The evolution of the adolescent growth spurt: Urinary biomarkers of bone turnover in wild chimpanzees (*Pan troglodytes*)

Aaron A. Sandel [a, b, *], Jacob D. Negrey [c, d], Milja Arponen [e], Isabelle R. Clark [a, b], Jeremy B. Clift [f], Rachna B. Reddy [g, h, i], Kaisa K. Ivaska [e]

[a] Department of Anthropology, University of Texas at Austin, WCP 4.102, 2201 Speedway Stop C3200, Austin, TX 78712, USA

[b] Primate Ethology and Endocrinology Lab, University of Texas at Austin, 2201 Speedway Stop C3200, Austin, TX 78712, USA

[c] School of Human Evolution and Social Change, Arizona State University, 900 S. Cady Mall, Tempe, AZ 85281, USA

[d] Department of Pathology/Section on Comparative Medicine, Wake Forest School of Medicine, Winston-Salem, NC 27101, USA

[e] Institute of Biomedicine, University of Turku, Kiinamyllynkatu 10, 20520 Turku, Finland

[f] Department of Psychological Science, University of Arkansas, 216 Memorial Hall, Fayetteville, AR 72701, USA

[g] Department of Human Evolutionary Biology, Harvard University, 11 Divinity Ave, Cambridge, MA 02138, USA

[h] Department of Psychology, Harvard University, 33 Kirkland St, Cambridge, MA 02138, USA

[i] Department of Evolutionary Anthropology, Duke University, 104 Biological Sciences, Durham, NC 27708, USA

Abstract

Life history theory addresses how organisms balance development and reproduction. Mammals usually invest considerable energy into growth in infancy, and they do so incrementally less until reaching adult body size, when they shift energy to reproduction. Humans are unusual in having a long adolescence when energy is invested in both reproduction and growth, including rapid skeletal growth around puberty. Although many primates, especially in captivity, experience accelerated growth in mass around puberty, it remains unclear whether this represents skeletal growth. Without data on skeletal growth in nonhuman primates, anthropologists have often assumed the adolescent growth spurt is uniquely human, and hypotheses for its evolution have focused on other uniquely human traits. The lack of data is largely due to methodological difficulties of assessing skeletal growth in wild primates. Here, we use two urinary markers of bone turnover—osteocalcin and collagen—to study skeletal growth in a large, cross-sectional sample of wild chimpanzees (*Pan troglodytes*) at Ngogo, Kibale National Park, Uganda. For both bone turnover markers, we found a nonlinear effect of age, which was largely driven by males. For male chimpanzees, values for osteocalcin and collagen peaked at age 9.4 years and 10.8 years, respectively, which corresponds to early and middle adolescence. Notably, collagen values increased from 4.5 to 9 years, suggesting faster growth during early adolescence compared to late infancy. Biomarker levels plateaued at 20 years in both sexes, suggesting skeletal growth continues until then. Additional data, notably on females and infants of both sexes, are needed, as are longitudinal samples. However, our cross-sectional analysis suggests an adolescent growth spurt in the skeleton of chimpanzees, especially for males. Biologists should avoid claiming that the adolescent growth spurt is uniquely human, and hypotheses for the patterns of human growth should consider variation in our primate relatives.

Keywords: Skeletal growth; Adolescence; Primates; Life history; Bone turnover markers

1. Introduction

Humans display a suite of unusual life history traits, including long offspring dependency, slow growth during childhood, rapid growth around puberty, delayed reproduction, short interbirth intervals, and long lives (Lovejoy, 1981; Smith, 1989; Bogin, 1997, 1999; Hawkes et al., 2003; Schwartz, 2012). When did this life history profile evolve? Adolescence, in particular, is an unusual and important life history phase. During the adolescent growth spurt, bone is sensitive to mechanical loading and at greater risk for fracture (MacKelvie et al., 2002), but it remains unclear whether these traits are adaptive or detrimental consequences of rapid growth. Adolescence is also a sensitive time for brain development, social behavior, and cultural learning (Dahl et al., 2018). In fact, brain growth and body growth may be linked, with slow skeletal growth during infancy and childhood hypothesized as a tradeoff to allow rapid brain growth, and a skeletal growth spurt around puberty serving as 'catch-up' growth once the energetic demands of the brain are reduced (Kramer and Ellison, 2010; Ellison et al., 2012; Kuzawa et al., 2014).

Given the importance of adolescence, paleoanthropologists look to bones to ascertain clues to its evolution. One major line of research involves analyzing hominin fossils to determine the age and size at death and thereby determine when the human pattern of growth evolved (Smith, 1992). Did an adolescent growth spurt arise with bipedality among our extinct australopith relatives, or potentially later in the genus *Homo* with increases in brain size or changes in behavior and ecology? Answering these questions necessitates finding fossils of immature individuals (Thompson and Nelson, 2000; Mateos et al., 2014; Cameron et al., 2017; Belcastro et al., 2020). An especially informative case regarding the evolution of the human adolescent growth spurt is *Homo erectus* specimen KNM-WT 15000, which includes unfused bones, indicating that it was not an adult (Brown et al., 1985; Walker and Leakey, 1993). 'Nariokotome Boy,' as it is popularly known, was either a

juvenile or adolescent, and decades of study have contributed to a productive debate regarding whether *H. erectus* experienced an adolescent phase, including a growth spurt (Tardieu, 1998; Clegg and Aiello, 1999; Ohman et al., 2002; Anton and Leigh, 2003; Smith, 2004; Dean and Smith, 2009; Graves et al., 2010; Ruff and Burgess, 2015). Much of the evidence for whether H. erectus, and KNM-WT-1500 in particular, experienced an adolescent growth spurt is based on the rate and pattern of growth in humans compared to extant apes, including our closest living relatives, chimpanzees and bonobos (Hamada et al., 1996; Leigh, 2001; Hamada and Udono, 2002). Thus, data on growth in living humans and primates are crucial for inferring the evolution and selective forces shaping growth, size, and stature in hominin evolution.

Although some primatologists study growth trajectories in captive primates (e.g., Leigh, 1996; Hamada and Udono, 2002), comparative primate data that focus specifically on adolescent growth are generally lacking (Gavan, 1982;Watts and Gavan, 1982). This is due, in part, to conflicting definitions of adolescence and adulthood. Some scholars consider adolescence uniquely human, but such definitions rely on human-centric metrics, defining adolescence in strictly cultural terms (Kett, 1977) or restricting definitions of adolescence to the growth spurt itself (Bogin,1999). A broader definition of adolescence is needed, and we adopt one grounded in life history theory that defines adolescence as the period between the onset of puberty and the cessation of growth (Bogin, 2020a). This biological definition will hopefully disentangle the physical and energetic changes that occur during development from the psychosocial and cultural changes that characterize human adolescence.

