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Early environmental quality and life-course mental health effects: The Equal-Life project

Irene van Kamp[a,*], Kerstin Persson Waye[b], Katja Kanninen[c], John Gulliver[d], Alessandro Bozzon[e], Achilleas Psyllidis[e], Hendriek Boshuizen[f], Jenny Selander[g], Peter van den Hazel[h], Marco Brambilla[i], Maria Foraster[j], Jordi Julvez[k], Maria Klatte[l], Sonja Jeram[m], Peter Lercher[n], Dick Botteldooren[o], Gordana Ristovska[p], Jaakko Kaprio[q], Dirk Schreckenberg[r], Maarten Hornikx[s], Janina Fels[t], Miriam Weber[u], Ella Braat-Eggen[v], Julia Hartmann[a], Charlotte Clark[w], Tanja Vrijkotte[x], Lex Brown[y], Gabriele Bolte[z] Equal-Life Scientific Team**

Background: There is increasing evidence that a complex interplay of factors within environments in which children grows up, contributes to children's suboptimal mental health and cognitive development. The concept of the life-course exposome helps to study the impact of the physical and social environment, including social inequities, on cognitive development and mental health over time.

Methods: Equal-Life develops and tests combined exposures and their effects on children's mental health and cognitive development. Data from eight birth-cohorts and three school studies (N = 240.000) linked to exposure data, will provide insights and policy guidance into aspects of physical and social exposures hitherto untapped, at different scale levels and timeframes, while accounting for social inequities. Reasoning from the outcome point of view, relevant stakeholders participate in the formulation and validation of research questions, and in the formulation of environmental hazards. Exposure assessment combines GIS-based environmental indicators with omics approaches and new data sources, forming the early-life exposome. Statistical tools integrate data at different spatial and temporal granularity and combine exploratory machine learning models with hypothesis-driven causal modeling.

Conclusions: Equal-Life contributes to the development and utilization of the exposome concept by (1) integrating the internal, physical and social exposomes, (2) studying a distinct set of life-course effects on a child's development and mental health (3) characterizing the child's environment at different developmental stages and in different activity spaces, (4) looking at supportive environments for child development, rather than merely pollutants, and (5) combining physical, social indicators with novel effect markers and using new data sources describing child activity patterns and environments.

Introduction

Mental health is one of the fastest-growing public health issues in Europe primarily in terms of awareness. Its contribution to the burden of disease weighs heavily on societies and economies. In Europe, the cost of ill mental health was estimated to be over 4% of GDP in 2018.[1] Those with ill mental health have poorer educational and work outcomes than those in good mental health. Mental health at a (very) early age is a good predictor of a person's work situation in later life and available resources and accompanying adult mental health status. It is worrying that at school age, one in ten children has a mental health problem that warrants support and treatment.[1]

There is increasing evidence that a complex interplay of factors in the environments in which children grow up contributes to irreversible mental health effects later in life.[2,3] Estimates of the prevalence of ill mental health in adults, due to different environmental factors, vary strongly between studies, depending on the factors considered.[4] Children are even at greater risk when exposed to the same concentration of environmental contaminants due to lower smaller size and their risk-increasing behavior (e.g. hand-to-mouth contact) than adults.[5] Furthermore, with rapid brain development in early life, environmental exposure at that age may result in irreversible effects on mental health and cognitive development.[6] Despite this, children and adolescents have systematically been understudied in this domain.

The exposome concept offers a framework to study this complex interplay. The exposome was introduced firstly in 2005 and later expanded to emphasize the importance of human

What this article adds

Equal-Life, as part of the European Human Exposome Network, focuses uniquely on the effect of the internal and external exposome on mental health and cognitive development in children, with data available from conception to age 21 years. The discovery of new biomarkers for mental health and cognitive development has added scientific value. Traditional exposures with a negative health impact are combined with features promoting health by a novel approach to multimodal exposures. By including a positive outlook on physical and social environments Equal-Life stimulates a more holistic approach to environmental planning for different life stages and health equity.

[a]Centre for Sustainability, Environment and Health, National Institute for Public Health and the Environment, Bilthoven, the Netherlands; [b]School of Public Health and Community Medicine, Gothenburg University, Gothenburg, Sweden; [c]A.I.Virtanen Institute for Molecular Sciences, University of Eastern Finland, Kuopio, Finland; [d]Centre for Environmental Health and Sustainability & School of Geography, Geology and the Environment, University of Leicester, Leicester, United Kingdom; [e]Joint Research Center for Urban Systems and Environment, Delft University of Technology, Delft, the Netherlands; [f]Centre for Nutrition, Prevention and Health Services, National Institute for Public Health and the Environment, Bilthoven, the Netherlands; [g]Unit of Occupational Medicine at the Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [h]International Network on Children's Health, Environment and Safety, Ellecom, the Netherlands; [i]Data Science Laboratory, Politecnico di Milano, Milan, Italy; [j]Barcelona Institute for Global Health, ISGlobal, Barcelona, Spain; [k]Institut d'Investigació Sanitària Pere Virgili (IISPV), Barcelona, Spain; [l]Department of Cognitive and Developmental Psychology, Technical University Kaiserslautern, Kaiserslautern, Germany; [m]National Institute of Public Health, Ljubljana, Slovenia; [n]Institute for Highway Engineering and Transport Planning, Graz University of Technology, Graz, Austria; [o]Department of Information technology, Faculty of Engineering and Architecture, Ghent University, Ghent, Belgium; [p]Institute of Public health of the Republic of North Macedonia, Skopje, North Macedonia; [q]Institute for Molecular Medicine Finland, Department of Public Health, University

environmental exposures.[7,8] The concept refers to the totality of exposures from a variety of external and internal exposures over a complete lifetime, from conception onward. It reinforces the idea that health or disease is the product of the individual's history of exposures, resources, vulnerability, and coping possibilities. Research on exposomes is facilitated by technological developments that complement traditional epidemiological study designs.[9] In this context, the studies of the genome and exposome intersect, but they also diverge because the exposome is a variable and dynamic entity that evolves throughout the lifetime of the individual. Although the genetic sequence is generally unaltered through the lifetime, the genome is dynamic and expresses itself in a range of biomarkers. Part of the changes in the genome reflects the variation of the exposome, whereas part of it reflects developmental genetic programming, such as growth and puberty.

