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Examining developmental plasticity in the skeletal system through a sensitive developmental windows framework

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Abstract

Developmental plasticity facilitates energetically costly but potentially fitness-enhancing adjustments to phenotypic trajectories in response to environmental stressors, and thus may significantly impact patterns of growth, morbidity, and mortality over the life course. Ongoing research into epigenetics and developmental biology indicate that the timing of stress exposures is a key factor when assessing their impact on developmental processes. Specifically, stress experienced within sensitive developmental windows (SDWs), discrete developmental periods characterized by heightened energy requirements and rapid growth, may alter the pace and tempo of growth in ways that significantly influence phenotypic development over both the short and long term. In human skeletal biology, efforts to assess how developmental environments shape health outcomes over the life course could be enhanced by incorporating the SDW concept into existing methodological approaches. The goal of this article is to outline an interpretive framework for identifying and interpreting evidence of developmental stress in the skeletal system using the SDW concept. This framework provides guidance for the identification of elements most likely to capture evidence of stress most relevant to a study's core research questions, the interpretation of developmental stress exhibited by those elements, and the relationship of skeletal indicators of stress to the demographic patterning of morbidity and mortality. Use of the SDW concept in skeletal biology has the potential to enrich traditional approaches to addressing developmental origins of health and disease hypotheses, by targeting periods in which individuals are most susceptible to stress and thus most likely to exhibit plasticity in response.

KEYWORDS
plasticity, sensitive developmental windows, skeletal system

1 | INTRODUCTION

Skeletal biomarkers of stress have traditionally been used as indicators of adaptive failure, specifically to identify circumstances where environmental and cultural constraints exceeded local buffering mechanisms (Goodman et al., 1984, 1988). Research generated from this approach emphasized direct comparisons of lesion prevalence and phenotypic averages to understand stress experiences in relation to environmental and cultural conditions (Hillson, 1992; Palkovich, 1984; Stuart-Macadam, 1985, 1989). However, this interpretive model has been critiqued by a new generation of researchers who have reframed the skeletal system as a physical record of interactions between genetic and extragenetic inheritance systems and stress as signal capable of informing, rather than simply disrupting, plastic developmental processes (Agarwal, 2016; Agarwal & Beauchesne, 2011; Gowland, 2015; Temple, 2014, 2019). Constraints place limitations on

the trajectories and end products of evolutionary processes, with genetic mechanisms, biases within developmental systems, the costs of various biological functions, and available energy restricting the both the production of phenotypic variation and selection for optimal trait values (Charnov, 1993; DeWitt et al., 1998; Futuyma, 2010; Galis et al., 2018; Smith et al., 1985; Stearns, 1992). Plastic genotypes may be more energetically expensive than fixed alternatives, and the capacity to detect and appropriately respond to environmental signals may incur significant costs to developing organisms, constraining the evolution of phenotypic plasticity even in the heterogeneous environments where it is favored (DeWitt et al., 1998; Murren et al., 2015). Costs associated with phenotypic development are central to studies of both plasticity and life history theory, as cumulative trade-offs resulting from the sharing of energetic resources between expensive biological functions may place significant limitations on growth and development (Charnov, 1993; Murren et al., 2015; Stearns, 1992). However, these trade-offs may ultimately prove to be adaptive if they produce phenotypes better equipped to address future environmental challenges, by effectively offsetting or delaying the physiological consequences of costs incurred in early life (Murren et al., 2015; West-Eberhard, 2003). Innovative methodological approaches are required in order to examine how the skeletal system is shaped by phenotypic-environmental interactions, and how early life experiences shaped by environmental adversity are capable of both constraining and expanding the potential range of adult phenotypic outcomes (Agarwal, 2016; Bogin et al., 2017; Gowland, 2015; Stearns, 1992).

As Gowland (2015) suggests, the relationship between developmental environments and phenotypic plasticity complicates traditional interpretive frameworks in skeletal biology that center immediate environmental circumstances as the primary determinant of health outcomes. This observation is highly relevant to any number of phenotypic outcomes of interest to skeletal biologists, as plasticity encompasses both adaptive and nonadaptive processes of phenotypic reaction to environmental signals and changing environmental circumstances may render these categories mutable (Nettle & Bateson, 2015; West-Eberhard, 2003). In humans, this interpretive problem is amplified by distinctive features of our life history. Extended gestation and a long juvenile phase provide ample opportunity for environmental signals to fine-tune phenotypic trajectories to address local environmental challenges, but long lifespans increase the odds of mismatch between signals received in early life and adult environments (Botero et al., 2015; Charnov, 1993; Stearns, 1992; West-Eberhard, 2003). Not all environmental cues are equally likely to play a role in setting phenotypic trajectories, with signal timing and intensity influencing their impact on developmental processes (Kuzawa & Thayer, 2011; Thayer & Kuzawa, 2011; West-Eberhard, 2003). Thus, understanding plasticity's role in shaping long-term phenotypic trajectories first requires that we develop a theoretical framework for identifying and interpreting evidence of plastic responses to environmental signals in hard tissue, a crucial step in assessing their potential impact on adult phenotype.

This article suggests that the sensitive developmental windows (SDWs) concept can be used as a framework for targeting periods in the life course when developing organisms are especially sensitive to the influence of environmental cues, and thus most likely to mount plastic phenotypic responses to stress. Since plasticity is energetically costly, phenotypic sensitivity to environmental signals is at its maximum during growth and development, when plastic responses have the greatest potential to alter phenotypic trajectories (West-Eberhard, 2003). SDW are periods of development in which organisms exhibit their maximal plastic potential, and are typically characterized by heightened environmental sensitivity, rapid growth, increased energetic demands—and in the case of humans—social and cultural transitions between stages of the life course (Agarwal, 2016; Kuzawa & Thayer, 2011; Thayer & Kuzawa, 2011; West-Eberhard, 2003). Research on living human populations supports the idea that life course development and plasticity are closely linked concepts, and that environmental signals received during SDW in early life may strongly influence the pace and tempo of life history events and set long-term phenotypic trajectories (Kuzawa, 2007; Wells, 2016; Worthman & Kuzara, 2005). Indeed, plastic processes facilitate many of the key trade-offs that shape both individual life histories and demographic patterns of morbidity and mortality, with SDW acting as programming windows in which stress exposures apply costs and constraints that may only become apparent at later phases in the life course (West-Eberhard, 2003; Worthman & Kuzara, 2005).

In the context of the skeletal system, elements may attain a substantial percentage of their adult size within SDW, and geometric relationships established within skeletal structures during these same critical periods may persist throughout growth and development. For this reason, elements capable of recording durable evidence of phenotypic–environmental interactions within relatively discrete periods of an organism's developmental lifespan may effectively act as osteological time-capsules, permitting analysis of the relationship between the timing of stress exposures in early life and phenotypic outcomes over the life course. Furthermore, since the SDW concept operates at multiple scales of analysis, such that SDW can be identified at the level of organisms, systems and tissues (Burggren & Mueller, 2019) it facilitates the comparison of stress responses across different targets of analysis—even if a target is not one that is typically preserved in the archeological record. This concept may prove especially useful in analyses involving the skeletal system, as many hard tissue responses to stress may not be adaptive in and of themselves, but may instead be indicative of stress exposures at critical periods in early life that stimulate physiological trade-offs (Temple, 2019).

