- 150 Child Cohort Study (MoBa, Norway), Northern Finland Birth Cohorts (NFBC1966/1986, Finland),
- 151 Nascita e INFanzia: gli Effetti dell'Ambiente (NINFEA, Italy), The Raine Study (Australia), Rhea
- 152 Mother & Child Cohort Study (RHEA, Greece), and the Southampton Women's Survey (SWS, United
- 153 Kingdom).







156 Figure 2. Geographic distribution and sample sizes of cohorts in LifeCycle contributing mental health

- 157 data
- 158

159 The geographic coverage is broad, spanning across much of northern, western, central and southern

- 160 Europe as well as Western Australia (Figure 2). Mental health data from more than 250,000 children
- are available (as of June 2021), including either mother-child or mother-father-child cohorts, and the
- study population is diverse with respect to the age of the participants, cohort types, and data collection
- 163 periods (Table 1). As described elsewhere for the LifeCycle consortium, most of the cohorts in the

164 LifeCycle project (ALSPAC, CHOP, DNBC, EDEN, GECKO, HBCS, INMA, MoBa,

- 165 NFBC1966/1986, NINFEEA, RHEA, and SWS) predominantly represent ethnic groups from the
- 166 background population (more than 95% European/White), but certain cohorts like BiB, ELFE, The
- 167 Generation R Study, and The Raine Study have significant representation of other ethnic groups as
- 168 well.<sup>10</sup>
- 169

Cohort	Location of Coordinating Centre	Cohort Type	Data collection period	Recruitment	N (Live Births)		
	5		1		· · ·		
ALSPAC <sup>11,12</sup>	Avon, United Kingdom	Population-based	-based 1990-present Pregnancy				
BiB <sup>13</sup>	Bradford, United Kingdom	Population-based	2007-2010	Pregnancy	13,786		
CHOP <sup>14</sup>	Belgium (Liege, Brussels), Germany (Munich, Nuremberg), Italy (Milano), Poland (Warsaw), Spain (Reus, Tarragona)	Mixed (Randomised controlled intervention trial (first year) with birth cohort)	2002-2015	First 8 weeks of life	1,678		
DNBC <sup>15</sup>	Copenhagen, Denmark	Population-based	1996-present	Pregnancy	96,804		
EDEN <sup>16</sup>	Nancy and Poitiers, France	Population-based	2003-2017	Pregnancy	1,907		
ELFE <sup>17</sup>	Paris, France	Population-based	2011-present	Birth	18,329		
GECKO <sup>18</sup>	Drenthe, The Netherlands	Population-based	2006-present	Pregnancy	2844		
The Generation R Study <sup>19,20</sup>	Rotterdam, The Netherlands	Population-based	2002-present	Pregnancy	9,749		
HBCS <sup>21</sup>	Helsinki, Finland	Population-based	1934-present	Birth	13,345		
	Sabadell, Spain	Population-based	2004-present	Pregnancy	622		
INMA <sup>22</sup>	Valencia, Spain	Population-based	2003-present	Pregnancy	787		
	Gipuzkoa, Spain	Population-based	2006-present	Pregnancy	612		
MOBA <sup>23</sup>	Oslo, Norway	Population-based	1999-present	Pregnancy	113,564		
NFBC1966 <sup>24</sup>	Oulu, Finland	Population-based	1966-present	Pregnancy	12,058		
NFBC1986 <sup>25</sup>	Oulu, Finland	Population-based	1985/1986-present	Pregnancy	9,432		
NINFEA <sup>26</sup>	Torino, Italy	Population-based (Internet-based recruitment)	2005-present	Pregnancy (Internet- based recruitment)	6,816		
The Raine Study <sup>27</sup>	Perth, Australia	Population-based (Randomised assignment to multiple ultrasounds during pregnancy)	1989-present	Pregnancy	2,868		
RHEA <sup>28</sup>	Crete, Greece	Population-based	2007-present	Pregnancy	1,458		
SWS <sup>29</sup>	Southampton, United Kingdom	Population-based	1998-present	Pre-pregnancy	3,158		

170 Table 1. Summary characteristics of LifeCycle cohorts participating with mental health data

171

172 The participating cohorts include child participants with follow-up data ranging from birth until

adulthood (Table 2). Questionnaires, medical records, doctor diagnoses and registries were variably

- used across the cohorts to collect data at different ages, but all of the cohorts collected baseline data
- during pregnancy or at birth, and included a follow-up data collection at least once by the time the
- 176 child participant was 24 months of age. Although the regularity of follow-up differs substantially
- across cohorts, ranging from annually to many years apart, at least half of the cohorts performed some
- type of follow-up data collection for all incremental age groups up until 6 years of age. The
- 179 overlapping age ranges enable comprehensive comparative analyses of mental health constructs
- 180 between and within the populations to which these index children belong.