Human growth is clearly distinctive, with rapid growth in infancy, slow growth during childhood, and rapid growth during adolescence (Marshall and Tanner, 1970; Bogin, 1999, 2020b; Walker et al., 2006; Dean and Smith, 2009; Goldman et al., 2009; Urlacher et al., 2016; Bogin and Smith, 2019), but it may not be as unique as commonly thought (Leigh, 1996; Ellison et al., 2012).

Many catarrhine primates, especially males, exhibit increased weight gain around puberty in captivity and in the wild (Leigh, 1996; Setchell et al., 2001; Altmann and Alberts, 2005; Huck et al., 2011; Bernstein et al., 2013). Additional studies suggest that primates exhibit growth spurts in specific bones, such as in the face or pelvis (Orlosky, 1982; Ellison et al., 2012). Where humans appear to stand out is in their consistent, rapid increase in limb length and stature during adolescence compared to other primates, including chimpanzees (Hamada and Udono, 2002). Several studies have reported minor growth spurts in nonhuman primates, especially in males (Gavan, 1953; Watts and Gavan, 1982; Tanner, 1990; Setchell et al., 2001; Hamada and Udono, 2002;Walker et al., 2006; Lu et al., 2016; Galbany et al., 2017), although the effect appears smaller than that of humans. Nevertheless, these data have forced proponents of the hypothesis that the growth spurt is uniquely human to refine their position: "...unlike humans, other primate species have either no pubertal acceleration in total skeletal growth or a very small increase in growth rate of the long bones" (Bernstein and Bogin, 2019: p. 44). Despite this reformulation, data on growth across the total skeleton in other primates, especially in the wild, are generally lacking.

The paucity of data is due, in large part, to methodological challenges. Measuring growth in free-living animals is challenging. In some species, animals are immobilized and captured to obtain weights and other measurements (Glander et al., 1991; Alberts and Altmann, 2012). Occasionally, it is possible to obtain mass by luring animals onto scales (Altmann and Alberts, 1987; Pusey et al., 2005; Fragaszy et al., 2016). But methods involving capturing or feeding pose a risk to animal health, and ethical considerations may preclude making direct measurements (Linda, 2010; Cunningham et al., 2015). Alternative technologies can estimate size noninvasively. These include digital photography combined with parallel lasers to estimate limb lengths and body areas (Rothman et al., 2008; Lu et al., 2016; Galbany et al., 2017; Wright et al., 2019, 2020; Sandel et al., 2022) and the use

of urinary creatinine as a proxy for muscle mass (Emery Thompson et al., 2012). None of these methods, however, assess overall bone growth, especially as measurements of body weight reflect both hard and soft tissue, and photographs of body parts often can only measure twodimensional size and fail to capture the overall accrual of bone.

Biochemical markers of bone turnover may be a useful method for assessing total body skeletal metabolism, including growth, in wild primates. Assessing overall bone growth requires capturing physiological metrics of bone turnover. Bone undergoes constant remodeling, with old bone being resorbed and new bone formed (Allen and Burr, 2013; Bolamperti et al., 2022). During growth (i.e., bone modeling), formation dominates resorption (Sims and Gooi, 2008). Biomarkers of bone formation and resorption are present as metabolites in serum and, importantly, in urine (Jürimäe, 2010), which can be collected noninvasively. An ideal biomarker of bone formation is osteocalcin, a small protein released during bone formation. It is expressed only in the bone and for this reason is a specific surrogate for bone metabolism. For example, measures of osteocalcin in urine have been shown to capture patterns of catch-up growth in preterm infants (Haley et al., 2012; Kilpeläinen et al., 2012). When bone resorption occurs, Type I collagen (hereafter 'collagen'), the most abundant protein in bone matrix, is released (Gunja-Smith and Boucek, 1981; Hanson et al., 1992). Short collagen fragments (both N- and C-terminal) excreted into urine have been used in humans to assess growth during adolescence and risk of osteoporosis (Bollen, 2000). Urinary biomarkers have not been widely used to assess growth rates in humans, as they appear to capture subtle variation within and between individuals less precisely than serum measures (Bollen and Eyre, 1994; Bollen, 2000; Ivaska et al., 2005). However, urinary biomarkers have been valuable in cases where drawing several blood samples or taking X-rays for bone density are risky or impractical, such as with human infants (Kilpeläinen et al., 2012).

Evidence from studies measuring osteocalcin and collagen in serum as well as urine indicate that their levels correspond to general trends in bone growth during human development (Szulc et al., 2000). For example, 11-year-old children with high serum levels of bone biomarkers exhibited high bone mineral content three years later (Kouda et al., 2017). Similarly, a cross-sectional study in humans found high levels of collagen biomarkers in infants, lower levels during childhood, and higher levels in adolescence than in either childhood or adulthood (Choi et al., 2019). The same study found a similar but muted pattern with osteocalcin. In another cross-sectional study of children and adolescents 7 to 19 years of age, serum osteocalcin peaked at mid-puberty and urinary osteocalcin peaked slightly earlier (Paldánius et al., 2021). Both serum and urinary markers then decreased toward adulthood. Urinary osteocalcin levels in this study correlated well with serum levels (Paldánius et al., 2021). Both osteocalcin and collagen are involved in other physiological processes, so they do not map perfectly onto patterns of skeletal growth. However, osteocalcin is generally associated with bone formation and collagen with bone resorption, making these two proteins important indicators of skeletal metabolism.

Given prior studies in humans, both urinary osteocalcin and collagen are promising biomarkers for assessing bone growth in wild, nonhuman primates. Urinary osteocalcin has never been assayed in nonhuman primates, but the protein is highly conserved across species (Nielsen-Marsh et al., 2005). Chimpanzee and human osteocalcin, in particular, are nearly identical proteins, differing in only one amino acid sequence. In addition, urinary biomarkers of collagen have been used in some primate species in clinical studies (Stroup et al., 2001; Smith et al., 2009; Hotchkiss et al., 2022) but, to our knowledge, have never been employed with wild primates. Combining bone biomarkers with other metrics of growth and size, including creatinine (Emery Thompson et al., 2012;

Machanda et al., 2015) and limb size (Sandel et al., 2022), will paint a more complete picture of growth in chimpanzees and other primates.

Here, we examine levels of osteocalcin and collagen fragments in urine to assess bone turnover in a large, cross-sectional sample of wild chimpanzees (*Pan troglodytes*). We do this to address two questions: 1) to determine when skeletal growth plateaus to provide an important metric of when adolescence ends and adulthood begins, and 2) to assess whether chimpanzees exhibit an adolescent spurt in overall skeletal growth. Chimpanzees are an ideal species to investigate the adolescent growth spurt, as they experience an unusually long adolescence. Adolescence begins with the onset of puberty, which is apparent in males from increases in testes size between eight and 10 years of age, and with the onset of sexual swellings in females between nine and 11 years of age (Pusey, 1990). Determining the end of adolescence and the beginning of adulthood, however, is less straightforward. Adulthood is often linked to social rather physical changes. Male chimpanzees in the wild are considered adults at around 16 years when they dominate adult females, become integrated into the social world of adults, and appear to reach full body size (Pusey, 1990; Muller et al., 2004; Reddy and Mitani, 2020; Sandel et al., 2022). Females are considered adults when they have their first offspring. Considerable variation in the timing of these events exists, however (Goodall, 1986; Walker et al., 2018). By providing information on the pace and timing of skeletal growth, this study will elucidate patterns of chimpanzee growth which are relevant to defining adolescence and adulthood and, ultimately to understanding hominin life history evolution.

