Review

Biological Psychiatry

Teeth as Potential New Tools to Measure Early-Life Adversity and Subsequent Mental Health Risk: An Interdisciplinary Review and Conceptual Model

Kathryn A. Davis, Rebecca V. Mountain, Olivia R. Pickett, Pamela K. Den Besten, Felicitas B. Bidlack, and Erin C. Dunn

ABSTRACT

Early-life adversity affects nearly half of all youths in the United States and is a known risk factor for psychiatric disorders across the life course. One strategy to prevent mental illness may be to target interventions toward children who are exposed to adversity, particularly during sensitive periods when these adversities may have even more enduring effects. However, a major obstacle impeding progress in this area is the lack of tools to reliably and validly measure the existence and timing of early-life adversity. In this review, we summarize empirical work across dentistry, anthropology, and archaeology on human tooth development and discuss how teeth preserve a time-resolved record of our life experiences. Specifically, we articulate how teeth have been examined in these fields as biological fossils in which the history of an individual's early-life experiences is permanently imprinted; this area of research is related to, but distinct from, studies of oral health. We then integrate these insights with knowledge about the role of psychosocial adversity in shaping psychopathology risk to present a working conceptual model, which proposes that teeth may be an understudied yet suggestive new tool to identify individuals at risk for mental health problems following early-life psychosocial stress exposure. We end by presenting a research agenda and discussion of future directions for rigorously testing this possibility and with a call to action for interdisciplinary research to meet the urgent need for new biomarkers of adversity and psychiatric outcomes.

Keywords: Adversity, Biomarkers, Mental health, Prevention, Stress, Teeth

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Exposure to early-life adversity is one of the biggest risk factors for both mental and physical health problems across the lifespan. Early-life adversity encompasses experiences of threat or deprivation that deviate from a child's expectable physical and psychosocial environment and require some form of adaptation (1). These early-life adversities can thus be both physical and psychosocial in nature—spanning experiences of food deprivation resulting from poverty to witnessing or experiencing violence or having a parent with mental illness. These adversities are estimated to affect nearly half of all youths in the United States (2). Although not all children who experience early-life adversity will go on to have mental health problems (3), exposure to adversity has been associated with about a twofold increase in risk for depression, anxiety, or substance use disorders (4,5). In fact, researchers estimate that if the association between adversity and mental health risk was causal, approximately one third of all mental disorders could be attributable to childhood adversity (5–7).

Emerging evidence suggests that there may be certain stages in development, or sensitive periods, when the brain is highly plastic and thus when adversity may have even more enduring effects (8,9). Studies finding support for sensitive periods suggest that exposure to early adversity during prenatal life (10) and from birth to 5 years of age (11,12), may be especially important in shaping long-term risk for psychiatric disorders. These sensitive periods are often conceptualized as high-risk periods—or windows of vulnerability—when adverse life experiences, such as exposure to stressors, are most harmful in increasing disease risk. However, sensitive periods can also be viewed as high-reward periods—or windows of opportunity—when enriching life experiences, including exposure to health-promoting interventions, are even more beneficial in preventing disease and promoting long-term health. Of note, relatively few studies on the time-dependent effects of adversity have been performed, and the evidence both for (11–13) and against (14–16) the existence of sensitive periods is mixed.

Given the well-established association between early-life adversity and a variety of psychiatric disorders, there is an urgent need to both 1) refine our understanding of whether and when in development these sensitive periods occur and 2) identify children who experience early-life adversity—particularly

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during possible developmental sensitive periods—to guide targeted prevention efforts.

Yet, the lack of tools to reliably and validly measure both the presence and timing of early-life adversity remains one of the biggest obstacles in the field. Current gold standard measures of childhood adversity rely on either retrospective or prospective self-reports, which are susceptible to major biases in recall or self-disclosure (17). In fact, a recent meta-analysis of 16 studies found that retrospective and prospective measures of childhood maltreatment, one of the most common types of childhood adversity, showed poor agreement, with more than half of individuals with prospective observations of maltreatment not reporting it retrospectively and, similarly, more than half of individuals with retrospective reports lacking concordant prospective measures (18). Moreover, asking a child to directly report his or her own adversity exposure may raise ethical and other concerns and pose a risk of harm to the child (19). Official reports, such as health and social services records, provide an alternative strategy, but these can also dramatically underestimate the prevalence of certain adversities (20,21). Although promising biomarkers of early-life adversity and subsequent risk for mental health problems—such as altered DNA methylation patterns (22–24) and changes in amygdala connectivity (25,26)—are beginning to emerge through epigenetic and neuroimaging studies, respectively (27), these measures are currently too costly, time-consuming to implement, and/or lacking in reproducibility. Thus, there is a need for objective measures that are noninvasive, inexpensive, and able to provide more accurate information about the presence and timing of childhood adversity. If such a measure existed, its public health implications would be profound. For the first time, clinicians would be able to confidently identify children—on a population-wide scale—who experienced childhood adversity during sensitive periods in development and are therefore at future risk for developing a psychiatric (or other) disorder. Such early, accurate risk identification could unlock the full potential of primary prevention programs, altering the course of children's development before psychopathology symptoms ever even onset.

