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Adopting a child perspective for exposome research on mental health and cognitive development - Conceptualisation and opportunities.

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ABSTRACT

Mental disorders among children and adolescents pose a significant global challenge. The exposome framework covering the totality of internal, social and physical exposures over a lifetime provides opportunities to better understand the causes of and processes related to mental health, and cognitive functioning. The paper presents a conceptual framework on exposome, mental health, and cognitive development in children and adolescents, with potential mediating pathways, providing a possibility for interventions along the life course. The paper underscores the significance of adopting a child perspective to the exposome, acknowledging children's specific vulnerability, including differential exposures, susceptibility of effects and capacity to respond; their susceptibility during development and growth, highlighting neurodevelopmental processes from conception to young adulthood that are highly sensitive to external exposures. Further, critical periods when exposures may have significant effects on a child's development and future health are addressed. The paper stresses that children's behaviour, physiology, activity pattern and place for activities make them differently vulnerable to environmental pollutants, and calls for child-specific assessment methods, currently lacking within today's health frameworks. The importance of understanding the interplay between structure and agency is emphasized, where agency is guided by social structures and practices and vice-versa. An intersectional approach that acknowledges the interplay of social and physical exposures as well as a global and rural perspective on exposome is further pointed out. To advance the exposome field, interdisciplinary efforts that involve multiple scientific disciplines are crucial. By adopting a child perspective and incorporating an exposome approach, we can gain a comprehensive understanding of how exposures impact children's mental health and cognitive development leading to better outcomes.

1. Introduction

Mental disorders are a major challenge globally also in young people (WHO, 2021). Many children and adolescents with these disorders remain underdiagnosed and undertreated with high individual and societal costs (Kieling et al., 2011; OECD/EU, 2016). Noteworthy is that a child's mental health, well-being and cognition have intrinsic values, beyond an instrumental value for subsequent health trajectories in adulthood (UN, 2012; UNICEF, 2022). Several studies indicate a bi-directional relationship between well-being and cognition or mental health. Children with mental ill-health show poorer academic performance and quality of life that can compromise social and mental functioning later in life (Luby et al., 2017; Copeland et al., 2021; Löve et al., 2016). In addition, childhood cognitive development predicts educational achievement and thus an individuals' future professional career later in life. Multiple factors relating to the child's immediate and general physical and social environment as well as genetic predisposition may further affect the risk for mental ill-health. Together, this highlights the relevance of an exposome perspective to better understand the causes of and processes related to mental health, well-being, and cognitive functioning and to be able to trace back later outcomes to early developmental stages (Mulraney et al., 2021).

The exposome concept, initially described by Wild in 2005 and 2012, refers to the totality of exposures an individual is subjected to from conception and over a complete lifetime. In his work, Wild classifies exposome into three domains: 1) the internal exposome (e.g., metabolism, endogenous hormones, gut microflora, inflammation, oxidative stress); 2) the specific external exposome (e.g. radiation, infectious agents, chemical contaminants and environmental and occupational exposures, diet, lifestyle factors); and 3) the general external exposome including the social, economic and psychological influences on the individual (e.g., social capital, education, financial status, psychological and mental stress, urban–rural environment, climate). The exposome concept was introduced as a complement to the genome initiative, highlighting the pressing need to consider the importance of both internal and external exposures for health (Wild, 2005, 2012).

An exposome approach, hence, allows us to assess a dose perspective, interaction of exposures and sensitisation by exposure and the cumulative risks (Smith et al., 2015), taking into account time aspects such as critical periods for the health impacts. Furthermore, an exposome approach provides a comprehensive framework to study the causes and mechanisms driving social inequalities in health (Deguen et al., 2022).

Given the insight that an exposome approach provides excellent opportunities to consider how children's development and mental health are affected by the complex interplay of external and internal exposures over the life course (Vineis et al., 2020, Vineis and Barouki, 2022), there are surprisingly few exposome studies within mental health

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on children and adolescence (Haddad et al., 2019).) Whereas prenatal and early-life exposures have been extensively approached, this is often in relation to somatic health outcomes (e.g., asthma, birth weight) (Burbank et al., 2017; Nieuwenhuijsen et al., 2019).

The Equal-Life project, part of the European Human Exposome Network, has undertaken the important task of using an exposome approach to explore the effects of exposome on mental health and cognitive development in children and adolescents, from conception to age 21 (Van Kamp et al., 2022). The project addresses pathogenic and salutogenic exposures in relation to mental health and cognitive development in a health-disease spectrum, adopting a child perspective on exposures, intakes and uptakes. The project applies an often neglected but required holistic perspective to children's mental health and cognition. Within Equal-Life, the exposome is classified as external and internal, where the external is subdivided into *physical exposome* (e.g., the built environment and environmental quality indoors and outdoors) and the *social exposome* (e.g. societal context, socio-economic, social and psychosocial factors at the individual and contextual level) and *internal* exposome (processes occurring in the body, such as measured by proteomics, metabolomics, epigenomics, gene expression and neuroimaging). The social exposome perspective on children's and adolescents' mental health and cognitive development is specifically covered by another conceptual paper of the Equal-Life project for this special issue (Gudi-Mindermann et al., 2023), and focuses on promoting the social environment domain into the exposome paradigm, by simultaneously stressing the equity perspective. Equal-Life further integrates data at different spatial and temporal granularities and combines exploratory machine learning and hypotheses-driven modelling (hierarchical regression, structural equation modelling growth modelling, etc.). Important project hypotheses include potential mediators focusing on prominent mechanisms from exposome to mental health and cognition.

With the aim of extending and deepening knowledge on how mental health and cognitive development are associated with the child's exposome, we undertook reviews of existing scientific literature, including empirical and theoretical papers. The procedure was hypotheses-driven and focused on the mechanistic pathways, investigating how important mediators such as sleep, psychophysiological stress, restoration and self-regulation/coping could affect the linkage between exposome, mental health and cognitive development. The literature review led us to recognise a lack of operationalisation and, to some degree, the conceptualisation of exposome and, particularly in relation to how an exposome approach would emanate from a child perspective. We also observed strong barriers between scientific fields with few overlaps of natural sciences, social sciences and medical and health sciences, even in seemingly relevant areas, such as child development and the linkages of exposure to health outcomes. For example, exposures described from a child perspective are typically classified from a natural/medical science perspective focusing on distribution, time and frequency of exposures, while the social aspects of how age-specific behaviour affects the exposure were neglected. Furthermore, age-related exposures could be seen as closely connected to social concepts of place, activity and the agency of children and parents, siblings and peers, as has also been suggested in the Social Exposome framework (Gudi-Mindermann et al., 2023), while biological perspectives, such as age, sex, perception, uptake, intake and metabolism, would be handled in other papers. Finally, we also see factors related to outcomes being poorly attended to, such as diagnoses and exposures, where the influence of age, gender and culture are often neglected.

In an endeavour to bridge the identified gaps, this paper addresses significant conceptualisation and operationalisation aspects that will assist in embracing a child perspective within the exposome field, with a focus on mental health and cognitive development.