2. Methods

2.1. Study site and subjects

The Ngogo chimpanzee population consists of approximately 200 individuals in the center of Kibale National Park, Uganda. The Ngogo chimpanzees are surrounded by other chimpanzee communities and have no contact with human settlements or farms. The chimpanzees occupy a habitat with abundant food compared to other sites (Chapman et al., 1999; Potts et al., 2011; Wood et al., 2017). Chimpanzees have been studied at Ngogo continuously since 1995 by John Mitani, David Watts, and a team of Ugandan and international collaborators including Mbabazi Godfrey, Ngandizi Lawrence, Tumusiime Alfred, and Kevin Langergraber (Watts, 2012). Ages are known to the nearest year or month for all chimpanzees born in the Ngogo community since the study began. Females who immigrated into Ngogo during the study were estimated to be 13 years old on the date of their arrival, following convention (Thompson, 2013). Ages for older adults are based on physical features and genetic relationships (Wood et al., 2017).

We collected data on 109 individuals from 2016 to 2018. We considered individuals to be infants prior to weaning (<5 years), juveniles once weaned (as indicated by the cessation of nursing and carrying and/or the birth of a new maternal sibling, 5 to < 9 years), and adolescents upon the emergence of secondary sexual characteristics (i.e., enlarged and visible testes in males or swelling of the genital skin of females, 9 to <16 years; (Goodall, 1986; Lonsdorf et al., 2020). Adolescence could be further divided into early/middle adolescence, when individuals predominantly traveled with their mothers or caregivers (9 to <12 years), and late adolescence (12 to <16 years), when individuals were predominantly independent from their mothers and appeared considerably larger, reaching the approximate height of adults (Reddy and Sandel, 2020; Sandel et al., 2022). We considered chimpanzees to be adults at age 16 years, or, for females, at age 16 years or as soon as they had given birth to their first offspring(Goodall, 1986; Walker et al., 2018). We considered chimpanzees to be old adults after 40 years (Thompson et al., 2020). Based on these criteria, our sample included 7

infants (median age = 3.0, range: 2.5 to 4.9 years), 21 juveniles (median age = 7.0, range: 5.1 to 8.9 years), 13 early/middle adolescents (median age =10.8 , range: 9.3 to 11.9 years), 16 late adolescents (median age =13.1 , range: 12 to 15.9 years), 17 young adults (median age = 18.2, range: 16.1 to 20.7 years), 22 middle-aged adults (median age = 27.7, range: 21.2 to 37.1 years), and 13 old adults (median age = 45.1, range: 40.2 to 66 years). These age categories are useful descriptors, and they informed our analytical decisions in some of our analyses (e.g., the number of breakpoints in the segmented regression, see below). However, we employed age as a continuous predictor variable in all of our analyses. Data are biased toward male individuals because urine samples were often collected during behavioral follows as part of a study on the transition to adulthood in male chimpanzees.

2.2. Urine collection

Urine was collected within minutes of the chimpanzees urinating. It was either pipetted from leaves, the ground, or caught in plastic bags when chimpanzees were in trees.Urine was only collected if researchers could identify the individual with 100% confidence. Urine was kept on ice during the day (from two to 10 hours), and then stored in a -20° C solar freezer. Samples were then shipped frozen to the University of Turku, Finland, using freezer-packs in a cooler (Yeti) and stored at -20° C until analysis. We complied with the ethical standards in the treatment of animals in this study, and received an exemption from the University Committee on Use and Care of Animals at the University of Michigan and the Institutional Animal Care and Use Committee at the University of Texas at Austin.

2.3. Assays

We assayed urinary biomarkers of bone formation and resorption in chimpanzee urine at the University of Turku, Finland. All samples were measured twice. To quantify bone formation, we measured the urinary mid-fragments of osteocalcin using the U-MidOC assay developed for measuring human bone metabolism (Ivaska et al., 2005). Two-site immunoassay is based on two monoclonal antibodies which bind to human osteocalcin at different regions, and antibodies were found to cross-react with chimpanzee osteocalcin. Calibrators (0.35–85 ng/ml) were derived from a synthetic peptide of human osteocalcin fragment of residues 1–43 (Advanced Chemtech, Louisville, KY, USA), and human urine samples were used as controls across assay plates. Measurements were done as described previously (Ivaska et al., 2005). In brief, a biotinylated capture antibody solution (bio-6F9, HyTest Ltd, Turku, Finalnd) was added to streptavidin-coated wells (Uniogen, Turku, Finland) and incubated for 30 minutes. Urine samples, standards, and controls were added together with a second labeled antibody (eu-3H8, HyTest Ltd, Turku, Finalnd) and incubated at room temperature for 120 min and washed six times. Finally, a Europium fluorescence intensifier (Uniogen, Turku, Finland) solution was added and incubated for 30 minutes, which dissociates Europium label allowing measurement of time-resolved fluorescence with a multimode microplate reader (Victor2, PerkinElmer). All incubations were done in Buffer Solution RED (Uniogen, Turku, Finland) on a plate shaker, and washing of the wells was done with Wash Solution (Uniogen, Turku, Finland). Preliminary results indicated that chimpanzee urine samples fell within the standard curve. For nine samples, osteocalcin was undetectable and an additional six were below the lowest standard.

Bone resorption was assayed by measuring collagen (cross-linked N-telopeptides of type I collagen, known as NTx) using a commercially available kit (OSTEOMARK® NTx Urine), which is a competitive-inhibition enzyme-linked immunosorbent assay. Assays were done according to

manufacturer's instructions. In brief, each plate was pre-coated with human collagen antigen. Urine samples, standards (1–3000 nM Bone Collagen Equivalents), and controls were added to wells, followed by a monoclonal antibody directed against NTx and conjugated with enzyme label. The collagen fragments in urine samples compete against the antibody for binding sites in the well resulting in inverse correlation between collagen levels in the urine sample and the measurement. After washing the wells, chromogen and substrate reagents were added for 15 minutes, followed by stop solution, and values were read by absorbance at 450nm (Victor2, PerkinElmer). Preliminary results indicated that chimpanzee samples fell within the standard curve. Samples exceeding the highest standard (3000 nM Bone Collagen Equivalents;) were diluted 1:2 (and up to 1:5) with a buffer solution and reanalyzed.