In this article, we propose that teeth could potentially serve as a promising and actionable new tool capable of achieving these goals. To support this claim, we first summarize empirical work from dentistry, anthropology, and archaeology on human tooth development and show how these fields have collectively studied human and animal teeth for decades, using teeth as time capsules that preserve a permanent, time-resolved record of life experiences in the physical environment. This body of literature discusses teeth not as they relate to oral health but rather as fossil records in which the history of an individual's early environmental exposures is permanently imprinted. Importantly, many of the studies cited here were conducted in samples considered large by the standards of their disciplines. This includes those studies investigating human archaeological populations and nonhuman primate samples where there are a limited number of available specimens. Although these sample sizes are small in comparison with most psychiatric studies, we argue that insights from this collection of studies nevertheless provide initial suggestive evidence of the untapped opportunities for the field of mental health research and, potentially, clinical practice to prevent brain disease and promote brain health. Building from this literature, we then integrate these insights with knowledge about the etiology of psychiatric disorders and the role of early-life adversity in shaping mental health risk to present a working conceptual model that links past psychosocial stress exposure to markers of tooth development and, ultimately, risk for neuropsychiatric disease. We end with a research agenda and discussion of future directions for rigorously testing this conceptual model and with a call to action for interdisciplinary research to meet the urgent need for new transdiagnostic biomarkers of adverse early-life experiences and psychiatric outcomes. Although the evidence to support this conceptual model is in its nascent stages, the time is right to begin empirically testing this model, given increasing investment in the formation of large birth cohort studies that have already collected teeth, the availability of techniques to characterize between-person variability in teeth-related features (28), and the growing recognition of the potential for biomarkers to guide prevention and intervention planning.

THE PROPERTIES OF TEETH AS RECORDS OF EARLY-LIFE EXPERIENCE

Human teeth possess at least five properties that make them promising potential biomarkers of exposure to early-life adversity and therefore helpful tools to guide prevention efforts in psychiatry.

Teeth Develop During Known Sensitive Periods in Development

Most humans have two sets of teeth: a set of 20 primary (deciduous, "baby," or "milk") teeth that are shed and replaced by 32 permanent teeth (29). Each tooth is made of enamel (the hard outermost layer of the tooth crown), dentin (the underlying layer extending into the tooth root), and pulp (the innermost core of the tooth containing blood vessels, nerve cells, and dentin-forming cells called odontoblasts) (Figure 1A).

Primary teeth begin to mineralize at approximately the fourth fetal month, begin to erupt at approximately 6 months of age, and are completely formed by 2 to 3 years of age (30) (Supplemental Table S1). In contrast, the formation of permanent second molars extends from 3 years up until 14 to 16 years of age, while the permanent third molars, or wisdom teeth, complete their formation at around 18 to 25 years of age (31). These time frames coincide with known sensitive periods for brain development (32,33) and programming of stress response circuitry (34,35).

Teeth Leave a Permanent Record of Their Incremental Formation, Much Like the Rings in a Tree

The process of tooth formation is well documented (Figure 1B). In the final stage of tooth formation, odontoblasts (dentin-producing cells) and ameloblasts (enamel-producing cells) secrete proteins that incrementally mineralize the dentin and enamel, producing growth marks that remain visible in the completed tooth crown. These growth marks act as permanent records of the formation process, much like the rings in a tree marking its age. Cross-striations record roughly daily growth (Figure 1C). Longer period growth lines (36), called striae of Retzius (37), correspond to roughly weekly growth in humans.