Despite the fact, that social inequalities in health are a major public health challenge, and that social inequalities in housing and environmental conditions also prevail in Europe, until now the exposome concepts did not comprehensively capture causes of health inequities.[10,11]

Moreover, the social environment is a critical dimension in the process of mental health and cognitive development. Previous exposome concepts do not fully acknowledge the relevance of the social environment.[12] On the other hand, research linking the social environment to children's mental health and cognitive development has largely missed the variety of physical exposures over and above social positions of population groups.[13]

Social and environmental inequalities originate at an early stage in life and tend to cluster together in children from families with low socioeconomic position. Early exposures and their distribution along the social gradient can have several effects on health in relation to childhood development into adulthood. Conversely, a specific health problem is often the resultant of several adverse exposures that originate from different sources to which an individual is exposed in different ways and in different stages of his or her development. Besides suffering from health effects of unfair environmental and social conditions, children from disadvantaged societal groups might be prone by their living context to unhealthy behaviors such as poor diet, lack of physical activity, and excessive screen time, which tracks into adulthood.[14] Families with the low socioeconomic position are more likely to maladapted coping strategies (smoking, alcohol use, and substance use) which have direct prenatal and postnatal effects, as on the young child.[15]

Unfavorable factors tend to cluster together in children from families with low socioeconomic position. Children growing up in poverty are exposed to a larger number of physical and psychosocial risk factors across their life span and across multiple settings (at home, daycare, school, and neighborhood).[16] However, despite the growing literature on neighborhood effects and child development, this work largely equates neighborhood quality with socio-economic status (SES) while ignoring the potential role of the physical quality of neighborhoods in affecting children's development.[17] A recent review concluded that future research must also more deeply explore the way children and their families interact with their neighborhood and how this is shaped by the variability in neighborhood characteristics, and its contribution to developmental inequalities.[18]

Compared to epidemiological studies in adults, relatively few studies have incorporated longitudinal data evaluating children over time. It has been found that chronic exposure to multiple risk factors leads to differences in children's biological and psychological regulatory systems, with low-income children's chronic stress systems differing significantly from their peers.[18–20] Poorer self-regulation, as evidenced by greater difficulties with attentional control, delayed gratification, and inhibitory control has been associated with growing up in poverty.[3,21,22] Also in high SES groups delayed self-control is an important predictor of negative health outcomes later in life.[23] These maladaptive coping strategies at different function levels carry on later in life. Differences in parenting interactions are associated with significant differences in child language and cognitive development across the life course.[24] The associations are systematically the result of an accumulation of multiple risk factors which mediate the final outcome. An underlying assumption is that the physical and social circumstances that a child is brought up in, affect proximal processes; that is development processes of systematic interaction between a child and their environments, needed for optimal development.

The role of mediators in this process is only partly known, but self-regulation and maladaptive coping, neurodevelopment, stress, restoration, sleep, and physical and social support, are mechanisms identified as potentially important.[25–27]

These mechanisms are relevant in every development stage, but their effect might be very different depending on age and mental health outcome.

Project description

Aim

Equal-Life studies the long-term effects on mental health and cognitive development of the child-environment interaction. Environment is broadly defined to include the physical, built, social, economic and cultural dimensions, and perceived quality of place and life.

Based on a person-context-process-time framework, Equal-Life addresses the mechanisms deemed relevant for the association between the exposome and child cognitive development and mental health.[28,29]

of Helsinki, Helsinki, Finland; [r]Centre for Applied Psychology, Environmental and Social Research (Zeus GmbH), Bochum, Germany; [s]Built Environment, Technical University Eindhoven, Eindhoven, the Netherlands; [t]Hearing Technology and Acoustics, RWTH Aachen University, Aachen, Germany; [u]City of Utrecht, Utrecht, the Netherlands; [v]Avans University of Applied Science, Tilburg, the Netherlands; [w]Population Health Research Institute, St George's University of London, London, United Kingdom; [x]Department of Public and Occupational Health, Amsterdam Public Health Research Institute, Amsterdam UMC, Amsterdam, the Netherlands; [y]School for Environmental Planning, Griffith University, Brisbane, Australia; and [z]Institute of Public Health and Nursing Research, University of Bremen, Bremen, Germany

***The members of "The Equal-Life Scientific Team" are listed in the Appendix.*

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Only the results of Equal-Life (e.g. aggregated data not traceable to individuals, algorithms and scientific findings relevant to policy makers) will be made publicly accessible and will be part of the evidence-based guidance to be developed in the project.

All cohort data, school data and sub-study data used and collected in Equal-Life will stay with their owners and will be linked to the exposome data and will only be aggregated at result level. Thereby, we will ensure that all work carried out in Equal-Life will comply with national law and comply with GDPR.

**Corresponding Author. Address: Centre for Sustainability, Environment and Health, National Institute for Public Health and the Environment, the Netherlands. E-mail: Irene.van.kamp@rivm.nl (I.v. Kamp).*

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Within Equal-Life, we distinguish between the external exposome, subdivided into the physical exposome (e.g. aspects of the built environment, environmental quality indoors and outdoors), and the social exposome (e.g. societal context, socioeconomic, social, and psychosocial factors at the individual and the community level), and the internal exposome. Intermediate effect markers of mental health include all the processes, measurable through metabolomics, epigenomics, proteomics, and gene expression, and measures such as neuroimaging, neuro -physiological and - psychological tests, that happen in the body after exposure.