2. Mental health and cognitive development

The terms mental health, mental ill-health, well-being, mental illness, mental disorders, and quality of life are sometimes used interchangeably or as complementary concepts, and definitions tend to vary in the literature. Within Equal-Life, mental health is defined as the presence of psychological or psychiatric illness or psychological ill-health (psychopathology), whereas well-being refers to positive psychological health. Mental health is usually assessed and defined within diagnostic systems, i.e., DSM-V and ICD-11, providing diagnoses of for example depression, anxiety or attention deficit hyperactivity disorder (ADHD). For younger children and adolescents, mental health can also be assessed using symptom measures (e.g., Strengths and Difficulties Questionnaire (SDQ), Goodman and Goodman, 2009 or Multidimensional Peer Nomination Inventory (MNPI), Pulkkinen et al., 1999) assessing for instance internalising and externalising symptoms.

Well-being is part of the World Health Organisation's (WHO) salutogenic definition of 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" (WHO, 2004). Evidently, this definition goes beyond the mere presence or absence of mental diseases. It also comprises positive dimensions of health, such as hedonic well-being covering dimensions like happiness, pleasure and life satisfaction, and eudemonic well-being covering dimensions like personal growth, purpose in life, and relations with others (Ryan and Deci, 2001; Ryff et al., 2021).

Mental health and well-being are not to be understood as extremes of the same dimension, meaning that it is possible to have a mental disorder diagnosis and still experience well-being. The impact of a mental disorder will depend on access to resources in the immediate social environment, considering the special needs of a person. Thus, some children with mild to moderate symptoms will cope well in supportive settings, but less well in challenging ones. This means that the likelihood of diagnosis or manifestation of behavioural symptoms is also context dependent.

Cognition is defined as "the mental action or process of acquiring information and understanding through thought, experience, and the senses." Cognition is thus not a unitary dimension and consists of various interrelated but separable cognitive functions. For cognitive development, in Equal-Life we focus on executive functions; i.e., cognitive processes that enable volitional control of goal-directed behaviour (e.g., selective attention, cognitive flexibility, working memory, reasoning, problem solving, and planning (Diamond, 2013)), language and literacy functions, including phonology, syntax, semantics, listening comprehension, reading, and spelling, verbal precursors of literacy (verbal short-term memory, phonological awareness) and school/academic achievement (Diamond and Ling, 2020; Moreau, 2022).

3. Current conceptualisations and operationalisations of exposome

Despite the growing interest, use and relevance of exposome perspectives in research, there are challenges in conceptualisation and operationalisation, particularly for populations and outcomes less well studied. Since 2005, these challenges have resulted in pragmatic research approaches, and already Wild proposed exposome categories (i.e., internal and external) and the need to "slice" the concept to deal with the complexity inherent in this field of research. This practice of "partial assessment of the totality of environmental exposures" was also noted by Haddad et al. (2019) in their scoping review of the exposome. The processes of characterising and categorising the exposome are commonly guided by disciplinary boundaries, outcomes in focus, research interests and agendas, data availability or the ability to collect data. Although most studies follow the definition from Wild, the categorisation and operationalisation of the concept are evolving with the

inclusion of other domains of exposures e.g., working life exposome (Pronk et al., 2022), the pregnancy exposome (Robinson and Vrijheid, 2015) or the urban exposome (Robinson et al., 2018) and of different omics (e.g., adductomics, Vineis et al., 2020). Authors also use different approaches to the environmental-health linkages in exposome research. Some suggest departing from the characterisation of the external exposome while others depart from the measurement of the internal exposome with indicators in biospecimens (Rappaport and Smith, 2010). Ideally, an integration of these approaches seems to have the greatest potential for answering the research questions in environmental health research as proposed by (Zhang et al., 2021).

A handful studies have investigated the impact of exposome on mental health in the young population (Wang et al., 2023; Kershenbaum et al., 2014; Shaw et al., 2018; Robinson et al., 2015). The Helix project targeted several health outcomes in children, including mental health and cognitive development (Maitre et al., 2018, 2021; Julvez et al., 2021; Binter et al., 2022). Using an exposome approach in relation to children's behavioural problems, cognition and motor/verbal development, they highlighted the negative and positive effects of selected prenatal and childhood exposures on indicators of these outcomes. Cognitive function among 6–11-year-old children was analysed in relation to 87 prenatal exposures and 122 childhood exposures (air pollution, built environment, meteorology, natural spaces, traffic, noise, chemicals and lifestyles) in ExWAS (Julvez et al., 2021). The results showed both expected associations between cognition and nutrition and indoor air pollution and unexpected associations, i.e., higher green exposure during pregnancy and low cognitive function. This led to the authors reflecting over unidentified confounders and reversed causality. In another study, using the Avon Longitudinal Study of Parents and Children, Steer et al. (2015) identified initially 621 out of 3965 environmental variables associated with a measure of communication difficulties among children aged 9. Of these only 19 items remained in the final model, with maternal education, social network and "feel good score" being positive predictors.

Other studies investigating mental health and cognitive development have either focussed on social exposures or explicitly on poverty (Bradley and Corwyn, 2002; Luby et al., 2013) or on physical exposures, most often chemicals (Shah-Kulkarni et al., 2020; Zhang et al., 2019), where an exposome approach would have allowed investigation of interacting multiple, complex, and concurrent exposures (Burkett and Miller, 2021; Reuben et al., 2022).

Social exposures are commonly treated as confounders and adjusted for in the final analysis. This is particularly problematic as health inequities are a major challenge for societies. For example, low socio-economic status and poverty impact early age development within critical skills, such as language development, higher incidence of learning disorders and poor school outcomes (Bradley and Corwyn, 2002; Tamburlini et al., 2002; Luby et al., 2012, 2013; Hart and Risley, 1995). Children within families of low socio-economic position tend to live and attend schools in low socio-economic areas, leading to multiple stressors. Clustering of stressors or cumulative exposures add to health risks (Appleton, et al., 2016; Evans et al., 2013; Evans, 2003; Evans and Kantrowitz, 2002; Wallander et al., 2019). In addition, adolescents with a greater number of risk behaviour (drug use, poor sleep, poor diet, risky sex) tend to be more stressed than adolescents with less risky behaviours (Kwan et al., 2016). Furthermore, women from low socio-economic position have poorer nutrition and tend to work within occupations with higher physical and psychological demands, which may negatively influence foetus growth, including neurological development (Borge et al., 2017; Cai et al., 2019; Selander et al., 2019). While cumulative exposures are seen to add to the health risks, criticism have been raised as to whether the concept is useful for intervention measures, raising the need for more refined strategies (McLaughlin and Sheridan, 2016). A general conclusion points to the importance of including both physical and social exposures and particularly with reference to children's physical or mental health and cognitive development.

Schulz and Northridge (2004) were early in examining the relationships between social inequalities, the built environment and social context. Later, Tulve et al. (2016) developed a framework of the child's total environment that included: internal (intrinsic biological factors), built, natural and social environment for the optimisation of health and well-being among children. These frameworks were among the first to acknowledge the importance of the social environment on micro, meso and macro levels, or individual, home/family, school/daycare, community and city/state/national level, including factors such as the economy, demographics, safety, welfare, peer relations and family support. In a systematic scoping review of papers (2003–2013), Ruiz et al. (2016) assessed non-chemical and chemical stressors associated with children's cognitive ability. The authors point to a general lack of studies adopting an exposome perspective or even performing analyses of multiple exposures and the need for more knowledge on complex interactions between exposures and activities and behaviour within the total environment of a child, also addressed by Gudi-Mindermann et al. (2023).