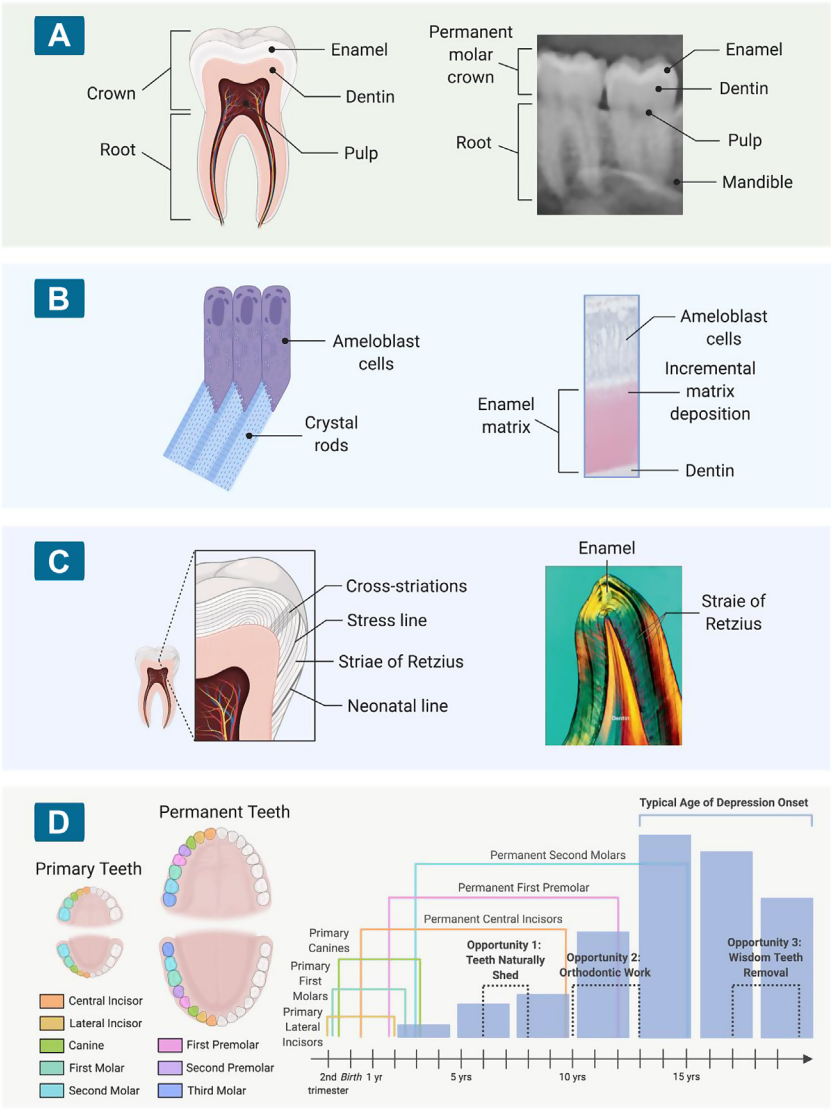

Figure 1. The properties of teeth as records of early-life experience (images created with BioRender). Human teeth possess at least five properties that position them to be promising biomarkers of early-life adversity and subsequent depression risk. **(A)** Each tooth is made of enamel (the hard outermost layer of the tooth crown), dentin (the underlying layer extending into the tooth root), and pulp (the innermost core of the tooth containing blood vessels, nerve cells, and dentin-forming cells called odontoblasts). **(B)** Teeth develop incrementally. In the final stage of development, enamel-producing cells known as ameloblasts secrete proteins that mineralize the dentin and enamel. Enamel is laid down in a matrix of crystal rods. **(C)** Because enamel does not regenerate, it leaves a permanent record of its formation process in the tooth, much like the rings in a tree marking its age. Stress exposure during development can disrupt this process, producing stress lines or permanent records of the existence and timing of the stressful experience. **(D)** Each tooth develops over a known time scale (see hollow bars). Collection of teeth could occur at multiple times across the first two decades of life when teeth are spontaneously shed or routinely removed (see dashed bars). Each time teeth are shed or removed possibly represents an easy and inexpensive opportunity for assessment and intervention to guide primary prevention efforts for psychiatric diseases. Here, we highlight prevention for major depressive disorder as an illustrative example. These prevention efforts are made possible because the time periods for tooth availability coincide with time periods during or before major depressive disorder often first onsets (see filled bars). Photos in panel **A** (right) and panel **B** (right) are from F.B. Bidlack (unpublished data). Photo in panel **C** (right) is from Nanci (43).

These growth marks are preserved in teeth across mammal species (38–41). Exposure to adversity may affect this growth process, resulting in abnormal growth marks or stress lines, as discussed below.

Because each tooth develops in a specific time window during ontogeny (Supplemental Table S1), these growth marks permanently record different phases of development. In other words, each tooth may tell its own story about human growth and development. Depending on whether the tooth root is present, the growth marks in a primary central incisor record daily and weekly development from prenatal life up to 2 years postnatally, whereas a permanent second molar records development up to 14 to 16 years (30,42,43). Thus, one remarkable consequence of this natural variation across teeth is that a continuous record of growth from prenatal life up to midadolescence can be pieced together between these different types of primary and permanent teeth. In cases where the tooth root is unavailable, as is the case for most shed primary teeth, this timeline is truncated (as noted in Supplemental Table S1).

Human Teeth Preserve Biological Memories of the Existence and Timing of Past Physical Stressors

Exposure to physical stressors during tooth formation, such as poor nutrition, disease, and ingested toxicants like heavy metals, can affect dentin and enamel cell function (44,45), resulting in alterations that are visible as structural defects or recorded as changes in chemical composition within the tooth crown (44,46,47). Among the most commonly studied developmental defects are enamel hypoplasias, which appear on the surface of erupted teeth as pits, grooves, or complete absence of enamel. The prevalence and predictors of enamel hypoplasias in both living human participants (48,49) and

archaeological populations (50) are well described in archaeology, anthropology, and dentistry. Through visual inspection of tooth characteristics—whether using macro-level tools (e.g., hand lenses) or more micro-level tools (e.g., scanning electron microscopes, microcomputed tomography)—this work has revealed that individuals exposed to famine (51), malnutrition (48,52), infectious diseases (52), and injuries (47) have significantly higher risk for enamel hypoplasias as compared with individuals without such physical stress exposures. Similarly, individuals exposed to poor diet, disease (53), and maternal hypertension (54) have also been shown to have teeth that are significantly smaller than those of their unexposed peers.

Perhaps most uniquely, these physiological stressors have also been shown to produce accentuated growth marks known as stress lines (55,56) (Figure 1C). These stress lines permanently record the specific day or week in development when the stressor occurred. One of the most studied stress lines in teeth is the neonatal line marking an individual's birth (57). Seminal work by Andra *et al.* (58) and Smith (59) revealed that by using the neonatal line as a kind of temporal benchmark, teeth can be used to capture the developmental timing of a variety of physical environmental exposures, including exposure to heavy metals (60,61), organic chemicals (62), injury and infections (63), and extreme wintertime cold (61).

