Social Epigenomics: Conceptualizations and Considerations for Oral Health

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Abstract
Advances in high-throughput technologies and the generation of multiomics, such as genomic, epigenomic, transcriptomic, and metabolomic data, are paving the way for the biological risk stratification and prediction of oral diseases. When integrated with electronic health records, survey, census, and/or epidemiologic data, multiomics are anticipated to facilitate data-driven precision oral health, or the delivery of the right oral health intervention to the right individuals/populations at the right time. Meanwhile, multiomics may be modified by a multitude of social exposures, cumulatively along the life course and at various time points from conception onward, also referred to as the socio-exposome. For example, adverse exposures, such as precarious social and living conditions and related psychosocial stress among others, have been linked to specific genes being switched “on and off” through epigenetic mechanisms. These in turn are associated with various health conditions in different age groups and populations. This article argues that considering the impact of the socio-exposome in the biological profiling for precision oral health applications is necessary to ensure that definitions of biological risk do not override social ones. To facilitate the uptake of the socio-exposome in multiomics oral health studies and subsequent interventions, 3 pertinent facets are discussed. First, a summary of the epigenetic landscape of oral health is presented. Next, findings from the nondental literature are drawn on to elaborate the pathways and mechanisms that link the socio-exposome with gene expression—or the biological embedding of social experiences through epigenetics. Then, methodological considerations for implementing social epigenomics into oral health research are highlighted, with emphasis on the implications for study design and interpretation. The article concludes by shedding light on some of the current and prospective opportunities for social epigenomics research applied to the study of life course oral epidemiology.

Keywords: epigenetics, DNA methylation, health inequalities, psychosocial factors gene environment interaction, oral health

Introduction
The advent of multiomics, such as the genome, epigenome, microbiome, metabolome, and transcriptome, has ushered a new data-driven era of precision oral health care that aims for interventions to become tailored to individuals and potentially populations (Divaris 2019a). These interventions stem from linking multiomics data that are derived from large biobanks with electronic health record, survey, census, administrative, or epidemiologic data to generate Big Data. Appropriate prediction modeling would then be applied to achieve risk stratification and identification of the factors involved in oral disease susceptibility or resilience. As opposed to the traditional one-size-fits-all strategy, precision oral health is anticipated to enable the delivery of oral health care interventions that are based on a set of biological and clinical phenotypes that characterize an individual, thereby delivering the right intervention to the right individuals/populations at the right time.

The promise of precision health has led to several initiatives around the world to generate layers of multiomics combined with health records with the aim of influencing health outcomes and patient responses to medical care. For example, the All of Us research program in the United States aims to enroll 1 million people to collect genetic, health record, and lifestyle information (Sankar and Parker 2017; All of Us Research Program Investigators 2019). Similarly, the Genome Canada All for One Precision Health Partnership collects genetic data with a focus on developing targeted diagnostics and therapeutics for rare diseases (Ginsburg et al. 2021). On the precision oral health front, strides have been recently made to understand the biological basis and clinical phenotypes of the most common chronic oral diseases, namely periodontal disease, dental caries, and oral cancer. For example, genome-wide association studies (GWASs) based on data from the UK Biobank, the GLIDE consortium (Gene-Lifestyle Interactions in Dental Endpoints), and others have suggested that the genes EFCAB4B, GLT6D1, DEFA1A3, IL37, and SIGLEC5 may be susceptibility loci for periodontitis risk (Shungin et al. 2015; Shungin et al. 2019). Similarly, KPNA4, ITGAL, PLUNC, and many others were suggested as putative dental caries
susceptibility genes (Wang et al. 2012; Shaffer and Marazita 2015). At the population level, precision public health proposes to understand and predict health risks more granularly and to customize interventions for specific and homogenous subpopulations based on biological risk (Meurer et al. 2019). However, the notion that tailored oral health interventions can be achieved through relying solely on biological/clinical risk prediction and stratification is consistent with the biomedical model of health, which posits individual biological factors as the primary determinants of health. While important, these factors arguably account for a limited variation in oral disease risk. For example, GWASs that exclusively relied on clinical and/or microbial phenotypes might not have found much of the variation in oral disease to be explained by genetic factors as was initially hypothesized. This accentuates that the inherited genome can remain mostly stable throughout the life course and may only partly determine the biological risk profile (Divaris 2019b). Meanwhile, in accordance with the biospsychosocial model, which postulates health as the interaction of social, psychological, and biological factors (Borrell-Carrió et al. 2004), external forces that lie within the social, environmental, commercial, and economic exposures present shifting conditions that possibly influence the multomics of long-term oral and nonoral health outcomes—thereby referred to as the socio-exposome (Senier et al. 2017). This is evident in GWASs that have attributed much of the variability in oral disease to behavioral risk factors (e.g., smoking, excessive dietary sugars, poor oral hygiene), which in turn are known to downstream from the structural and social determinants of health, such as socioeconomic position (SEP), social capital, food security, and access to quality health care, all of which individuals and populations experience intermittently and cumulatively along the life course (Watt et al. 2016).