Cohort	Baseline (no. live births)	Age of child at assessment (years)														
		0 to <1	1 to <2	2 to <3	3 to <4	4 to <5	5 to <6	6 to <7	7 to <8	8 to <9	9 to <10	10 to <12	12 to <14	14 to <16	16 to <18	18+
ALSPAC <sup>a</sup> Sex (% M:F)	14,953	11,466 51.6:48.4	11,097 51,7:48,3	9,993 51.8:48.2	9,779 51.7:48.3	9,632 51.8:48.2	8,683 51.6:48.4	8,410 51.4:48.6	8,282 50,7:49,3	7,481 49.8:50.2	7,718 49.3:50.7	7,552 49.4:50.6	6,829 49.1:50.9	5,506 47.1:52.0	5,212 43.6:56.4	
BiB Sex (% M:F)	13,786 51.6:48.4	1,436 49.6:50.4	3,484 50.3:49.7	2,911 50.1:49.9	1,167 47.9:52.1	2,505 49.9:50.1	79 51.9:48.1									
CHOP <sup>b</sup> Sex (% M:F)	1,678 50.7:49.3	1,175 49.0:51.0	1,067 48.1:51.9	934 48.2:51.8	747 46.6:53.4	674 47.2:52.8	655 47.2:52.8	1,028 48.5:51.5	594 49.0:51.0	589 47.0:53.0		719 46.5:53.5				
DNBC Sex (% M:F)	96,804 51.3:48.7	70,276 51.1:48.9	65,548 51.0:49.0				1,628° 52.0:48.0		57,156 51.2:48.8			46,345 <sup>d</sup> 49.7:50.3 48,579 <sup>c</sup> 48.2:51.8				35,558 <sup>f</sup> 41.6:58.4
EDEN <sup>g</sup> Sex (% M:F)	1,907		1,612 52.8:47.2	1,429 52.2:47.8	1,257 52.4:47.6	1,192 51.3:48.7	1,114 52.7:47.3					557 51.3:48.7				
ELFE Sex (% M:F)	18,329 51.4:48.6	16,547 51.2;48.9	14,439 51.2:48.8	13,277 50.7:49.3	11,935 51.2:48.8											
GECKO Sex (% M:F)	2,844	2,812 50.3:49.7	2,558 50.3:49.7	2,319 50.1:49.9	1,819 51.2:48.8	1,486 51.4:48.6	2,322 50.3:49.7					2,299 49.8:50.2				
Generation R Sex (% M:F)	9,749 50.7:49.3	7,893 50.5:49.5					8,305 50.5:49.5				7,393 50.1:49.9		6,842 50.3:49.7			
HBCS Sex (% M:F)	13,345 52.3:47.7	13,345 52.3:47.7	13,342 52.3:47.7	13,342 52.3:47.7	8,947 52.0:48.0	7,252 51.7:48.3	9,947 52.6:47.4	10,055 52.7:47.3	10,046 52.6:47.4	10,033 52.7:47.3	9,985 52.8:47.2	9,902 52.8:47.2				13,345 52.3:47.7
INMA-Sabadell Sex (% M:F)	622		559 51.3:48.7			481 51.4:48.7		473 51.6:48.4			433 52.0:48.0					
INMA-Valencia Sex (% M:F)	787		694 52.6:47.4				530 51.7:48.3		469 50.8:49.3		429 50.6:49.4					
INMA-Gipuzkoa Sex (% M:F)	612 50.3:49.8		556 49.1:50.9	506 52.0:48.0		394 49.2:50.8			397 49.4:50.6	382 54.0:46.0						
MoBa Sex (% M:F)	113,564	87,801 51.0:49.0	74,750 51.0:49.0		58,835 51.0:49.0		41,617 50.9:49.1		53,517 51.3:48.7	43,609 50.9:49.1						
NFBC1966 Sex (% M:F)	12,058		10,729 50.8:49.2											10,927 50.4:49.6		9,517 51.3:48.7
NFBC1986 Sex (% M:F)	9,432		1,803 50.9:49.1				5		8,416 <sup>d</sup> 51.3:48.7 8,525 <sup>h</sup> 51.5:48.5					6,985 <sup>d</sup> 50.0:50.0 7,344° 48.5:51.5 6,795 <sup>i</sup> 49.4:50.6		Data collection ongoing (2019- 2020)
NINFEA Sex (% M·F)	7,527 <sup>j</sup>	6,907 50 7·49 3	6,279			4,398			2,348 50 3·49 7			837 50 8·49 2		49.4.50.0		
The Raine Study Sex (% M:F)	2,868 50,7;49.3	50	2,430 50,9:49,1	1,974 52,1:47,9	2,260 50,9:49,1	511110.5	2,236 51.6:48.4			2,140 51,4:48,6		2,048 51.7:48.3		1,864 51.4:48.6	1,693 49.9:50.1	1,462 48.9:51.1
RHEA Sex (% M:F)	1,458 50,1:49.9	1,257 50,2:49.8	569 54.5:45.5			904 52.3:47.7		626 55.1:44.9								
SWS Sex (% M·F)	3,158	2,959 51 7:48 3	2,875	2,779 51 8:48 2	2,625 52 1:47 9	1,182 51 9:48 1		2,034 51 3:48 7		1,214 49.4:50.6						