The overarching aim of the Equal-Life project is to develop evidence-based guidance for policymakers, particularly those in local governments and the child and youth (care) sector. The guidance will be used by them in the identification and design of intervention strategies, and preventative measures focused on the risk factors of mental health and the cognitive- and socio-emotional development of children. Evidence-based environmental health policy responses (e.g. in planning, housing, transport, schooling, regulation, and prevention strategies) can manage adverse environments and create restorative ones; improving mental health and reducing the overall burden of disease.

To achieve this aim, Equal-Life pursues four objectives as follows:

Objective #1: Equal-Life seeks to innovate internal and external exposure assessment. The approach will combine aspects of early-life physical environments with social aspects of the environment. Developmental environments of children and adolescents/young adults are the point of attention because they have systematically been understudied in this domain. Resilience to exposures later and self-regulation capabilities are important mediators.

Objective #2: Define and map the pathogenic and salutogenic environmental factors of mental health and cognitive development

(1) by mapping the environmental features which are relevant for restoration;
(2) by describing and analyzing the association between the exposome and mental health at different developmental stages;
(3) by studying early markers of poorer mental and cognitive development while accounting for environmental sensitivities.

Objective #3: Compose and explore a set of interventions for different life-stages with the purpose to enhance the quality of settings and spaces relevant for children's activities in their social context, leading to more health equity.

Objective #4: Develop evidence-based guidance that anticipates trajectories of changes in health distribution if the exposome, or its elements, are altered at different levels. The guidance will be in such a form as to inclusion of new information can be easily added for different purposes (policy, research, or intervention studies).

Who is in the study?

Equal-life makes use of existing data from cohort and school studies and will collect new data (1) to enrich the exposure data in the cohorts (2) to more precisely focus on and describe relevant exposures (3) to better characterize the social and societal context, and (4) to provide further information regarding certain children's mental health and cognition outcomes.

The cohorts and school studies

Equal-Life has access to eight European cohorts, one national longitudinal school study, and two cross-sectional studies. Table 1 shows the included cohorts and school studies and the different age groups covered at baseline and follow-up. The geography covered is primarily Western Europe (seven countries). The birth cohorts include at least 226,807 children (mother/child pairs) for whom longitudinal data are available of mental health and cognitive development endpoints, including biomarkers and epigenetics, and related exposures. The other studies include an additional 15,866 children, some of which also provide parental information and retrospective information on perinatal circumstances.

In total, data are available for 242,673 children from preconception to 21 years. Most data are collected at a regional, and three at national (Finland, the Netherlands, and Germany) scale as presented in Figure 1.

What has and will be measured

The cohorts and school studies were selected, based on their focus on children and data availability on indicators of mental health and/or cognitive development and on information on the key mechanism studied (including stress, sleep, self-regulation, and restoration). Table 2 provides an overview of the main concepts related to outcomes and mediating processes.

The cohorts and school studies also include data at different locations and times on a range of exposures, including aspects of the built environment, outdoor and indoor environmental quality, and lifestyle-related factors. The cohort and school studies available within Equal-Life also comprise data on sociodemographic characteristics and socioeconomic circumstances at the individual level of the children. These data are currently being grouped and described in detail in an overall matrix of exposure data for the cohorts. Table 3 presents a preliminary overview of what is available.

These existing data will be enriched at the exposure side, as described below.

Table 1.

Overview of the cohorts and school studies included in Equal-Life project.

Cohort name	Cohort type	Study design	Geographical scale	Country	Age range (years)	Calendar year	Number of children
PIAMA	Birth	Longitudinal	National	Netherlands	Prenatal–20	1997–2018	4 000
FAIR	Birth	Longitudinal	Regional	Sweden	Prenatal–12	2007–2018	200 000
ABCD	Birth	Longitudinal	Regional	Netherlands	Prenatal–14	2003–2018	8 266
WALNUTS	Child/adolescence, School	Cross-sectional	Regional	Spain	11–14	2016–2018	700
BREATHE	Child, school	Longitudinal	Regional	Spain	7–11	2012–2013	2 878
FINNTWIN12	Twin-family	Longitudinal	National	Finland	11–24	1994–2006	5 600
ALPINE	Birth (Retrospective)	Cross-sectional	Regional	Austria and Italy	(prenatal) 8–11	2004–2005	1 251
ALSPAC	Birth	Longitudinal	Regional	U.K.	Prenatal–11	1991–2008	14 541
RANCH	Child, School	Cross-sectional	Regional	Netherlands	9–10	2002	737 NL
NORAH	Child, School	Cross-sectional	National	Germany	8	2012	1 243
STARS	Adolescence	Cross-sectional	Regional	Sweden	13	2015–2019	2 283