4. Adopting a child perspective to an exposomic approach

A child's exposure and vulnerability to internal, social and physical components vary over developmental phases, ranging from preconception, foetal period, neonatal period, infant, toddler, early childhood, middle childhood and early and late adolescence. Children are over these time periods subjected to a wide diversity of physical and social exposures in places and times, exposures over which they have little control. Also, a child's vulnerability varies due to their extensive bio-psycho-social development. Children also have a comparatively higher uptake of exposures due to their physiology (Etzel, 2020) and less developed detoxification metabolism (Huen et al., 2012).

To propose and adopt a child perspective to the exposome we articulate in this section the concepts of vulnerability, including the notions of susceptibility and equity. The child development, extensive growth and in particular, the brain development is explicitly discussed in relation to the concepts of vulnerability and critical periods. For the integration between various exposures (e.g., physical and social exposures) and between exposures and the individual, we apply the structure-agency theory and the concepts of social practices, places, actors and activities.

4.1. *Vulnerability*

The concept of vulnerability is fundamental in relation to both child development and health equality. Still, the articulation of the concept of vulnerability tends to vary across and within disciplines (Gudi-Mindermann et al., 2023; WHO, 2019). It also depends on whether the research focus is on the individual or the population. An individual focus comprises the inborne and constantly evolving biological susceptibility in different phases of human development from the pre-natal period to adolescence (e.g., critical and sensitive periods), whereas a population perspective comprises the differential vulnerability between groups within and between societies which is essential for understanding how health inequities evolve and persist. To better understand and act on health inequities between groups in societies, Diderichsen et al. (2019) suggest a three-dimensional definition of vulnerability. The first dimension captures how *differential exposure* is unequally prevalent among different groups in societies (e.g., exposures to noise, chemicals and restorative areas). The second dimension captures *differential susceptibility* (i.e., inequality in the health effect of exposure), due to e.g., influence of comorbidity, allostatic load, genetic makeup and epigenetics (Evans et al., 2021) Thus, susceptibility might change over time and increased susceptibility might be the result of previous exposure (Chae et al., 2021). The third dimension comprises *differentiation in capacity* to response, which reflect how power and access to resources (e.g., financial, social and material) enable avoiding exposures and coping

with potential adverse health effects (Diderichsen et al., 2019). Again, it is important to note that these three levels are not static. Rather, unequal exposure, susceptibility and capacity to act are closely related to formal (e.g., laws, regulations, educational systems) and informal structures (e.g., norms and expectations). Consequently, this three-dimensional approach to vulnerability allows us to describe the contribution of each dimension as well as their interdependencies and in this way might help us to avoid the pitfall of labelling and stigmatising specific groups or communities as "vulnerable populations". Instead, it acknowledges that vulnerability from a population perspective is a matter of context (Chae et al., 2021). While this approach has been questioned for conflating exposure, susceptibility and capacity of response, it captures the notion that the individuals' behaviours, activities and places also have an effect on the exposures.

4.2. The developing brain

The pregnant mother's exposure to chemicals and metals may affect prenatal development and long-term cognitive development for the child (Shah-Kulkarni et al., 2020; Zhang et al., 2019). Pre-pregnancy exposures and pre-natal stressors may also be related to several adverse outcomes both in the short term, and long term (van den Bergh et al., 2020). Higher levels of self-reported stress and or higher levels of pregnancy cortisol have been found to be associated with growth restrictions and poor infant neurodevelopment (cognitive development) (Caparros-Gonzalez et al., 2021). Some studies also indicate an association between pre-natal stress (in mother or child) and anxiety symptoms in the child at ages 8–11 years (McGuinn et al., 2022). Within-family studies of exposed and non-exposed children born to the same mother can provide tests of the putative causal hypothesis underlying such associations (Skoglund et al., 2014; Li et al., 2020). Regarding prenatal stress, cortisol output during pregnancy is one stress hormone identified as associated with neurodevelopment, but we lack knowledge of all the mechanisms (Caparros-Gonzalez et al., 2021). In contrast to epinephrine, cortisol crosses the blood–brain barrier and has been associated with changes in brain structures involved in cognition (Gunnar and Quevedo, 2007). The effect may be more or less harmful during different time periods of brain development. For example, elevated cortisol levels early in gestation was linked to lower rate of development over the first year and lower mental scores at one year of age. Elevated cortisol levels late in gestation showed accelerated cognitive development and higher mental scores at 12 months for children (ibid).

Research suggests that early life stress is linked to pronounced effects on the development of prefrontal–hippocampal–amygdala circuits (McEwen and Morrison, 2013). Apart from playing a large role for the peripheral stress responses, including the HPA axis, the prefrontal hippocampal-amygdala circuits are associated to emotions, self-regulation, memory, and learning (ibid) and chronic activation of these circuits to mental and physical health issues (Nusslock and Miller, 2016). Hippocampal volume may be reduced among children exposed to early life stressors (Hanson et al., 2015), and changes in hippocampal volume are thought to be linked to deficits in child learning processes. (Pechtel and Pizzagalli, 2011).

The cortical organisation and structures of the human brain are formed sequentially from conception to young adulthood allowing them time to be affected by external and internal exposomes (Fig. 1). The process of neuronal growth and migration to the developing parts of the cortex occur predominantly prenatally (Houston et al., 2014). Cortical morphology and density continue to develop during early childhood and adolescence and into the late twenties. During this time, cortical development progresses from lower-order cortical structures, with sensory and motor functions, to higher-order, trans modal association cortical structures with executive, socioemotional and mental functions. (Sydnor et al., 2021). During the developmental phases, the social, physical, and internal exposures interact and help fine-tune and shape the various structures in the brain. When these interactions are hampered or if there is interaction with hazardous exposures, the developmental process is compromised. While the child brain is resilient and malleable to salutogenic influence, such as supportive care and stimulating environment partly balancing the negative exposures (Evans and Kantrowitz, 2002), its rapid development and growth during