Indeed, early life exposures to stress in human populations have been linked to a variety of physiological and behavioral phenotypic outcomes in adulthood, including, modifications to the neuroendocrine system (Graignic-Philippe et al., 2014; McEwen, 2008; Thayer & Kuzawa, 2014), cognitive function (Rooij Sr. et al., 2010), the pace and tempo of reproductive life histories (Chua et al., 2016; Forman et al., 2013; Gettler et al., 2015), the patterning of somatic growth (Chung & Kuzawa, 2014; Lampl & Schoen, 2017; Wells, 2016), susceptibility to chronic disease (Danese & McEwen, 2012; Gluckman

et al., 2009), brown adipose tissue mass and metabolism (Levy et al., 2021), and increased mortality risk (Brown et al., 2009; Garland, 2020; Lorentz et al., 2019; O'Rand & Lynch, 2018; Stringhini et al., 2018). Stress exposures within specific SDW may have outsized impacts on these aspects of the adult phenotype, which may in turn impact individual fitness. Therefore, understanding when developing organisms are most susceptible to stress is a crucial step in understanding the relationship between early life biology and health outcomes across the life course. Integrating the SDW concept into existing developmental origins of health and disease (DOHaD) approaches in skeletal biology will enhance our ability to interpret both the patterning of stress biomarkers—the artifacts of plastic responses to environmental signals—and their relationship to phenotypic development over the life course.

2 | THE ROLE OF PLASTICITY IN PHENOTYPIC DEVELOPMENT

Defining phenotypic plasticity presents a theoretical challenge, because environmentally mediated phenotypic modification encompasses a wide variety of complex interactions between systems of genetic and extragenetic inheritance. The physiological and behavioral products of these interactions may represent relatively short-term solutions to environmental challenges that bridge the gap between physiological accommodation and genetic selection, such as in the case of increased melanin production in response to UV radiation (Randhawa et al., 2015), or alteration in gut microbiome composition following a change in diet (David et al., 2013; De Filippo et al., 2010). Yet, they may also have significant, lasting impacts on the phenotype, especially if they influence developmental processes (West-Eberhard, 2003). Thus, it may be helpful to define developmental plasticity as a subset of environmentally mediated phenotypic responses that occur in early life, with the potential to meaningfully impact the pace and direction of long-term developmental trajectories. Developmental plasticity may be further distinguished from other types of phenotypic plasticity because it is informed by two categories of environmental signal: (1) direct cues of immediate environmental conditions and (2) intergenerational signals of mean environmental conditions (Berghänel et al., 2016; Bogin et al., 2017; Doughty & Reznick, 2004; Duazo et al., 2010; Kuzawa, 2005; Kuzawa & Fried, 2017; Low et al., 2012; Wells, 2019; West-Eberhard, 2003). These two generalized categories of signal provide organisms with information about their environment over an extended timeline, guiding the development of tissues and organs to meet the challenges posed by current—and theoretically, future—conditions.

It is this second possibility that is of particular interest to evolutionary biologists, as the ability to anticipate future environmental conditions and adjust phenotypic trajectories in response would confer adaptive benefits on developing organisms. Here, the term "adaptive" reflects the potential of phenotypic plasticity to positively influence fitness outcomes within a particular environmental context (Ellis et al., 2017). Since a single genotype may support multiple phenotypes, phenotypic development that anticipates local environmental challenges—even in the face of substantial trade-offs—represents a potentially adaptive capability (Ellis et al., 2017; West-Eberhard, 2003). Selection for this capability confers clear benefits to short-lived species with fast paced life histories, since signals received during development are more likely to be reliable indicators of future environments (Nettle & Bateson, 2015; Snyder-Mackler et al., 2020). Conversely, species with slower life histories may be less likely to benefit from developmental programming, due to the potential for significant mismatches between early life and adult environments. Indeed, in long-lived, socially complex species, environmental conditions experienced in early life are often poorly correlated with those experienced as an adult (Botero et al., 2015). For this reason, whether developmental plasticity in humans best represents a constrained phenotypic response to adverse conditions or an adaptive response to future environmental challenges is a subject of continuing controversy (Berrigan & Scheiner, 2004; Bogin et al., 2017; Lea et al., 2015, 2018; Low et al., 2012; Nettle & Bateson, 2015; Snyder-Mackler et al., 2020).

In studies of human populations, two general categories of model have arisen to explain the relationship between stress exposures in early life, corresponding plastic responses, and the patterning of morbidity and mortality over the life course: developmental constraints and predictive adaptive response (PAR) models. Developmental constraints models frame the adult phenotype as the end product of incremental life history trade-offs between growth and survival, ensuring that individuals achieve reproductive maturity, even at the cost of reduced somatic growth, increased susceptibility to chronic disease, and heightened mortality risk (Kuzawa, 2007; Thayer & Kuzawa, 2011). PAR models posit that signals of future environmental conditions transmitted from mothers to offspring in early development (e.g., maternal glucocorticoid levels), influence whether developing offspring adopt "fast" or "slow" life histories, with accelerated growth increasing the odds of successful reproduction at the cost of increased disease susceptibility and decreased longevity (Berghänel et al., 2016; Brumbach et al., 2009; Gluckman et al., 2005, 2014; Kuzawa, 2005, 2007; Snyder-Mackler et al., 2020). A variant PAR model proposed by Nettle and Bateson (2015) suggests that significant developmental constraints in early life signal organisms to adjust their developmental trajectories to cope with the unavoidable impacts of impaired somatic growth and increased mortality risk. Rather than relying on external signals to predict future environmental states, organisms adjust their developmental trajectories in response to their own impaired growth and development in early life, with developmental constraint itself acting as a reliable signal of future physiological adversity (Nettle et al., 2013; Nettle & Bateson, 2015). Both developmental constraints and PAR models adopt a life history perspective, positing that in environments characterized by adversity, energy budgets are less flexible and may require organisms to make significant trade-offs between growth, maintenance, and reproduction that directly influence mortality risk over the lifespan (Charnov, 2004; Kuzawa, 2007; Lea et al., 2018; Stearns, 1992). However, these models offer different explanations for the phenotypic–environmental

interactions underlying these trade-offs, and this framing has significant implications for the identification and interpretation of plastic responses in developing systems.

Currently, the available body of human plasticity research supports the idea that phenotypic development is guided by incremental life history trade-offs between growth and other expensive physiological functions (Hayward & Lummaa, 2013; Lea et al., 2015, 2018; Snyder-Mackler et al., 2020). However, recent studies of the relationship between stress exposures in early life and long-term alterations to immune function, the neuroendocrine system, and related behavioral phenotypes complicate this narrative (Brumbach et al., 2009; Danese & McEwen, 2012; Ellis et al., 2017; Gluckman et al., 2009; Graignic-Philippe et al., 2014; McEwen, 2008; Nederhof & Schmidt, 2012; Thayer & Kuzawa, 2014). Indeed, some of these studies suggest that early life stress exposures may sensitize the phenotype to high-stress environments in ways that provide fitness benefits even while exacting considerable long-term costs. Viewed through this lens, development informed by adversity produces "stress-adapted" phenotypes best equipped for harsh environments (Ellis et al., 2017). An individual with a "stress-adapted" phenotype may display evidence of strong stress responses in early life but may exhibit increased resilience to environmental stressors after acclimatizing to adverse conditions through plastic developmental processes. However, since these plastic processes involve resource reallocation, producing this alternative phenotype may come at the cost of reductions in the function of a variety of biological systems and a shift toward an accelerated life history (Ellis et al., 2017; Worthman & Kuzara, 2005). In effect, this type of adaptive plasticity trades enhanced resilience that facilitates successful reproduction for delayed costs in the form of increased chronic disease risk and reduced longevity (Brumbach et al., 2009; Ellis et al., 2017; Ellis & Del Giudice, 2019; Worthman & Kuzara, 2005).