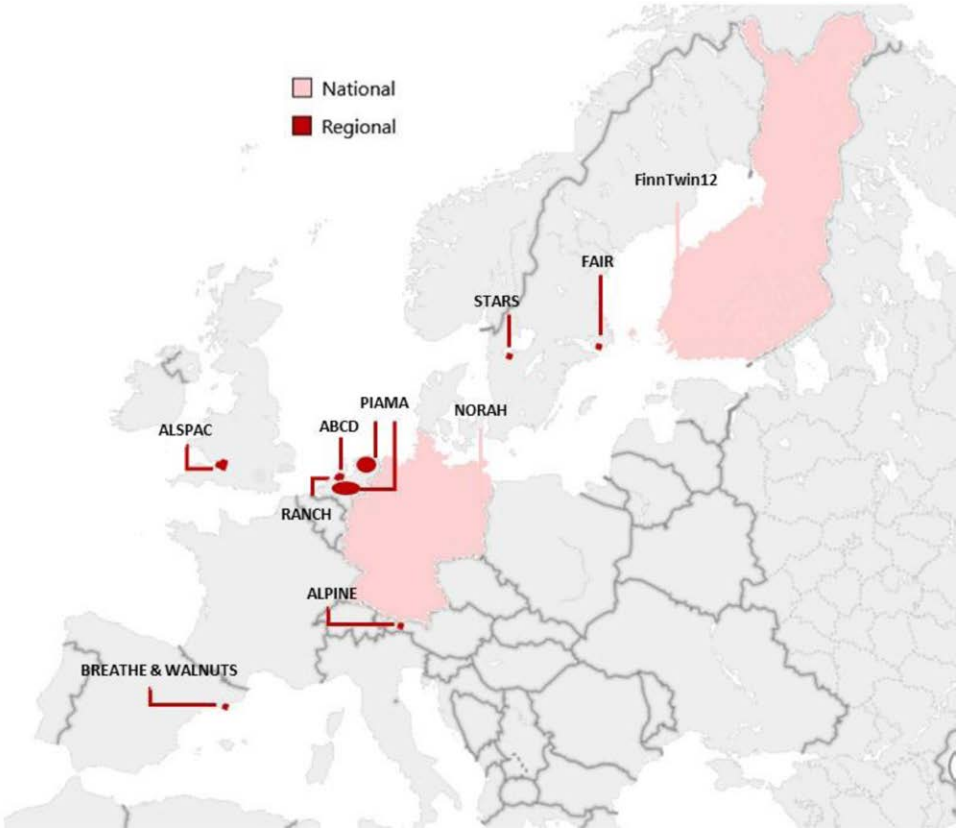

Figure 1. Geographical representation of the cohort and school studies.

External exposome and exposure enrichment

We aim to enrich the data provided in Table 3 with additional exposure data on the following environmental physical and social factors:

(1) the built environment[30] in urbanized and rural areas, including housing quality, age of building, level of urbanization, crowding, type of neighborhood, physical safety, access to amenities such as playground, sports ground, parks, culture, and relevant moderators such as length of residency;
(2) outdoor environmental quality including air pollution, noise, and sound green and blue space, landscape, temperature, light at night, and electromagnetic fields, among others.
(3) indoor environmental quality, including drinking water quality, light at night and blue light, view from the house, dampness, air quality, sound and noise, dust, dampness and molds, among others;
(4) socioeconomic characteristics of the neighborhood or at a macro level (e.g. deprivation and welfare state policies)

The data enrichment will consider the following factors:

(1) children's activity patterns and their locations (home, daycare and (pre) school environment, during commuting/ recreation), and across different developmental phases;
(2) the social environment (e.g. minority stress in face of discrimination, attachment, parenting style, lone parenting, social safety, social cohesion, social networks);
(3) lifestyle (nutrition, specific foods, sugar intake, physical activity and screen time, gaming and social media use).

The key mechanisms between exposure and mental health (brain development, sleep, stress/restoration, and self-regulation) are highly related to the built and social environment. They can be considered as indirect, mediating processes in exposure-outcome-relationships, or as direct, biological effects related to air quality, noise, crowding, and light.[16,31,32] The indirect mechanisms illustrate the necessity to adopt a dimensional approach to mental health and cognitive development, complementing the categorical approach to final, clinical "endpoints". Apart from tracing these indirect mechanisms, we seek to elaborate on the biological aftermath of these as well. In further defining the physical and social exposome, Equal-Life takes mental health and cognitive development as a point of departure. By defining mental health-enhancing environments at different life stages and time-activity patterns in children and adolescents the exposome is developed in a systematic manner. The resulting set of indicators (and created exposome) will be joined with new (micro) datasets, from crowd-sourcing and social-media platforms, to spatial data on the environment. The aim is to provide qualitative and quantitative insight into how children and adolescents interact with the social and physical environments and the mental health consequences.

Internal exposome

Effect markers of mental health will be explored on a selection of children, for which biological (mainly blood-derived plasma) samples are available. The selection is based on high, medium, and low scores on the total Strength and Difficulty Index as a proxy for an overall measure of mental health, also known as the p-factor.[33,34] Metabolic alterations such as changes in lipids, fatty acids, and abundant metabolites are reported to occur during neuropsychiatric conditions. In Equal-Life, we will first measure signatures of the internal processes linked to metabolism, inflammation, and oxidative stress. This will be achieved by measuring mitochondrial, protein-based, and metabolomics-based alterations in biological fluids and comparing the results from healthy children to those children with a high risk of mental dysfunction. Second, the altered signatures will be linked to the external exposome analysis of health effects. This process

Table 2.

Key concepts (outcomes and mediators).

OUTCOMES
DOMAIN: MENTAL HEALTH
Mental ill-health or illness
Psychological or psychiatric illness or psychological ill-health (psychopathology)
Well-being, or positive mental health
"a state of well-being in which every individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his community"[41]
The general factor of psychopathology (the p-factor)[33]

DOMAIN: COGNITION
General Cognitive Functions
Processing speed (simple reaction time, speeded crossing-out-tasks, speeded visual matching tasks)
Basic executive functions
- Inhibitory control (e.g., flanker task, stroop task, go-nogo task, stopsignal task, and flanker task)
- Cognitive flexibility (switching tasks, e.g, dimensional card sorting, and number-letter task)
- Working memory (e.g., n-back task, digit span backwards, running memory, and operation span)

Higher-level executive functions
- Reasoning (fluid intelligence, e.g., Raven´s Matrices, Culture-Fair Test, SON-R)
- Planning and problem-solving (e.g., Towers of Hanoi, Maze Test)

Language Acquisition
Oral language functions (phonology, vocabulary, Grammar, Listening Comprehension)
Written language functions
- Precursors of literacy (e.g., phonological awareness, rapid naming)
- Basic literacy functions (decoding skills, e.g., reading and spelling real words and pseudowords)
- Reading comprehension and fluency
- Clinical diagnosis of developmental dyslexia