Based on control samples, we calculated within- and between-assay variation (coefficients of variance; CV%). For osteocalcin (assayed in 2018) the mean within-assay CV was 4.2% and the mean between-assay CV was 4.8%. For collagen, we used two control samples (low and high concentration), and assays were conducted in 2018 and 2021. The mean within-assay CVs were 7.0% and 3.1% (assayed in 2018) and 2.7% and 4.2% (assayed in 2021). The mean between-assay CVs were 19.9% and 21.5% (assayed in 2018) and 10.4% and 11.2% (assayed in 2021), respectively.

Since metabolites in urine vary based on how concentrated or dilute the urine is, we controlled for urine concentration using specific gravity (Haddow et al., 1994), which was recorded in the field using a handheld refractometer with a resolution of 0.001 (Atago PAL-10S). To calculate biomarker values, we removed particularly dilute samples (<1.003; Emery Thompson et al., 2012; $n = 27$) and outliers (>1.10; $n = 1$).

2.4. Statistical analyses

Statistical analyses were completed using R v. 4.1.2 (R Core Team, 2021). For both osteocalcin and collagen, we analyzed individual means and modeled nonlinear age-related variation in two ways: general additive models and segmented regression. We used two methods to increase confidence in detecting nonlinear patterns in the data, including peaks at certain ages. We transformed collagen and osteocalcin concentrations to approximate a normal residual distribution using the Box-Cox transformation (Box and Cox, 1964).

First, we used general additive models (GAMs), which are generalized linear models which allow for smooth nonlinearity in the predictors of a linear outcome (Wood, 2006). General additive models are preferable to other analytical approaches to studying nonlinear relationships—for instance, parametric polynomial regression, which requires the generation of many models, the application of model selection techniques, and clear assumptions about the form of a nonlinear relationship. Similarly, a LOESS curve, which uses weighted least squares modeling, requires that the user makes subjective specifications concerning model fit. General additive models, in contrast, do not require that the degree of the nonlinearity be specified beforehand and will generate predictor fits automatically, selecting the best fit for the data (Wood, 2006). In addition to other test statistics common to linear models (e.g., F and *p*-values), output of the 'gam' function in R package 'mgcv' includes a summary statistic entitled Estimated Degrees of Freedom (EDF), which indicates the degree to which a curve is nonlinear (Wood, 2006). A greater EDF indicates greater nonlinearity; a linear fit has an EDF of 1, and a substantially nonlinear fit has an EDF greater than 2.

We built GAMs fitted with restricted maximum likelihood using the 'gam' function in package 'mgcv' v. 1.8.38 (Wood, 2006); we included chimpanzee age (averaged across urine sample collection dates) as a cubic regression spline. To determine whether biomarker values were greater, equal, or lower in adolescence compared to infancy or juvenility, we extracted the age at which each

GAM peaked. To isolate periods of increase and decrease in each GAM (suggesting changes in growth trajectories), we calculated first derivatives using the 'derivatives' function in the 'gratia' package (Simpson, 2022). We defined periods of increase and decrease as those in which the first derivative's 95% confidence interval did not include 0.

In our second modeling method, we used segmented regression to identify breakpoints suggesting changes in growth trajectories. We used the 'lm' function to build linear models for each biomarker, and then used the 'segmented' function in package 'segmented' v. 1.4.1 (Muggeo, 2003, 2008) to estimate breakpoints. We instructed each model to estimate three break points to roughly approximate three developmental transitions: infancy to juvenility, juvenility to adolescence, and adolescence to adulthood.

We implemented three GAMs and three segmented regressions for each biomarker. In each model, the response variable was mean biomarker values, and the predictor variable was mean chimpanzee age. The first model included samples from both males and females. Initially, we included sex as a parametric predictor, but we removed this predictor from the final models, as it exhibited minimal effect on either collagen or osteocalcin levels. To then assess subtle sex biases in growth trajectories, we ran two additional models: one including samples only from males, and one with samples only from females. We performed model diagnostics by plotting residuals and using the functions 'gam.check' (for GAMs) and 'shapiro.test' (for segmented regressions). Alpha was set to 0.05.

3. Results

Bone turnover markers varied among individuals and by age. For qualitative comparisons, we summarize mean values for different age classes. Mean osteocalcin levels (ng/ml corrected for specific gravity ±SE) were higher among infants (0.26 ± 0.07), juveniles (0.33 ± 0.04), and early adolescents (0.32 ± 0.03) compared to late adolescents (0.20 ± 0.03), young adults (0.14 ± 0.02), middle-aged adults (0.14 ± 0.03), and old adults (0.08 ± 0.03). Similarly, collagen mean levels (nM corrected for specific gravity ±SE) were generally higher among infants (27.2 ± 4.5), juveniles (32.7 ± 3.3), early adolescents (40.5 ± 5.1), and late adolescents (32.9 ± 5.2) compared to young adults (17.6 ± 1.9), middle-aged adults (13.1 ± 1.2), and old adults (15.3 ± 3.0). Notably, early adolescents exhibited the highest levels of collagen, with mean values exceeding those of infants.

Using GAMs to examine average biomarker values for all 109 chimpanzees, we found that both osteocalcin and collagen exhibited highly nonlinear relationships with age (Tables 1 and 2; Fig. 1). General additive model fits for collagen and osteocalcin peaked at 10.1 years and 8.0 years, respectively (Tables 1 and 2; Fig. 1). The 95% confidence intervals of the first derivatives of each model indicated periods of decrease from 10.4 to 16.5 years as well as 29.9 to 44.0 years for osteocalcin and 12.4 to 20.7 years for collagen (Tables 1 and 2; Fig. 1).

Separate GAM fits for males and females suggested that the delayed decreases in both biomarkers observed in the pooled dataset were driven by males. Analyzed independently, male collagen values significantly increased from 4.5 to 8.9 years, peaked at 10.8 years, and decreased from 12.4 to 18.2 years (Fig. 2; Table 1). In contrast, female collagen levels peaked at 2.9 years and significantly decreased 6.7 to 29.6 years (Fig. 3; Table 1). Osteocalcin values exhibited similar patterns. Male values peaked at 9.4 years and significantly decreased from 12.4–16.9 years whereas female values peaked at 2.9 years and significantly decreased from 4.2–34.6 years (Table 1; Fig. 2).

Results of segmented regressions largely mirrored patterns observed in GAMs (Table 2). For osteocalcin and collagen, males exhibited breakpoints at 11.6 and 12, respectively (Table 2). Segmented regression modeling indicated an increase in both biomarkers to approximately 11.5–12 years, after which values for both biomarkers decreased (Fig. 2). Curiously, for females, results of segmented regression differed more prominently from GAM results than for males. For females, segmented regression of collagen identified a peak breakpoint at 13.0 years (Table 2); the model fit increases to 13.0 years and decreases thereafter (Fig. 2). For osteocalcin, segmented regression yielded a peak breakpoint at 6.9 years (Table 2), after which the fit decreased into adulthood (Fig. 3).

