Title: Associations between social behavior and proinflammatory immune activation are modulated by age in a free-ranging primate population.

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Abstract

The effect of the social environment on the proinflammatory immune response may mediate the relationship between social environment and fitness, but remains understudied outside captive animals and human populations. Age can also influence both immune function and social behavior, and hence may modulate their relationships. This study investigates the role of social interactions in driving the concentrations of two urinary markers of proinflammatory immune activation, neopterin and suPAR, in a free-ranging population of rhesus macaques (*Macaca mulatta*). We collected 854 urine samples from 172 adult monkeys, and quantified how urinary suPAR and neopterin concentrations were related to affiliative behavior and agonistic behavior received over 60 days. In females, but not males, higher rates of affiliative interactions were associated with lower neopterin concentrations, while conversely, experiencing more agonistic interactions was associated with higher neopterin concentrations. The association between affiliation and neopterin concentrations was modulated by age, with older females experiencing a stronger negative association between affiliative behavior and neopterin concentrations. There were no associations between suPAR concentrations and social environment for either sex. This study demonstrates that proinflammatory immune activity is a potential mechanism mediating the association between social environment and fitness under naturalistic conditions, and that age can be an important modulator of the effect of social environment on the immune system.

Key words: neopterin, suPAR, sociality, rhesus macaque, aging, immune response, affiliation, agonism, social buffering

Introduction

The quality and quantity of social interactions an individual experiences (the social environment) is found to be associated with individual fitness across a range of taxa including in group-living

bird species (Lewis et al., 2007; Riehl & Strong, 2018), large herding mammals (Cameron et al., 2009; Wal et al., 2015), rodents (Siracusa et al., 2021), and primates (Brent et al., 2017a; Feldblum et al., 2021). Understanding how the social environment 'gets under the skin' to influence fitness is central to our understanding the evolution of social behavior. One of the postulated mechanisms that may mediate the association between social environment and fitness is through the effects of social environment on the immune system, and in particular, the influence of the social environment on proinflammatory immune activation (Coe, 1993; Eisenberger et al., 2017; K. J. Smith et al., 2020; Uchino, 2006). Proinflammatory immune activation is a normal defense reaction that serves to protect a host from infections developing following pathogen exposure (Ahmed, 2011; Laroux, 2004). However, chronic activation of proinflammatory components of the immune system can lead to chronic inflammation, which is associated with a wide variety of degenerative conditions, including cardiovascular disease (Golia et al., 2014; Libby, 2006), autoimmune diseases (Ishihara & Hirano, 2002), neurological disorders (Skaper et al., 2018), and cancers (Chai et al., 2015; Multhoff et al., 2012). High levels of inflammation is used as a key hallmark of aging and senescence (Dodig et al., 2019), and is also often used as a general indicator of individual health and disease status (Barzilay et al., 2001; Finch, 2007; Il'yasova et al., 2005; Strandberg & Tilvis, 2000). The relationship between proinflammatory immune activation and the social environment in human populations has garnered a great deal of research attention (Ahmed, 2011; Eisenberger et al., 2017; Laroux, 2004; C. E. Smith et al., 1994; Uchino, 2006). Social support, social integration, and affiliative relationships are generally associated with lower levels of inflammation in human studies (C. E. Smith et al., 1994; K. J. Smith et al., 2020; Uchino, 2006), as well as in experimental studies of captive nonhuman primates (Boccia et al., 1997; Coe, 1993; Cohen et al., 1992). However, there is a dearth of evidence from nonhuman or noncaptive populations that an affiliative social environment reduces proinflammatory immune activation (Snyder-Mackler et al., 2020). Consequently, the extent to which proinflammatory immune activation mediates the relationship between social environment and fitness, and thus plays a role in the evolution of sociality more broadly, is poorly understood.

It is not clear whether social environment will have the same effect on proinflammatory immune activity in wild animal populations as it does in humans and captive animal studies. Under naturalistic conditions, animals are likely directly in competition with social partners for food, mates, or other resources to a greater extent than we see in human populations living in high-income societies, or in captive animal studies where competition for resources is heavily reduced or removed, and the animals typically have access to veterinary care. Wild animals may face greater costs associated with social behavior compared to humans or captive animals as it may increase their competition for resources, as well as increase their risk of disease or pathogen transmission through social interactions (Balasubramaniam et al., 2019; Briard & Ezenwa, 2021; Habig et al., 2018; Kappeler et al., 2015; Lucatelli et al., 2021; MacIntosh et al., 2012). Consequently, it is unclear if positive social interactions might reduce inflammation in animals under natural conditions. Investigating the role of affiliative social interactions in modulating inflammation in nonhuman animals living under naturalistic conditions is necessary to evaluate if the relationship between social connection and inflammation seen in laboratory animals and humans may have adaptive evolutionary roots. Additionally, investigating this relationship in nonhuman primates living under naturalistic conditions would be especially valuable in helping

us understand the evolutionary history of a link between social support and inflammation in humans.