Human Teeth May Also Preserve Biological Memories of the Existence and Timing of Past Psychosocial Stressors

To our knowledge, no studies have yet examined the extent to which psychosocial-based early-life adversities, such as changes in family or household structure (e.g., divorce, bereavement following family death) and experiences of deprivation or threat (e.g., physical or sexual abuse and neglect, other interpersonal and noninterpersonal traumas), are recorded in human teeth. However, at least three preliminary yet intriguing lines of evidence suggest that teeth may preserve biological memories of past psychosocial stressors, with the timing of these stressors recorded in stress lines.

As noted, the majority of research on stress lines in humans has focused on the neonatal line, which can be seen in the primary teeth of about 90% of children (64). Most commonly, anthropologists and forensic experts use the neonatal line to determine the causes and timing of infant death (65) because the neonatal line is absent in the case of stillbirth (66). A small number of researchers have used the neonatal line as a marker of different types of potential perinatal stress. From these studies, there is initial evidence showing an association between certain stressful perinatal factors (64,66–70)—including preterm birth, winter birth, and a more complicated or longer duration of delivery—and a wider neonatal line (see Supplemental Table S2). Of note, models of prenatal stress that include high-risk pregnancies and maternal prenatal exposure to chronic social disadvantage have, in turn, identified an impact of these factors on adverse offspring brain development and risk for psychiatric disorders later in life (71,72). Determining whether these associations represent the effects of psychosocial stress experienced by the mother or physiological stress experienced by the infant will require more routine measurement of the neonatal line in cases where the conditions of delivery are well documented, as is the case for many current birth cohort studies.

As summarized in Supplemental Table S3, a second body of evidence comes from seven studies in nonhuman primates exploring the associations between potential psychosocial stressors and markers of disrupted tooth development. Like humans and other mammals, nonhuman primates have two sets of teeth that develop incrementally and leave behind time-resolved growth marks (38); nonhuman primates are also affected by the same types of social stressors known to affect humans such as disruptions in parent–child bonding (73). Thus, primate studies provide a strong animal model to complement human studies. As shown in Supplemental Table S3, three studies did not have animal life histories and thus made inferences about stress exposures using evidence such as local rainfall records and knowledge of typical weaning patterns (74–76). Among the four studies in which animal life histories were known, all four documented the emergence of stress lines corresponding to the timing of psychosocial stress exposure such as separation from the mother (77), transfers to new enclosures (78), postsurgery hospital checkups (78), death of a sibling (79), and other disruptions in the caregiving environment (63,79). In one suggestive study of captive juvenile rhesus macaques, Austin *et al.* identified stress lines in enamel that corresponded to the timing of individuals' temporary separations from their mothers and the social group to undergo biobehavioral assessments (63). These biobehavioral assessments included measures of behavioral and physiological stress response to a novel environment (80) and coincided with stress lines that typically appeared within a day of the assessment. These stress lines also correlated with the timing of changes in chemical composition. Based on these primate findings, there is reason to hypothesize that the time resolution of social stressors may also be captured in human teeth. Empirical research in both humans and animals is needed to investigate this question further and, as we discuss later, to clarify which types of social experiences produce stress lines.

A third body of evidence suggesting that teeth may preserve biological memories of past psychosocial stressors comes from a very small collection of studies showing that psychosocial stressors may have time-resolved effects on human hair and nails, which are formed from the same ectodermal tissue as tooth enamel (81). Like enamel, hair and nails also grow incrementally and are affected by circadian cycles (36,82,83). The same physical stressors known to compromise ameloblast functioning—including injury, malnutrition, and physical illness—also disrupt hair and nail growth cycles. In hair, these stressors can trigger an abnormal shift of scalp follicles from the growing (anagen) stage into the dying (telogen) stage, resulting in acute temporary hair loss 2 to 4 months after the inciting event (84). In nails, these disruptions can manifest as linear grooves called Beau's lines. Given that nails grow at a known rate, the timing of exposure can be estimated by measuring the distance of the lines from the nail bed (85). Similar to the neonatal line, Beau's lines appear in the fingernails of 92% of infants at 4 weeks of age and then disappear with growth (86). Notably, acute temporary hair loss (telogen effluvium) has been empirically linked to acute psychological stressors such as car accidents and bereavement (87). The