Importantly, appreciating the role of the socio-exposome in the biology of oral disease is consistent with applying an integrative social and behavioral lens to investigations of oral health and related inequalities (McNeil et al. 2022). To be sure, studies that are agnostic on the role of the socio-exposome in altering biological processes (e.g., gene expression, microbiome composition) risk producing biased effect estimates that may inaccurately attribute the variation in oral disease outcomes to differences in biological factors alone, such as the accumulation of dental plaque or inflammatory factors. Such estimates can thereby lead to reductionist and misguided interventions that can exacerbate oral health inequalities (Divaris 2019b; Gansky and Shafik 2019; Gomaa et al. 2019). For example, clinical approaches that focus only on addressing these biological causes of oral disease, while important, ignore the possible effect modification of social exposures and their contribution to biological susceptibility or resilience. Likewise, studies may attribute the variation in oral health multomics to biological differences in relation to genetic ancestry while ignoring the social constructs that are related to race/ethnicity, such as exposures to discrimination or oppression, and how these in turn can affect biology through the stress pathway (Park et al. 2022). Interventions stemming from such studies are arguably unable to tackle the fundamental causes of disease and may even place minoritized groups at a disadvantage in benefiting from that intervention. Therefore, conceptualizing and modeling socio-exposomic factors as predictors or modifiers of the multomics–oral health relationship will be key for realizing equitable and targeted oral health interventions.

Mounting research suggests that social and psychosocial factors contribute to inflammatory processes that are pivotal to various oral and nonoral diseases (Sabbah et al. 2018). For example, low SEP has been linked to increased levels of the stress biomarker cortisol and a proinflammatory oral immune cell phenotype that is conducive to periodontal disease, indicating a triggered hypothalamic pituitary adrenal axis (stress pathway) in individuals exposed to social adversity (Gomaa et al. 2018). Earlier studies proposed a similar process in dental caries through an interaction of cortisol with cariogenic bacteria (Boyd et al. 2010). While these results suggest that external stimuli can “get under the skin” to become biologically embedded and alter biological responses, it remains unclear whether they can get down to the molecular level of the genes, particularly in relation to oral disease mechanisms. To this end, epigenetics is postulated as a mechanism of biological embedding through which social and environmental exposures may influence biology and increase disease risk.

Epigenetic marks are a set of modifications to DNA and its packaging that can influence gene expression without altering the genomic sequence (Feinberg 2008). These mediate the interplay of genetic variation and external environmental exposures, thus potentially offering explanations for the questions of why some individuals seem to become sicker than others despite similar exposures and why those exhibiting the same clinical phenotype may respond differently to the same treatment (Boyce and Kobor 2015). As opposed to DNA sequence, which is set at conception and is therefore mostly static, epigenetic marks can undergo significant changes during development and along the life course. Although some epigenetic marks are highly stable, such as those that regulate cell fate, many continue to change over the life span in response to external forces (Zannas and West 2014). The growing interest in epigenetic processes as compelling mechanisms that may alter genetic expression is amplified by the increasing affordability of epigenetic technology, such as microarrays that are used for the quantification of DNA methylation (DNAm). DNAm is the chemical addition of a methyl group to the cytosine residue, typically at cytosine-phosphate-guanosine (CpG) dinucleotides. DNAm has been extensively studied as one mechanism that potentially underlies social inequalities in health, as demonstrated by studies in child development, aging, cancers, cardiovascular and metabolic diseases, and others—hence the term social epigenomics (Essex et al. 2013; Boyce and Kobor 2015; Notterman and Mitchell 2015; Garg et al. 2018; Cerutti et al. 2021). This emerging field has continued to expand over the past few years showing that the social environment may become biologically imprinted through a biological cascade that reflects the consequences of social inequalities and leads to adverse health outcomes. This in turn provides a
nucleus for evidence that a biomedical intervention may not alleviate disease on its own and that the fundamental causes of disease lie within the social environment need to be accounted for.