# Table 2. Age ranges and sex (% male:female) of participants during assessment in LifeCycle cohorts

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\*ALSPAC follow-up data is based on number of parents completing at least some of the questionnaire(s) on young person up to age 7 years, and number of children attending clinic from age 7 years and onwards

<sup>b</sup>CHOP follow-up data is based on number of children with at least one anthropometric measurement at the considered age

°DNBC follow-up data at 5 years based on a subsample, selected based on parental alcohol characteristics

<sup>d</sup>Parent-reported data

°Self-reported data

<sup>f</sup>DNBC data collection for 18-year follow-up is currently ongoing <sup>g</sup>EDEN follow-up data is based on number of children with at least one neurodevelopment assessment at the considered age

182 183 184 185 186 187 188 189 190 191 <sup>h</sup>Teacher-reported data

<sup>i</sup>Clinical data

<sup>j</sup>NINFEA baseline data refers to no. pregnant women recruited

## 192 Main outcome measures

# 194 Psychological, motor and cognitive measures

Mental and cognitive disorders comprise some of the most frequently diagnosed conditions in children under 18 years of age. The combined data resource will contain information pertaining to the children from more than 200 mental health measures, covering eight clinical domains across 60 dimensions (Table S1). A majority of these measures assess domains under a broad banner of 'mental health', encompassing psychological functions, cognitive and executive functions and psychological development (67.0%; 136 of 203), covering dimensions such as neurodevelopmental disorders, internalising and externalising symptoms, temperament and mental diagnoses. Further domains include language skills (31.0%; 63 of 203), executive functions (29.1%; 59 of 203), memory (11.3%; 23 of 203) and general intelligence (8.4%; 17 of 203) (Table S1). There are many commonalities between mental health domain-types and significant overlap in the age groups with measures in specific domains (Figure 3). This makes it possible to harmonise the data.<sup>30</sup> Most of the cohorts continuously follow up their participants, and the availability of harmonised data will tend to increase with time.



Figure 3. Overview of overlap in LifeCycle mental health, behavioural and cognitive domains across age

233 Basic illustration of the range of developmental domains and participant ages for data in the LifeCycle Project.

236	There are a number of approaches to harmonise data and several of these have been described and
237	successfully implemented in large collaborations. <sup>31,32,33,10</sup> The LifeCycle Project has developed a
238	protocol to generate harmonised variables across a selection of important cognitive and mental health
239	domains. This harmonisation approach creates standardised scores and percentiles for important
240	domains such as internalising and externalising symptoms, ADHD and ASD symptoms and diagnosis,
241	and language and motor functions. Percentiles and standardised scores were used as they allow the
242	pooling of mental health outcome data collected using different scales or instruments. One of the
243	biggest harmonisation challenges this project faced was obtaining a thorough inventory of the
244	available mental health data in individual cohorts, which was overcome by mapping the available data
245	by instrument, measure, age group, and domain. A subset of cohorts has also employed items from the
246	same mental health, cognitive and motor function measures, and these data can be pooled or co-
247	analysed without the need for harmonisation (Figure 4). All of the measures harmonised thus far by
248	age and cohort can be found in the LifeCycle online catalogue ( <u>https://catalogue.lifecycle-project.eu/</u> ).
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Figure 4. Overview of overlap in mental health and cognitive measures in the LifeCycle cohorts providing mental health data

are described in supplementary table 1.

268 (ANT: Attention Network Task; ASQ: Ages and Stages Questionnaire; BAS: Behavioural Approach System; BDI: Becks Depression

269 Inventory; BRIEF: Behaviour Rating Inventory of Executive Function; BSID: Bayley Scales of Infant Development; CAST: Childhood

270 Asperger Syndrome Test; CBB: CogState Brief Battery; CBCL: Child Behaviour Checklist; CPRS-R: Revised Conners' Parent Rating Scale;

271 DAWBA: Development and Well-Being Assessment; DDST: Denver Developmental Screening Test; DISC-IV: Diagnostic Interview

272 Schedule for Children; DST: Digit Span Test; FTT: Finger Tapping Test; GMDS: Griffiths Mental Development scales; GPT: Grooved

273 Pegboard Test; M-CHAT: Modified Checklist for Autism in Toddlers; MB-CDI: MacArthur-Bates Communicative Development

274 Inventories; N-Back: Working Memory Test; NEPSY-II: Developmental NEuroPSYchological Assessment, Second Edition; PLIKS:

275 Psychosis-like symptoms measure; RPM: Raven's Progressive Matrices; SDMT: Symbol Digit Modalities Test; SDQ: Strengths and