While an increase in affiliative social interactions may be associated with lower levels of inflammation, experiencing agonistic social interactions might have the opposite effect. In humans, experiencing a range of negative social environments, including bullying from peers (Copeland et al., 2014), conflict with friends and family (Song et al., 2015), and living in a community with a high risk of violence (Finegood et al., 2020), is associated with higher levels of chronic inflammation. In nonhuman animals, losing agonistic encounters (Kinsey et al., 2008; Stewart et al., 2015) and being of a low social rank (Sanchez Rosado et al., 2023; Snyder-Mackler et al., 2016) are both shown to be correlated with increased inflammation. Since increased exposure to conspecifics also inherently increases the likelihood of experiencing conflict and agonistic behavior in the wild (Altizer et al., 2003; Sah et al., 2018), investigating the role of both affiliative and agonistic social experiences on proinflammatory immune activation is necessary for understanding the mechanistic links between social environment and fitness.

Quantifying proinflammatory immune activation under naturalistic conditions can be challenging. Most direct measures of immune activation require invasive blood sampling (reviewed in (Peters et al., 2019)), which poses logistical and ethical challenges, especially for large mammal populations, where blood sampling often involves trapping and anesthetizing the animals. In recent years there has been an effort to validate urinary markers of proinflammatory immune activation in nonhuman primates to facilitate non-invasive measurement of immune functioning. These include urinary concentrations of neopterin (Higham et al., 2015), and soluble urokinase Plasminogen Activator Receptor (suPAR) (Higham et al., 2020), two compounds that are already well-established in human clinical settings to assess prognosis across a wide variety of conditions including viral infections (Andersen et al., 2008; Fuchs et al., 1988), parasitic infections (Brown et al., 1990; Ostrowski et al., 2005), malignant tumors (Liu et al., 2017; Sucher et al., 2010), and autoimmune diseases (Pliyev & Menshikov, 2010; Reibnegger et al., 1986). Both neopterin and suPAR are also good indicators of low-grade inflammation among otherwise healthy individuals (Capuron et al., 2014; Thunø et al., 2009). While neopterin and suPAR are both general indicators of proinflammatory immune signaling (Sucher et al., 2010; Thunø et al., 2009), correlations between the circulating levels of the two compounds are low to moderate in humans (Nyamweya et al., 2012; Tahar et al., 2016) and nonhuman primates (Cooper, Watowich, et al., 2022). This indicates that there are observable differences in the biological mechanisms driving the concentrations of these two compounds, and measuring both in tandem may provide a fuller picture of proinflammatory immune activation processes.

Associations between the social environment and inflammation might be substantially modulated by an individual's age due to age-related changes in the immune system (Capuron et al., 2014; Gruver et al., 2007), in other aspects of physiology (Giordano et al., 2005; Majnarić et al., 2021), and in social behavior (Lang & Carstensen, 1994; Rosati et al., 2020; Siracusa et al., 2022). There are sweeping changes to immune system signaling across adulthood, resulting in age-related declines in immune system competency and increases in inflammation, often referred to as immunosenescence (Capuron et al., 2014; Gruver et al., 2007). Associated with these age-related declines in the immune system, older individuals may have a greater inflammatory

response to agonistic social interactions (Kinsey et al., 2008). Additionally, age-related changes in the hypothalamic-pituitary-adrenal (HPA) axis response to stressors (Giordano et al., 2005) or reduced ability to maintain homeostasis with age (Majnarić et al., 2021) can heighten influences of an agonistic social environment on inflammation in older individuals. Social behavior also changes with age. Across a range of social species, including humans (Lang & Carstensen, 1994), nonhuman primates (Rosati et al., 2020; Siracusa et al., 2022), deer (Albery et al., 2022), whales (Weiss et al., 2021), and rodents (Kroeger et al., 2021; Weiss et al., 2021), individuals become more socially selective as they age, relying on fewer, but perhaps more meaningful, social connections. This change in the quality and quantity of social relationships with age may directly influence the effects of affiliative social behaviors on inflammation in older individuals. Despite the potential importance of age in modulating effects of both the social environment and inflammation, there is a dearth of empirical studies, and as such the effect of age in modulating associations between social environment and inflammation is poorly understood.