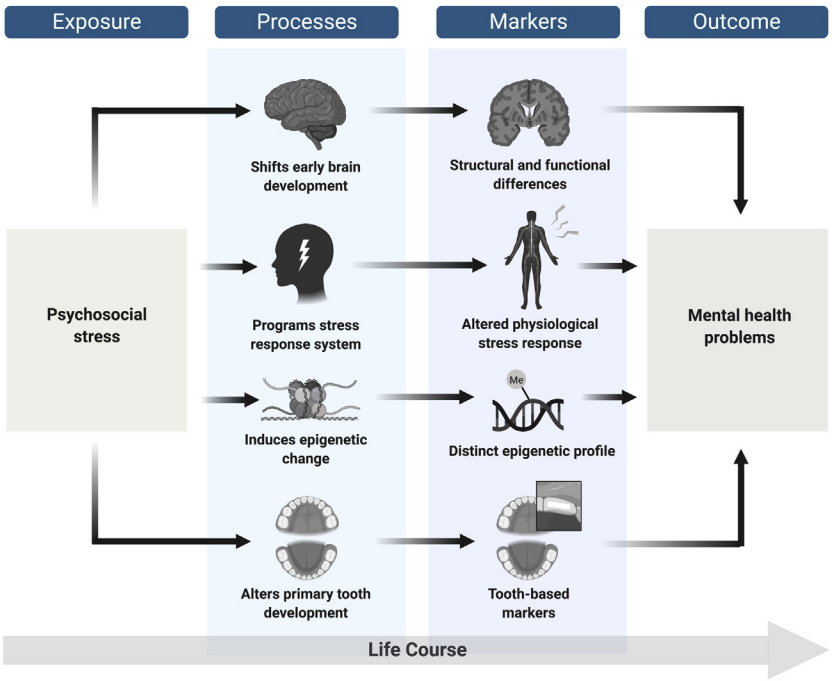

Figure 2. The TEETH (Teeth Encoding Experiences and Transforming Health) conceptual model (images created with BioRender). The three main tenets of the TEETH conceptual model are presented. The first states that exposure to psychosocial stressors (e.g., growing up in poverty, witnessing or experiencing violence) during early life disrupts multiple developmental processes, including those involved in brain development and programming of the body's stress-response circuitry and epigenome. We propose that psychosocial stressors may also affect tooth formation. The second tenet of the model states that these disruptions in development leave behind biological imprints—or markers—that can be objectively captured. Importantly, some of these markers, such as stress lines in teeth, may also preserve information about the timing of early exposures and consequent developmental disruptions. Finally, the third tenet of the model proposes that these markers of disrupted processes can be used to predict important mental health outcomes.

appearance of Beau's lines has also been anecdotally attributed to similar adverse psychosocial experiences (88).

Teeth Are Spontaneously Shed or Routinely Removed Across the First Two Decades of Life, Making Them Potentially Ideal Tools to Guide Primary Prevention Efforts in Psychiatry

A final useful property of human teeth is that healthy or non-decayed teeth are naturally shed or routinely extracted during the first 2 decades of life. As an alternative to discarding or storing those unused teeth, three possibly easy and inexpensive screening opportunities exist when teeth could instead be used to measure early-life exposure to both physical and psychosocial stressors and thus to identify children at highest risk for a psychiatric disorder. To illustrate this point, we highlight these possibilities below and in Figure 1D in relation to major depressive disorder (MDD), one of the most common and burdensome psychiatric disorders that onsets at different stages of the early-life course (89).

First, most primary teeth begin shedding at around 6 to 8 years of age (30). This time period precedes the onset of puberty, a known high-risk period for the onset of depression, particularly in girls (90). It is therefore reasonable to imagine the possibility that one day pediatricians or dentists could collect children's shed teeth from parents, send these teeth to specialized labs for analysis, and use the results as an additional MDD risk assessment tool.

A second opportunity exists during early adolescence, when otherwise healthy primary and permanent teeth are surgically extracted for orthodontic reasons (91). Approximately 14% of U.S. children have at least one tooth extracted by 13 years, before the age of onset for most adolescent MDD cases (92,93). Moreover, approximately one third of preschool children experience a traumatic injury to one or more primary teeth, and approximately one quarter of school-age children experience a traumatic injury to the permanent teeth (94). Although the treatment of traumatic injury varies depending on the nature of the injury and clinician training, some of these cases result in the extraction of the injured tooth, providing yet another opportunity for assessment of brain health and risk for future brain health problems.

A third opportunity exists during late adolescence and early adulthood, when about half of all insured individuals in the United States have their third molars, or wisdom teeth, removed (95). This period spanning 15 to 20 years of age coincides with the developmental stage when approximately 25% of MDD cases onset (96).

Of course, these prevention opportunities could also be realized for other psychiatric disorders as well. These include disorders that onset during the early teen years, including attention-deficit/hyperactivity disorder, and oppositional defiant disorder (93), as well as disorders that onset during young adulthood, including schizophrenia, bipolar disorder, and substance use disorders (93).

THE TEETH CONCEPTUAL MODEL

Based on these prior findings and the previously described potential of teeth to serve as new biomarkers, we introduce the TEETH (Teeth Encoding Experiences and Transforming Health) conceptual model (Figure 2). This model proposes that early-life psychosocial stressors disrupt multiple developmental processes (97), potentially including those involved in tooth

Table 1. Human Empirical Studies on Properties of Teeth and Mental Health Outcomes, Organized by Mental Health Outcome Examined