276 Difficulties Questionnaire; TEA-ch: Test of Everyday Attention for Children; TMT: Trail Making Test; TRF: Teacher Report Form; WASI:

277 Wechsler Abbreviated Scale of Intelligence; WPPSI: Wechsler Preschool and Primary Scale of Intelligence; YRBSS: Youth Risk Behavior

278 Surveillance System; YSR: Youth Self-Report).

<sup>266</sup> Summary of overlapping measures and age ranges in participating cohorts. The full list of available measures (including non-overlapping)

#### 279 Early-life exposures – lifestyle, migration, socioeconomic, and urban environment

The LifeCycle online catalogue<sup>10</sup> also contains information on harmonised data on diverse measures of exposures early in life. These will enable the analysis of risk models for mental health that assess the nature and impact of indirect and direct exposures experienced in early life, and comorbidities with adverse mental health symptoms and other health conditions. Comprehensive exposure-outcome analyses will also be used to develop predictive markers for mental health in children and adolescents, which may help shape the prediction of mental disorders, allowing for targeted early intervention.

286

## 287 Mediating Pathways - Brain Development

Early life is a particularly vulnerable time-window for brain development. The vital stages of 288 289 neurogenesis, proliferation and migration occur almost exclusively during foetal development, and experience-dependent brain connectivity (i.e. myelination) is largely shaped and completed in early 290 childhood.<sup>34</sup> Research-based evidence has repeatedly linked brain structure, volume, and connectivity 291 indicators to a number of behavioural and cognitive outcomes.<sup>35,36,37</sup> However, study samples are often 292 limited in size and population diversity, and only few longitudinal studies exist.<sup>38</sup> A subset of cohorts 293 294 in LifeCycle have participant data on structural brain imaging (ALSPAC n=950; Generation R  $n\approx 4000$ ;<sup>39</sup> NFBC1966 n=1000; NFBC1986 n=600), and will be contributing information on 295 296 neuroanatomical markers such as total brain volume, cortical grey matter, white matter volume, 297 ventricular volume, and volumes of subcortical brain structures including the hippocampus and 298 amygdala. In addition, structural and functional connectivity metrics have been assessed. Data have been collected through neuroimaging techniques, such as foetal ultrasound and Magnetic Resonance 299 Imaging (MRI) in childhood and /adulthood MRI. These data enable LifeCycle to describe changes in 300 301 structural and functional development of the brain from foetal life and infancy, and to subsequently 302 associate this brain development in early life with psychopathology outcomes in childhood, 303 adolescence and adulthood.

- 305
- 306

# 307 Mediating Pathways - Epigenetics

An increasing number of studies are beginning to demonstrate the importance of epigenetic modification in mediating the risk of disease, including mental health outcomes. Epigenetically-modified loci have been linked to a wide range of mental disorders such as schizophrenia,<sup>40</sup> as well as childhood onset disorders such as ADHD,<sup>41</sup> and ASD,<sup>42</sup> but conflicting and non-replicated associations mean that the causal relationships remain poorly understood.<sup>43</sup> LifeCycle mental health studies can currently analyse DNA methylation data on 14,368 offspring cohort participants (Figure 5), measured at birth (cord or placenta blood; N=7,783), childhood (0-12 years; N=3,055), adolescence (12-18 years; N=2,680), or adulthood (>18 years; N=850). Six of the thirteen contributing cohorts additionally contain longitudinal epigenetic data [ALSPAC, CHOP (multiple age groups in childhood), EDEN, Generation R, INMA, and RHEA]. The particular focus will be to identify epigenetic mechanisms that mediate the effect of early life exposures on behavioural and cognitive development, as well as mental health outcomes such as ASD, ADHD, depression and anxiety. This means it will be possible to track epigenetic changes in participants with behavioural and/or neurodevelopmental outcomes across time, and study causal relationships between environmental exposures in pregnancy or early life and later-life mental health outcomes mediated by DNA methylation. 





#### **Figure 5.** Overview of sample sizes for DNA methylation data in the offspring from birth to adulthood

337 Circle sizes are proportionate to the DNA methylation sample sizes as indicated in the scale at the bottom of the figure.

\*Numbers relevant as of June, 2021 (sample processing and data collection is ongoing in several LifeCycle cohorts)

339 340

# 341 Framework for collaborative analyses

LifeCycle aims to perform most of the analyses through DataSHIELD.<sup>44,45</sup> With the recent launch of 342 the platform and its analytical features for use with LifeCycle harmonised data, a number of novel 343 collaborative studies have begun to form within the theme of mental health. Examples of planned and 344 ongoing exposure-outcome analyses include infant feeding patterns and school-age externalising 345 behaviours, maternal smoking in pregnancy and adverse child behaviours, associations between sleep, 346 behaviour and cognition, sibling effects and prematurity, and socioeconomic inequalities and general 347 348 mental health trajectories. Results from these studies are currently pending, but they have already 349 shown that independent participant data resources have been successfully harmonised and can be co-350 analysed. The quantity and breadth of mental health and cognitive data available that have been mapped and harmonised by the LifeCycle mental health research group is a singular resource to enable 351 developmental studies of mental health. These data will play an important role in replicating previous 352

353 findings with an enhanced statistical power, expanding upon previous associations through larger and

354 more diverse samples, and in the development of novel models to describe how multi-faceted early-

355 life exposures can shape and influence the landscape of mental health in later life.

