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ORIGINAL ARTICLE

Dehydroepiandrosterone-sulfate (DHEA-S), sex, and age in zoo-housed western lowland gorillas (*Gorilla gorilla gorilla*)

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Abstract Among humans, dehydroepiandrosterone-sulfate (DHEA-S) declines with age and is hypothesized to be involved in somatic maintenance and healthy aging. Men have significantly higher DHEA-S than women, contradicting longer lifespans in the latter. Declines of DHEA-S with age also are observed in chimpanzees. In both chimpanzees and bonobos, males and females show no differences in DHEA-S production. Based on human and chimpanzee data, gorillas were predicted to show declining DHEA-S with age. Similar to chimpanzees and bonobos, it also was predicted DHEA-S would not be significantly different between males and females. DHEA-S was assayed from serum banked during physical examinations of gorillas housed at three North American zoos ($n = 63$). Gorillas ranged from 6 to 52 years of age. Differences between males and females were examined using t tests. Linear regression was used to determine the relationship of DHEA-S with age. There was no significant difference in DHEA-S between males and females. Additionally, there was no significant relationship between DHEA-S and age. As predicted, there were no sex-based differences in DHEA-S in gorillas, which is similar to chimpanzees and bonobos but different from modern humans. Unlike chimpanzees and humans, there was no significant relationship between DHEA-S and age in gorillas. The absence of a relationship between age and DHEA-S may be due to the lack of gorillas under age 6 years in this sample as declines in chimpanzees occur prior to age 5 years, more rapid growth and development among gorillas compared with other African hominoids, or a unique pattern of DHEA-S production.

Keywords Great apes · Captivity · Aging · HPA axis

Introduction

Dehydroepiandrosterone (DHEA) and its sulfate ester, dehydroepiandrosterone-sulfate (DHEA-S), are the most abundant steroids in the human body (Orentreich et al. 1984; Barrett-Connor et al. 1986; Šulcová et al. 1997; Gordon et al. 1999; Beishuizen et al. 2002; Conley et al. 2004; Tagawa et al. 2004; Blevins et al. 2013). Produced and secreted by the adrenal cortex (Orentreich et al. 1984; Barrett-Connor et al. 1986; Šulcová et al. 1997; Gordon et al. 1999; Conley et al. 2004), DHEA-S is considered a reservoir for DHEA due to its higher concentrations and longer half-life (Blevins et al. 2013). DHEA-S plays a role in vertebrate stress responses. When the hypothalamic–pituitary–adrenal (HPA) axis is activated, corticotropin-releasing hormone (CRH) stimulates release of adrenocorticotropin hormone (ACTH) into circulation (Seaward 2006; Nelson 2011; Everly and Lating 2013). The adrenal cortex simultaneously releases glucocorticoids and DHEA-S in response to ACTH (Barrett-Connor et al. 1986). DHEA-S is a glucocorticoid antagonist (Svec and Lopez 1989; Seeman et al. 1997; McEwen 2004; Singer et al. 2004; Buford and Willoughby 2008), and while many of its functions remain unknown (Nelson 2011), it likely plays a protective role against some of the damaging effects of prolonged glucocorticoid exposure; For example, DHEA-S may protect hippocampal neurons from damage (Bastianetto et al. 1999) and/or enhance immune function

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(Beishuizen et al. 2002; Tagawa et al. 2004; Buford and Willoughby 2008).

In humans, basal DHEA-S varies by life history stage (Fig. 1; Orentreich et al. 1984; Barrett-Connor et al. 1986; Šulcová et al. 1997; Gordon et al. 1999; Butcher et al. 2005). Plasma DHEA-S is high in neonates, falls within months of birth, and remains low until approximately age 7 years. DHEA-S then increases during adrenarche, peaks between ages 15–25 years, and finally decreases steadily after the third decade of life. Multiple studies report declining DHEA-S with age in humans, suggesting these declines may be involved in loss of somatic maintenance while higher DHEA-S likely promotes healthy aging (Orentreich et al. 1984; Barrett-Connor et al. 1986; Labrie et al. 1997; Šulcová et al. 1997; Parker et al. 2000; Poršová-Dutoit et al. 2000; Giordano et al. 2001; Mazat et al. 2001; Enomoto et al. 2008). Research documents relationships of low DHEA-S with bone loss, atherosclerosis, systemic lupus, coronary heart disease, obesity, cancer, diabetes, and immune disorders (Gordon et al. 1999; Poršová-Dutoit et al. 2000). In addition, DHEA-S is associated with parameters of well-being, cognition, memory, and sleep patterns (Gordon et al. 1999).