Study	*N*	Population Studied	Age of Participants	Tooth Examined	Exposure of Interest	Outcome	Main Findings
Autism Spectrum Disorder							
Adams *et al.* (116)	26	Children with ASD and healthy control subjects	Case mean = 6.1 years; control mean = 7 years	Unreported	Heavy metals (mercury, lead, zinc); oral antibiotic exposure	ASD diagnosis—clinically diagnosed	Children with ASD had significantly higher concentrations of mercury and higher early life antibiotic exposure than typically developing children.
Abdullah *et al.* (117)	84	Children with ASD, high levels of disruptive behavior, and healthy control subjects	9–14 years	Primary molar	Heavy metals (lead, mercury, manganese)	ASD diagnosis—clinically diagnosed; high levels of disruptive behavior—evaluated by teachers with Disruptive Behaviors Disorder rating scale	No significant difference in heavy metal concentrations between ASD and control groups, but marginally significantly lower manganese concentrations in children with ASD relative to control subjects. No significant differences in concentrations between children with high levels of disruptive behavior and control subjects.
Arora *et al.* (60)	76	Adolescent twin pairs (RATSS cohort)	8–12 years	Unreported	Heavy metals (manganese, lead, zinc)	ASD diagnosis—clinically diagnosed	Differences in heavy metal concentrations during prenatal and first 5 postnatal months between ASD and control groups.
Curtin *et al.* (118)	193	ASD-diagnosed children and unaffected twin siblings, ASD-diagnosed children and unaffected non-twin siblings, ASD-diagnosed individuals and age- and gender-matched control subjects (RATSS, ALSPAC, and Autism Tooth Fairy Project cohorts)	Tooth-shedding age	Unreported	Heavy metals (zinc, copper)	ASD diagnosis—clinically diagnosed	The duration, regularity, and complexity of cyclic variation of coupled zinc and copper concentrations were reduced in individuals with ASD versus unaffected individuals.
Internalizing and Externalizing Problems							
Mora *et al.* (119)	248	Children with possible agricultural pesticide exposure (CHAMACOS cohort)	7–10.5 years	Primary incisor	Heavy metals (manganese)	Internalizing, externalizing, hyperactivity behavior—reported by mothers and teachers	Higher prenatal and early postnatal manganese concentrations were associated with poorer behavioral outcomes in children.
Horton *et al.* (120)	133	Healthy children (ELEMENT cohort)	8–11 years	Unreported	Heavy metals (manganese, zinc, lead)	Internalizing, externalizing, hyperactivity behavior—reported by parents	Manganese concentrations during the prenatal period through the first 2 or 3 months of the postnatal period were associated with reduced behavioral symptoms. However, postnatal manganese concentrations after 4 months and postnatal lead exposure were associated with increased internalizing symptoms, specifically anxiety; two possible sensitive periods for metal exposure were identified.

Table 1. Continued

Study	*N*	Population Studied	Age of Participants	Tooth Examined	Exposure of Interest	Outcome	Main Findings
Schizophrenia and Psychotic Disorders							
Modabbernia *et al.* (114)	14	Adults with schizophrenia and healthy control subjects (GROUP cohort)	Case mean = 25.2 years; control mean = 28 years	Unreported	Heavy metals (manganese, lead, cadmium, copper, magnesium, zinc)	Schizophrenia diagnosis—clinically diagnosed	Higher early life lead concentrations were found among individuals with schizophrenia.
Velthorst *et al.* (115)	25	Adults with psychotic disorders and unaffected siblings	Case mean = 24.35 years; control mean = 28 years	Unreported	Heavy metals (copper, magnesium manganese, zinc, lead, arsenic, lithium, tin)	Psychotic disorder diagnosis and symptom severity—clinically diagnosed	Higher concentrations of early life lithium in patients with psychosis compared with control subjects; higher concentrations of magnesium and lower concentrations of zinc associated with more severe symptoms.

This table presents a summary of recent work using tooth-based markers of environmental toxin exposure, particularly exposure to heavy metals, to predict risk for mental health disorders such as ASD, internalizing and externalizing symptoms, and schizophrenia and other psychotic disorders.

ALSPAC, Avon Longitudinal Study of Parents and Children; ASD, autism spectrum disorder; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; ELEMENT, Early Life Exposures in Mexico and Environmental Toxicology; GROUP, Genetic Risk and Outcome of Psychosis; RATSS, Roots of Autism and ADHD Twin Study in Sweden.

formation, and that these developmental disruptions leave behind measurable biological imprints that can then be leveraged to predict risk for later psychiatric disease. Through this model, we propose that primary and permanent teeth may serve as dual markers of both past psychosocial stress exposure and future mental health risk. Below, we describe and review the evidence supporting each of the three main tenets of our model in the hopes of translating the current literature on tooth formation into testable research hypotheses for the mental health field.

Tenet 1: Early-Life Adversity May Be Associated With Disrupted Processes Involved in Brain and Tooth Development

Psychosocial stress during an organism's early development is associated with disruptions in key biological processes, including programming of brain structure and function (98,99), the body's stress response circuitry (97,100), and the epigenome (22,23). As discussed, there is also preliminary support for the notion that psychosocial stressors can leave a detectable trace in the microstructure and chemical composition of primate teeth (63,77,78). We propose that these stressors may also affect human tooth formation (Figure 2). Nascent evidence suggests parallels between biological processes involved in the development of teeth and the brain, the key organ giving rise to psychiatric disease and modulating stress responses. For instance, receptors for neuropeptides, including serotonin and melatonin, are expressed by ameloblasts and potentially modulate enamel formation (101,102). Other markers specific to glial cells (the most abundant central nervous system cell type) are also expressed in dental pulp (103).

Like enamel, brain structures are also derived in ontogeny from ectodermal tissue (104), supporting observations that developmental defects in enamel are disproportionately common among people with Down syndrome, cerebral palsy, and other brain-related congenital conditions (105,106). Therefore, enamel formation not only appears to track ameloblast function but also may be susceptible to processes affecting early brain development (107,108). Together, these findings led Morishita and Arora to suggest that "it is possible that the timetable of key neurodevelopmental events is imprinted in an individual's teeth" (109).