School Achievement/Academic Achievement
Grades, School-leaving qualification, Educational Level qualification, Educational Level
MEDIATORS
DOMAIN: COPING/SELF-REGULATION
Self-regulation: related terms (e.g., emotion regulation), determinants, long-term outcomes, measures (e.g., Marshmellow-test, parent questionnaires)
Coping and coping styles (e.g., engagement vs. disengagement)
DOMAIN: SLEEP
Measures of sleep quantity and sleep pattern
Measures of sleep quality
Sleep related outcomes (short term)
Sleep related behavior
Time
DOMAIN: RESTORATION
Actual restoration
Perceived restoration
Restorativeness/restorative quality (perceived and objective)
Instoration
DOMAIN: STRESS
Stress as process
Psychological stress (perceived stress)
Psycho-physiological stress (responses)

might be repeated for cognitive effects as well, such as language acquisition, attention, memory, and IQ, together describing fluid intelligence or the so-called g-factor.[35] An improved understanding of markers for mental health and cognitive development and the relationship of these biomarkers to external exposures are required to advance mental health and cognitive development research.

In depth studies

Within the Equal-Life project, we aim to assess the effect of the total environment on mental health and cognitive development. The effect type or size may vary between ages and social groups. Therefore, the first step in this process is to investigate what environments children of different ages, gender, and social groups visit, how often they go there and how much time is spent at these places. Table 4 provides an overview of the location, objective and, design of the in-depth studies. These in-depth studies are experimental studies to collect additional data on the effect of the total environment on mental health and cognitive development.

Method

The first steps of the project focus on defining key concepts and questions related to mental health and cognitive development, while describing specific needs and vulnerabilities related to age. These include the potential influence of the exposome, related mechanisms as well as activity spaces and patterns relevant and characteristic for children.

The questions to be answered by Equal-Life will be discussed with a broad range of stakeholders at an early stage to ensure that the information needs of all relevant stakeholders (e.g. policymakers) are addressed.

Table 5 shows the seven steps of the method applied in Equal-Life. These steps are explained in Table 5 and are linked to objectives, activities, and findings to date and data sources.

Based on the activities, tasks, and deliverables in earlier stages of the project, a set of research questions and specific hypotheses is currently under development. This is a still ongoing process. Figure 2 shows the different information sources used for deriving research questions, which are also described in Table 5.

Mechanisms and life-course form the key elements of our hypothesis-driven approach. Building on existing theories and knowledge on neurobiological and -psychological development of children and adolescents i.e[36–38] the literature was reviewed to extend our knowledge on how exposome could affect development and mental health. Three mechanisms were explored in particular: psychosocial and psychophysiological stress, self-regulation/coping, and sleep quality. The assumption is that these mechanisms could mediate the linkage between exposome and child neurodevelopment and thus affect mental health and cognitive function.

The second important aspect in our approach is a life-course perspective of the full linkage of the exposome, mediators, and outcomes. Existing life-course epidemiological models [39,40] are being studied, stressing the accumulation of hazards/risks over the years and the influence this might have at certain ages, either indirectly via mediators or directly on the outcomes at other ages. Not only risks but also supportive environments at different ages will be considered.

Strengths and limitations

Strengths

(1) Equal-Life features a holistic approach to child environments and performs the full value chain from the development of the exposome, via health assessment to develop a set of interventions. At the same time, the broadness of the exposome is circumscribed as the project takes mental health and cognitive development as a starting point. The Equal-Life approach is novel in: the combination of physical and social elements of the exposome; the sex/gender-sensitive conceptualization with an intersectionality perspective of the exposome as a temporally and spatially dynamic and multidimensional process; and the focus on mental health and cognitive development. Exposome projects thus far have been primarily focused on somatic disease and did not take dimensions of environmental justice and health equity into account.
(2) The project will explore new biomarkers for mental health. These are intermediate effect markers, which will

Table 3.

Overview of the data on external exposome categories available in the cohort and school studies before data enrichment.

Study →	PIAMA	FAIR	ABCD	WALNUTS	BREATHE	FinnTwin12	ALPINE	ALPAC	RANCH	NORAH	STARS
Physical environment											
Noise	X	X	X		X	X	X	Y	X	X	
Air pollution (outdoor)	X	X	X	X	X		X	X	X		
Air pollution (indoor)					X		X				
ETS (smoking parents)		X	X			X	X	X			
Green space	X		X		X		X	X		X	
Molds and dampness	X						X	X			
Type of house						X	X	X	X		
Vibration		X					X				
Electromagnetic fields			X				X				
Life style factors											
Nutrition/eating behavior	X		X	X		X	X	X			X
Physical activity[a]	X	X	X	X	X	X	X	X			X
(Mother's) BMI/anthropometrics	X	X	X	X				X			
Mother's alcohol use			X	X		X		X			
Mother's caffeine use			X			X		X			
(Mother's) drug use			X			X		X			
TV/radio consumption			X				X	X			
Mobile phone and internet use			X			X		X			
Screen use				X				X			
Social environment											
Being bullied	X		X			X		X			
Crowding/density							X	X	X	X	
(Parental) education	X	X	X			X	X	X	X	X	
(Parental) occupation		X	X			X	X	X	X	X	
Parental income		X	X					X	X	X	X
Nationality/ethnicity		X	X			X		X	X	X	X
Parental marital status		X	X			X		X			X
Social/parental support			X			X		X	X	X	
Neighborhood SES	X		X			Y		X			
Satisfaction[b]	X		X			X	X				X
Social environment[c]			X				X	X	X		X

[a]physical activity indicator, including sedentary activity.
[b]Satisfaction with different aspects of (social) life.
[c]Not further specified.

Table 4.

Overview in-depth studies.