Sex differences in DHEA-S emerge during adulthood (Behringer et al. 2012), with men consistently showing higher circulating DHEA-S than women (Orentreich et al. 1984; Barrett-Connor and Goodman-Gruen 1995; Labrie et al. 1997; Šulcová et al. 1997; Poršová-Dutoit et al. 2000; Mazat et al. 2001; Enomoto et al. 2008). As higher DHEA-S may promote better health, higher DHEA-S in men contradicts their shorter lifespans. However, as a precursor to testosterone (Longcope 1996), sex differences in adrenal steroid production may explain differences in DHEA-S levels between men and women. It has been suggested higher DHEA-S concentrations are protective against cardiovascular pathology in men but not women (Barrett-Connor and Goodman-Gruen 1995; Poršová-Dutoit et al. 2000). In addition, Mazat et al. (2001) reported DHEA-S and mortality risk are inversely related in men but not women.

Only humans and a few other primate species are characterized by having adrenals that produce large amounts of DHEA-S (Labrie et al. 1997; Conley et al. 2004). While basic data on DHEA-S are lacking for most species, two postulates for the relatively high DHEA-S production unique to primates have been suggested. First, that high production of DHEA-S is related to the relatively long lifespans observed among nonhuman primates (Conley et al. 2004). Second, that nonhuman primates experience age-related patterns of DHEA-S production similar to humans (Blevins et al. 2013). For example, recent reports on chimpanzees (*Pan troglodytes*; Bernstein et al. 2012), bonobos (*Pan paniscus*; Behringer et al. 2012), and gorillas (*Gorilla gorilla*; Bernstein et al. 2012) suggest all experience adrenarche. In rhesus (*Macaca mulatta*) and pig-tailed (*M. nemestrina*) macaques, DHEA-S declines from ages 4–5 years throughout later life (Muehlenbein et al. 2002). Wild chimpanzees also exhibit declining DHEA-S with age, with the most dramatic decreases occurring from infancy to age 5 years (Seraphin et al. 2008). These data suggest great apes and even cercopithecoids exhibit declines in DHEA-S with age. However, the fact that these declines occur dramatically at much earlier ages than in humans may help explain why nonhuman primates show signs of senescence while still reproducing and, on average, do not live long after their fertile years (Blevins et al. 2013).

Comparing women and female chimpanzees, Blevins et al. (2013) observed DHEA-S declined more gradually in chimpanzees, but that chimpanzees produced only approximately half the DHEA-S as women. DHEA-S concentrations in women did not decrease below the