A notable outlier in our study presented an unexpected and intriguing case study. A 29-year old male exhibited high osteocalcin levels comparable to that of infant chimpanzees. This male had a chronic, open infection from a snare injury on his hand received at a young age, which he rarely put pressure on, and which may have contributed to his small size. In 2015, the snare was removed, and the injury healed. His high levels of osteocalcin 2–3 years later may indicate bone formation associated with healing and subsequent load bearing (Fig. 4).

4. Discussion

We found evidence of a skeletal growth spurt during adolescence in a population of chimpanzees from Ngogo in Kibale National Park, Uganda. In a large, cross-sectional sample spanning a wide age range of wild chimpanzees, we found that two independent urinary markers of bone turnover—osteocalcin and collagen—exhibited peak levels around 9 to 10 years of age, which corresponds to early adolescence. High levels of urinary markers of bone turnover during early adolescence resembles the pattern found in humans (Szulc et al., 2000; Rauchenzauner et al., 2007;

Paldánius et al., 2021). The high levels during adolescence appeared to be driven by males in our sample, and when we separated the sample by sex, there were clear peaks for males in both biomarkers at age 9 or 10 years using two statistical methods. We did not have sufficient data on infants to assess changes from birth through infancy. Larger sample sizes are also required to determine whether juveniles exhibit comparable or faster growth than infants, which would contrast with the slowing of growth in weight and stature exhibited by human juveniles. Nevertheless, there was strong evidence from general additive models that collagen levels prominently increased from the start of the juvenile period to the start of adolescence, which is consistent with an adolescent growth spurt. This peak in skeletal growth occurs just prior to the attainment of adult stature. By 12 years of age, male chimpanzees at Ngogo appear to be within the adult range for limb lengths (Sandel et al., 2022), which is similar to findings from captivity (Gavan, 1953). We found that both bone turnover markers began to decrease at age 12 years in male chimpanzees and plateaued at 17 or 18 years. Given the large difference in size between early- and late-adolescent male chimpanzees (Fig. 4), it is not surprising that we detected a growth spurt in bone turnover. However, bone turnover reflects total bone metabolism, and thus is also capturing nonlinear growth, such as cross-sectional area.

Although we found compelling evidence for an adolescent growth spurt in males, the pattern for females was inconclusive. Our two statistical methods suggest different patterns among females: general additive models indicated a decrease in both biomarkers from infancy to adulthood, whereas segmented regressions suggested an adolescent peak for collagen and juvenile peak for osteocalcin. The discrepancy between the two models is likely due to our limited sample size for females, especially juvenile and adolescent females. Additionally, female patterns may be affected by more approximate age estimates due to chimpanzee dispersal patterns and individual variation in the timing of key life history events: first pregnancy and birth can occur any time between 11 and 22 years of

age (Walker et al., 2018), and we do not account for this variation in our analyses. Given the hint of an adolescent peak in collagen based on the segmented regression, we cannot dismiss the possibility of an adolescent growth spurt for females without a larger sample size.

4.1. Skeletal growth in chimpanzees

Our findings complement the few other studies that have investigated growth in chimpanzees. Data on growth spurts of limb lengths in chimpanzees have been indeterminate (Watts and Gavan, 1982; Hamada et al., 1996; Hamada and Udono, 2002). A longitudinal study of 12 chimpanzees living in a lab setting found a steady decrease in growth rates with age, but reanalysis of those same data found a small increase in growth around adolescence (Watts and Gavan, 1982); however, the magnitude of this increase was small, on the scale of several millimeters (Bogin, 2020b). A large, cross-sectional study of captive chimpanzees found no evidence for a growth spurt (Hamada et al., 1996), but a subsequent longitudinal study found mixed results. Five of 12 chimpanzees exhibited slow growth in stature as juveniles followed by rapid growth in adolescence (Hamada and Udono, 2002). The fact that some chimpanzees exhibited a spurt whereas others did not indicates that chimpanzee growth patterns are more variable, and potentially more flexible, than those of humans. For chimpanzees, an adolescent growth spurt may reflect a mechanism for achieving comparable adult body size in the face of variable environmental conditions earlier in life. This flexibility may explain why prior studies of captive chimpanzees have suggested that there is no growth spurt: given the variation in growth patterns and sizes of chimpanzees, cross-sectional studies may overlook growth spurts. Longitudinal data on urinary markers of bone metabolism will be necessary to confirm the existence of an adolescent growth spurt in the chimpanzee skeleton. However, our findings that early adolescent males exhibited higher bone turnover than their older or younger groupmates across

two independent biomarkers and two distinct statistical methods provide strong circumstantial evidence.

It is possible that the chimpanzees at Ngogo exhibit a different pattern of growth from that of other chimpanzee populations. For example, compared to the nearby Kanyawara community, Ngogo has abundant food resources (Chapman et al., 1999; Potts et al., 2011), which likely provide the Ngogo chimpanzees with greater energy balance (Emery Thompson et al., 2009) and long lives (Wood et al., 2017). Whereas the Kanyawara chimpanzees frequently eat the piths of terrestrial vegetation, the Ngogo chimpanzees have ample opportunities to eat fruits and figs regularly, and when they do eat vegetation it is often the protein-rich leaves of sapling Pterygota trees, rather than the low-quality pith of terrestrial herbaceous vegetation such as Acanthus (Watts et al., 2012; Carlson et al., 2013). Likely due to the abundant food available, the Ngogo chimpanzee community was much larger than any other chimpanzee group ever studied (Potts et al., 2011; Patterson et al., 2014; Wood et al., 2017). At the time of our study, the Ngogo chimpanzees had almost 200 individuals, including 30 adult males. Future work determining the quality of food per individual chimpanzee at Ngogo compared to other sites would be key for understanding energy availability relevant for growth. In addition, it would be worth testing whether the large number of chimpanzees influences growth through social and physiological pathways. Future studies of growth in chimpanzees would thus benefit from investigating social and ecological predictors of the pace of growth in chimpanzees.

4.2. Defining adolescence and a holistic perspective on growth

Adolescence has been a largely overlooked life history period in the animal world. Part of this is due to the important psychosocial changes during this period for humans (Dahl et al., 2018), which may have led scholars to conflate this life history stage with the important psychological and cultural

changes that occur during human adolescence. In addition, several key studies in human biology have defined adolescence as the growth spurt itself (Bogin, 1999). A more appropriate definition of adolescence, however, should ground the definition based on life history theory, which defines life stages based on how energy is received from the environment and how it is spent on growth, maintenance, and reproduction (Bogin, 2020a, 2020b).