In-depth study	Objective	Study type
Activity patterns	To investigate what environments children from different social and age groups, visit, how often they go and how much time they spend there.	Three-phase cross-sectional study is planned (N = 385) including a survey, a time-activity-exposure pattern pilot and validation by means of GPS, diaries and personal exposures
Auditory cognition in activity based acoustic settings	To examine the influence of real-life class room scenarios on auditory processing and cognitive performances. To identify key indicators of classroom acoustic scenario's. To evaluate sound reproduction methods suitable for children in listening experiments.	A series of 8–10 listening experiments is performed with two paradigms: (1) auditory selective attention and (2) speech intelligibility. For each experiment 30 children (3–10 years) and 24 young adults (18–26 years) are recruited via educational institutions and under advice of the educators and teachers.
Preschool study in Germany and Belgium	To study the effects of physical and social exposures at (pre-) school and at home on children´s well-being, cognition, and EEG parameters of auditory processing.	The study design is longitudinal with two measurement waves separated by a period of 14 months (t1: preschool, age 5; t2: primary school, age 7) at 2 study sites (Germany and Belgium). Noise exposure and air quality will be assessed using sensor devices at both measurement waves. Environmental quality at home and at school as well as social indicators will be assessed by questionnaires for children, teachers, and parents.
Sleep study in Sweden and Austria	To increase our understanding of how the exposome affects mental health and cognition via sleep.	Children are selected based on combined indicators of noise and air-pollution exposure and green space. Sleep quality and sleep patterns will be measured in the participants' home using questionnaires and objective sleep measures making use of sensors. Exclusion criteria include sleep apnea and skin irritation. The Swedish sleep study comprises children (10–17 years) recruited from the STARS cohort. The Austrian sleep study comprises children (8–14 years) recruited from a study among adults (N~1200).

be linked to exposures retrospectively. These data were available, but not yet explored and tested in a larger group and linked to exposures. The use of a large set of cohorts and school data, all containing comparable data on mental health and cognitive development, will allow for more detailed analysis with enough statistical power.

Table 5.

Seven step approach.

Step #	Process step name	Objective	Information and data sources	Activities and findings up till now
1	Define	To define pathways from exposure indicators towards outcomes	Literature theory	The key concept of mental health, cognitive development, the mechanisms of sleep, self-regulation and stress and restoration and defining the physical, social and internal exposome. Four scoping reviews are being finalized on the key mechanisms (stress, self-regulation, and sleep) and the role of the social exposome. Existing cohort and school study data are being grouped along the key dimensions addressed in Equal-Life.
2	Consult and Select	To include input from relevant stakeholders at an early stage in the project	Delphi consultation Online focus groups Dialogues	A Delphi consultation (with three rounds) among experts and the stakeholders was developed and performed to match the key scientific and policy oriented questions to be addressed in Equal-Life. A code and protocol was developed to select children for biomarker analyses in blood plasma, based on the total score on the Strength and Difficulty Questionnaire (SDQ) as indicator of the so-called p-factor which is considered as risk factor for future mental health problems. Two cohorts were selected for biomarker analysis aimed at exploring new markers of mental health. The process of data and material transfer (xy coordinates and plasma) between the data owners and enrichers is nearly completed.
3	Collect	To collect data within the environments defined as relevant for mental health and cognitive development for children and adolescent	GIS based historic information Measures Sensors Internet of Things Diaries	A protocol was developed for the transfer of xy coordinates and metadata form the cohorts and school studies.
4	Match	To compose the exposome based on three and match with the key outcome data in the available data sets.	Birth cohort data School study data Retrospective longitudinal	
5	Analyze	To analyze the association between the external exposome and mental and cognitive effects.		Machine learning is used to explore the relevant variables in individual cohort or school studies in a non-targeted and data-driven manner. Random forest was chosen as method. A code was developed to apply machine learning in the nontargeted phase of the study to identify relevant features in the cohorts and school studies. The output can be used to explore what predictors are important for mental health, and serve as input for the conceptual model. The code is stored on GitHub, making it easily accessible for all Equal- Life partners and beyond.
6	Translate: interventions and tools	To inform stakeholders and policymakers of the best- and promising intervention analysis.		
7	Communicate	To communicate the outcomes to a range of audiences.		

Steps distributed over the different Work-Packages of Equal-Life (WP) step 1: WP1 and 4; step 2: WP8; step 3: WP 1–5; step 4: WP7; step 5: WP2, 6 and 7; step 6: WP8, 9, 10; step 7: WP10, 11, All.

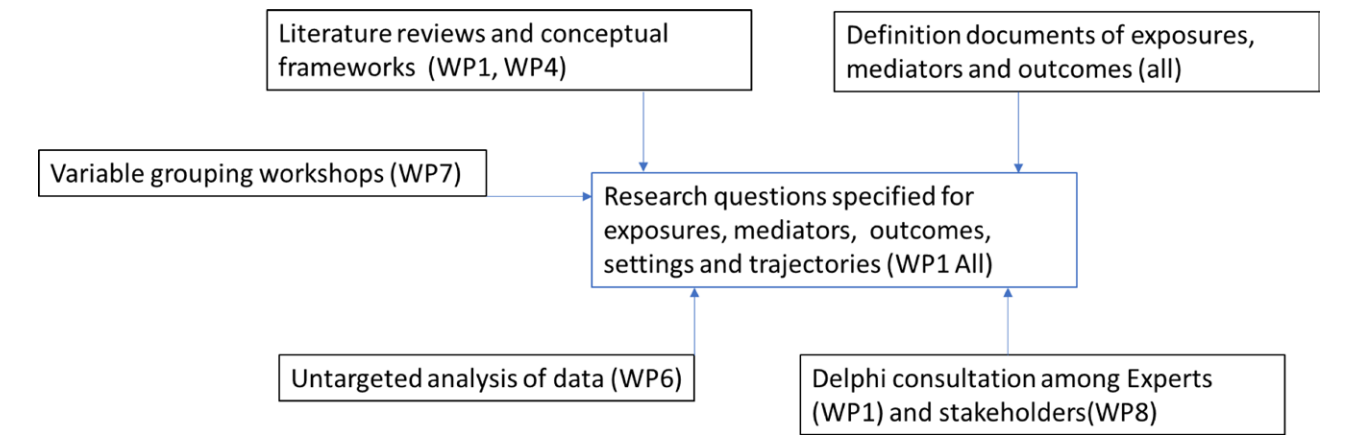

Figure 2. Sources of information used for deriving research questions.