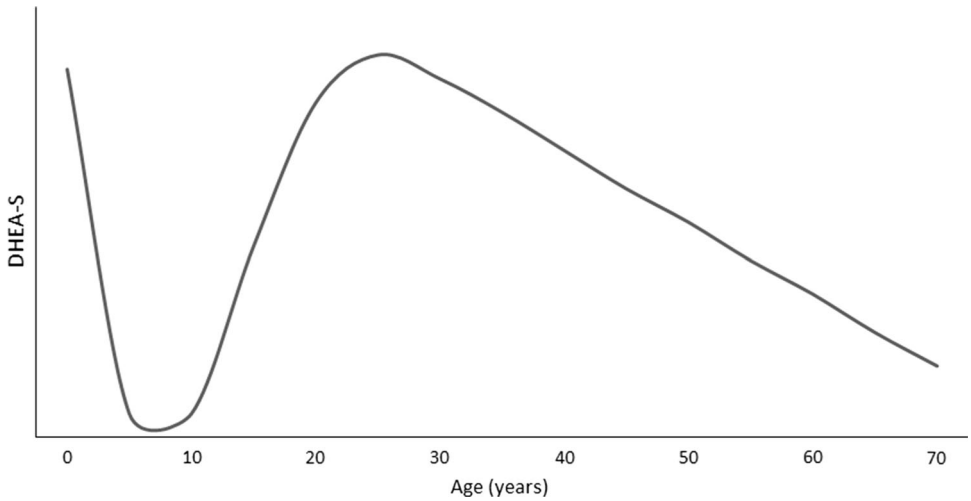

Fig. 1 Basal DHEA-S varies by age in humans

highest level reported for chimpanzee females until after age 65 years (Blevins et al. 2013), which may partially explain extended lifespans in humans. The differences are even greater for other apes, with gorillas having only 34 % the DHEA-S concentration of *Pan*, and orangutans (*Pongo*) being even lower, only 16 % the concentration of *Pan* (Bernstein et al. 2012). Interestingly, research has not documented significant differences in DHEA-S between male and female chimpanzees (Bernstein et al. 2012) or bonobos (Behringer et al. 2012), a characteristic similar to that seen among human children.

Unfortunately, data are few or missing for examining relationships of DHEA-S with age and sex in many non-human primate species, including gorillas. For example, at the time of this submission, the Species 360 database (formerly International Species Information System) lacks physiological reference values of DHEA-S and only one published paper has reported a mean for DHEA-S in gorillas ($\bar{x} = 22.76$ µg/dL, $n = 49$, ages 2–42 years; Bernstein et al. 2012). Based on recent research among chimpanzees and the well-documented human pattern of DHEA-S variation, it was hypothesized western lowland gorillas (*Gorilla gorilla gorilla*) would experience a gradual decline in DHEA-S with age. Furthermore, unlike adult humans but similar to *Pan*, no significant differences in circulating DHEA-S between male and female gorillas were predicted.

Methods

DHEA-S was assayed for 29 male and 34 female western lowland gorillas housed at the Columbus Zoo and Aquarium, Louisville Zoo, and Omaha's Henry Doorly Zoo. As there was no statistically significant difference in DHEA-S by location [analysis of variance (ANOVA): $p = 0.516$], all gorillas were combined into a single sample. This research was minimally invasive, as all serum was obtained from samples banked during previous anesthetizations for physical examinations. Research protocols adhered to legal requirements for conducting research within the United States of America and were approved by The Ohio State University Institutional Animal Care and Use Committee (IACUC). Columbus Zoo and Aquarium, Louisville Zoo, and Omaha's Henry Doorly Zoo are accredited by the Association of Zoos & Aquariums (AZA). The gorillas ranged from 6 to 52 years of age [$\bar{x} = 22.76$, standard deviation (SD) 12.79 years; Fig. 2] at time of sampling. Males and females were not significantly different in age (*t* test: $p = 0.480$). After collection during physical examinations, serum samples were immediately stored at −70 °C. Because not all gorillas experienced physical examinations at the same time, samples were kept in storage for varying durations. The earliest sample was collected during an examination in April 1991, and the most recent sample was collected in July 2015. Assaying DHEA-S from frozen sera is consistent with other studies reporting DHEA-S in nonhuman primates (Bernstein et al. 2012). Among humans, the majority of studies completed assays using fresh sera (e.g., Labrie et al. 1997; Šulcová et al. 1997; Parker et al. 2000; Giordano et al. 2001; Enomoto et al. 2008), although others processed frozen sera. While degradation is possible with frozen storage, DHEA-S reportedly maintains its integrity when placed in long-term storage at −50 °C or lower (Orentreich et al. 1984; Harder 2012), and some human research has used frozen sera for assays (e.g., Barrett-Connor and Goodman-Gruen 1995; Mazat et al. 2001). There were no major