This article argues that considering the impact of the socio-exposome in biological profiling for precision oral health applications is necessary to ensure that definitions of biological risk do not override those of social ones and that a holistic nonreductionist approach is taken to interventions. To facilitate the uptake of the socio-exposome in multiomics oral health studies and subsequent interventions, 3 pertinent facets are discussed. First, a summary of the landscape of the epigenetics of oral health is presented. Next, findings from the nondental literature are drawn on to elaborate on the pathways and mechanisms that link the socio-exposome with gene expression—or the biological embedding of social experiences through epigenetic processes. The article then emphasizes some of the methodological considerations for implementing social epigenomics into oral health research, highlighting implications for study design and interpretation. Finally, it concludes by shedding light on some current and prospective opportunities for social epigenomics research applied to the study of life course oral epidemiology.

Deciphering the Pathways from the Socio-exposome to Gene Expression

Epigenetic Landscape of Oral Health and Disease

The state of oral health and disease is likely no longer a question of nature or nurture but rather an interaction of both. At the crux of this line of investigation is the question of how genetic predisposition and salient experiences together mold health outcomes. This realization has led to a series of investigations on gene-environment interactions (Shaffer et al. 2015). Together, the genome, the environment, and gene-environment interactions across time are reflected in the epigenome, which is highly malleable in response to external stimuli and strongly influenced by genetic variation.

The study of epigenetics in oral health and disease is still in its infancy. However, work in this area is rapidly evolving, with studies demonstrating the involvement of epigenetic marks in tooth development, craniofacial syndromes, dental caries, periodontal diseases, and oral cancer (Hughes et al. 2013). A recent study showed that differentially methylated CpGs in cord blood for the genes PBX1, ACAT2, LTBP3, and DDR (involved in dental tissue development) were associated with advanced dental caries in children at 6 y of age (Silva et al. 2022). Studies have also shown differential hypermethylation of genes ZNF718, ZFP57, HOXA4, and others encoding proinflammatory cytokines in association with periodontitis (Larsson et al. 2015; Martins et al. 2016). It is noteworthy that these epigenetic changes in relation to oral diseases have been linked to environmental exposures such as smoking and diet, which are well known to be socially patterned, typically concentrating in socially and economically disadvantaged and/or oppressed groups and those who otherwise experience psychological or behavioral difficulties (Watt et al. 2016). Furthermore, epigenetic marks have been postulated as radio- and chemotherapeutic targets for precision oral cancer treatment (D’Souza and Saranath 2015; Hema et al. 2017). Taken together, these studies provide insights into the role of epigenetics in oral disease risk and the contribution of external stimuli to these diseases. The promise of epigenetics to oral health as a dynamic expression of external exposures, and potentially social ones, therefore lies in developing biomarkers for clinical applications to predict risk, enhance diagnosis and prognosis, and monitor responses to clinical interventions. Interestingly, new treatments such as epidrugs are being introduced as vehicles that can modify disease-associated epigenetic proteins (Salarinia et al. 2016). Although there are no studies to date assessing epidrugs in oral diseases, a few emerging findings are indicating potential for their use in inflammatory conditions such as rheumatoid arthritis.