Yet even in controlled trials involving short-lived model species, it is often difficult to clearly link environmental signals received in early life, downstream phenotypic effects, and their impact on fitness (Doughty & Reznick, 2004). Conducting longitudinal studies of early life stress in human populations is complicated not only by our extended lifespans, but by the intense interaction between cultural, behavioral, and physiological variables that shape phenotypic development. As Schulz (2010) observes, there is no way to design an ethical, prospective test for SDW in early life. Indeed, key studies linking early life stressors to phenotypic outcomes in human populations are often predicated on evaluating the health status of individuals from populations subjected to systemic social inequities, unpredictable social environments, violence, and intergenerational trauma (Brown et al., 2009; Brumbach et al., 2009; Danese & McEwen, 2012; Rooij Sr et al., 2010). The traits that emerge in response to these high-stress environments are often assessed in the context of measures of health and well-being developed by and for WEIRD (Western, educated, industrialized, rich, and democratic) populations—factors which may be relevant to Western public health models and intervention strategies, but not necessarily to examinations of evolutionary fitness (Ellis et al., 2017; Ellis & Del Giudice, 2019; Henrich et al., 2010). However, an increasing number of studies in epidemiology and biomedicine have begun to employ biomarkers to assess the relationship between early-life stress exposures and phenotypic outcomes in living human populations, as biomarkers may indicate the timing and severity of stress exposures as well as physiological efforts to mediate the effects of stress within biological systems (Davis et al., 2019; Worthman & Costello, 2009). Traditional approaches in skeletal biology excel in the application of biomarker models to assess links between environmental stress and measures of population health, and have explored this relationship in a broad variety of spatiotemporal contexts. In the following sections, I describe how the SDW concept could be used to devise more specific tests of DOHaD hypotheses related to the timing of early life stressors and the production of adaptive responses, by using evidence of plastic stress encoded in hard tissue to identify periods of development in which key life history trade-offs are initiated and related constraints on adult phenotype.

3 | TARGETING DEVELOPMENTAL PLASTICITY USING SDW

Following Waddington's (1957) concept of the epigenetic landscape, organisms are guided through developmental processes by: (1) successive developmental perturbations that gradually push them toward a phenotypic destination and/or (2) high-fidelity signals of future conditions that alter long-term phenotypic trajectories at developmental switch-points. Although these processes are not necessarily mutually exclusive, developmental constraints models frame adult phenotypes as largely the product of developmental perturbations, while PAR models frame them as a response to high-fidelity signals of future conditions that influence long-term developmental trajectories. This distinction is important, because the patterning of nonadaptive—or even maladaptive—phenotypic artifacts generated by these processes may be discernable from one another, provided that they are recorded in a durable format. Additionally, these models operate on the concept that different life history trade-offs guide developmental processes in early life, and so determining when these trade-offs are initiated and identifying associated physiological costs is key to analysis.

Two primary questions face skeletal biologists at this juncture: (1) when are stress exposures most likely to produce potentially adaptive plastic responses and (2) what will evidence of such responses look like in the skeletal record? Based on previous studies of DOHaD and the concept of the stress-adapted phenotype, we might expect that individuals subject to stress in early life acclimatize to stress as a result of adaptive plastic responses to informative environmental signals received within early SDW (Amoroso & Garcia, 2018; Ellis et al., 2017). If this is the case, members of a population exhibiting evidence of stress in elements with early SDW should then exhibit subsequent acclimatization to their environment through catch-up growth (i.e., limited evidence of stunting) and reduced mortality risk in early life (i.e., low juvenility index). Both the alternative PAR model described by Nettle and Bateson (2015) and the key cost-benefit trade-offs governing life history patterns described by Worthman and

Kuzara (2005) further suggest that this acclimatization likely comes at a delayed cost, with reduced investment in developmental processes (e.g., inhibited fetal growth) and accelerated life histories (e.g., early achievement of developmental milestones relative to chronological age) driving reductions in longevity (e.g., earlier age-at-death) and enhanced disease susceptibility (e.g., associations between early life stress and chronic disease). If phenotypic plasticity better fits the developmental constraints model, we might instead expect to see consistent evidence of stress responses across the developmental lifespan, resulting in increased evidence of stunting and increased mortality risk. Furthermore, the timing of stress events in early life may have a weaker association with adult phenotypic outcomes, since costs and constraints are determined based on cumulative exposures rather than programming periods. In the process of examining these alternative models, differences in stress responses across elements may be used to more specifically identify periods in which stress has a strong association with potentially adaptive phenotypic outcomes. Here, SDW provides a valuable framework for addressing questions at the heart of the DOHaD hypothesis: when is stress most likely to drive short-term trade-offs between physiological functions, and when is it most likely to act as a programming signal?

Here, applying the SDW framework to the skeletal system is especially advantageous because it permits comparison of stress events within and across systems over extended timelines, even in the event that only some skeletal signals of stress are preserved. This is possible because the neuroendocrine system effectively acts as a "pacemaker" of life-history trade-offs, with the hypothalamo-pituitary-gonadal (HPG) and hypothalamo-pituitary-adrenal (HPA) axes regulating the allocation of energetic resources between developing systems across multiple timescales (Worthman & Kuzara, 2005, p. 98). In addition, stress and its associated hormonal mediators are highly generalized, with glucocorticoids producing both short and long-term effects in a variety of biological systems (Crewther et al., 2011; Falkenstein et al., 2000; Martinelli Jr. & Moreira, 1994; Mazziotti & Giustina, 2013; Worthman & Kuzara, 2005). Although the pace and intensity of phenotypic reactions to the same environmental signal may vary across receptive biological targets, it may be possible to correlate them provided that we are able to estimate signal timing. Thus, identifying how—and when—the hormonal mediators of environmental signals produce enduring phenotypic responses in both hard and soft tissues allows us to make better informed predictions about population-level patterns related to growth, reproduction, and survivorship.

It is hypothesized that glucocorticoid secretion regulates growth hormone (GH) production through complex interactions with the hypothalamus, pituitary gland, and liver, with the potential for both glucocorticoid concentration and duration of effect to impact growth trajectories in developing organisms (Martinelli Jr & Moreira, 1994; Mazziotti & Giustina, 2013). Indeed, the interaction between glucocorticoids, GH and the skeletal system underlies the analysis of many skeletal biomarkers commonly used to assess population stress in skeletal biology, as GH has a moderating effect on endochondral ossification, bone metabolism, and enamel deposition (Donatti et al., 2011). Just as glucocorticoids influence hard tissue growth and development, they also moderate these processes in a variety of biological systems, with recent research suggesting that early life exposures to glucocorticoids may strongly impact plastic responses in the neuroendocrine and reproductive systems in ways that influence the pace and tempo of individual life histories, disease risk, and the aging process (Davis et al., 2019; Davis & Sandman, 2010; Entringer et al., 2011, 2012; Forman et al., 2013; Mittal et al., 2015; Thayer & Kuzawa, 2014). Research conducted by Entringer et al. (2011, 2012), even suggests that telomere length and homeostasis in humans is plastic and receptive to stress experienced during intrauterine life, potentially accelerating cellular dysfunction and aspects of the aging process, with clear implications for longevity. Thus, the very systems that regulate the pace and timing of life history events exhibit plasticity in response to stress experienced within SDW. Since the same suite of hormonal mediators trigger phenotypic reactions to environmental signals within and across systems, it may be possible to significantly amplify the interpretive power of studies related to developmental plasticity by: (1) identifying SDW in a broader variety of biological targets and (2) identifying correlations between known SDW over developmental timelines of interest.