Rhesus macaques (*Macaca mulatta*) offer an excellent study system to investigate the role of social behavior on inflammation and to investigate how age might modulate this relationship. Rhesus macaques live in multi-male multi-female groups and form strong social bonds as well as strict dominance hierarchies within groups, resulting in frequent affiliative and agonistic interactions between group mates (Bernstein & Sharpe, 1966; Cooper, Brent, et al., 2022). All males rank above all females within a social group (Bernstein & Sharpe, 1966; Maestripieri, 2012). Importantly, affiliative relationships in rhesus macaques are known to positively affect individual fitness (Brent et al., 2013, 2017a; Ellis et al., 2019; Pavez-Fox et al., 2022), while low social rank and agonistic social interactions are known to negatively affect individual condition (Pavez-Fox et al., 2022; Sanchez Rosado et al., 2023; Snyder-Mackler et al., 2016). As such, rhesus macaques are an exceptional model system on which to explore if proinflammatory immune activation may be a mechanism linking the social environment and fitness under naturalistic conditions. Additionally, rhesus macaques are a good model species for understanding these processes in humans, given their phylogenetic similarities, and consequent similar physiology, immune system, and aging trajectories (Chiou et al., 2020). Rhesus macaques are a female philopatric species, and as such the social interactions of females are more kin-based and their social partners are more stable over long periods of time when compared to males (Kapsalis & Berman, 1996). It has been posited that the social environment may have greater fitness impacts on females than males in female philopatric primates (Sterck et al., 1997). Investigating the influence of social environment on immune functioning in both sexes separately offers the opportunity to investigate how sex differences in philopatry may relate to sex differences in the influence of the social environment on physiology, and ultimately, fitness.

In this study we aim to quantify the effects of recent affiliative and agonistic social interaction on proinflammatory immune-related processes in a free-ranging rhesus macaque population living under naturalistic conditions on Cayo Santiago, Puerto Rico. We sought to address relationships between urinary neopterin and suPAR with affiliation and agonism received, while addressing age-modulation of these relationships for males and females in each section.

Methods

Study Population

We studied a population of free-ranging rhesus macaques located on Cayo Santiago, a 15.2-hectare island off the southeastern coast of Puerto Rico. The population is entirely composed of the descendants of 409 wild-caught Indian rhesus macaques that were brought to the island for the purpose of behavioral research in 1938. Cayo Santiago is a naturalistic environment where the monkeys roam freely, form their own social groups, choose their own mates, and live and die with minimal intervention. The births, deaths, and movements between social groups of all individuals are tracked through census records maintained by the Caribbean Primate Research Centre (CPRC). The population is provided *ad libitum* access to drinking water. Their diet of wild-growing flora is supplemented by commercial monkey chow at a rate of 0.23 kg per animal per day. The current population size is approximately 1,600 individuals living in 6-9 mixed-sex social groups.

Data Collection

Trained field technicians collected urine samples from adults (ages 6 – 29 years) in 2 social groups in the population over a duration of 3 years (2020-2022). During these three years samples were collected by between two and six technicians opportunistically from focal individuals 5 days per week from the months of February through September, between the hours of 7:00 and 14:00. Unrelated to the present manuscript, some animals from the population were trapped and briefly anesthetized once a year for routine measurement including collecting blood samples and morphological measures. This trap-and-release protocol occurred on Cayo Santiago inclusive of the months of October through January each year. We did not collect urinary or behavioral data during these months in an effort to avoid the confound of any potential changes in behavior or immune activity associated directly with the animals experiencing these trap-and-release protocols. Immediately upon observation of a focal individual urinating, samples were collected from the ground or foliage using a disposable pipette, and then transferred to a vial and put on ice until transfer to a −80°C freezer at 2:30 p.m. Both urinary neopterin and suPAR are relatively robust to freeze-thaw cycles and prolonged periods above freezing making them well suited for this kind of field collection (Heistermann & Higham, 2015; Higham et al., 2020). Additionally, individual fluctuations in suPAR (Sier et al., 1999) and neopterin (Auzeby et al., 1989) concentrations across daylight hours are negligible, such that measurements occurring at any time during the day are comparable to one another, and researchers need not restrict their sample collection to a narrow window of time. For a detailed description of the collection, storage, and shipment of samples see (Cooper, Watowich, et al., 2022).

Behavioral data were collected by two trained field technicians over the same time periods that urine was collected. Behavioral data was collected using two methods, focal sampling and ad libitum observations. Focal sampling consisted of 10-minute focal animal samples where the behaviors of a single individual were recorded continuously (Altmann, 1974). Focal data collection was stratified to ensure equal sampling of individuals throughout the day and over the course of the year. During these focals, all social interactions that the focal individual experienced were recorded, including the duration of these experiences, and the identity of the other individual(s) involved in each social interaction. Affiliative social interactions included grooming and sustained passive physical contact with another individual (hereafter ‘huddling’).