Epigenetics in Biological Embedding

The next section draws on findings from the nondental literature to illustrate the pathways and mechanisms by which the socio-exposome may alter gene expression and subsequent health outcomes. As described earlier, biological embedding refers to the processes by which “macro” social exposures can alter various “micro” biological functions in predictable and enduring ways that can influence health and in turn manifest in childhood and/or later in adult life (Gomaa et al. 2016; Aristizabal et al. 2020). The importance of biological embedding stems from its ability to explain patterns of health inequalities, potentially providing clues to the following questions: Is the impact of social exposures on health reversible or modifiable? Are there specific periods over the life course that are more sensitive to social exposures than others? Can the impact of such exposures on health be passed down intergenerationally? Moreover, the relevance of biological embedding extends to informing clinicians, policy makers, and the public alike about the magnitude of the impact to which social factors can alter biological ones. Indeed, arguments on the links between social exposures and health can come across as being more persuasive and powerful when joined by evidence of the related biological pathways—that is, demonstrating that the biological consequences of social adversity can get as deep as leaving imprints on the epigenome that can trigger oral disease and that may be passed down intergenerationally.

Epidemiologic and experimental studies suggest that favorable and unfavorable social exposures can become biologically embedded through enacting epigenetic changes with consequences for development, behaviors, and health outcomes (Szyf et al. 2008; Turecki and Meaney 2016). Hypothetically, these epigenetic changes can contribute to individual differences in susceptibility and resilience for a range of diseases and, potentially by extension, oral disease. In an early example from nonhuman studies, high-quality maternal care in rats (maternal licking and grooming of pups) was associated with
reduced cytosine methylation in the pups at the promoter of the glucocorticoid receptor gene (NR3C1), which regulates the stress response (Kaffman and Meaney 2007). Interestingly, alteration of maternal care through cross-fostering of the pups from low- to high-care mothers was associated with the pups showing significant cytosine hypomethylation at NR3C1, suggesting a causal link. Human studies also correlated the social environment with variations in DNAm at specific sites or globally across the epigenome. For example, in a sample of adult males from the 1958 British birth cohort for extremes of childhood and adulthood SEP, methylation differences in gene promoters were more frequently evident in relation to childhood SEP, indicating the crucial role of the early environment in the magnitude of epigenetic alteration that can manifest later on (Borghol et al. 2012). Similarly, history of child maltreatment in those who later died by suicide was linked to increased cytosine methylation within the NR3C1 promoter in hippocampal tissue, which is the stress-regulating region of the brain (McGowan et al. 2008). Several other DNAm studies noted persistent associations between low SEP and altered DNAm of genes involved in inflammation, glucocorticoid signaling, and other functional categories (Cerutti et al. 2021). Likewise, epigenetic aging—or the difference between chronological age and epigenetic age (measured through age-informing CpG sites)—has been linked to a range of social exposures, including low SEP, adverse childhood experiences, and psychosocial stress (Colich et al. 2020; Marini et al. 2020).

Life course oral health epidemiologic studies have consistently found that oral health in childhood has a long-term impact on oral health in adulthood and that early life social exposures can contribute to the oral-systemic disease connection later in life (Ben-Shlomo 2002; Nicolau et al. 2007). This is consistent with results from the nondonal literature postulating early life and childhood as sensitive windows in which social exposures arguably have a larger magnitude of the effect on health outcomes in adult life as compared with those occurring at later time points (Dunn et al. 2019). One of the most compelling findings on this comes from studies on the children of survivors of the Dutch Hunger Winter, in which individuals who were prenatally exposed to the famine in 1944 to 1945 and assessed 6 decades later showed hypomethylation of the imprinted insulin-like growth factor II (IGF2; a key for human growth and development), as compared with their unexposed same-sex siblings (Roseboom et al. 2011). The association was specific for periconceptional exposure, thus reinforcing the idea that early-life conditions are linked to epigenetic changes that may persist throughout life. Therefore, deciphering the epigenetic impact of social experiences during this sensitive period is crucial for understanding the biological risk for various health conditions, including oral diseases. In agreement with this model, a recent study linked maternal psychosocial stress during pregnancy and structural changes in primary teeth (Mountain et al. 2021). Similarly, early life stress has been shown to contribute to earlier eruption of permanent molars, suggesting an accelerated aging process (Medermott et al. 2021). Collectively, these studies make a strong case for the socio-exposome as a prominent driver of epigenetic dysregulation that should be considered when identifying the risk of disease and the delivery of treatment. Although there is scarcity of investigations showing an epigenetic impact of social and/or environmental exposures in dental, oral, and craniofacial health, the aforementioned studies demonstrate that by extension, a hypothesis can be driven on the magnitude of oral disease risk that can be shaped in early life through social and environment impacts on the epigenome (Fig. 1). Hence, emphasis on prevention and intervention in early life and childhood may have a far-reaching impact on oral health.