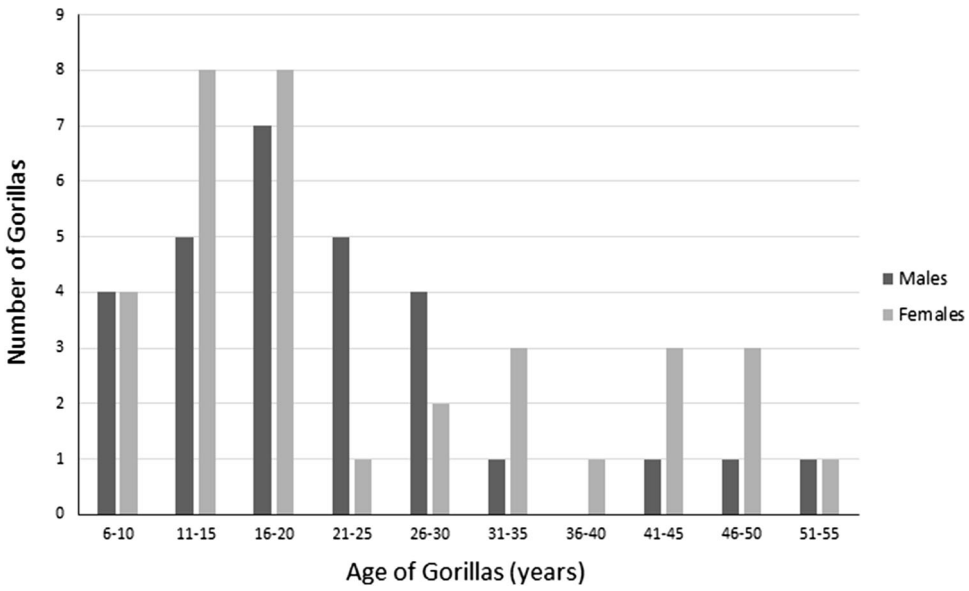

Fig. 2 Age distribution of male and female gorillas in 5-year intervals

changes in housing or husbandry conditions between when the first and last samples were collected at any of the three zoos. One sample was assayed per gorilla. Columbus Zoo and Aquarium gorilla sera were assayed in October 2014; Louisville Zoo and Omaha's Henry Doorly Zoo gorilla sera were assayed in June 2016. Samples were assayed by The Ohio State University Center for Clinical and Translation Science: Clinical Research Center (CRC). DHEA-S was measured using solid phase, competitive chemiluminescent enzyme immunoassay. Analytical sensitivity for DHEA-S was 3 μg/dL; intra-assay variation was 5.1 % for the low pool and 3.7 % for the high pool, and inter-assay variation was <7.9 %. The calibration range for DHEA-S was 15–1000 μg/dL. Differences in DHEA-S by sex were tested using *t* tests. Levine's test was used to determine whether the variance in DHEA-S was significantly different between males and females. Linear regression was used to examine the relationship between DHEA-S and age. DHEA-S values were positively skewed with four outliers, all from females. Two of the four outliers were extreme outliers. As there were no differences in outcomes when the dataset contained all outliers, they were retained in analyses unless otherwise mentioned. When DHEA-S values were log transformed to normalize the data, there also was no difference in results, therefore log-transformed analyses are not presented. All analyses were completed in SPSS 22.

Results

DHEA-S for all gorillas in the sample ranged from 15.0 to 172.0 μg/dL ($\bar{x} = 35.5$ μg/dL, SD = 30.5; Fig. 3). DHEA-S for female gorillas ranged from 15.0 to 172.0 μg/dL ($\bar{x} = 37.6$ μg/dL, SD = 38.9; maximum without outliers = 83.3 μg/dL), and DHEA-S for male gorillas ranged from 15.0 to 69.0 μg/dL ($\bar{x} = 33.1$ μg/dL, SD = 16.3). There was no significant difference in DHEA-S between males and females (*t* test: $p = 0.564$; Fig. 4). When outliers were retained, variance in DHEA-S in females was significantly larger than variance in DHEA-S in males (Levine's test: $p = 0.020$, $F = 5.681$). When the two extreme outliers were removed from the data, there was no significant difference in variance of DHEA-S between males and females (Levine's test: $p = 0.326$, $F = 0.981$). There was no significant relationship between age and DHEA-S (linear regression: $p = 0.769$, $R^2 = -0.015$; Fig. 5).

Discussion

These results confirm earlier reports that gorillas have lower average DHEA-S than *Pan* ($\bar{x} = 66.94$ μg/dL) but higher average DHEA-S than *Pongo* ($\bar{x} = 10.91$ μg/dL; Bernstein et al. 2012; see also Blevins et al. 2013).