Agonistic behaviors included physical attack with contact (e.g. biting, hitting, or pushing), physical attack without contact (e.g. lunging, charging, or chasing), threatening body language or verbalization (e.g. open mouth threat, stare threat, or threatening bark), and submissive body language (e.g. fear grin or displacement). With the exception of 'huddling' behavior, all social interactions had a 'giver' and a 'receiver', which were recorded. In addition to the 10-minute focal sampling, field technicians also recorded every time they observed an agonistic social interaction in the field between adults of the same sex as an ad libitum observation. Since agonistic interactions were recorded ad libitum exclusively when they occurred between same-sex pairs, our dataset on agonistic behaviors was biased towards same-sex agonism (as opposed to male-female agonism).

Immunoassays

We measured urinary neopterin and suPAR using commercial ELISA kits (neopterin: IBL International Cat. No. RE59321; suPAR: RayBiotech Cat. No. ELH-uPAR-1), performed according to the manufacturer's instructions for each. Both the neopterin kit (Higham et al., 2015) and the suPAR kit (Higham et al., 2020) have been previously described and analytically and biologically validated for use in rhesus macaques (Higham et al., 2015, 2020). Sample duplicates with a coefficient of variation (CV) greater than 15% were rerun, and >95% of samples had CVs below 10%. Samples were initially run at a 1:30 dilution for the neopterin assay, and undiluted for the suPAR assay. Samples which fell outside of the linear range of the assay were rerun at either twice or half the previous dilution value to bring the sample within the linear range of the assay standard curve. Inter-assay variation, determined by the CVs calculated by high- and low-value quality controls, was 12% (high) and 9% (low) for neopterin, and 15% (high) and 12% (low) for suPAR. Intra-assay CVs were less than 11% for neopterin, and less than 10% for suPAR. We corrected each sample for urine concentration by indexing neopterin and suPAR values to urinary creatinine concentrations, measured using the Jaffe reaction, as described elsewhere (Bahr et al., 2000).

Statistical Analysis

To measure affiliation, we considered the total duration of all affiliative behaviors (giving grooming, receiving grooming, and huddling with direct physical contact) recorded during all focal behavioral scans taken for an individual within the 60-day period prior to that individual's urine sample collection. Using this focal behavioral data, we divided the total duration of affiliative behavior by the total duration of focal observation for that individual to get the affiliation rate in the 60 days prior to sampling. If an individual had less than 10 minutes of focal data collected in the relevant 60-day period, that individual sample was excluded from analysis. The 60-day period was chosen because it allows for a sufficient amount of behavior to have been recorded, while also being a moderate time line over which to observe the influence of social environment on physiology. Each urine sample measurement had an average of 44 ± 18 (mean ± SD) minutes of focal data collected in the preceding 60 days. Since there can be a 1-15 day lag in urinary suPAR and neopterin response to physical injury or infection (Higham et al., 2015, 2020), the 60-day period effectively covers a period in which any effect of the social environment on urinary concentrations of neopterin and suPAR is likely to be captured. Rather than observing acute effects of a specific behavior on immune activity, our goal in this study was

to understand how average rates of affiliative and agonistic behaviors over the course of weeks influences average immune system functioning in that individual. The final sample size included 854 urine samples from 91 females and 81 males with paired focal sampling data. Since the urinary assay for suPAR required a larger urine volume than neopterin, we were not able to assay suPAR for a subset of the samples. Consequently, the final sample size for suPAR measurements included 683 urine samples from 82 females and 79 males.

We used mixed-effects linear regression models to quantify the effect of affiliation rate in predicting inflammation. We modelled the effects of affiliation on neopterin and suPAR for males and females separately, resulting in four total models. Inflammation marker concentrations were log-transformed prior to analysis in order to satisfy normality assumptions (i.e., so that residual variance was normally distributed). To control for the varied duration of total focal behavioral data collected across samples, we weighted observations in the model by duration of total focal data collected in the 60-day period as an unscaled absolute value (in minutes). Weighting observations in these models allows us to control for variance in sampling effort across time periods in this study. In addition to the variable affiliation rate, each model also included age at sample collection (calculated from a known birthday, accurate within a week), social group, dominance rank, and the interaction between age and affiliation rate as fixed effects. Affiliation rate and age were each standardized by centering values at 0 and dividing by their standard deviation prior analysis to facilitate interpretability of both the lower-order estimates for these terms, as well as the higher-order interaction estimates for these terms simultaneously. Dominance rank was established for a given year within each social group and within each sex by using the direction and outcome of agonistic and submissive interactions recorded across both focal sampling and ad libitum observations (Brent et al., 2013; Ellis et al., 2019). Rank was assigned as "high" (≥80% of other adults of the same sex dominated), "medium" (50 to 79% of other adults of the same sex dominated), or "low" (≤ 49% of other adults of the same sex dominated). Social group was a categorical variable denoting group membership to one of two social groups in the study (V or F). Individual identity and year were included as multilevel random effects. These effects controlled for the nonindependence of repeated measures of the same individual and for annual variation in immune marker means associated with differences in environmental conditions, respectively. In cases where a significant association between affiliation rate and an immune marker was found, we ran an additional mixed-effect linear regression model where we partitioned the model by types of affiliation (grooming given, grooming received, and huddling) in order to better understand the specific behaviors driving the association between affiliation rate and inflammation.