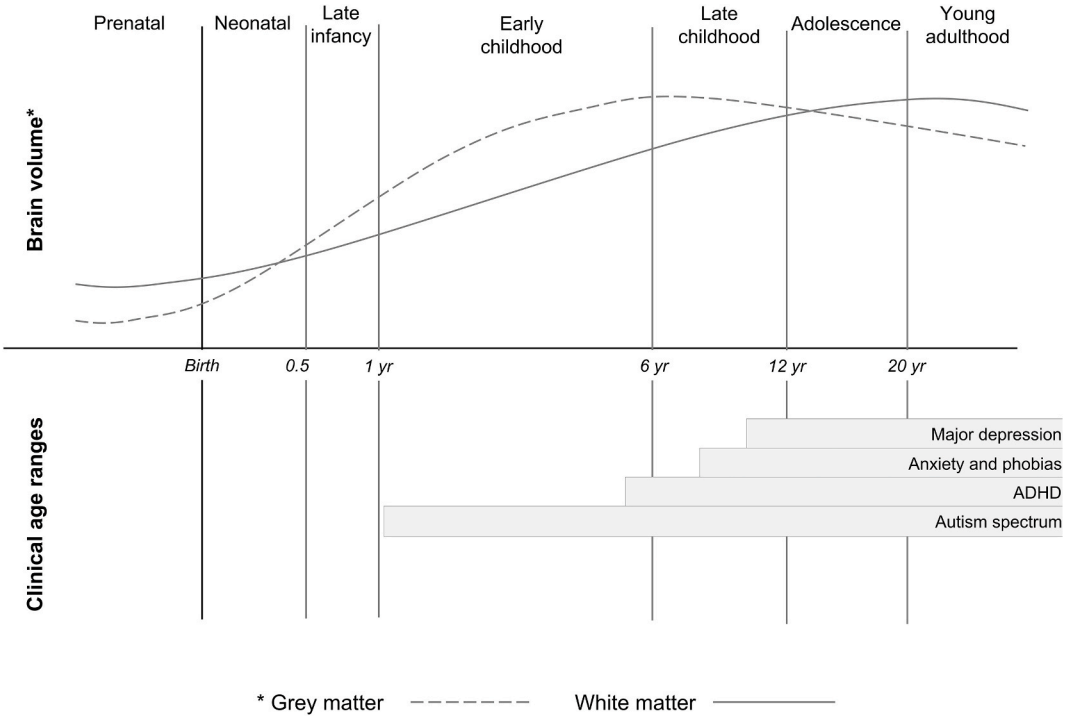

Fig. 1. Brain volume (grey and white matter) development from the prenatal period to young adultohood in parallel with examples of common time periods for clinical diagnosis for a selection of mental health disorders. Adapted from Bethlehem et al. (2022).

prenatal and very early age also makes it highly sensitive for external impacts.

Compared to adults, though, less is known about how cortical structure develops in early childhood. Using the largest dataset available, 123,941 Magnet Resonance Imaging (MRI) scans were collected and analysed to create a chart of neurodevelopment over age, focusing on structural MRI data of main tissues like the total grey matter volume (GMV) and total white matter volume (WMV) (Bethlehem et al., 2022). It was found that cortical GMV increased strongly from mid gestation and during the first years of life, with a peak at 5.9 years. White matter volume (WMV) also increased from mid gestation through childhood with a peak at 28.7 years. (Fig. 1). A limitation of the data is the lack of diversity globally with the majority of populations from North America and Europe. Interestingly, a large proportion of individual variation in cortical GMV and surface area (SA) at six years of age seemed already to be present at one year of age, while measures of cortical WMV at the age of 6 were explained to a lesser degree by variation at 1 years of age (ibid).

Variation in cortical morphology is of interest as it may be related to cognitive function, sleep patterns and neurodevelopmental disorders. For example, autism spectrum disorder being associated with alterations in cortical (GM) structure, including increased cortical thickness (CT) and (SA), while attention deficit-hyperactivity disorder and conduct disorders are suggested to be associated with non-normal cortical GM (Gilmore et al., 2020). Individual variation in sleep pattern among adolescence was also seen to be associated with brain morphology, with for example grey matter volume in hippocampus being associated with faster non-REM sleep spindle frequencies (Saletin et al., 2013). Furthermore, cognitive ability in infants and children has been associated with individual differences in regional and cortical GM volumes, CT and SA (Girault et al., 2020; Fenchel et al., 2022). The observation that individual variations occur at a very early age emphasises the importance of the right timing for any support.

Even though using such methods as MRI gives us a better insight into the development of brain structures and functional networks, we are still at the beginning of a more comprehensive understanding. A better understanding of factors of importance for the development neural systems (Houston et al., 2014) may aid in understanding impaired neurodevelopment and related neurodevelopmental disorders, such as Attention Deficit Hyperactivity Disorders (ADHD), Autism Spectrum Disorders and developmental learning disorders. This may be possible through new methods, such as functional MRI, which can provide information on neural activity by measuring changes in blood oxygenation levels. These measurements can be done when performing, e.g., cognitive tasks and may provide more precise information on the coherence of neural activity with cognitive development.

Caution is advised, however, in drawing conclusion from cortical morphology or neural activity alone as a consequence of hazardous interactions, as animals studies indicate that the inherent plasticity of the brain allows for catching up at later stages (Hensch, 2005; Werker and Hensch, 2015). It is also important to acknowledge that there are large individual variations in brain morphology among healthy children, that the impact of cortical thickness (CT), for example, is comparatively weak when compared to other influencing aspects, such as gestational age and maternal education (Girault et al., 2020).

4.3. Critical periods for susceptibility

The period of childhood may be viewed as a succession of phases or stages with distinguishable anatomical, physiological, and psychological characteristics (Firestone et al., 2007; Hubal et al., 2014). To facilitate analyses and communication, Firestone et al. (2007) defined these periods as "a distinguishable timeframe in an individual's life characterized by unique and relatively stable behavioural and/or physiological characteristics that are associated with development and growth". The stages or periods are commonly referred to as "critical periods" or "windows" during which a child may be susceptible or more likely to be affected by an exposure. The stages are seen as sequences that depend on and influence each other, meaning that factors affecting health development in early life (such as excessive stress, restricted physical activity, or poor care) may affect a child's future mental and physical well-being (e.g., Smith et al., 2015; Evans, 2003). In biology science, critical periods or windows commonly adhere to "periods of development when it is observed intrinsic changes in biological systems towards increasing complexity, greater adaptivity and more efficient functioning (Scott, 1986), while in life course epidemiology critical period has been defined as "a limited time window in which an exposure can have adverse or protective effects on development and subsequent disease outcome." (Kuh et al., 2003). For example, high levels of prolonged prenatal parental stress during pregnancy and early postnatal stress to the new-born can lead to impaired neurodevelopment during sensitive periods of rapid cell division throughout foetal and postnatal life. This can have lasting negative effects on health and well-being throughout the lifespan (Bleker et al., 2019; Romero-Gonzalez et al., 2020; McGuinn et al., 2022). In addition, stressors at an early age may also increase the likelihood of phenotypic expression of a genetic predisposition to a neurodevelopmental disorder (Lachmann et al., 2022).

Sensitive periods are sometimes used interchangeably with critical windows but are more often used in psychological and behavioural literature (e.g., Skogen and Øverland, 2012; Nelson, 2000) and tend to describe periods where an exposure may have the most prominent effect. New views on critical windows highlight that although adaptive changes may primarily be modified early in life, the door seems to be open for lifelong plasticity (Werker and Hensch, 2015). Questions are therefore "what processes open, mediate, close or reopen the critical windows" (ibid).

As a proxy for critical periods or windows, age spans are commonly referred to, however the use of age spans differs between cultures and scientific fields. In developmental psychology age spans important for development was suggest among others by Erikson and Erikson in the early fifties (Dunkel and Harbke, 2017). These age spans have influenced clinical practice, research, and education, including school curriculums.

Departing from a biological/natural and paediatric expertise and focusing on a chemical exposure assessments and risk assessments, the US Environmental Protection Agency (2005) and later the World Health Organisation (WHO, 2006) undertook the task of determining age spans based on anatomy and physiological development that would affect dose and health impact. These attempts were subsequently revisited by Hubal et al. (2014), who attempted to harmonise exposure assessments to compare judgements across place, culture, and time. While they stress that there is no single "correct" means of defining the age spans, they point out that using a standardised categorisation facilitates comparisons between studies and countries. They propose to use the WHO detailed age span comprising 12 age spans or a simplified version of eight age spans (see details in Table S1 in the supplementary material).