356

#### 357 Strengths and limitations

There are many strengths inherent in large consortia such as LifeCycle.<sup>1</sup> Key among these is that 358 359 LifeCycle is building the EU Child Cohort Network, a sustainable research network that will enable 360 continued exploitation of the LifeCycle data, metadata and collaborative progress beyond the usual 361 timelines of a funded grant. Another important strength is the ability to study age differences and agerelated mental health and cognitive changes; this developmental aspect will help to understand the 362 long- and short-term consequences of early life exposures, and how other factors such as epigenetic 363 changes may mediate later health outcomes. Geographic diversity is also a key feature; it provides 364 enhanced location coverage and generalizability of results, and also facilitates intra- and inter-365 population comparisons. This makes it possible to make more reliable causal inferences due to 366 367 different confounding structures.

368

The number of critical mental health domains covered is another strength, allowing for exposure-369 370 outcome research into many important and well-studied areas within this field. The availability of the 371 harmonisation protocols, coupled with the extensive overview of mental health measures, including 372 detailed information on the dimensions and age ranges across cohorts, provides users with an integrated catalogue of psychological, cognitive, and psychomotor data in participating cohorts. 373 374 Furthermore, the use of DataSHIELD enables a flexible and data-secure approach that allows new 375 cohorts and centres to link into the analysis network and contribute with their own data, as well as the 376 addition of newly harmonised data as these are collected and updated. This open-source analysis 377 platform "takes the analysis to the data, not the data to the analysis", providing researchers with the ability to remotely analyse data from multiple datasets without being able to access the data itself.<sup>45,46</sup> 378 Removing the need to physically share data externally means participating cohorts bypass ethical 379 concerns related to the protection of privacy and other issues that arise when participant data are being 380

sent internationally to multiple users, and thus addresses some important ethico-legal considerationsthat are often associated with individual-level data sharing and analysis.

383

384 The heterogeneity of the psychological and cognitive measures available presents a potential limitation. Depending on the specific research question under investigation and measurement 385 equivalence of constructs between different instruments, robust harmonisation<sup>30,32</sup> of certain measures 386 387 may not be possible or may be limited to a small number of cohorts. This reduces the sample size or 388 the range of participant ages that are possible to include. Within-country geographical bias of many of 389 the cohorts may also present a weakness. Specifically, the urban-centric nature of many of the studies could mean that the generalizability of findings will be somewhat skewed, and the population-level 390 inferences will need to take this bias into account. Furthermore, DNA methylation and brain imaging 391 data are only available for less than 10% of total study participants. These smaller sample sizes may 392 393 limit the number and strength of associations that can be found, as well as the distribution of participant ages and geographic and ethnic origins. However, the cohort studies are continuously 394 395 expanding and adding new data on their participants, including phenotypic, genetic, epigenetic and 396 biological data. The collaborative groundwork laid by LifeCycle will make it possible to continue building upon the analyses that have been performed, and help to mitigate some of the limitations that 397 have been described. 398

399

#### 400 Data Access

401 LifeCycle has developed an application procedure for data use proposals as described by Jaddoe et al.<sup>1</sup> 402 It should be noted that approvals for data use and associated fees remain under the purview of the 403 participating cohorts. This is the case regardless of whether one applies through LifeCycle or directly 404 to the cohort, and these practices may vary across cohorts. The project strives to conduct as many analyses as possible within DataSHIELD. DataSHIELD is freely available to download and use 405 (http://www.datashield.ac.uk/). This enables external cohorts to collaborate with LifeCycle and 406 perform co-analyses. For more information, please visit the official website for the LifeCycle Project 407 (https://lifecycle-project.eu/), or refer to the consortium design paper.<sup>1</sup> 408