As noted previously, the relationship between psychosocial stress and tooth development in humans is largely unexplored. However, one previous study did examine the association among features of primary teeth, socioeconomic status (an indicator of both material and social deprivation), and cortisol reactivity (a commonly used proxy for stress response system dysregulation) (110). This study found an interaction between socioeconomic status and cortisol reactivity, such that the children with the greatest enamel thickness tended to have both low socioeconomic status and low salivary cortisol reactivity. Thus, these initial findings suggest important interrelationships among socioeconomic disadvantage, biological sensitivity to stress, and tooth-based markers of development that require further elucidation.

Table 2. Future Directions for Research on the Use of Teeth as a Biomarker of Early Life Adversity and Mental Health Risk

Research Questions	Studies Needed to Address Research Question	Special Considerations
What do teeth capture: To what extent do teeth record experiences of early life adversity that are common in the world today and are known to increase risk of having psychopathology in the future? Is there a one-to-one correspondence between the occurrence of a specific stressor and its presentation in teeth? What are optimal strategies to disentangle the presence of early life adversity in teeth as compared with co-occurring physical stressors?	Observational studies could focus on collecting and analyzing the teeth of children with known and well-documented psychosocial exposures, to test whether these exposures correspond to the existence and timing of tooth-based marks, in conjunction with changes in enamel or dentin chemical composition. Causal inference methods, such as the decomposition of joint effects in the presence of interactions (127,128), could be used to tease apart the effects of psychosocial versus physical stressors. New or existing experimental studies in nonhuman primate or rodent models that manipulate the caregiving environment to induce early life stress could assess differences in tooth formation between stressed and control animals. Stress paradigm studies that will already sacrifice the study animals would present easy affordable opportunities for tooth collection and testing this conceptual model.	These studies would need to address unique measurement and design issues, including the reliable and valid assessment of potential covariates (e.g., bruxing or grinding, malocclusion or tooth misalignment, diet and sugar-sweetened beverage consumption, other factors that may be either localized to the mouth or systemic in nature). Accounting for the effects of socioeconomic disadvantage may be particularly challenging because it may include elements of both psychosocial stress (e.g., family stress associated with difficulty in affording basic needs) and physical stress (e.g., poor nutrition).
Under what conditions do teeth capture it: Which features of early life adversity exposure matter most? (That is, is there a dosing effect whereby only stressors of a certain magnitude are recorded in teeth? Are only certain types of adversities with specific characteristics recorded?)	Translational epidemiological studies could test the effects of timing, duration, chronicity, and type of adversity exposure in animal and human models [e.g., (14)]. Fragmented care rodent models meant to mimic the experience of neglect (129,130) could be particularly useful for studying potential sensitive periods for stress exposure given the accelerated rodent life cycle in comparison with primates.	Although teeth have been proposed as a useful tool for capturing the early exposome (58), broadly defined as all environmental exposures experienced by an individual from the prenatal period onward (131), early life adversity represents a multifaceted construct that cannot be reduced to a simple summation of exposures. Given evidence of differential effects associated with different adversity types (132), future research should push toward understanding the level of exposure specificity that can be attained from teeth.
How do teeth capture it: What are the mechanisms that give rise to these tooth-based markers? (That is, through what biological processes are stress lines recorded? And are these biological processes capturing systemic changes throughout the body or those localized within the mouth?)	Basic research could elucidate the possible pathways through which psychosocial stress disrupts ameloblast and odontoblast function and alters tooth formation. Observational studies could explore the associations between tooth-based markers and other biomarkers of developmental disruption such as neural, stress reactivity, and epigenetic markers.	Biological sensitivity to the consequences of early life adversity may also be partially genetically determined (133). Future studies will thus also need to consider the role of genetic variation as a potential moderator of the association between adversity exposure and tooth development.
What are the practical considerations: If validated as a biomarker of psychosocial adversity, what social, cultural, and logistical factors would need to be understood to make the widespread clinical application of teeth feasible in psychiatric and pediatric research?	Qualitative studies could assess parents' willingness to collect and share their children's teeth for screening purposes and to identify the barriers and facilitators to such data collection efforts. Feasibility studies could explore how to better integrate dentists, who tend to operate as separate entities with their own insurance and medical record systems, with pediatricians and mental health service providers.	Multiple markers can be derived from teeth, which span macro to micro levels of analysis, so future research will need to examine the trade-offs associated with each of these for etiological and prevention work. Some tooth-based markers are quite time intensive to derive, so length of time for data acquisition must also be considered to evaluate the long-term feasibility of a given measurement approach to be implemented on a population scale.

This table presents a possible future research agenda to test elements of the proposed TEETH (teeth encoding experiences and transforming health) conceptual model. This future research will require identifying and testing foundational questions, which may entail consideration of epistemological issues (e.g., how to best approach research on the exposome) and logistical challenges (e.g., how to account for the effects of lifestyle factors that may act on teeth).