From an exposome approach, a categorisation of vulnerable age spans would ideally acknowledge psychosocial, cognitive, and biological developmental age periods and their vulnerability for different exposures and pathways of exposures. The initiative was already suggested in the bio-psycho-social model developed by Havighurst (1956) and has later been explored but mainly for adult ageing (e.g. Friedman and Ryff, 2012). We would propose that future efforts attempt to define an interdisciplinary exposome-inspired age operationalisation with a clear child perspective.

4.4. Structure and agency – a theoretical approach for understanding the exposome in children

In the development of a child perspective within the exposome field, we see the need to avoid *methodological individualism* where individuals are perceived as passive receivers of exposure or studied separated from

contextual factors (Frohlich et al., 2001). To that end, it has been suggested to adopt a sociological approach: *structure and agency (*Abel and Frohlich, 2012; Øversveen et al., 2017*)*. In this approach, *agency* captures an individual's expression of will and capacity to act. However, these actions are not executed randomly. Instead, individual reasoning and actions are guided by the constant interaction with social *structures*, which may impose opportunities and/or constraints to agency. The social structures can be enacted in the form of laws, regulations, and state institutions, but also in the form of norms, expectations and patterned behaviour or discourses. In addition, and of great relevance to our discussion about the exposome, these structures are also manifested in the form of natural or built environments (Bernard et al., 2007). Importantly, structures may enable and restrain agency disproportionally between groups in society, e.g., living within neighbourhoods with limited access to recreational areas may restrain physical outdoor activity.

Behaviour affects a child's exposure and may also affect outcome. For example, using social media late at night might negatively affect sleep and increase the risk of mental disorders. On the other hand, social media use can be seen as an opportunity for social interactions, thereby promoting well-being. Nevertheless, many behaviour change models are critiqued as naïve due to the primacy of the individual and individual choice, and this seems to be the case even when "contextual factors" are considered (Blue et al., 2016). *Social practice theory* (Blue et al., 2016; Maller, 2015) offers a significant contribution to the development of a child perspective to the exposome as it further develops the structure-agency nexus, focusing on its materialisation as practice. Social practice theory thus combines "Materials", "Competences" and "Meanings", where materials refer to objects, consumer goods and infrastructures, competences refer to the understandings of situations and practical know-how, and meanings add the social significance of the practice and past experiences of participation (Blue et al., 2016). These entities (materials, competences and meanings) are the basis for understanding a given practice. It should be noted that a social practice is not a synonym for individual behaviour (Blue et al., 2016). Rather, Maller defines *a practice* as:

> being constituted by meanings about how and why to do things (cultural conventions, expectations and socially shared meanings), materials (objects, tools and infrastructures), and competences both tacit and explicit (knowledge and embodied skills) (Maller, 2015).

Applying the social practice theory to social media usage among children and adolescents might include: 1) a shared understanding or *meaning* of why to engage in social media, when to do so, how often, but also what to post and what influencers to follow; 2) *materials* like mobile devices, software applications, algorithms, electricity; and 3) *competences* in how to download applications, navigate the internet, charge your device and source criticism. In addition, the practice of social media usage could be an interrelated part in other practices, such as going to sleep. With this approach, the practice entities (meanings, materials, and competencies) will affect our assessment of the child exposome in a comprehensive way that assists in the formulation of adequate interventions. For instance, if we aim to study child relevant exposures like artificial light, we need to acknowledge the various parts that determine media usage, i.e., how long, how often, the use of screen filtering, parental guidance, school demands and peer pressure.

Apart from the developing agency of very young children (who have less ability to define and express their will and capacity to act), we highlight the relevance of surrounding and significant actors (e.g., parents, preschool staff and teachers), whose practices might affect the younger child and can be investigated from a social practice approach, e.g., breast feeding, reading aloud and going to the park (van Nijnatten, 2010).

4.5. Places, actors and activities

Places are understood according to human geography and urban planning as locations instilled with meaning (Tuan, 1977). Places reflect interactions among locations (locality), the linkages to daily social activity (locale), and individual/community sense of place (Cloke and Johnston, 2005; Dohmen et al., 2021; Psyllidis et al., 2022). It is also where social interactions take place (Gudi-Mindermann et al., 2023). Over the life course, different places (e.g., home, schools, nature) have differential relevance to people, something that also varies across historical periods, across countries, across people and across practices (Cresswell, 2009). Conceptually, places are aligned with actors and activities that are understood according to structure-agency and social practice theories. *Activities* are thereby understood as specific actions of relevance for exposure and for health equity (Dohmen et al., 2021), e.g., exercising and eating. A social practice approach will help explain how to understand these activities and their link to exposure, including social structures, individual choices and behaviour (Blue et al., 2016). In Fig. 2, we present a concept for elaborating on how a child perspective can be approached in exposome research evaluating mental health and cognitive development. The figure should be seen as an evolving concept that may inspire researchers and other stakeholders in considering relevant dimensions for the exposome conceptualisation, such as places, exposures, actors, activities, social practice, and life stages. Consequently, the actual content might differ depending on the research focus, with the suggested places, exposures, actors, and activities being altered. As indicated in Fig. 2, digital engagement is added as it has become a place of growing relevance for the exposome from a child perspective (Odgers and Jensen, 2020). However, it is important to acknowledge that the concept is not exhaustive and that it can enable other types of extensions when needed.

4.6. A child-perspective on exposures

Due to their physiology (Etzel, 2020) and less developed detoxification metabolism (Huen et al., 2012), children have a comparatively higher uptake of exposures as compared to adults for most environmental pollutants. These physiological differences are well known within the paediatric medicine and pharmacology, but sometimes overlooked in environmental studies. For example, the air intake of an infant is about twice that of an adult, and similarly a child has a considerable higher intake of water and food per kilogram weight (Moya et al., 2004; Bearer, 1995). Children up to the age of about seven also differ in relation to adults regarding diffraction and reflection properties of the head, pinna, and torso (the head-related transfer functions; HRTF) (Fels, 2008). As the variations in HRTFs, affects noise exposures at the opening of the ear and with the addition of the resonance of the ear canal further affects the auditory exposure, this may have implications for perception and discomfort to higher frequency sounds (Persson Waye and Karlberg, 2021), sound localisation and possibly also for the risk of hearing problems.

Highly relevant is also how a child's activity pattern and social behaviour may affect the exposure and intake (Lipina, 2016; Tulve et al., 2016). For example, it has been shown that preschool children are exposed to significantly higher noise levels as compared to their preschool teachers - a difference amounted to as much as 6 to 8 $dB_{LAeq\ indoors}$ over the day (Persson Waye and Karlberg, 2021). This difference is most likely explained by several factors such as several children being in one room, playing close to each other also during loud activities and not having the capacity to control, anticipate, understand or cope with the noise (Persson Waye et al. 2013, 2019). The need for child relevant assessment methods in general is evident and is specifically for noise exposure currently an issue for research (Loh et al., 2022). With a few exceptions, current health frameworks do not deal with these age-specific aspects well.