- 409 In some cases, data sharing and transfer agreements will need to be developed. These may vary due to
- 410 country-specific practices and restrictions as outlined by local General Data Protection Regulation
- 411 (GDPR) legislation. Application procedures directly to cohorts for data can be found at the following
- 412 websites:
- 413
- 414 ALSPAC
- 415 http://www.bristol.ac.uk/alspac/researchers/access/
- 416 For more information on the ALSPAC cohort (including data dictionary, ethical considerations, and
- 417 funding), refer to Supplementary file 2.
- 418 **BiB**
- 419 https://borninbradford.nhs.uk/research/how-to-access-data/
- 420 CHOP
- 421 https://www.birthcohorts.net/birthcohorts/birthcohort/?id=137
- 422 **DNBC**
- 423 https://www.ssi.dk/English/RandD/Research%20areas/Epidemiology/DNBC/For%20researchers.aspx
- 424 EDEN
- 425 http://eden.vjf.inserm.fr/index.php/fr/contact
- 426 ELFE
- 427 https://www.elfe-france.fr/en/the-research/access-to-data-and-questionnaires/
- 428 **GECKO**
- 429 http://www.birthcohorts.net/birthcohorts/birthcohort/?id=138
- 430 The Generation R Study
- 431 https://www.generationr.nl/researchers/collaboration/
- 432 INMA
- 433 http://www.proyectoinma.org/presentacion-inma/politica-colaboracion/en\_politica-colaboracion.html
- 434 HBCS
- 435 https://thl.fi/en/web/thlfi-en/research-and-expertwork/projects-and-programmes/helsinki-birth-cohort-
- 436 study-hbcs-idefix

- 438 https://www.fhi.no/en/op/data-access-from-health-registries-health-studies-and-biobanks/data-from-
- 439 moba/research-and-data-access/

440 NFBC1966/1986

- 441 https://www.oulu.fi/nfbc/
- 442 NINFEA
- 443 https://www.progettoninfea.it/contact\_us
- 444 The Raine Study
- 445 https://www.rainestudy.org.au/
- 446 RHEA
- 447 http://www.rhea.gr/en/research/data-access/
- 448 SWS
- 449 https://www.mrc.soton.ac.uk/sws/
- 450

#### 451 Acknowledgements

- 452 We would like to thank all of the mothers, fathers and children for generously donating their time and
- 453 effort as participants in the cohorts included in LifeCycle. The long-term dedication and commitment
- 454 of both the staff and participants involved in these studies have made this work possible. For more
- 455 information on individual cohorts' acknowledgements, refer to Supplementary File 2.
- 456

# 457 Funding

- 458 LifeCycle is a five-year research project that is funded through the European Union's Horizon 2020
- 459 Research and Innovation Programme (grant agreement no. 733206). For more information on
- 460 individual cohorts' funding information, refer to Supplementary File 3.

461

#### 462 Conflict of interest statement

463 The authors have no conflict of interest to declare.

465	References
466	
467	<sup>1</sup> Jaddoe V, Felix JF, Andersen, AM, et al. The LifeCycle Project: EU child cohort network a federated analysis
468	infrastructure and harmonized data of more than 250,000 children and parents. European Journal of Epidemiology 2020;
469	35(7):709-724.
470	<sup>2</sup> Jousilahti P, Laatikainen T, Peltonen M, et al. Primary prevention and risk factor reduction in coronary heart disease
471	mortality among working aged men and women in eastern Finland over 40 years: population based observational study. BMJ
472	2016;352:i721.
473	<sup>3</sup> Bhatnagar P, Wickramasinghe K, Wilkins E, Townsend N. Trends in the epidemiology of cardiovascular disease in the UK.
474	Heart 2016;102(24):1945-1952.
475	<sup>4</sup> Gershon A, Hwee J, Victor JC, et al. Mortality trends in women and men with COPD in Ontario, Canada, 1996-2012.
476	<i>Thorax</i> 2015;70(2):121-6.
477	<sup>5</sup> Whiteford HA, Degenhardt L, Rehn J, et al. Global burden of disease attributable to mental and substance use disorders:
478	findings from the Global Burden of Disease Study 2010. Lancet 2013;382(9904):1575-86.
479	<sup>6</sup> Litt E, Baker MC, Molyneux D. Neglected tropical diseases and mental health: a perspective on comorbidity. <i>Trends</i>
480	Parasitol 2012;28(5):195-201.
481	<sup>7</sup> Correll CU, Solmi M, Veronese N, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with
482	pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World
483	<i>Psychiatry</i> 2017;16(2):163-180.
484	<sup>8</sup> Vancampfort D, Correll CU, Galling B, et al. Diabetes mellitus in people with schizophrenia, bipolar disorder and major
485	depressive disorder: a systematic review and large scale meta-analysis. World Psychiatry 2016;15(2):166-74.
486	<sup>9</sup> Lewis AJ, Galbally M, Gannon T, Symeonides, C. Early life programming as a target for prevention of child and adolescent
487	mental disorders. BMC Med 2014;12:33.
488	<sup>10</sup> Pinot de Moira, A., Haakma, S., Strandberg-Larsen, K. et al. The EU Child Cohort Network's core data: establishing a set
489	of findable, accessible, interoperable and re-usable (FAIR) variables. Eur J Epidemiol 2021;36:565–580.
490	<sup>11</sup> Boyd A, Golding J, Macleod J, et al. Cohort profile: the 'children of the 90 s'-the index offspring of the avon longitudinal
491	study of parents and children. Int J Epidemiol 2013;42(1):111-27.