Tenet 2: Developmental Disruptions During Tooth Formation May Produce Time-Resolved Biological Imprints That Can Be Objectively Captured

Both prenatal and postnatal disruptions in brain development following exposure to adversity are increasingly being identified through neuroimaging markers of structural changes (e.g., cortical thinning) (111,112) and functional changes (e.g., decreased amygdala connectivity) (25,26). Early-life adversity has also been associated with altered stress response functioning, which may manifest in the form of chronically low or high cortisol

reactivity (35,113). Similarly, altered epigenetic processes following early-life psychosocial stress appear to become encoded in the epigenome, detectable at birth (24) and beyond (22,23).

We propose that psychosocial stress–induced disruptions in tooth formation may result in macro-level alterations, such as changes in tooth dimensions, as well as micro-level biological signatures, including changes in microstructure and chemical composition as visible in stress lines (Figure 2). Importantly, because teeth form during known developmental periods, all markers of tooth developmental disruptions can be considered time resolved, with the level of temporal specificity varying depending on the measure used and the tooth analyzed. For example, macro-level measures may reveal the existence of exposures within the 3- to 5-year window corresponding to that tooth type's mineralization. Examination of more micro-level measures, such as stress lines, could more precisely pinpoint the timing of exposures to within a 1-week margin of error (78).

Tenet 3: Disrupted Developmental Processes May Predict Mental Health Risk

Most research on biological markers of psychiatric risk have focused on the brain, indicators of stress reactivity, or epigenetic markers. Our model proposes that teeth may serve as an additional, albeit novel, biomarker linking early-life psychosocial stress exposure to mental health risk (Figure 2). Although this proposition has not yet been widely tested, recent work from at least eight studies on tooth-based markers of environmental toxins (e.g., pollutants, heavy metals) has provided some evidence that these physical exposures can be captured in teeth and used to predict risk for mental disorders such as schizophrenia and psychotic disorders (114,115), autism spectrum disorder (60,116–118), and both internalizing and externalizing symptoms (119,120) (Table 1). Whether tooth-based markers of psychosocial stress can function as indicators of psychiatric risk will be a rich area of future inquiry.

CLINICAL AND TRANSLATIONAL IMPLICATIONS AND FUTURE RESEARCH DIRECTIONS

If validated as biomarkers, teeth would transform the study of sensitive periods by allowing for new noninvasive, temporally specific measures of early-life adversity. Teeth as biomarkers would also provide clinical utility in numerous areas, given the ease with which they can be obtained; because nearly every person forms and sheds teeth, the collection of shed teeth is noninvasive, and the information stored in teeth could be easy to access and relatively inexpensive to analyze. As novel biomarkers, teeth could change the standard for how children are screened for the occurrence of early-life adversity and its mental health consequences. Thus, as noted previously, teeth could be used in primary prevention programming to help identify youths at risk for mental disorders that typically onset any time during middle childhood or later, including conduct disorder, generalized anxiety disorder, posttraumatic stress disorder, substance use disorders, schizophrenia, and MDD.

For such work to advance, however, a number of foundational questions must be addressed. These questions range from empirical questions about the extent to which early-life adversity exposures correlate with tooth-based markers, to mechanistic questions about the pathways through which early-life adversity might affect tooth formation, to feasibility questions about social, cultural, and logistical facilitators and barriers to the widespread clinical application of teeth in psychiatric and pediatric research. In Table 2, we outline a research agenda in the hopes of charting a course for this work to progress during the years to come. We hope that these jumping-off points will encourage others to join this scientific space and will foster coordinated interdisciplinary efforts to leverage teeth as an underused tissue type in ways that can efficiently and cost-effectively make the most of existing and emerging data and methodologies. Such efforts could capitalize on existing large-scale tooth collections available in multiple birth cohort studies [e.g., (121–124)], where rich phenotypic information about early experiences and subsequent mental health outcomes already exists.

CONCLUSIONS

There is widespread recognition of the urgent need for new biomarkers of both adverse experiences (125) and psychiatric outcomes (126). This article summarizes key properties of human tooth development and presents a working conceptual model that leverages these properties to propose the use of teeth as a novel biomarker of early-life adversity and associated mental health risk. Given this conceptual model and the availability of technologies to study teeth, now is the time to explore the untapped potential of teeth to capture past adversity exposures and future risk of psychiatric problems. Although much interdisciplinary work will be required to validate our TEETH conceptual model, we hope that this framework will catalyze new research into the potentially transformative application of teeth to guide primary prevention interventions in psychiatry.

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ARTICLE INFORMATION

From the Center for Genomic Medicine (KAD, RVM, ORP, ECD), Department of Psychiatry (RVM, ECD), and Henry and Allison McCance Center for Brain Health (ECD), Massachusetts General Hospital; Department of Psychiatry (ECD), Harvard Medical School, Department of Developmental Biology (FBB), Harvard School of Dental Medicine, Boston; and Forsyth Institute (FBB), Cambridge, Massachusetts; Department of Orofacial Sciences (PKDB) and Center for Children's Oral Health Research (PKDB), School of Dentistry, University of California, San Francisco, San Francisco, California.

Address correspondence to Erin C. Dunn, Sc.D., Psychiatric and Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, 185 Cambridge Street, Simches Research Building, 6th Floor, Boston, MA 02114; E-mail: edunn2@mgh.Harvard.edu.

Website: www.thedunnlab.com.

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