As seen in Fig. 2, examples of external and internal exposures and

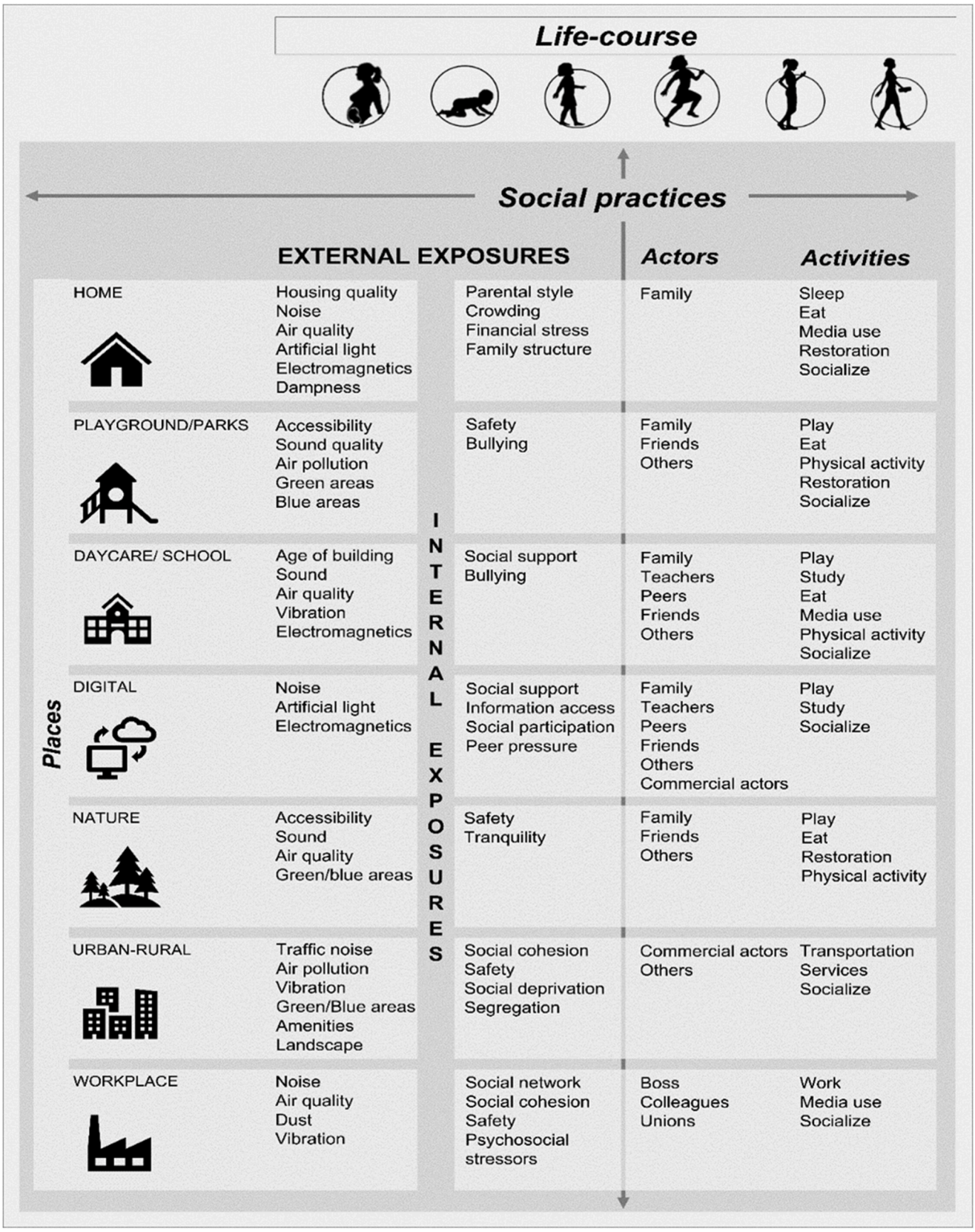

Fig. 2. Relevant dimensions for the exposome conceptualisation, such as places, exposures, actors, activities, social practices and life stages, emphasizing their interrelationships. Social practice is seen as an underlying and modifying concept that affects and is affected by the different components. Inherited in the places are to various extents, aspects of the exposure domains used in Equal-Life (indoor and outdoor environmental quality, natural environment, built environment, social environment and lifestyle). The internal exposures (e.g., proteins and metabolites) are in this concept less well tied to place but may still be affected by the social practices and the life course. The life course highlights the need to consider the child development as a crucial aspect in the articulation of the social practices and the exposures in connection to the places, actors and activities.

combinations are potentially relevant for a child's mental health and cognition. A preliminary list of relevant exposures for children was presented by van Kamp et al. (2022) and this was extended during the course of the project, using the domains: indoor and outdoor environmental quality, natural environment, built environment, social environment and lifestyle. In the previously mentioned literature review of how sleep, psychophysiological stress, and self-regulation/coping (papers in preparation) and restoration (Dzambov et al., 2023), may mediate the association of exposome and mental health, preliminary analyses show that physical and social exposures, were most frequently included in the exposome, while internal exposures were less commonly considered. Physical exposures included: outdoor and indoor environmental quality (i.e., noise, air pollutants inclusive passive tobacco smoke, and restorative green and blue areas), lifestyle (i.e., diet, smoking, screen time and physical activity) and built environment (urban/rural). Of the social exposures, socioeconomic (i.e., household or parental income, parental education), social circumstances (i.e., crowding, social cohesion, child separation, ethnic minority), psychosocial mechanisms (i.e., adverse caregiver-child interaction, abuse, family hostility, parent mental illness, parenting) and combined factors (i.e., stressful life events, adverse childhood experiences) were most often reported. Internal exposures classified within the groups: metabolomics (e.g serotonin), proteomics (e.g cytokines), epigenetics (e.g methylation changes) as well as transcriptomics and microbiome, were mainly reported for the studies on stress.

This paper has though no ambition of providing an exhaustive list of exposures but rather to propose a framework of how to approach these. Some of these exposures are as shown in Fig. 2 based on life-course phase, place, and social practices, which should be viewed in relation to actors and activities.

In addition, the exposures may differ between urban and rural settings and between different cultures and countries. In recent years the urban environment (city-level) and its places are commonly identified as being of particular risk for health. Factors related to urbanisation, such as rapid growth, a high density of people, buildings and transport, lack of social cohesion, criminality, high demand on drinking water supplies and sizeable waste handling, highlight the risks for an unhealthy environment (e.g., Firdaus and Ahmad, 2014). However, focusing on urbanity discounts around 43% of the global population and tends to ignore the relevance of an exposome perspective in rural areas, including those adverse for children's health (e.g., chemical exposures from farming, accidents at farms, noise from transportation, unsafe or long transportation to schools and leisure activities, lack of choice of education, poor accessibility to health care and inequality in SES). Importantly, potential salutogenic exposures also differ, such as access to green and blue areas, places for playing and physical activity, and social cohesion in smaller communities. Although, data from the US repeatedly describe how children in rural areas are at particular risk to their health and well-being (US Census Bureau, 2008; Cherry et al., 2007), a more complex picture is presented in a United Nation report (UN, 2018) covering a global perspective. When analysing several indicators of child well-being in 77 countries (mostly low and middle-income countries), it confirms on the one side that urban children in most countries fare better than rural children, but that the figures also hide huge inequalities in urban areas. One of the few studies that investigated cumulative risks for children in rural areas corresponded with conclusions from studies in urban areas that cumulative risks increased psycho-social distress and showed an association with a lower rating of self-worth (Evans, 2003). Taken together, a general conclusion is that few studies have undertaken an exposome perspective to study children's health in rural areas. An important question when promoting children's health globally is whether interventions tailored for the urban environment also are applicable or appropriate for the rural environment. This question needs further study.