4 | IDENTIFYING SDW IN THE SKELETAL SYSTEM

The capacity to withstand stress is modulated by adaptive plasticity that reallocates energy toward investment in short term survival (Charnov, 1993, 2004; Murren et al., 2015). Limitations on this process are, however, associated with physiological constraints, which reduce the modulation of energy to competing systems following investment in short-term survival (Charnov, 2004; Kuzawa, 2007; Murren et al., 2015; Stearns, 1992). Bioarchaeological research identifies adaptive plasticity using skeletal biomarkers that represent stress events where short-term trade-offs permitted continued survival of the organism, and may also use the human skeleton as a record to measure morbidity and mortality risks at later stages of the lifespan (Temple, 2019). Although the capacity to mount a plastic response to stress is potentially adaptive, not all plastic responses contribute to fitness, and many are the result of inhibitory influences like insufficient food, immunological insults, or chronic activations of the stress response system, the artifacts of which are clearly identifiable in the osteological record (Temple, 2019). Thus, one of the key challenges facing skeletal biologists is to develop methodology that facilitates the identification of signals likely to produce potentially adaptive plastic responses recorded in hard tissue, even in environments where developmental perturbations resulting from fluctuating access to energy have a strong influence on phenotype.

As previously discussed, since both the concentration and duration of exposure to glucocorticoids may influence phenotypic end products, it is essential that both acute and chronic indicators of stress are accounted for in SDW models in order to address the problem of equifinality. In many ways, the traditional toolkit used by skeletal

biologists to assess stress is well equipped to address this challenge. Biomarkers associated with acute stress episodes (e.g., Harris lines and enamel defects) are direct evidence of short-term trade-offs between somatic growth and survival moderated by interactions between glucocorticoids and GH (Newman & Gowland, 2015; Smith, 2006; Temple, 2019). The severity and periodicity of enamel defects are directly linked to interruptions in GH production and capture highly specific information about the developmental chronology of teeth (Smith, 2006; Smith et al., 2006). Since enamel secretion occurs rhythmically in 12-h subdivisions during tooth development (Smith, 2006), the patterning of defects may be used to assess the frequency and patterning of stress events with great specificity (Davis et al., 2019; Lorentz et al., 2019). In addition, the neonatal line—a histological landmark corresponding to the highly stressful event of birth—may be used to differentiate between pre and postnatal enamel deposition, facilitating analysis of stress experienced in late gestation versus early infancy (Eli et al., 1989; Lorentz et al., 2019).

Conversely, skeletal measures of stunting are more indicative of developmental environments characterized by chronic stress, since these conditions develop over longer time spans and thus reflect extended periods of disrupted growth and development in which recovery was not achieved. Since long bones remain responsive to the influence of environmental signals until epiphyseal fusion occurs in adolescence and are also highly responsive to mechanical inputs (Haapasalo et al., 2000, 2009), they embody complex phenotypic–environmental interactions over an extended timeframe encompassing multiple SDW. Metric traits of long bone diaphyses have traditionally been used to assess patterns of growth and development in a wide variety of studies in skeletal biology, nutrition, and public health (Danaei et al., 2016; Dhavale et al., 2017; Gough et al., 2015; Lampl & Schoen, 2017; Mays & Brickley, 2008; Prentice et al., 2013; Richard et al., 2014; Schillaci et al., 2011; Temple, 2019). In addition, maternal exposures to adverse environments have been linked to stunting in offspring, as signals of both immediate environmental conditions and "mean" conditions experienced over the mother's lifetime are transmitted to infants throughout gestation and the weaning period (Gowland, 2015; Kuzawa, 2013). Gowland (2015) characterizes this dynamic as akin to "inheriting well-being" as a result of cumulative exposures to adverse social, ecological, and biological environments across multiple generations. Crucially, long bones may also be capable of mounting compensatory responses to previous developmental disruptions in the form of catch-up growth, provided that sufficient resources are available (Prentice et al., 2013; Richard et al., 2014). Thus, in the context of an SDW model, evidence of diaphyseal stunting reflects both short-term life history trade-offs between early life adversity and somatic growth in the form of developmental disruptions (e.g., Harris lines) and their cumulative impact on long-term phenotypic trajectories (e.g., diaphyseal stunting and catch-up growth).

Recent efforts to study plasticity in the skeletal system have adopted the DOHaD perspective, linking evidence of stress experienced during early life to the patterning of stunted growth, disease susceptibility, and mortality risk in adulthood (Table 1). In particular, recent studies involving the analysis of enamel defects offer a promising model for identifying SDW within the skeletal system, by linking the timing of stress events to long-term phenotypic trajectories (Brickley et al., 2019; Davis et al., 2019; Lorentz et al., 2019; Garland, 2020). Temple (2019) has argued that while skeletal changes associated with stress are not necessarily adaptive in and of themselves, they may signal the presence of an adaptive response to stress involving energetic trade-offs between early life adversity and reduced investment in growth (Temple, 2019). By examining episodes of stress in early life and their association with key covariates across a

TABLE 1 Recent tests of DOHaD hypotheses in skeletal biology

Study	Measure of developmental stress	Key covariates
Armelagos et al. (2009)	Enamel defects (enamel hypoplasias)	Age at death, number of defects, developmental timing of defects, and sex
Amoroso and Garcia (2018)	A-P and T-R VNC diameters	Age at death, cause of death, occupation, place of birth, place of death, sex, and year
Brickley et al. (2019)	Mineralization defects (interglobular dentine)	Frequency of defects and developmental timing of defects
Davis et al. (2019)	Enamel defects (perikymata)	Number of defects, developmental timing of defects, psychopathology, and sex
Garland (2020)	Enamel defects (accentuated lines)	Age at death, frequency of defects, and developmental timing of defects
Lorentz et al. (2019)	Enamel defects (accentuated lines)	Age at death, frequency of defects, and developmental timing of defects
Newman and Gowland (2015)	Vertebral body height and T-R VNC diameter	Cribra orbitalia, estimated age at death, rickets, and sex
Temple (2014, 2019)	Enamel defects (perikymata)	Estimated age at death, estimated stature, and sex
Watts (2013, 2015)	A-P and T-R VNC diameters	Estimated age at death, estimated stature, and sex
Weisensee (2013)	Craniofacial fluctuating asymmetry (FA)	Age at death, cause of death, place of birth, place of death, occupation, and sex

variety of hard tissue elements (Table 1), it may be possible to identify relatively discrete SDW in which stress acts as a signal that facilitates the development of the "stress-adapted" phenotypes described by Ellis et al. (2017). In the following sections, I briefly describe recent research in skeletal biology focused on a variety of hard tissue elements that suggests the existence of such windows, and how they may be used to further enhance our understanding of DOHaD.