Life history theory accounts for how and when energy is devoted to growth during infancy and then shifted to reproduction in adulthood in the face of various sources of mortality. Body size is a key component of reproductive success and survival from predators, and it may be important to growrapidly or take a long time to grow as large as possible (Smith and Fretwell, 1974; Sibly and Brown, 2007, 2009). Although life history theory often simplifies development into infancy and adulthood, primates have protracted life stages between infancy and adulthood, juvenility and adolescence, when energy is still devoted to growth. Building on life history theory, we define adolescence as the period initiated by puberty and ending when growth plateaus. With this definition, animals may exhibit an adolescence regardless of whether they have an adolescence growth spurt (Hamada and Udono, 2002). Importantly, life history theory is focused less on growth per se and more on how energy is allocated across development. However, when considering human growth within a broader primate perspective, there may be an overemphasis on growth in stature.

Life history evolution is not about height; it is about energy (Bogin, 2020b). For example, humans appear to invest incredibly high ‘total energy’ during infancy, but they do so incrementally less as they develop (Pontzer et al., 2021). There is no increase in total energy expenditure around puberty (Pontzer et al., 2021). Thus, there may be energetic trade-offs occurring during development allowing for rapid growth during that time in humans, which could relate to the allocation of energy to different organs in the body or changes in diet and activity (Kuzawa et al., 2014; Pontzer and

McGrosky, 2022). Future work should reconcile patterns of growth with energy expenditure (Pontzer et al., 2021). Doing so will enable adequate tests of hypotheses for the evolution of growth spurts

4.3. The value of urinary markers of growth

Bone biomarkers represent a useful addition to other measures of growth, size, and energy metabolism. Although urine is somewhat difficult to collect, it is easier in many respects than other noninvasive methods of assessing growth, such as digital photography with parallel laser devices (Sandel et al., 2022). Bone biomarkers are valuable as they represent a snapshot of bone turnover and allow for cross-sectional metrics of growth. Bone biomarkers are also advantageous as they capture overall bone turnover, which may be especially important for understanding how energy is allocated to growth. Other methods, such as photogrammetry or even the rare case where hand measurements can be made, only assess the lengths and area of limbs and other body parts. Finally, bone biomarkers are potentially useful metrics for understanding health, including assessing osteoporosis later in life, and understanding how the skeleton responds in real time to environmental conditions (Ivaska et al., 2005). For example, our finding that a 29-year-old chimpanzee who had a wire snare removed from his hand 2e3 years before the study had osteocalcin levels comparable to those of infants in the same sample parallels findings in humans that bone biomarker levels are elevated for at least 1 year following fracture (Emami et al., 1999; Obrant et al., 2005). With this in mind, there are numerous questions related to health and skeletal physiology that could be addressed using urinary markers of bone turnover. Hoes does habitat heterogeneity influence variation in skeletal growth within populations? How does stress influence skeletal growth during development and bone health during aging? When can an animal be considered fully grown, and to what extent does that align with social metrics of adulthood?

5. Conclusions

Humans have long been considered unique in experiencing a growth spurt during adolescence. Humans may stand out in their consistent, rapid period of growth in multiple dimensions for both males and females during adolescence. Considering this growth pattern unique, however, is premature, as comparable data and analyses on nonhuman species are still lacking. This is the first study to evaluate bone metabolism in wild chimpanzees and, to our knowledge, any wild primate. Urinary biomarkers represent a promising method for comparing growth patterns noninvasively across species. These methods can complement studies of growth from wild skeletal remains (Mcfarlin et al., 2008, 2016; Ruff et al., 2013), photographic measures of body size (Galbany et al., 2016; Lu et al., 2016), and hand measurements of size when available (Pusey et al., 2005). It remains unclear why certain species tend to exhibit a rapid period of growth around adolescence. Could the growth spurt relate to rapid brain growth during infancy, terrestriality, or sexual size dimorphism? More comprehensive longitudinal data are needed to consider these functional explanations for adolescent growth spurts in humans and other animals.

Declaration of competing interest

The authors have no conflicts of interest.

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Author contributions

A.A.S. conceptualized the study, acquired funding, collected data, supervised data collection, assayed samples, analyzed data, and wrote the paper. J.D.N. collected data, supervised data collection, acquired funding, analyzed data, and wrote the paper. M.A. assayed samples and edited the paper. I.R.C. collected data, assayed samples, and edited the paper. J.B.C. collected data and edited the paper. R.B.R. supervised data collection, acquired funding, and edited the paper. K.K.I. designed methods, assayed samples, supervised methods, acquired funding, and edited the paper.

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Figure Legends

Figure 2. Biomarker levels in chimpanzees, including males and females. Collagen is an indicator of bone resorption and osteocalcin is an indicator of bone formation. We transformed collagen and osteocalcin values to approximate a normal residual distribution (Box and Cox, 1964). The solid blue lines (upper panels) represent the generalized additive models with confidence intervals as dashed lines; red lines (lower panels) represent segmented regressions. Dotted vertical lines are placed at age 5 years (end of infancy) and age 10 years (around early adolescence) to aid interpretation. (For interpretation of the references to color in this figure legend, the reader is referred to theWeb version of this article.)

Figure 2. Biomarker levels in male chimpanzees.We transformed collagen and osteocalcin values to approximate a normal residual distribution. The solid blue lines (upper panels) represent the generalized additive models (GAMs) with confidence intervals as dashed lines; red lines (bottom

panels) represent segmented regressions. Among male chimpanzees, GAMs and segmented regressions indicate peaks of both biomarkers in early adolescence (9.4e10.8 years). Dotted vertical lines are placed at age 5 years (end of infancy) and age 10 years (around early adolescence) to aid interpretation. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Figure 3. Biomarker levels in female chimpanzees. We transformed collagen and osteocalcin values to approximate a normal residual distribution. The solid blue lines (upper panels) represent the generalized additive models (GAMs) with confidence intervals as dashed lines; red lines (lower panels) represent segmented regression. Among female chimpanzees, GAMs suggest an incrementally lower turnover with age, but segmented regressions indicate a peak at 13 years for collagen and 7 years for osteocalcin. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Figure 4. Chimpanzees vary in size. A late adolescent male, Barron (top left) and his early adolescent maternal brother, Orff (top right) sit next to each other. Their older brother (bottom), an adult male, Garrett, is one of the smallest adult chimpanzees in the community, likely due to a chronic snare injury that was only able to be removed in 2015, when he was 26 years old. His osteocalcin levels were unusually high 2e3 years after the snare was removed and he began putting regular weight on his hand and upper limb.

Table 1

Results of general additive modeling assessing non-linear associations of collagen and osteocalcin with chimpanzee age.