**Methodological Considerations**

The implementation of social epigenomics into dental, oral, and craniofacial research needs to be informed by the unique characteristics of epigenetic data and the specific social epidemiologic research question at hand. The next section elaborates on some of the methodological key areas to consider when embarking on a social epigenomics study for oral health.

**Candidate Genes versus Epigenome-wide Association Studies**

Early DNAm studies examined specific candidate genes in association with an exposure or health outcome of interest. These included several popular candidates related to adverse social exposures and stressful events as described earlier (e.g., 5-HTTLPR, OXTR, MAOA, and NR3C1), (Nikolova and Hariri 2015). However, there are a few noteworthy methodological limitations of the candidate gene approach. Candidate gene promoters may exhibit little variability, as most promoters are typically unmethylated. Additionally, strategies used to collapse DNAm measurements into 1 methylation variable, such as taking an average or conducting a principal component analysis of multiple CpGs, can be problematic, due to groups of CpGs overlapping with different types of functional regions, thereby eliminating important functional information (Jones et al. 2018). The candidate gene approach for DNAm studies has therefore partly faded over the years to be replaced with the global DNAm and epigenome-wide association study approaches. These have become more appealing as well due to their increased affordability and significantly larger informational output (Jones et al. 2018; McDade et al. 2019).

**Effect Size**

An important consideration for DNAm and epigenome-wide association studies is that the effect sizes can be small. The typical effect sizes with DNAm findings that have been validated are generally not >10% in terms of the mean difference in the proportion of methylated DNA strands between groups of individuals (Breton et al. 2017). Small effects are partly determined by how and where DNAm is measured, which is usually an association at 1 locus. For example, associations between smoking and DNAm have been shown to have an
effect size that ranges from 1% to 10% (Gao et al. 2015). Since
the more distant exposures such as SEP will typically require
larger sample sizes, DNAm differences in social epigenomic
studies are expected to be quite small. Researchers should
therefore not be dissuaded by small effect sizes; rather, as they
design their studies, they should carefully consider the vari-
ability within a targeted region and assume a small effect size
to be able to achieve adequate power.

**Type of Biosample**

The tissue specificity of DNAm creates a significant challenge
for the use of surrogate tissues in cases where the primary tis-
sue of choice is not feasible. This is particularly relevant to
studies in which DNAm of central organs/tissues (e.g., heart,
brain) is of ultimate interest, yet samples from these tissues
cannot be collected for living human studies. Accessible
peripheral tissues—such as saliva, epithelial cells from buccal
swabs, or blood from venipuncture, heel sticks, or finger
pricks—are therefore viable options (Lowe et al. 2013). This is
good news for studies on oral health as samples from saliva,

![Figure 1. Hypothetical illustration based on the life course model shows how the epigenome may be altered by social and psychosocial exposures in 4 individuals (A–D), each with a different trajectory that leads to varying degrees of oral disease risk. Positive signs in red (+) indicate increased adverse exposures; negative signs in green (−) indicate limited exposure to adversity. The epigenome in each individual diverges early in life due to varying genetic makeup and subsequent exposures to endogenous and exogenous stimuli and is therefore nonlinear from birth onward. The size of the red symbol (+) represents the magnitude of the effect that an adverse exposure may have on the epigenome, depending on the timing of that exposure. Individual A represents the accumulation model, in which the same exposure occurs repeatedly and cumulatively over the life course. Individual B represents the sensitive periods model, in which exposures during sensitive periods of development, such as early life and childhood, may have a larger impact on oral disease risk than exposures later in life. Individual C represents exposures occurring later in life, in which the magnitude of the effect is smaller than in individual B. For individual D, little to no exposure contributes to low risk of oral disease.](image-url)
concordance between central and surrogate tissues have shown mixed results (Hannon et al. 2015), and research into the validity of DNAm patterns in saliva or buccal swabs as proxies for those occurring in central tissues will be key for future social epigenomic studies concerned with the oral-systemic disease connection.