4.1 | Dental measures

Using the periodicity of defects in dental enamel to estimate the frequency and duration of stress exposures in early childhood, Temple (2019) found that individuals who formed defects at earlier ages were at higher risk of mortality, a result which supports the idea that the timing of environmental signals in early life influences adult phenotypic outcomes. Similarly, Lorentz et al. (2019) used developmental defects in enamel microstructures to assess the relationship between the timing of early life adversity and mortality risk, finding a link between prenatal stress and earlier age at death. Of equal significance is their finding that there was no association between stress experienced within the first 8 months of postnatal life and earlier age at death in their study population. This result strongly suggests that the timing of stress exposures in early life is a key factor in predicting mortality risk when extrapolated to the population level, and furthermore, that there may be a relatively discrete SDW in late gestation in which elevated glucocorticoid levels trigger a trade-off between early life adversity and mortality risk (Lorentz et al., 2019). Another promising avenue of DoHaD research is represented by the model developed by Davis et al. (2019) that uses a variety of dental measures to assess the timing and frequency of early life stress exposures to better understand how they relate to impaired mental health over the life course. The ultimate goal of this project is to identify key dental biomarkers that facilitate identification of vulnerable individuals most at risk of developing symptoms of impaired mental health—a novel diagnostic application of hard tissue biomarkers with potential for further development.

4.2 | Bone mineral Density

Studies related to mechanical loading of long bones as a result of athletic activity and subsequent changes in bone mineral density (BMD) also appear to suggest the presence of SDW related to BMD development and maintenance (Haapasalo et al., 2000, 2009; MacKelvie et al., 2002). Physical activity subjects the body to stress, with estrogen and insulin-like growth factor 1 (IGF-1) interactively moderating the development and maintenance of the musculoskeletal system in response to mechanical loading (Damien et al., 1998, 2000). Bone cells possess estrogen receptors, which regulate osteoblast proliferation and activity in response to mechanical loading, and in turn interact with IGF-1, which is produced in bone cells in response to mechanical strain (Damien et al., 1998). This process occurs in both sexes, and basal levels of osteoblast proliferation do not significantly vary between males and females, although different skeletal elements demonstrate varying levels of responsivity to mechanical strain (Damien et al., 1998, 2000). In a study of exercise-induced BMD changes in the upper limbs of male tennis players, Haapasalo et al. (2000) hypothesized that loading-induced adaptations had developed in individuals who had started playing in childhood, resulting in site-specific gains in BMD in their dominant arm. In a 2009 study of female tennis players, Haapasalo and colleagues found that subjects' humeri were most responsive to mechanical loading during the adolescent growth spurt, but that mechanical loading during late childhood (e.g., Tanner stages I and II, mean ages 9.8 and 10.4 years) had no significant effect on BMD in comparisons of athletes and controls. The authors suggest that rapid skeletal growth and turnover during adolescence promote significant acquisition of bone in response to mechanical loading—a result that is highly suggestive of an SDW for BMD development and maintenance, with potential benefits in the form of greater resistance to osteoporosis in later life. Interestingly, the effect of mechanical loading on the lumbar spine in the same study population only produced significant differences between athletes and controls later in development (Tanner stages IV and V, mean age 13.5 and 15.5), suggesting that the lumbar spine may have a different SDW for bone density acquisition and maintenance. Since cortical bone in general is responsive to strain, it is possible that similar SDW may be found in other skeletal elements subject to mechanical loading related to physical activity (Pearson & Lieberman, 2004; Ruff et al., 2006). Furthermore, numerous properties of bone—cortical bone thickness, cortical bone area, and total bone area, to name a few—are responsive to mechanical loading, with the potential to exhibit SDW relevant to osteological analyses (Pearson and Lieberman, 2004; Ruff et al., 2006).

4.3 | Measures of asymmetry

Although relatively underutilized in DOHaD studies, measures of asymmetry may represent a promising approach to assessing the relationship between developmental stress and health in archeological populations (Chovalopoulou et al., 2017; Weisensee, 2013). A recent study of cranial asymmetry in a modern Greek population found no association between early developmental environments and age at death, as assessed through measures of fluctuating asymmetry (FA) in the cranium (Chovalopoulou et al., 2017). However, a study of a much larger historical Portuguese population by Weisensee (2013) found an association between FA and cause of death, with more severe FA observed in individuals known to have died from degenerative versus infectious diseases. This result suggests that developmental instability in early childhood that promoted asymmetric development of elements of the cranium produced physiological trade-offs which left affected individuals more susceptible to chronic disease in adulthood; a result consistent with previous studies which indicate that early life adversity impacts chronic disease risk over the lifespan (Danese & McEwen, 2012; Gluckman et al., 2009). A particular advantage of using

asymmetry as a biomarker of developmental stress is that the neutral phenotypic expectation in bilaterally symmetrical animals is minor directional asymmetry (Auerbach & Ruff, 2006; Klingenberg, 2015). Thus, the presence of significant, canalized FA in conservative elements under limited mechanical stress may be indicative of an adverse developmental environment characterized by chronic stress. Provided that the window in which canalization of asymmetry occurs is relatively discrete, this approach could prove particularly useful in expanding SDW models in the skeletal system—a topic explored in greater detail in the following section. However, caution should be exercised in the selection of target elements, as studies of handedness and upper limb morphology indicate that regular mechanical loading in the dominant limb may in fact act upon existing asymmetrical structures developing in early life, with human populations typically displaying varying degrees of limb bone bilateral asymmetry in adulthood (Auerbach & Ruff, 2006; Haapasalo et al., 2000, 2009; Perchalski et al., 2018). For these reasons, elements characterized by asymmetric development that are highly responsive to mechanical loading may not be appropriate choices for methods that use measures of asymmetry as indicators of developmental stress.

4.4 | Vertebral measures

The anterior–posterior (AP) and transverse (TR) diameters of the vertebral neural canal (VNC) and vertebral body height have also been used to assess the presence, severity, and timing of developmental stress events in archeological samples and their impact on mortality risk (Amoroso & Garcia, 2018; Newman & Gowland, 2015). These approaches build on prior research conducted by Watts (2013, 2015), in which constrained VNC dimensions were interpreted as signals of life history trade-offs involving reductions in somatic growth in order to enhance survival in adverse environments. Given that the VNC can be assessed in terms of subdivisions of vertebrae representing series of adjacent SDW (Amoroso & Garcia, 2018; Newman & Gowland, 2015), this approach may prove to be highly useful in a variety of modern and archeological study contexts. The study conducted by Amoroso and Garcia (2018) is particularly instructive as a potential model for future SDW approaches, as their analysis of the relationship between VNC dimensions and age-at-death was explicitly framed as a test of developmental constraint versus PAR models through the examination of life history trade-offs. Since VNC dimensions had no statistically significant effect on age-at-death in their skeletal sample, they suggest that individuals exposed to early life stress underwent predictive adaptive responses that "allowed them to cope with adversity without affecting longevity" (2018, p. 8). This result suggests that the long-term impacts of these potentially adaptive plastic responses may have been mitigated for affected individuals over the life course through behavioral or cultural factors, effectively relaxing constraints, or possibly, that the primary cost of enhanced resilience was not reduced longevity. Examination of trade-offs in such cases may be enhanced by use of multi-marker SDW models, so that other life history trade-offs and the potential for physiological mitigation can be further explored.

Together, these studies represent a major step forward in addressing the theoretical propositions raised by DOHaD, by linking evidence of developmental stress in the skeletal record to demographic patterns of growth, morbidity, and mortality over extended timeframes. In fact, in several of the cases detailed above, potential SDW have been identified in which stress exposures increase mortality risk (Lorentz et al., 2019; Temple, 2019), chronic disease risk (Weisensee, 2013), facilitate the development of stress-adapted phenotypes (Amoroso & Garcia, 2018), and shape patterns of bone acquisition (Haapasalo et al., 2000, 2009). Knowing that stress responses encoded in teeth, vertebral dimensions, and the BMD of upper limb bones may be used to predict long-term phenotypic outcomes, it stands to reason that other elements may be similarly utilized in SDW models. However, certain traits related to growth and development may make some skeletal elements more suitable candidates for inclusion than others.