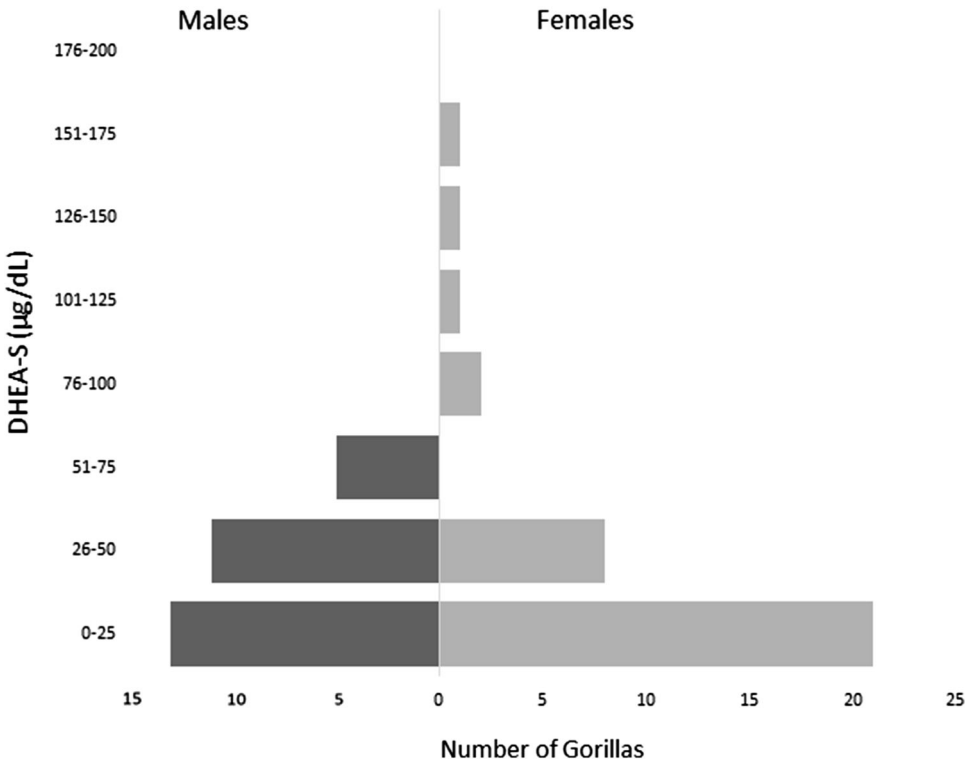

Fig. 3 Distribution of dehydroepiandrosterone-sulfate (DHEA-S) in male and female zoo-housed western lowland gorillas (aged 6–52 years)

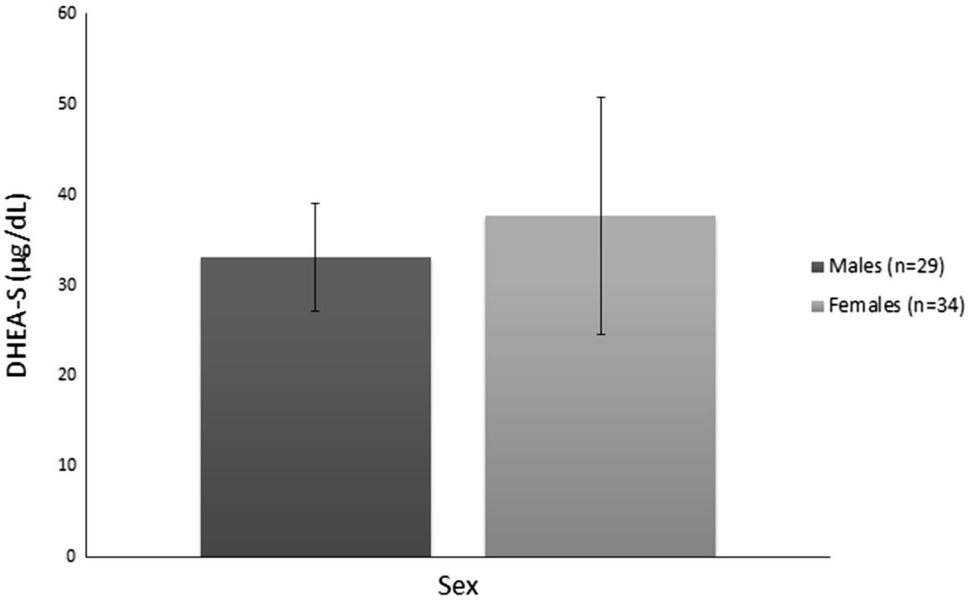

Fig. 4 Average dehydroepiandrosterone-sulfate (DHEA-S) of male and female zoo-housed western lowland gorillas (aged 6–52 years). *Error bars* represent 95 % confidence intervals