Analyte	Subjects (*n*)	EDF	Reference DF	F	*p*-value	Age of peak fitted value	Periods of significant change[a]	
							Increase	Decrease
Collagen	All (109)	5.14	5.94	11.9	<0.001	10.05	NA	12.4–20.7
	Males (63)	5.52	6.40	10.1	<0.001	10.75	4.45–8.94	12.4–18.2
	Females (46)	2.08	2.56	6.80	0.001	2.93	NA	6.7–29.6
Osteocalcin	All (106)	5.37	6.17	11.01	<0.001	7.95	NA	10.4–16.5; 29.9–44.0
	Males (63)	4.52	5.36	3.63	0.005	9.41	NA	12.4–16.9
	Females (43)	2.71	3.26	16.4	<0.001	2.93	NA	4.20–34.6

EDF = estimated degrees of freedom. Indicates linearity of relationship between predictor and response variable.

[a]Ages at which the 95% confidence interval of the first derivative did not include 0.

Table 2

Results of segmented regression assessing nonlinear associations of collagen and osteocalcin with chimpanzee age.

Analyte	**Subjects (*n*)**	**Breakpoint 1**	**Breakpoint 2**	**Breakpoint 3**
Collagen	All (109)	4.4	11.6	18.5
	Males (63)	12.0	14.1	40.6
	Females (46)	13.0	18.7	NA
Osteocalcin	All (106)	4.7	12.0	13.4
	Males (63)	11.6	13.2	40.7
	Females (43)	6.9	13.9	47.1

Figure 1

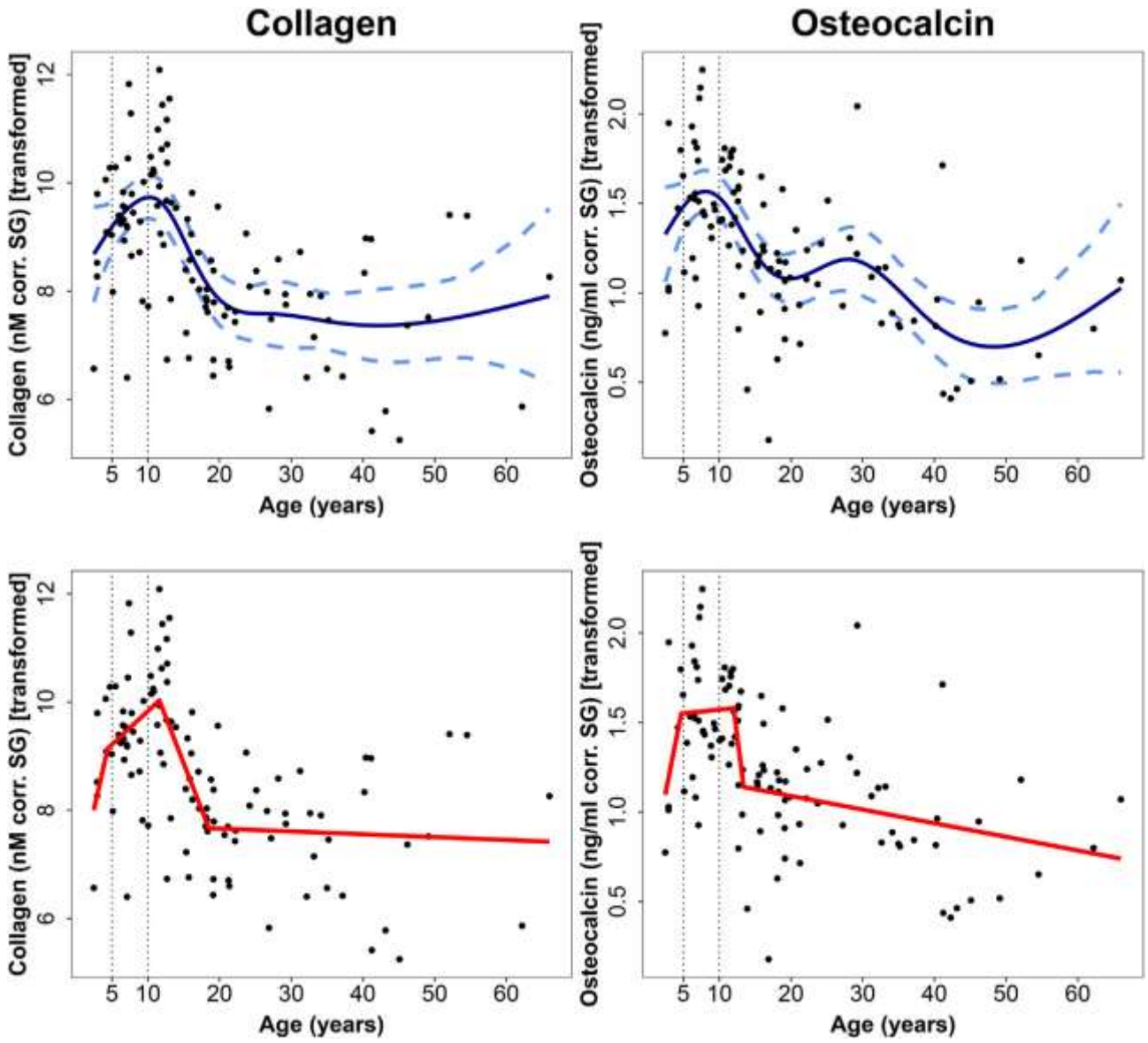
Collagen
Osteocalcin
Collagen (nM corr. SG) [transformed]
Osteocalcin (ng/ml corr. SG) [transformed]
Age (years)
5 10 20 30 40 50 60
6 8 10 12
0.5 1.0 1.5 2.0