(3) Equal-Life features a consortium of partners that includes a broad and complementary range of disciplinary backgrounds necessary to explore the full causal chain, from exposure to policy interventions and feedback.
(4) For the first time in the field of the exposome, we introduce the concept of focusing not only on risks and hazards that children run in their daily environment but also on the positive potential of the environment on child wellbeing and recuperation from daily stressors.
(5) Equal-life will use novel microdata and enrich the exposome with "untapped" physical and social exposome parameters. The novelty of using new forms of data such as user-generated content from social media, online mapping, street-level imagery, and crowdsourcing campaigns in the study of environmental exposures primarily lies in the enrichment possibilities that these data offer. In particular, they can capture aspects of people's daily life and the physical environment, such as human perceptions, experiences, and interactions at large scales, as evidenced by numerous studies in various scientific fields. The use of such data in exposure studies to date has been limited. Equal-Life aims to fill this gap by leveraging the granularity of such data and by bringing them into the core of the proposed enrichment strategy.
(6) Thus far many studies in the field of environment and health have been focused on specific subgroups. Our cohort data include a broad group of European (EU) children and in some cohorts stratification on ethnicity, migrant background or aspects of acculturation, and other demographic features is possible.
(7) To be able to adequately address health inequities, multilevel analyses will be applied to distinguish health effects of social factors at the individual level from those of neighborhood- or macro-level. Moreover, Equal-Life will conduct case studies to assess equity impacts of interventions or policies of different sectors.
(8) Our proposed method of data analyses first explores data in a nontargeted way using machine learning and next with a targeted (hypothesis driven) approach to tackle the complexity of the associations. This is a unique approach as far as mental health and cognitive development are concerned.
(9) Including stakeholders over the project lifetime is not innovative, but involving them actively in setting the scene by coformulating the relevant questions from a policy and planning point of view, and codesigning future tools to assess policy interventions, takes the exposome endeavor away from the laboratories and into the field (real life, real people, real time and real locations).

Equal-Life will explore the ways to sustain (and maintain) these tools also after the end of the project. By linking them as much as possible to local tools they will be more tailored to the needs of different EU regions. The participating public health institutes could support guidance tools with updates within their programs which are financed on a regular basis. In other words: the tools will be active instead of passive aiming at optimal exploitation.

Challenges and limitations

Equal-Life faces several external barriers that may threaten the achievement of the desired impact from the project. These include low engagement of stakeholders, lack of data availability, low uptake of the toolkit, and difficulties to maintain and update the toolkit with new data and information. Even the most sophisticated statistical methods cannot solve gaps caused by issues of data availability, comparability, and quality.

Statistical data analyses need to take the quality of the available data into account. Equal-Life has access to high-quality data, but the harmonization of the data across the cohorts and school studies is one of the key challenges. A dual approach, combining an explorative and a more analytical approach is seen as the most realistic way to move forward. In the analytic approach, state-of-the-art methods for analyzing causalities, such as propensity score methods among others and mediation analyses are considered.

The project has many interdependencies between work packages including many partners from a diverse set of disciplinary backgrounds. This poses a challenge for Equal-Life as well.

Equal-Life will also face complicated data management issues and when maintenance after the project finishes, and we face the challenge of trying to generalize the outcomes to all European countries, whereas many countries are not covered by the data.

Finally, the currently ongoing COVID-19 pandemic will complicate the execution of studies that involve immediate contact with children.

Conclusion

Mental health is the result of the complex interplay between genetic, psychological, physical and social environment, and other factors and experiences. The life-course exposome concept, referring to the totality of exposures from conception onwards, is emerging as a very promising approach in studying the role of the environment in human disease. The EU-funded Equal-Life project will develop and utilize the exposome concept in an integrated study of the external exposome and of measurable internal biological factors and link those to a child's development and life course mental health. This will be carried out using a novel approach combining exposure data to characterize, measure, model, and understand influences and inequities at different developmental stages. The goal is to propose the best supportive environments for all children.

Collaboration

The Equal-Life consortium consists of 22 partners, 2 subcontractors, 4 international advisors, and 1 stakeholder chairing the advisory team.

The consortium brings together various types of institutions including governmental institutes, universities, and research Small and Medium Enterprises. Equal-Life combines extensive multidisciplinary expertise from leading experts in the fields ranging from public health, epidemiology, child psychology, microbiology, environmental psychology, architecture, environmental-, and spatial planning, neurobiology, geographic, political sciences, physics, information and communications technology, to statistical modeling. These experts bring knowledge on environment and health in children from their own country, and from their broader international networks. Equal-Life's potential end-users comprise local authorities, NGOs such as the WHO European Healthy City Network, urban planners, and others.

Equal-Life is a member of the European Human Exposome Network which brings together nine research projects, receiving over €100 million from Horizon 2020, the EU's framework program for research and innovation. These projects address issues such as exposures to air quality, noise, chemicals, urbanization, and health impacts. The projects' results will contribute to advancing the European Green Deal's ambition to protect citizens' health and well-being from pollution and environmental deterioration by providing new evidence for better preventive policies.