- 492 <sup>12</sup>Fraser A, Macdonald-Wallis C, Tilling K, et al. Cohort profile: the avon longitudinal study of parents and children:
- 493 ALSPAC mothers cohort. *Int J Epidemiol* 2013;42(1):97–110.

- 494 <sup>13</sup>Wright J, Small N, Raynor P, et al. Cohort Profile: the Born in Bradford multi-ethnic family cohort study. *Int J Epidemiol*495 2013;42(4):978–91.
- <sup>14</sup>Koletzko B, von Kries R, Closa R, et al. Lower protein in infant formula is associated with lower weight up to age 2 y: a
  randomized clinical trial. *Am J Clin Nutr* 2009;89(6):1836–45.
- 498 <sup>15</sup>Olsen J, Melbye M, Olsen SF, et al. The Danish national birth cohort–its background, structure and aim. *Scand J Public*
- **499** *Health* 2001;29(4):300–7.
- 500 <sup>16</sup>Heude B, Forhan A, Slama R, Douhaud L, Bedel S, Saurel-Cubizolles MJ, Hankard R, Thiebaugeorges O, De Agostini M,
- 501 Annesi-Maesano I, Kaminski M, Charles MA. EDEN mother-child cohort study group. Cohort Profile: The EDEN mother-
- 502 child cohort on the prenatal and early postnatal determinants of child health and development. Int J Epidemiol
- **503** 2016;45(2):353–63.
- 504 <sup>17</sup>Charles MA, Thierry X, Lanoe JL, Bois C, Dufourg MN, Popa R, Cheminat M, Zaros C, Geay B. Cohort proafile: the
- 505 French National cohort of children ELFE: birth to 5 years. Int J Epidemiol 2020;49(2):368–9.
- 506 <sup>18</sup>L'Abee C, Sauer PJ, Damen M, Rake JP, Cats H, Stolk RP. Cohort profile: the GECKO Drenthe study, overweight
- 507 programming during early childhood. *Int J Epidemiol* 2008;37(3):486–9.
- 508 <sup>19</sup>Kooijman MN, Kruithof CJ, van Duijn CM, Duijts L, Franco OH, van Ijzendoorn MH, de Jongste JC, Klaver CC, van der
- 509 Lugt A, Mackenbach JP, Moll HA, Peeters RP, Raat H, Rings EH, Rivadeneira F, van der Schroeff MP, Steegers EA,
- 510 Tiemeier H, Uitterlinden AG, Verhulst FC, Wolvius E, Felix JF, Jaddoe VW. The generation R study: design and cohort
- 511 update 2017. *Eur J Epidemiol* 2016;31(12):1243–64.
- 512 <sup>20</sup>White T, Muetzel RL, El Marroun H, Blanken LME, Jansen P, Bolhuis K, Kocevska D, Mous SE, Mulder R, Jaddoe VWV,
- 513 van der Lugt A, Verhulst FC, Tiemeier H. Paediatric population neuroimaging and the generation R Study: the second wave.
- 514 *Eur J Epidemiol* 2018;33(1):99–125.
- 515 <sup>21</sup>Eriksson JG, Forsén T, Tuomilehto J, Osmond C, Barker DJP. Early growth and coronary heart disease in later life:
- 516 longitudinal study. *BMJ* 2001;322(7292):949.
- 517 <sup>22</sup>Guxens M, Ballester F, Espada M, Fernández MF, Grimalt JO, Ibarluzea J, Olea N, Rebagliato M, Tardón A, Torrent M,
- 518 Vioque J, Vrijheid M, Sunyer J. INMA project. Cohort profile: the INMA-INfancia y Medio Ambiente-(Environment and
- 519 Childhood) Project. Int J Epidemiol 2012;41(4):930–40.
- 520 <sup>23</sup>Magnus P, Birke C, Vejrup K, Haugan A, Alsaker E, Daltveit AK, Handal M, Haugen M, Høiseth G, Knudsen GP, Paltiel
- 521 L, Schreuder P, Tambs K, Vold L, Stoltenberg C. Cohort profile update: the Norwegian mother and child cohort study
- **522** (MoBa). Int J Epidemiol 2016;45(2):382–8.