In the following sections, I describe how a model for interpreting plastic responses to developmental stress may be constructed using a series of early differentiating, highly conservative skeletal elements likely to capture and retain evidence of developmental perturbations within early life SDW. Building on prior research within skeletal biology, models based on the SDW concept have the potential to enhance our ability to assess how the timing of stress events and downstream compensatory responses relate to health and fitness outcomes over the life course.

5 | CONSTRUCTING AN SDW MODEL FOR SKELETAL BIOLOGY

The SDW concept offers a powerful interpretive framework for assessing the relationship between the timing of stress exposures in early life and adult phenotypic outcomes, because it is predicated on the idea that different elements are most likely to mount plastic responses to stress at different stages in development as their SDW "open" and "close." Since some elements are more likely to encode and retain evidence of crucial environmental signals in early life, examining the patterning of phenotypic plasticity exhibited by these elements may be especially informative when contextualized by population-level patterns of morbidity and mortality. Conservative, early-differentiating skeletal elements less susceptible to remodeling may record evidence of complex interactions between behavior, physiology and the environment within relatively narrow SDW, as responses to stress are canalized in their morphology. On the other hand, elements that continue to grow and develop throughout the juvenile period remain susceptible to environmental signals over an extended timeframe and are more likely to incorporate evidence of successive developmental perturbations. Morphological variation in some elements tends to reflect neutral genetic expectations, while other elements are more likely to embody the effects of

environmental inputs (Van Dongen & Gangestad, 2011; Von Cramon-Taubadel, 2009, 2011). For these reasons, it is essential that any study of developmental plasticity accounts for differences in the sensitivity of developing tissues to the effect of environmental stressors. The systems approach to the SDW concept advocated by Burggren and Mueller (2019) explicitly addresses this methodological challenge, and so may be particularly applicable to the skeletal system.

The modularity of a biological system acts as both a facilitator of, and a check on, developmental plasticity, safeguarding that whole systems are not adversely impacted by acute stress events while ensuring that environmental information potentially relevant to development is collected over an extended timeframe. Since different elements have individual or unique SDW, plasticity displayed by one element may have cascading impacts on related components within the system, just as later-developing elements may exhibit compensatory responses to plasticity exhibited by earlier developing elements (Burggren and Mueller, 2019; West-Eberhard, 2003). Although all organisms are complex, highly integrated biological systems, the skeletal system is relatively modular and element-scale developmental processes are well-documented in the biological literature. Patterns of skeletal growth and epiphyseal fusion are frequently used to assess the impact of stress on the pace and tempo of development (Lewis, 2017). In addition, many existing studies of stress in the skeletal system are predicated on the concept that plasticity declines as individuals age due to increasing constraints on phenotypic adjustment, and indeed, many of the most frequently utilized skeletal stress biomarkers (e.g., enamel defects, cribra orbitalia, and porotic hyperostosis) best reflect early developmental environments (Hillson, 1992; Ritzman et al., 2008; Stuart-Macadam, 1985, 1989; Wells, 2014, 2016).

As previously discussed, an interpretive framework based on the SDW concept is capable of operating on multiple scales of analysis, facilitating the identification and interpretation of plastic responses at the level of individual elements, extended systems, and organisms. Since the human skeleton consists of a modular system of elements that develop in a well-defined sequence, with groups of components contributing to shared functions, an SDW model can be tailored to address specific questions about the relationship between developmental plasticity and its impact on the phenotype. This may be accomplished by selecting sequences of skeletal elements with SDW that are "open" during developmental episodes of interest, measuring plastic responses exhibited by these elements, and then comparing these responses to relevant phenotypic outcomes (e.g., height for age, estimated age at death; Table 2). Furthermore, since signals of stress are highly generalized, identifying when stress was encoded in a particular skeletal element permits comparison to SDW identified in other biological systems. For example, if the timing of prenatal stress episodes encoded in dental enamel in an archeological sample correlates with a SDW associated with reduced telomere lengths and accelerated aging, this might allow you to make informed inferences about observed demographic patterns related to age-at-death.

Of course, not all exposures to stress result in biomarker formation and important passages in an individual's life history may be obscured or erased as a result of skeletal remodeling. Thus, the first step in constructing an SDW framework that facilitates analysis of the link between early developmental environments and phenotypic outcomes is to identify skeletal elements most likely to capture and retain evidence of plastic responses to environmental signals in early life. When selecting elements for inclusion in this model, it is important to account for the following factors: (1) their relative positions in a developmental sequence, (2) whether elements are adjacent and/or share a common function, and (3) the degree to which observable morphological variation in each element is influenced by genetic versus extragenetic factors. The modularity of the skeletal system reduces the odds that an acute response to stress exhibited by one element undermines an essential physiological function (West-Eberhard, 2003). Thus, elements linked by proximity or common function are likely to mount compensatory responses to plasticity (e.g., asymmetry) exhibited by earlier-developing elements. This cascading effect is perhaps best illustrated by studies of asymmetry in the human cranium, which demonstrate that the early-developing basicranium acts as a "constructional template" for later-developing craniofacial elements (Galiè et al., 2015, p. e63). Ideally, elements whose morphology may be strongly influenced by compensatory responses should not be included unless appropriate adjacent or functionally-related elements are also examined as controls.

In addition, the genotype may exert significant influence over plastic expression within a biological system. If the morphology of an element strongly correlates with genetic data, then this must be accounted for in sample selection in order to control for genetic influence. It may be most appropriate to examine the effect of developmental plasticity within populations where variation in morphological expression may be better controlled for—although even in such cases, the potential for significant morphological variation within populations exists. Although the role that the genotype plays in influencing plastic expression in the skeletal system is not well defined at the level of individual elements, those associated with single sensory functions

TABLE 2 Standard covariates used in DOHaD studies in skeletal biology

Covariate	Proxy measure of:
Cause of death (e.g., infectious or chronic disease, injury, and accident)	Morbidity and immune function
Estimated stature	Quality of developmental environment, somatic growth trajectory, and potential for catch-up growth
Estimated age at death	Mortality risk
Juvenility index	Mortality risk
Stress biomarkers (enamel defects, cribra orbitalia, and porotic hyperostosis)	Quality of developmental environment and exposure to physiological and psychosocial stressors
Socioeconomic status (SES) indicators (e.g., income and occupation)	Psychosocial stress exposure

(e.g., auditory or visual) may be less likely to reflect neutral genetic histories, and thus may be particularly suitable for inclusion in an SDW model (Scheuer et al., 2016; Von Cramon-Taubadel, 2011).

In light of the three factors discussed here, it follows that developmental plasticity in early life is best represented by elements that are both early-differentiating and highly conservative, and responsive to environmental inputs largely within defined developmental windows. Recent DOHaD studies in skeletal biology have tended to focus on dental enamel, because it develops in a well-defined sequence and does not remodel. These traits make it an ideal medium in which to assess the impact of developmental timing on phenotypic development, but the SDW approach is strengthened by the analysis of multiple elements over an extended time period. Skeletal elements associated with delicate soft tissue structures are often developmentally conservative because even relatively minor alterations to their geometry could have significant impacts on fitness. Nonetheless, they are—with perhaps the exception of the VNC—underutilized in tests of DOHaD hypotheses.