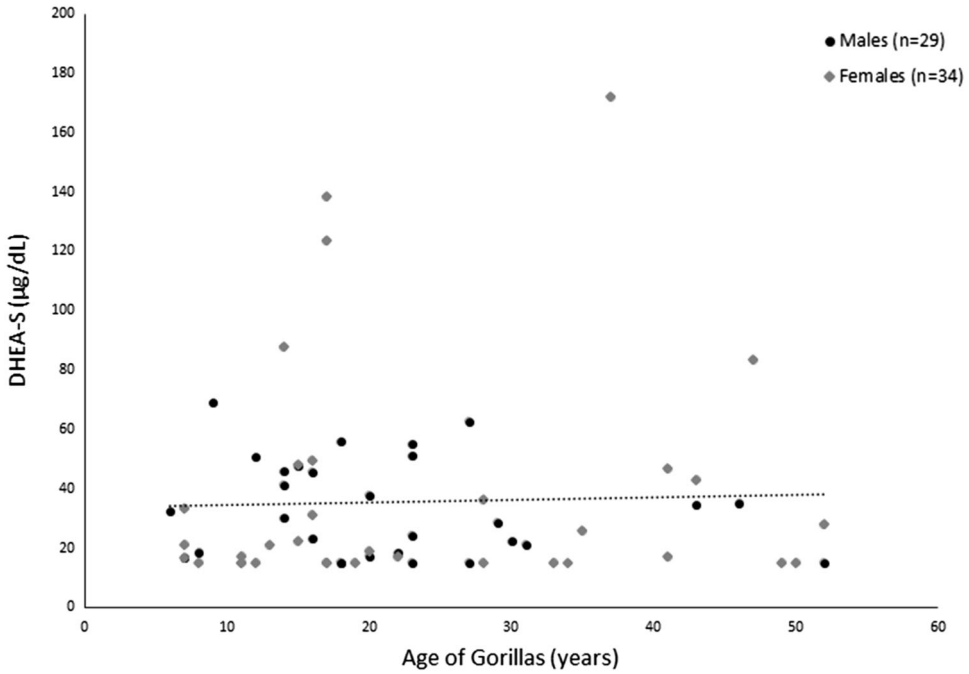

Fig. 5 Distribution of dehydroepiandrosterone-sulfate (DHEA-S) by age in zoo-housed western lowland gorillas. Regression is not significant ($p = 0.769$, $R^2 = -0.015$)

However, among these gorillas, average DHEA-S ($\bar{x} = 35.5$ µg/dL) was higher than the average previously published by Bernstein et al. (2012; $\bar{x} = 22.76$ µg/dL, $n = 49$, ages 2–42 years). As absolute values of both DHEA-S and testosterone (Hagey and Czekala 2003) in great apes are highest in humans, higher DHEA-S in *Homo* compared with other great apes may reflect its role as a testosterone precursor. Among humans, men have higher DHEA-S than women (Orentreich et al. 1984; Labrie et al. 1997; Šulcová et al. 1997; Mazat et al. 2001; Enomoto et al. 2008), whereas *Pan* does not exhibit a significant difference between males and females (Behringer et al. 2012; Bernstein et al. 2012). These results indicate gorillas also do not show a significant difference in DHEA-S by sex (Fig. 4), suggesting differential titers of DHEA-S between males and females is recently evolved in hominins.