Figure 2

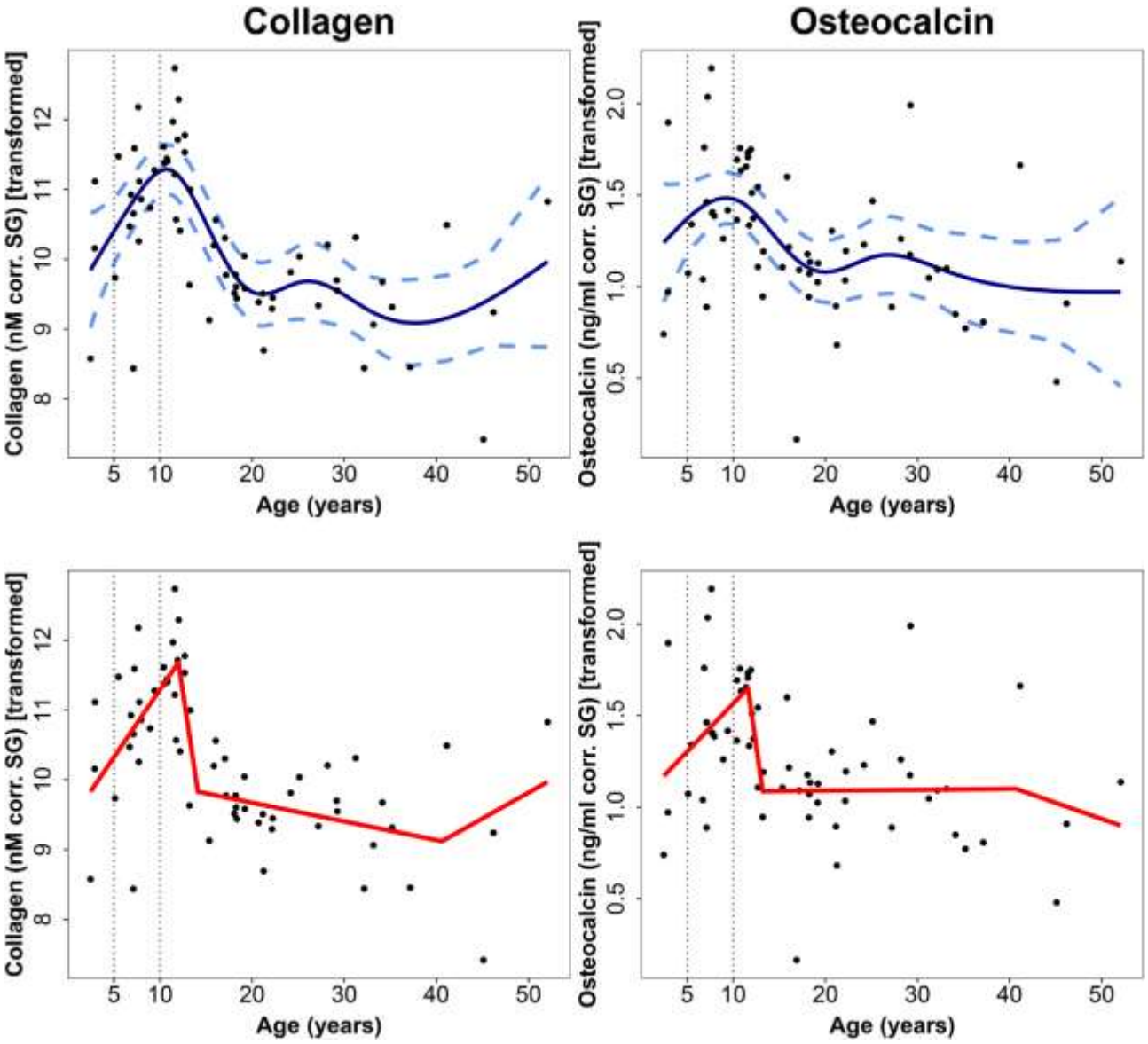
Collagen
Osteocalcin
Collagen (nM corr. SG) [transformed]
Osteocalcin (ng/ml corr. SG) [transformed]
Age (years)
5
10
20
30
40
50
8
9
10
11
12
0.5
1.0
1.5
2.0

Figure 3

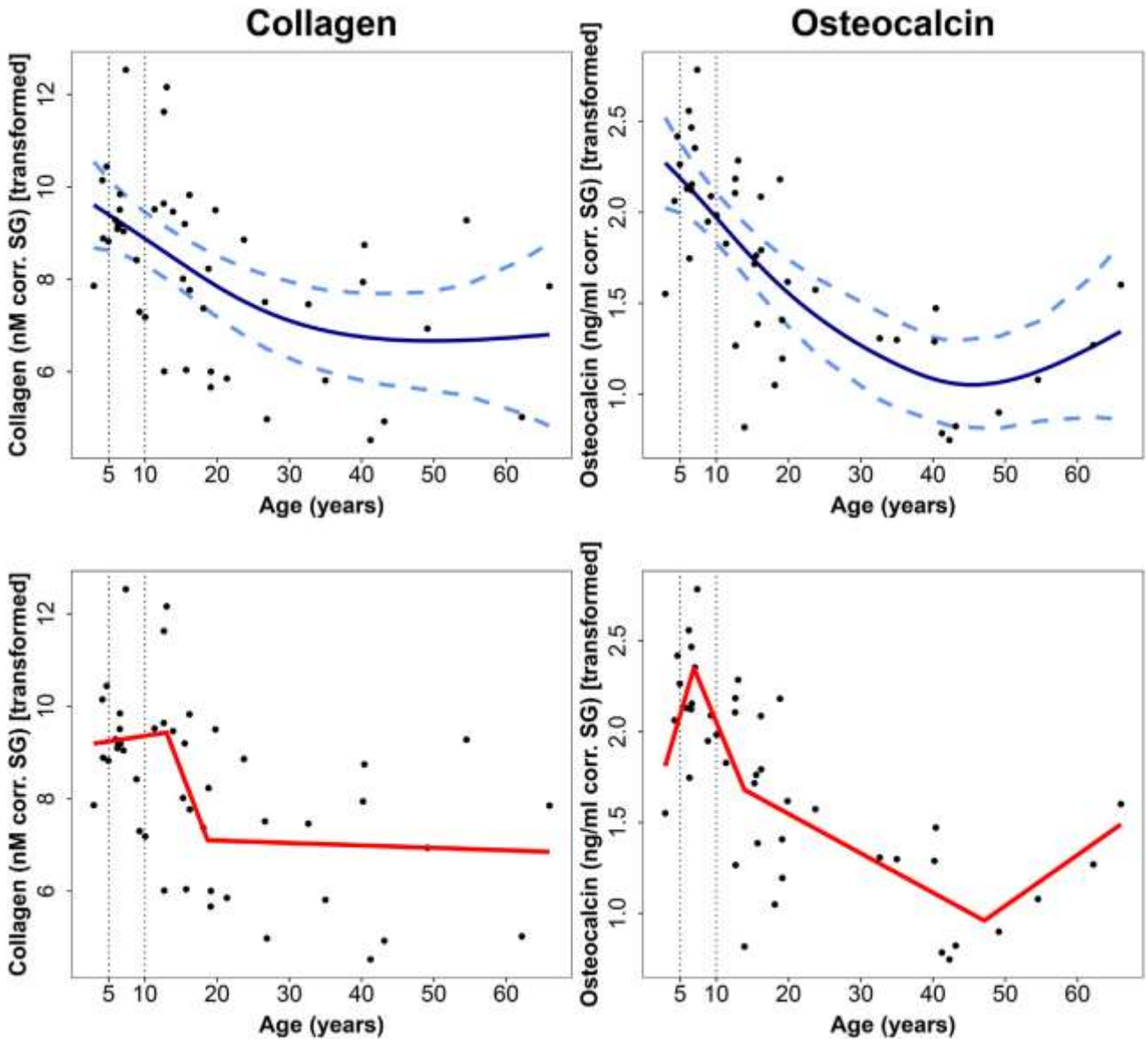
Collagen
Osteocalcin
Collagen (nM corr. SG) [transformed]
Osteocalcin (ng/ml corr. SG) [transformed]
Age (years)
5 10 20 30 40 50 60
6 8 10 12
1.0 1.5 2.0 2.5

Figure 4