For the purposes of this article, I will describe three skeletal elements that could be used to construct an SDW model for examining developmental stress over an extended timeline in early life: elements of the basicranium forming the foramen magnum, the petrous portion (PP) of the temporal, and the VNC. The SDW framework is graphically represented for these elements in Figure 1. Multi-marker models of stress, such as the alternative frailty index proposed by Marklein et al. (2016), are better at capturing evidence of stress as embodied by the skeletal system because they can account for differences in the ability of various hard tissues to record evidence of both acute and chronic stress exposures. As modeled by the studies referenced in Table 1, evidence of developmental stress embodied in these three elements can be assessed in terms of long-term phenotypic outcomes using covariates (e.g., estimated stature, age-at-death, and juvenility index) related to morbidity and mortality (Table 2). Altogether, these elements are suitable for inclusion in an SDW model because they are more likely to mount plastic responses to important environmental cues rather than compensatory responses by virtue of their early differentiation. Since they exhibit limited potential for remodeling outside of early SDW, they effectively behave as osteological time-capsules—recording evidence of complex interactions between behavior, physiology, and the environment within defined developmental episodes with the potential to impact long-term developmental trajectories.

5.1 | The basicranium and foramen magnum

The foramen magnum is formed by the fusion of four elements of the immature occipital: the occipital squama, which is itself composed of the supraoccipital and interparietals, the left and right partes laterales, and the pars basilaris. These components of the immature occipital develop from multiple centers of ossification, which appear between 8 and 12 weeks of fetal life (Cunningham et al., 2017). Early development of the occipital is a complex process, with the supraoccipital component ossifying within a cartilaginous framework, the interparietals developing from several intramembranous ossification centers, and the partes laterales ossifying endochondrally. The size and geometry of these components change considerably throughout gestation and early childhood, but several key transformations take place

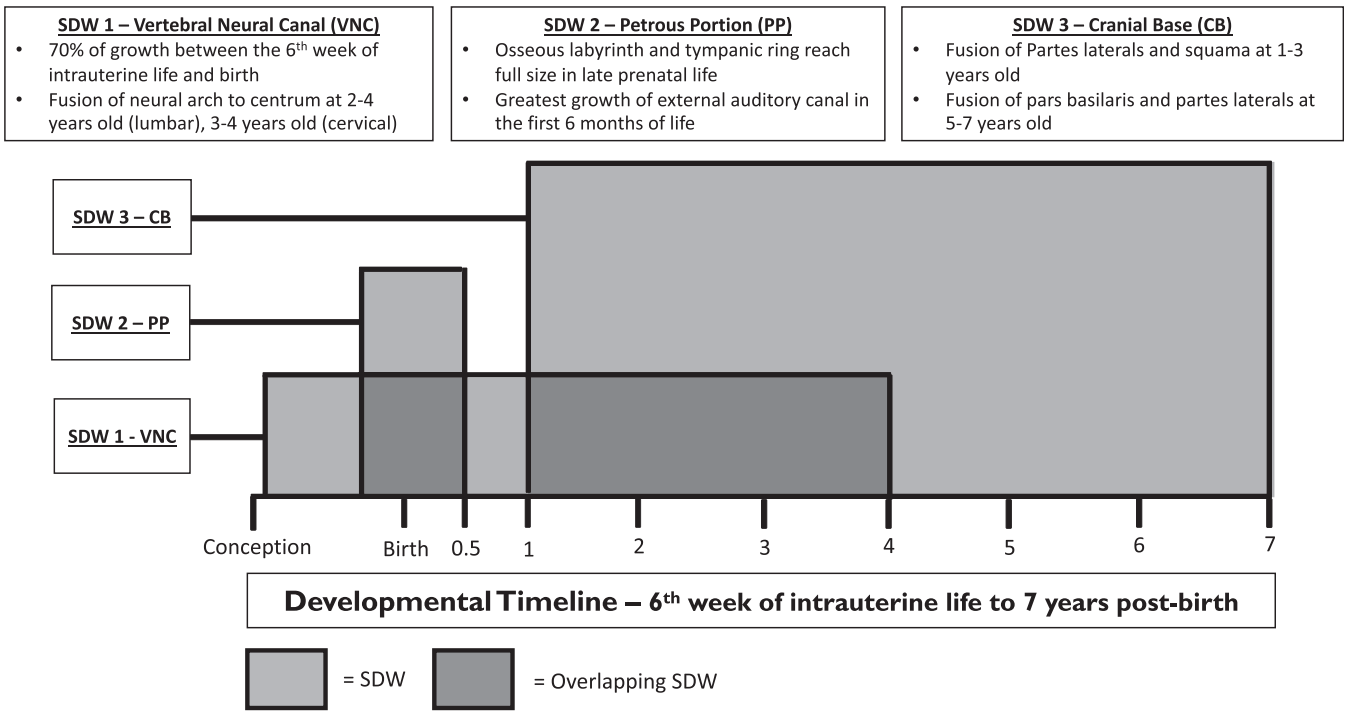

FIGURE 1 An example sensitive developmental window (SDW) model for interpreting skeletal evidence of developmental stress in early life

by the first 6 months postbirth. The pars basilaris develops its distinctive lateral angle 7 months into gestation, and the partes laterales become longer than they are wide—similar to their adult proportions—by 8 months into gestation. Similarly, the width of the pars basilaris becomes greater than its length at approximately 6 months postbirth. The partes laterals and squama of the occipital fuse at the anterior intraoccipitalis sutures between 1 and 3 years postbirth, while the pars basilaris and partes laterals fuse posterior intraoccipitalis sutures between 5 and 7 years postbirth, largely establishing the dimensions and geometry of the foramen magnum (Cunningham et al., 2017). Although the development of this feature occurs over a timeline extending into early childhood, each component of the occipital forming the foramen magnum undergoes significant development from early gestation to the first 6 months of postnatal life. For this reason, particular patterns of developmental disruption (e.g., AP vs. TR asymmetry) may point to periods of stress that influenced one component more strongly than another, and so it may be possible to establish more precise estimates of when these stressors were experienced. Indeed, studies produced by Weisensee (2013) and Chovalopoulou et al. (2017) work suggests that elements of the basicranium may be especially likely to develop and canalize FA in response to developmental instability.

5.2 | The Vertebral Neural Cana

As suggested by Amoroso and Garcia (2018), VNC dimensions may prove to highly useful as indicators of developmental stress because they are largely established in early life and are highly sensitive to environmental conditions (Papp et al., 1994). The development of the VNC is likewise complex, and begins with initial development of the vertebral anlage at 6 prenatal weeks. The cartilaginous framework from which ossification of each vertebrae proceeds develops by 11–12 prenatal weeks, and periosteal bone first begins to develop by 13–14 prenatal weeks, originating in paired ossification centers on the lateral aspects of the developing VNC. The ossification centers for the neural arches and centrum, which together form the VNC, develop between 2 and 4 prenatal months. It is important to note that the VNC experiences 70% of its total growth between the 6th week of intrauterine life and birth, and 95% of its growth by 5 years postbirth (Cunningham et al., 2017; Dimeglio, 1992). The final dimensions of the VNC are therefore largely established after neurocentral fusion, which is completed in all vertebrae by the age of six, with only a minor increase in the transverse diameter in late adolescence (Newman & Gowland, 2015; Scheuer et al., 2016). Since the pattern of vertebral fusion proceeds in such a well-defined sequence, it is possible to associate evidence of plastic responses to environmental stressors in the form of constrained growth with relatively narrow developmental episodes (Amoroso & Garcia, 2018; Newman & Gowland, 2015). Additionally, since plasticity in one vertebra may influence the development of later-developing, adjacent vertebrae, compensatory plasticity can be identified and controlled for in studies involving these elements.