- 523 <sup>24</sup>University of Oulu: Northern Finland Birth Cohort 1966. University of Oulu. http://urn.fi/urn.nbn:fi:att:bc1e5408-980e-
- **524** 4a62-b899-43bec3755243.
- <sup>25</sup>University of Oulu: Northern Finland Birth Cohort 1986. University of Oulu. http://urn.fi/urn.nbn:fi:att:f5c10eef-3d254bd0-beb8-f2d59df95b8e.
- 527 <sup>26</sup>Richiardi L, Baussano I, Vizzini L, Douwes J, Pearce N, Merletti F. NINFEA cohort. Feasibility of recruiting a birth cohort
- through the Internet: the experience of the NINFEA cohort. *Eur J Epidemiol* 2007;22(12):831–7.
- 529 <sup>27</sup>Newnham JP, Evans SF, Michael CA, Stanley FJ, Landau LI. Effects of frequent ultrasound during pregnancy: a
- randomised controlled trial. *Lancet* 1993;342(8876):887–91.
- <sup>28</sup>Chatzi L, Plana E, Daraki V, et al. Metabolic syndrome in early pregnancy and risk of preterm birth. *Am J Epidemiol*2009;170(7):829–36.
- <sup>29</sup>Inskip HM, Godfrey KM, Robinson SM, Law CM, Barker DJ, Cooper C. SWS Study group. Cohort profile: the
- 534 southampton women's survey. *Int J Epidemiol* 2006;35(1):42–8.
- <sup>30</sup>Fortier I, Burton PR, Robson PJ, et al. Quality, quantity and harmony: the DataSHaPER approach to integrating data across
- bioclinical studies. *Int J Epidemiol* 2010;39(5):1383-93.
- 537 <sup>31</sup>Doiron D, Burton P, Marcon Y, et al. Data harmonization and federated analysis of population-based studies: the
- 538 BioSHaRE project. *Emerg Themes Epidemiol* 2013;10(1):12.
- 539 <sup>32</sup>Fortier I, Raina P, Van den Heuvel ER, et al. Maelstrom Research guidelines for rigorous retrospective data harmonization.
- 540 *Int J Epidemiol* 2017;46(1):103-105.
- <sup>33</sup>Beenackers MA, Doiron D, Fortier I, et al. MINDMAP: establishing an integrated database infrastructure for research in
- ageing, mental well-being, and the urban environment. *BMC Public Health* 2018;18(1):158.
- <sup>34</sup>Stiles J, Jernigan TL. The basics of brain development. *Neuropsychol Rev* 2010:20, 327-48.
- <sup>35</sup>Banaj N, Piras F, Piras F, et al. Cognitive and psychopathology correlates of brain white/grey matter structure in severely
- 545 psychotic schizophrenic inpatients. *Schizophr Res Cogn* 2018;12:29-36.
- <sup>36</sup>Cheetham A, Allen NB, Whittle S, et al. Amygdala volume mediates the relationship between externalizing symptoms and
- daily smoking in adolescence: A prospective study. *Psychiatry Res Neuroimaging* 2018;276, 46-52.
- 548 <sup>37</sup>Bayard F, Thunell CN, Abé C, et al. Distinct brain structure and behavior related to ADHD and conduct disorder traits. *Mol*
- 549 Psychiatry 2018; doi: 10.1038/s41380-018-0202-6.

- <sup>38</sup>Volkow ND, Koob GF, Croyle RT, et al. The conception of the ABCD study: From substance use to a broad NIH
- collaboration. *Developmental Cognitive Neuroscience* 2017; 32, 4-7.
- <sup>39</sup>White T, Muetzel RL, El Marroun H, et al. Paediatric population neuroimaging and the Generation R Study: the second
  wave. *Eur J Epidemiol* 2018;33(1):99-125.
- <sup>40</sup>Pries LK, Gülöksüz S, Kenis G. DNA Methylation in Schizophrenia. *Adv Exp Med Biol* 2017;978, 211-236.
- <sup>41</sup>Wiers CE, Lohoff FW, Lee J, et al. Methylation of the dopamine transporter gene in blood is associated with striatal
- dopamine transporter availability in ADHD: a preliminary study. *Eur J Neurosci* 2018;48(3):1884-1895.
- <sup>42</sup>Duffney LJ, Valdez P, Tremblay MW, et al. Epigenetics and autism spectrum disorder: A report of an autism case with
- 558 mutation in H1 linker histone HIST1H1E and literature review. *Am J Med Genet B Neuropsychiatr Genet* 2018;177, 426-433.
- <sup>43</sup>Barker ED. Epigenetics, Early Adversity and Child and Adolescent Mental Health. *Psychopathology* 2018;51, 71-75.
- <sup>44</sup>Wolfson M, Wallace SE, Masca N, et al. DataSHIELD: resolving a conflict in contemporary bioscience-performing a
- 561 pooled analysis of individual-level data without sharing the data. *International Journal of Epidemiology* 2010;39(5):1372-
- **562** 1382.
- <sup>45</sup>Gaye A, Marcon Y, Isaeva J, et al. DataSHIELD: taking the analysis to the data, not the data to the analysis. *Int J Epidemiol*2014;43(6):1929-1944.
- <sup>46</sup>Wilson RC, Butters OW, Avraam D, et al. DataSHIELD New Directions and Dimensions. *Data Science Journal* 2017;16,
- 566 p.21. DOI: http://doi.org/10.5334/dsj-2017-021.