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APPENDIX

The members of Equal-Life Scientific Team are as follows: Agnes Wiberg, School of Public Health and Community Medicine, Gothenburg University, Gothenburg, Sweden; Albert Ambròs, Barcelona Institute for Global Health, ISGlobal, Barcelona, Spain; Albert Wong, Centre for Nutrition, Prevention and Health Services, National Institute for Public Health and the Environment, Bilthoven, The Netherlands; Alyce Whipp, Institute for Molecular Medicine Finland, Department of Public Health University of Helsinki, Helsinki, Finland; Andrei Pyko, Unit of Occupational Medicine at the Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; Angel Dzhambov, Institute for Highway Engineering and Transport Planning, Graz University of Technology, Graz, Austria; Anna Hansell, Centre for Environmental Health and Sustainability & School of Geography, Geology and the Environment, University of Leicester, Leicester, United Kingdom; Anna Sandionigi, Quantia Consulting srl, Milan, Italy; Anneke Blokstra, Centre for Nutrition, Prevention and Health Services, National Institute for Public Health and the Environment, Bilthoven, The Netherlands; Antonia Valentin, Barcelona Institute for Global Health, ISGlobal, Barcelona, Spain; Arto Alatalo, A.I.Virtanen Institute for Molecular Sciences, University of Eastern Finland, Kuopio, Finland; Arzu Arat, Unit of Occupational Medicine at the Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; Barbara Mihevc, National Institute of Public Health, Ljubljana, Slovenia; Bruno Raimbault, Barcelona Institute for Global Health, ISGlobal, Barcelona, Spain; Calvin Jephcote, Centre for Environmental Health and Sustainability & School of Geography, Geology and the Environment, University of Leicester, Leicester, United Kingdom; Charlotta Eriksson, Unit of Occupational Medicine at the Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; Christin Belke, Centre for Applied Psychology, Environmental and Social Research (Zeus GmbH), Bochum, Germany; Christoph Giehl, Department of Cognitive and Developmental Psychology, Technical University Kaiserslautern, Kaiserslautern, Germany; Elise van Kempen, Centre for Sustainability, Environment and Health, National Institute for Public Health and the Environment, Bilthoven, The Netherlands; Gerd Kortuem, Joint Research Center for Urban Systems and Environment, Delft University of Technology, Delft, The Netherlands; Helena Skröder, Unit of Occupational Medicine at the Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; Igor Spiroski, Institute of Public Health of the Republic of North Macedonia, Skopje, North Macedonia; Izaque de Sousa Maciel, A.I.Virtanen Institute for Molecular Sciences, University of Eastern Finland, Kuopio, Finland; Jan Spilski, Department of Cognitive and Developmental Psychology, Technical University Kaiserslautern, Kaiserslautern, Germany; Jana Roczen, Institute of Public Health and Nursing Research, University of Bremen, Bremen, Germany; Jesper Löve, School of Public Health and Community Medicine, Gothenburg University, Gothenburg, Sweden; John Bolte, Center for Sustainability, Environment and Health, National Institute for Public Health and the Environment, Bilthoven, The Netherlands; Jolanda Boer, Centre for Nutrition, Prevention and Health Services, National Institute for Public Health and the Environment, Bilthoven, The Netherlands; Karin Loh, Hearing Technology and Acoustics, RWTH Aachen University, Aachen, Germany; Kathryn Adams, Centre for Environmental Health and Sustainability & School of Geography, Geology and the Environment, University of Leicester, Leicester, United Kingdom; Kim White, Centre for Sustainability, Environment and Health, National Institute for Public Health and the Environment, Bilthoven, The Netherlands; Larissa Leist, Department of Cognitive and Developmental Psychology, Technical University Kaiserslautern, Kaiserslautern, Germany; Lena Gudi-Mindermann, Institute of Public Health and Nursing Research, University of Bremen, Bremen, Germany; Luc Dekoninck, Department of Information technology, Faculty of Engineering and Architecture, Ghent University, Ghent, Belgium; Maddie White, Institute of Public Health and Nursing Research, University of Bremen, Bremen, Germany; Mar Álvarez-Pedrerol, Barcelona Institute for Global Health, ISGlobal, Barcelona, Spain; Marco Balduini, Quantia Consulting srl, Milan, Italy; Marja Heinonen-Guzejev, Institute for Molecular Medicine Finland, Department of Public Health University of Helsinki, Helsinki, Finland; Maud Dohmen, Built Environment, Technical University Eindhoven, Eindhoven, The Netherlands; Michael Smith, School of Public Health and Community Medicine, Gothenburg University, Gothenburg, Sweden; Michail Evangelos Terzakis, Built Environment, Technical University Eindhoven, Eindhoven, The Netherlands; Mihail Kochubovski, Institute of Public Health of the Republic of North Macedonia, Skopje, North Macedonia; Natalia Vincens, School of Public Health and Community Medicine, Gothenburg University, Gothenburg, Sweden; Nataša Frigelj, National Institute of Public Health, Ljubljana, Slovenia; Rik Bogers, Centre for Sustainability, Environment and Health, National Institute for Public Health and the Environment, Bilthoven, The Netherlands; Roos Teeuwen, Joint Research Center for Urban Systems and Environment, Delft University of Technology, Delft, The Netherlands; Sammie Jansen, Centre for Sustainability, Environment and Health, National Institute for Public Health and the Environment, Bilthoven, The Netherlands; Sarah Leona Benz, Centre for Applied Psychology, Environmental and Social Research (Zeus GmbH), Bochum, Germany; Sarah Verhulst, Department of Information technology, Faculty of Engineering and Architecture, Ghent University, Ghent, Belgium; Shaban Memeti, Institute of Public health of the Republic of North Macedonia, Skopje, North Macedonia; Tatiana Alvares-Sanches, Centre for Environmental Health and Sustainability & School of Geography, Geology and the Environment, University of Leicester, Leicester, United Kingdom; Thomas Lachmann, Department of Cognitive and Developmental Psychology, Technical University Kaiserslautern, Kaiserslautern, Germany; Timothy Van Renterghem, Department of Information technology, Faculty of Engineering and Architecture, Ghent University, Ghent, Belgium; Vasileios Milias, Joint Research Center for Urban Systems and Environment, Delft University of Technology, Delft, The Netherlands; Wim Swart, Centre for Sustainability, Environment and Health, National Institute for Public Health and the Environment, Bilthoven, The Netherlands.

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