Unlike humans (Orentreich et al. 1984; Labrie et al. 1997; Šulcová et al. 1997; Parker et al. 2000; Giordano et al. 2001; Mazat et al. 2001; Enomoto et al. 2008), chimpanzees (Seraphin et al. 2008; Bernstein et al. 2012; Blevins et al. 2013), and even macaques (Muehlenbein et al. 2002), gorillas do not appear to exhibit age-related declines in DHEA-S (Fig. 5). While the lack of relationship between DHEA-S and age among gorillas may be

related to their more rapid growth and development compared with chimpanzees and humans (Harcourt and Stewart 2007; Watts 2012), macaques develop more rapidly than any great ape and still show age-related declines. A possible explanation for the lack of association between DHEA-S and age in this sample may be that this sample does not include gorillas under 6 years of age. Given the largest declines in both macaques and chimpanzees occur prior to age 5 years, it is possible gorillas exhibit age-related decline in DHEA-S during early life. Sera for gorillas under 6 years of age are unavailable in this dataset. If these data accurately reflect the absence of age-related DHEA-S declines in *Gorilla* after age 6 years, additional data on *Pongo* also should demonstrate no relationship between DHEA-S and age. Conversely, if the lack of an age decline as reported here is due to the age range, then additional evidence may support its evolutionary conservation throughout catarrhines. Another possibility is that gorillas evolved a unique pattern of DHEA-S production in the 10 million years since they diverged from other African apes (Schaefer and Steklis 2014).

The distribution of DHEA-S in this sample of gorillas is unexpected (Fig. 3). Because DHEA-S is a glucocorticoid antagonist, high levels are generally considered a sign of well-adapted physiology whereas low levels may indicate severe and/or chronic stressors or pathology (Svec and Lopez 1989; Poršová-Dutoit et al. 2000; Beishuizen et al. 2002; Goldman et al. 2005; Marik 2009; Nelson 2011). Therefore, healthy animals are expected to have high DHEA-S. However, if DHEA-S increases in direct relation to cortisol, higher DHEA-S may actually reflect experiencing substantial stressors. Cortisol and DHEA-S assayed from the same serum samples were significantly positively associated ($p < 0.001$; $R^2 = 0.313$). Correspondingly, each female with an outlier DHEA-S value was experiencing an event that would likely be perceived as stressful. For two females, serum was obtained during anesthetization immediately following parturition. In women, DHEA-S declines steadily during pregnancy to suppress the maternal immune system (Nieschlag et al. 1974; Bird et al. 1980; Tagawa et al. 2004), but increases significantly during the stressor of parturition (Rivarola et al. 1968). When measured at a second date when neither female was pregnant, DHEA-S values were within the range reported with outliers excluded. The two other females with outlying DHEA-S values were experiencing severe, chronic illness. In humans, DHEA-S is depressed during acute phases of illnesses (Marik 2009) and in patients with multiple traumas and septic shock (Beishuizen et al. 2002), but the stressor of chronic illness may itself promote increased DHEA-S in response to the continued output of cortisol. In one of these females, DHEA-S measured at a second time point when she was without illness was within the reported range without outliers. For the other female, no second DHEA-S measure was available.

While a strength of this research is the broad upper age range of animals included, a limitation is the lack of samples for gorillas under 6 years of age. Bernstein et al. (2012) reported gorillas go through a transient increase in DHEA-S prior to sexual maturation, although it is a modest increase by *Pan* standards. Additionally, in chimpanzees the most substantial age-related decline in DHEA-S occurs between birth and age 5 years (Seraphin et al. 2008). It is possible gorillas exhibit a similar pattern of DHEA-S variation, with higher DHEA-S at birth followed by a rapid decline during early life. Following DHEA-S in a sample of gorillas from birth through late life is necessary to provide a complete understanding of DHEA-S variation across all gorilla life history stages.

This research provides evidence high DHEA-S and age-based fluctuations in circulating titers may be recently evolved among some hominins and catarrhines, respectively (Conley et al. 2004; Behringer et al. 2012; Bernstein et al. 2012; Blevins et al. 2013). While multiple primate species produce DHEA-S, many other mammals do not (Labrie et al. 1997; Conley et al. 2004). Although some features of DHEA-S production, such as adrenarche, appear to be homologous throughout African great apes (e.g., bonobos, chimpanzees, gorillas, and humans), sex-based differences in adults likely are a recent innovation in genus *Homo*. While the age range of the sample must be considered, these data suggest the significant age-related declines in DHEA-S observed in *Homo*, *Pan*, and *Macaca* may not be phylogenetically conserved throughout catarrhines. Alternatively, age-related declines in DHEA-S may occur before the age of 6 years in *Gorilla*, as has been observed in *Pan* and *Macaca*.

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Compliance with ethical standards

Conflict of interest I declare no conflict of interest.

Ethical approval All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted.

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