Similarly, a better understanding and inclusion of a global perspective are called for, as there are few studies providing this information. We have come to realise that our understanding of the exposome perspective regarding children is based on high and middle-income countries and is taken from geographically restricted areas of the globe. A global perspective on exposure, its distribution and its timing as well as social support and individual resilience are needed to place children and adolescents at the centre of the sustainable developmental goals "for current and future generations" (Alfvén et al., 2019).

5. The conceptual framework

In Fig. 3 we present a conceptual framework on exposome, mental health, well-being and cognitive development in children and adolescents, including potential mediators (Fig. 3). With mediators, we refer to variables that may link the exposome to mental health/cognitive development. Of main focus in Equal-Life was the mediators: sleep, psychophysiological stress, restoration and self-regulation/coping and how they potentially mediated the linkage of exposome to mental health and cognitive development. These results are published separately (e.g. Dzhambov et al., 2023) in this special issue.

The development of the framework was based on an interactive research process, oscillating from inductive and deductive reasoning, considering the findings of literature reviews in connection with further evidence, existing models (e.g., Dahlgren and Whitehead, 1991; Institute of Medicine, 2000; Krieger, 2012), previous work of Equal-Life (Gudi-Mindermann et al., 2023) and interdisciplinary expertise discussions within and outside the Equal-Life framework.

In Fig. 3, 'Exposome' depicts the environment in which the individual is embedded includes social, physical and internal exposures (see also Section 3) and that are expected to change and increase in complexity along the life course (Wild, 2005, 2012; Senier et al., 2017). The social, physical and internal exposures interrelate along the life course, not as separate parts of the environment but as the total environment in itself, or the exposome. The relationships between exposome, mediators and outcomes are magnified in the centre of this framework and should be understood as embedded in the environment along with the individuals. The exposome interlinks with the mediators to affect mental health and cognition and provides a possibility for interventions along the life course. Mental health and cognitive development also interact with each other in a bidirectional mode as depicted by the arrows in the figure and as previously noted in Section 2.

A balance is proposed between the exposome and the mental health/cognitive development outcomes which is illustrated in the form of a seesaw. The balance introduces graphically the notion that physical, social and internal exposures may have both detrimental and supportive qualities over the life course. It also represents the notion that the outcomes vary from positive to negative. The mediators, in the middle, convey the mechanistic, mediating role of potential mediators and the possibilities of these mediators to function as contributing factors in the balance between environment and health.

'Vulnerability' (Fig. 3) is intended to capture both the evolving biological susceptibility in different phases of individual human development and a population perspective with a three-dimensional approach to vulnerability comprising 1) differentiation of exposure, 2) differentiation of effect (i.e., susceptibility); and 3) differentiation in capacity to respond to exposure or health adversities. As discussed in Section 4, it is important to note that these dimensions are not static but fluid in several respects. A life-course exposure implies that prenatal or antenatal exposures may induce susceptibility to subsequent exposures. Consequently, social patterns (e.g., due to socioeconomic position, gender) and unequal exposures in children and adolescents might also result in subsequent inequalities in susceptibility. The vulnerability layer closely interacts with the other layers where "social structures and values" relate not only to unequal exposures during childhood and adolescence but also to access to resources and thereby the capacity to respond to exposures and adversities. Similarly, vulnerability may be a product of social practices by the children themselves or other relevant

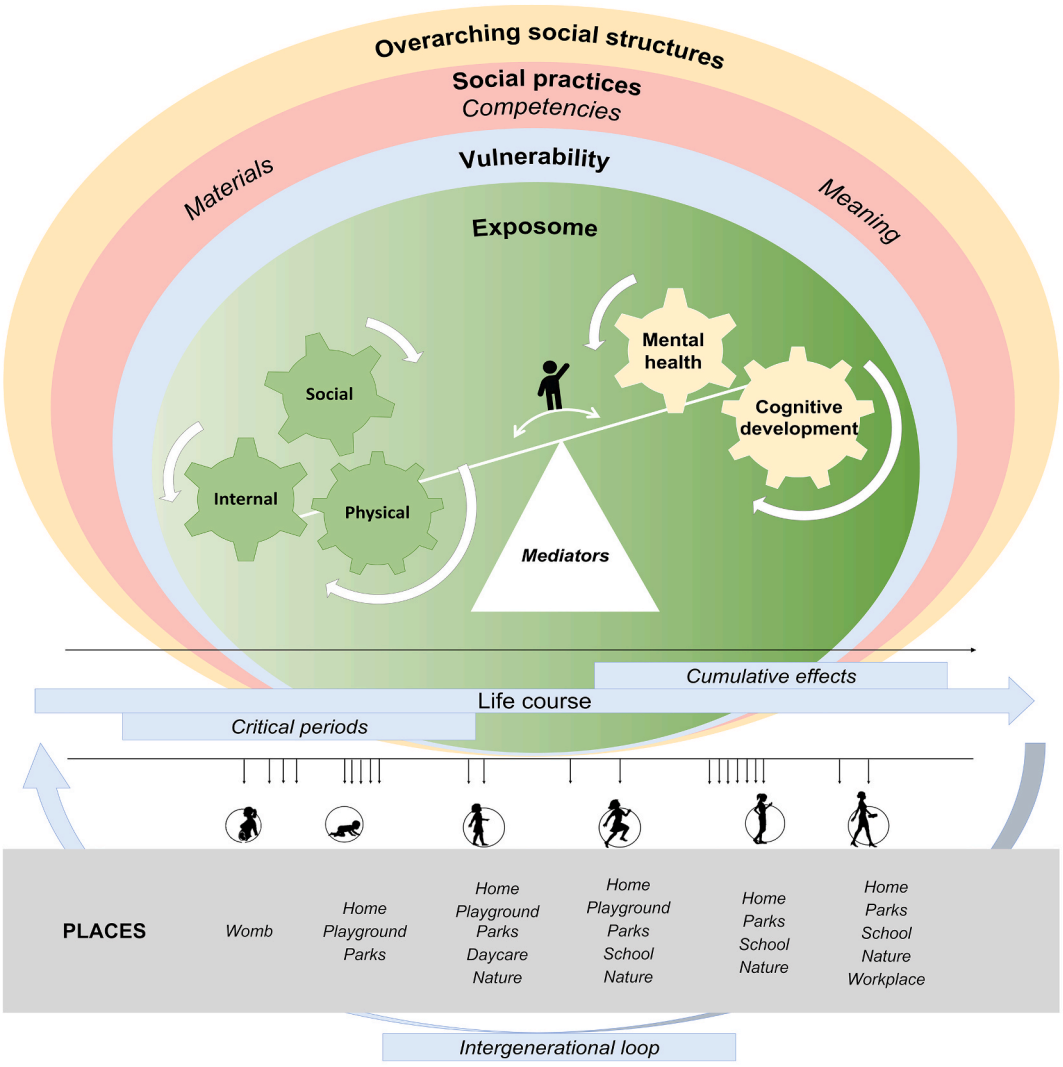

Fig. 3. The conceptual framework of the interlinkages between exposome, mental health and cognitive development of children and adolescents, highlighting the possibility for mediating pathways.

actors (e.g., parents, siblings, teachers).