5.3 | The Petrous Portion of the Temporal

Although the PP is underutilized in studies of developmental stress in comparison to the cranial base and VNC, it exhibits several key traits that suggest it may be effectively utilized as an indicator of environmental conditions in early life. Although the squamous, tympanic, and mastoid components of the temporal bone continue to grow in size and change dimensions throughout the juvenile period, the osseous labyrinth and tympanic ring reach their adult proportions in the middle of prenatal life and display no capacity for remodeling (Cunningham et al., 2017; Jeffery & Spoor, 2004; Spoor, 1993). Furthermore, the greatest growth in the external auditory canal occurs in the first 6 months of life, and only a slight increase in the width of the tympanic cavity during this period (Cunningham et al., 2017; Eby & Nadol, 1986). The membranous labyrinth of the inner ear begins to develop in week three of gestation, and by weeks 17–19, the labyrinth reaches its adult size (Cunningham et al., 2017; Jeffery & Spoor, 2004). By fetal week 24, this labyrinth ossifies, and there are no further increases in size or dimensional changes to the otic capsule at this stage (Spoor, 1993). Similarly, the round window and associated fossulae are thought to reach their adult dimensions during late fetal development, with a burst of rapid growth taking place in the weeks prior to birth (Bonaldi et al., 1997). Thus, aspects of the temporal bone that exhibit high degrees of conservatism because of their relationship to the inner ear may be particularly well-suited for analysis using an SDW framework, despite their relationship with more plastic elements of the temporal that continue to develop over longer time periods.

6 | DISCUSSION

A key challenge facing skeletal biologists seeking to address questions related to plasticity is how to apply insights derived from developmental biology to the skeletal system, when hard tissue is both a relatively conservative record of stress and unlikely to be in a state of perfect preservation in many research contexts. Since the potentially adaptive value of plasticity lies in its ability to tailor developing phenotypes to local environmental conditions, it is essential that we examine developmental plasticity's impact on morbidity and mortality across a wide variety of environmental regimes, not all of which are conducive to the preservation of delicate soft tissue and genetic material. Although the skeletal system is an imperfect record of phenotypic-environmental interactions, it is also able to withstand a relatively wide range of preservation conditions. Thus, while hard tissue provides only an incomplete picture of developmental plasticity and its phenotypic products, it permits comparison between a broader variety of populations existing across time and space. It is therefore crucial that we develop methods that allow us to work around the limitations posed by destructive taphonomic processes, so that we can access a deeper, richer account of how our species has shaped, and been shaped by, our environment.

The proposed SDW model provides one approach to operationalizing insights derived from developmental research across the biological sciences, by providing a flexible framework for assessing plastic responses to stress in the skeletal system that takes advantage of the system's modularity and varying degrees of conservatism. It is essential that any study of plasticity in the skeletal system accounts for variations in responsivity to stress across different elements over the developmental lifecycle, and so in order to effectively utilize this approach, researchers must carefully consider which elements are most suitable proxies for early developmental environments prior to data collection. The SDW concept facilitates selection of elements most likely to mount a phenotypic response to stress within periods most relevant to questions asked by researchers, and since the SDW for many elements overlap, it may be possible to construct multiple viable models to address each question. The ability to customize the model to suit research questions and work around preservation or access limitations will enable developmental plasticity research to be conducted in a broader cross-section of modern and archeological contexts. Indeed, since the SDW concept is already well established in developmental biology, adopting this approach in skeletal biology will facilitate analyses of how evidence of early life stress encoded in hard tissue relates to phenotypic outcomes in a variety of biological systems.

Traditional methods of identifying and evaluating biosocial stress in the skeletal record are predicated on the concept that hard tissue is more likely to record evidence of phenotypic–environmental interactions during development (Hillson, 1992; Ritzman et al., 2008; Stuart-Macadam, 1985, 1989). Thus, the SDW model proposed here simply refines this approach by contextualizing phenotypic outcomes over the life course and their relationship to stress exposures within relatively discrete developmental episodes. This crucial extension of existing DOHaD approaches has the potential to improve our understanding how developmental plasticity may act as a buffer against—or merely a reflection of—sociobiological stressors. Yet as Amoroso and Garcia (2018) caution, early life stress is an imperfect predictor of health outcomes, and a holistic approach is required to understand how risk factors associated with stress may be mitigated or amplified by social and cultural factors. It is for this reason that SDW models should carefully consider how local biocultural factors may mitigate costs, relax constraints, and obfuscate the physiological signals associated with life history trade-offs. In doing so, the SDW concept may represent a useful strategy for answering some of the fundamental questions posed by the Osteological Paradox; namely, how selective mortality and heterogeneous frailty shape a mortuary sample (Woods et al., 1992). Indeed, if it is possible to identify consistent associations between stress experienced within particular SDW and population-level patterns of morbidity and mortality, we may begin to better understand the role plasticity has played in adapting human populations to novel environmental conditions throughout our species' history.

As previously discussed, variations in local conditions may limit the ability of investigators to capture plasticity data for every relevant element, but groups of investigators interested in the same sets of DOHaD related questions may use SDW models in order to promote consistency in data collection across samples. The most significant challenge facing early adopters is related to model construction; namely, which elements best reflect developmental plasticity within relevant episodes, and what markers should be used to assess varying degrees of plasticity. The three elements discussed in this article are only a starting point, and other elements may prove to be more or less appropriate based on the aims of the project and the state of sample preservation. Depending on the elements selected, different measures (e.g., FA, anterior–posterior vs. transverse measures, perikymata in tooth enamel) may best represent phenotypic outcomes of plastic responses to stress. As some measures better reflect acute responses to environmental stress, and others the cumulative impact of stress over extended periods, the same care should be taken in biomarker selection as in element selection. Indeed, this also applies to sample selection, since significant differences in diet, activity, and genetic histories may variably influence the development of skeletal elements, and it is often impossible to disentangle their relative influences on phenotype if this information is unknown. Since variation in stature and measures of skeletal asymmetry also vary by population, direct comparison between populations using this method may be less informative than analyses conducted within a population subject to similar environmental, social, and genetic variables.

Finally, the working definition of SDW outlined in this article is one which prioritizes growth rates and geometry, two factors that may be measured with relative ease in the skeletal system. However, it is as yet unclear the extent to which stress encoded in the skeletal system within these windows reliably endures throughout the lifespan in a way that is interpretable to osteologists, especially in instances when elements undergo multiple periods of rapid growth and proportional change throughout their developmental lifecycle. It is for this reason that early-differentiating, conservative elements with relatively abbreviated developmental timelines may prove to be the most suitable elements for use in an SDW model, but this does not mean that others should not be examined using this methodology. Development can only proceed from prior forms, and so stress encoded in an early SDW is likely to influence phenotypic development within any subsequent SDW. Although it is likely that disentangling the impact of growth within multiple SDW may not always be possible, in certain cases examining stress in a single element across multiple SDW (e.g., early childhood and adolescent growth spurts impacting long bones) may provide valuable information about resilience in the face of adverse environments and the capacity for catch-up growth when conditions improve. Although the SDW concept may not be applicable in every research context, it is my hope that by contextualizing it within skeletal biology, it may prove a valuable addition to the ever-expanding set of tools employed by biologists to study phenotypic-environmental interactions in the past.

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AUTHOR CONTRIBUTIONS

Cait McPherson: Conceptualization; writing-original draft; writing-review & editing.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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