**Timing of Biosample Collection**

Inferences made from DNAm studies largely depend on the time point at which the DNA was sourced along the course of the study, the timing in which the exposure occurred, and that in which the outcome was assessed. The impact of a social exposure over time can intersect with, be modified by, or confounded by other social or behavioral ones. An example is the intersectionality of SEP with exposures to racism or oppression of minoritized groups in determining the risk of oral disease over time, which may be further modified by health behaviors, factors of access to dental care, or others. Thus, DNAm patterns at a time point that are accompanied by recalled or recollected indicators of a social exposure that has occurred earlier may not be attributable to that specific exposure due to the host of social and behavioral factors that can contribute to this pathway over time. Recent small experimental studies have demonstrated that DNAm may be modified through psychosocial interventions (Vinkers et al. 2021); however, the temporality issue in cross-sectional studies cannot capture the dynamic nature of epigenetics (Ng et al. 2012), leading most inferences that are drawn from linking DNAm to social exposures to be primarily correlational. Fortunately, in the absence of longitudinal and/or interventional studies, more advanced and robust statistical methods, such as those of causal inference for epidemiologic studies (Hernán and Robins 2010) and mendelian randomization, can play an important role. These can help decipher the causal role of social exposures in oral disease risk through DNAm as a biological mechanism. Regardless of the design selected, it is imperative that social epigenomic findings be approached with caution and that the allure of jumping to mechanistic interpretations and conclusions be avoided by ensuring that study design limitations are acknowledged and that the aforementioned methodological key points are considered.

**Future Directions**

As the associations of the socio-exposome with epigenetic changes in different health outcomes and various age groups are unraveled, the application of social epigenomics to the study of oral disease risk will become more plausible. To enable this, large data sets that integrate epigenetics with oral health and social and behavioral information are necessary (Fig. 2). The mouth is a surrogate model for several systemic diseases, and saliva and buccal swabs are noninvasive and readily accessible biosamples that can enable epigenomic studies on routine medical and dental visits in which sociodemographic data can also be collected. Importantly, a rigorous delineation is needed of whether epigenetic changes in these biosamples reflect those that are specific to the local tissues of the oral cavity or more globally reflect multifinal epigenetic changes in several organs/systems. As we learn more about other multiomics, such as the oral microbiome, future studies can take an integrative multiomics approach to study the interaction between the oral microbiome and epigenomics in oral disease. Research in this direction will pave the way for tailoring more equitable oral health interventions that do not exclusively rely on individual differences in multiomics but can...
rather take an upstream approach by considering the impact of the social environment on biology. Furthermore, social epigenomics in oral health research will allow us to zoom into the developmental origin of oral diseases and the long-term impact of early social and psychosocial exposures on dental, oral, and craniofacial health and development. The mounting interest and emphasis worldwide on standardized population oral health data collection in longitudinal studies and birth cohorts that are accompanied by biobanks will be catalysts for propelling this new direction of research.

Concluding Remarks

Social epigenomics offers an exciting avenue for investigations into the origin and development of dental, oral, and craniofacial conditions. The prominent role of DNA methylation in early cell differentiation and plasticity makes it an intriguing molecular mechanism for the biological embedding of social experiences. To move forward the application of this field to oral health research, careful attention to study design and interpretation will be critical. There is a lot to explore and investigate in this emerging area of research, in anticipation of not only a better explanation of the social underpinnings of biological differences in oral health but ultimately more equitable oral health care.

Author Contributions

N. Gomaa, contributed to conception, design, data acquisition of data and literature search and curation, drafted and critically revised the manuscript. The author gave final approval and agree to be accountable for all aspects of the work.

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