'Social practices' (Fig. 3) comprises the notion of social practices (e.g., Blue et al., 2016; Maller, 2015). As discussed above (Section 4), this approach assists in understanding the complex interrelationships between structure and agency that shape the exposome, potential mediators and outcomes of children and adolescents through everyday practices. A social-practices approach highlights that physical, social and internal exposures in a life-course perspective (i.e., the total exposome) are dependent on the "Materials", "Competences" and "Meanings" (Blue et al., 2016) and involved in the practices of children and adolescents, like playing games, being with friends, attending school or pre-school, eating dinner or interacting with social media. For younger children we also need to recognise the relevance of other actors and their social practices for exposome in children, e.g., parenting, working and teaching. With social practices at the heart of investigation, we will neither emphasise the overarching structures and values that distribute exposure nor the behaviours of the individual. Instead, we will focus on the very nexus where these two meet and overlap. This will make it easier to understand inter- and intragroup differences in relation to exposome, mediators and outcomes, since structures and values will enable, restrain and shape practices differently between groups of children and adolescents.

'Overarching Social Structures' (Fig. 3) comprises overarching structures at the macro level. These macro-level structures can comprise international institutions and agreements, national laws and regulations, quality of governance and macro-economic structures but also cultural values, and religion. They are interconnected to the individual at the micro level (see Section 4). For example, child exposure to chemicals, second-hand smoke and sugars is influenced by laws, regulations, and economic structures but also norms around parental behaviour. It should also be noted that these structures are not static but constantly influenced by political actors and non-governmental organisations (NGO) but also commercial actors that lobby to influence laws, regulations, and norms in the society (Kickbusch, 2016).

The framework highlights the **relevance of a life-course perspective** to the exposome-outcome nexus, articulating the notions of critical windows, cumulative effects and intergenerational loops. The small arrows from the life course to each developmental phase depict this notion

of timely relevance of exposures. Some of these were touched upon in relation to child development in Section 4. The developmental phase from conception to early adulthood (Seckfort et al., 2008; Taylor, 2010) can be seen as a **critical periods or window for effects,** but the period also comprises several critical periods characterised with specific development and growth during which a child may be susceptible or more likely to be more highly exposed.

The effects of the exposome may **accumulate** over the life course as the number, duration and severity of exposures add up with time. The accumulation of risk can be due to clustering of exposures, as often seen in social exposure (Evans, 2003), or due to repetition of exposures over time. Chain of risk or the trigger model deviates slightly from the accumulation model as it includes a sequence of linked exposures (one experience or exposure leading to another) that may increase the risk of disease (Kuh et al., 2003).

In addition, the **intergenerational effects** need to be considered. Evidence points to various exposures (including malnutrition, childhood trauma and drug exposures) with both physiological and behavioural effects that can be carried over into subsequent generations. There is also the possibility of intergenerational effects in which both pre- and postnatal exposures can lead to epigenetic changes that may impact health over the life course and into future generations (Galler and Rabinowitz, 2014). Genetic liability to such exposures and experiences may also be transmitted from parents to children (Handakas et al., 2023).

6. Concluding remarks

An exposome approach to children's and adolescents' mental health and cognitive development is imperative, given the complexity and diversity of risk and salutogenic factors and their interrelation with child development and health in a time, level, and frequency domain. This paper provides a framework for how a child perspective can be incorporated within the exposome field. This framework helps us understand and communicate the combined physical, social and internal exposures that are relevant for health estimates from an exposome perspective. We emphasise that for the young population, the exposome is made up by an intricate relation of place, activity and actors, and importantly, these vary with age, social position (e.g., gender, socioeconomic position, ethnicity) and societal structures, creating patterns of vulnerability among groups of children and adolescents. We suggest that a social practice approach might contribute to understanding and acting on these intriguing processes. Together with the child's age-dependent physiology, these practices influence the child's exposures and their effect on mediators and outcomes. Importantly, social practices may also directly affect the potential mediators.

While there is a growing interest in research within the exposome field, we note that the operationalisation of exposome is still commonly guided by disciplinary boundaries, the outcomes in focus, data availability or data collection. To advance the field, novel statistical methods together with an open epidemiological approach are needed. Traditionally, epidemiological analyses define an independent variable (i.e., predictor or determinant) and a dependent variable (i.e., outcome), and hence bi-directional relations tend to be disregarded, favouring a unilinear causal relation (Lundberg, 2020). While simplifications are often necessary in research, when attempting to capture a life-course perspective we should acknowledge that associations are not only linear but sometimes bidirectional and that the direction and even relevance of associations may change between life periods. Furthermore, to understand individual-level outcomes, we may need to understand their relation to higher-level factors like family or community and the potential interaction between these.

To successfully undertake an exposome perspective for evaluating children's and adolescents' mental health and cognitive development, a truly interdisciplinary effort is encouraged (van Kamp et al., 2022). This poses a challenge, given the scarcity of interdisciplinary efforts in exposome research. In this paper, we point out important areas that currently are solely or predominantly defined within either the social or biological scientific fields, such as the developmental phases of a child or the use of vulnerability. Good attempts to integrate scientific fields are the paradigms on exposome research (Wild, 2005, 2012), the life-course perspective (Kuh et al., 2003), the ecological model for human development (Bronfenbrenner, 1979) and the Ecosocial theory by Krieger (2001). All these acknowledge that a variety of disciplines, e.g., medicine, biology, sociology, psychology, ecology, political science, natural science, and economics, are crucial for this task.

Further, a global, cultural and rural/urban perspective on exposure, its distribution and timing, and societal support are needed to advance the exposome field outside its current focus. This would facilitate setting children and adolescents at the centre of sustainable goals for future generations (Alfvén et al., 2019). However, our contemporary understanding of the exposome perspective comes from high and middle-income countries and from geographically restricted areas of the globe, which limits our ability to draw general conclusions on risks or health-promoting interventions and the applicability of these interventions.

As noted in this paper, an exposome approach is highly relevant to understanding the production of inequalities in mental health and cognition in children and adolescents and consequently inequalities in adulthood. Beyond the challenge of understanding the processes behind the disproportional distribution of physical and social exposome between groups of children and adolescents, we also need to acknowledge how the exposome interacts with susceptibility due to human development from pre-natal to late adolescence. At the same time, there is a lack of empirical research on inequalities within the exposome field. Still, an inequality approach to exposome research should refrain from treating inequalities as unidimensional phenomena based on groups in a society characterized by socioeconomic status, gender, *or* ethnicity, and instead acknowledge how health-related experiences and exposures vary greatly within these groups at the intersection of multiple social positions in the lives of individuals. The lack of intersectionality in exposome research was recently noted (Bowleg, 2021; Gudi-Mindermann et al., 2023), and some guidance on how this can be pursued was also provided by Zota and VanNoy (2021).

Lastly, we have outlined biological, social and behaviour conditions that affect the exposure and the outcome for a child that calls for a child specific health risk assessment. It is imperative that current health frameworks deal with these age-specific aspects. The challenges and suggestions presented here may be seen as opportunities to develop the exposome field, with respect to a child perspective, within and between disciplinaries and hopefully inspire to further studies on children's health in relation to the exposome.

Credit author statement

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Irene van Kamp reports financial support was provided by European Comission. One of the co-authors of the present submission (Angel M. Dzhambov) is also a VSI co-editor and a collaborator of another co-editor of the VSI (Iana Markevych

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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