For each observation, we quantified agonism received as a count measure of the number of agonistic behaviors received as well as submissive behaviors given using both focal behavioral scan data and ad-libitum behavior data collected over the same length of time as affiliative behavior was quantified, the 60-day period prior to urine sampling. These behaviors included receiving a contact or non-contact physical attack, receiving threatening body language and/or verbalization, and giving submissive body language including a fear grimace and displacement behavior. Due to the global COVID-19 pandemic, behavioral sampling effort was lower during a substantial period of the year 2020 when compared to years 2021 and 2022. While this lower sampling effort could be controlled for in the measure of affiliation rate, which takes into account total focal behavior scan time, because our count measure of agonism received also

includes ad libitum observations of behavior, it is not possible to as precisely estimate sampling effort for each measure of agonism received. Consequently, we excluded urine measures collected in 2020 when modelling the relationship between immune markers and agonism received. The final sample size included 838 measures of neopterin from 92 females and 83 males with paired agonism data, and 678 measures of suPAR from 91 females and 79 males with paired agonism data.

We used mixed-effects linear regression models to quantify the effect of agonism received in predicting inflammation. Similar to the models for affiliation rate, we modelled the effects of agonism received on neopterin and suPAR for males and females separately, resulting in four total models. Inflammation marker concentrations were log-transformed prior to analysis in order to satisfy normality assumptions. In addition to the variable agonism received, each model also included age, social group, dominance rank, and the interaction between age and affiliation rate as fixed effects. Dominance rank is distinct from agonism received here in important ways. First, dominance rank considers both agonistic interactions received and given in determining rank placement. In contrast, our measure of agonism received is narrower in that it only considers agonistic interactions received (but not given). Second, dominance rank is calculated based on an entire year of social interactions, while agonism received only considers interactions within a 60-day period. Taken together, these differences between dominance rank and agonism received mean that agonism received is a more narrowly defined measure of agonistic interactions received in a recent period, while dominance rank more broadly reflects an individual's average place in the social hierarchy over a longer period. Dominance rank was not predictive of agonism received, and within each dominance category (i.e. 'high', 'medium', or 'low'), counts of agonism received varied considerably for both males and females (supplementary figure 1). We also reran all models including dominance rank quantified as the percentage of same-sex group members an individual held dominance status over within their social group, specified in models as a continuous variable. Similar to our models with rank specified as an ordinal variable, rank was not significant in any models, and this change did not influence the interpretation of any results. Full model results with the percentage dominated rank specified as a continuous variable are available in Supplementary Tables 1-4.

In cases where a significant association between agonism received and an immune marker was found, we ran an additional mixed-effect linear regression model where we partitioned the model by types of agonism in order to better understand the specific behaviors driving the association between agonism and inflammation. This model was equivalent to the original sex-specific model estimating neopterin concentration, except that we divided agonism into the three types of agonistic behavior measured in this study: severe agonism received, mild agonism received, and submissive behaviors. Severe agonism received included instances of being physically attacked by another adult individual including being bitten, being hit, being pushed, or grabbed. Severe agonism received also included attacks that resulted in no physical contact but had apparent attempted contact such as being lunged at, charged, or chased. Mild agonism received was characterized by instances of being threatened by another individual, without an escalation to a physical attack or attempted physical attack. Instances of mild agonism received included body language and vocal cues such as an open mouth and head bob while staring at the recipient, raising eyebrows while staring at the recipient, slapping the ground while staring at the recipient,

and threat vocalizations in the direction of the recipient. Submissive behaviors were distinct from other agonistic behaviors in that they were behaviors performed by the focal individual themselves, rather than a conspecific. These behaviors included displacement or submissive body language in response to the approach of a conspecific as well as submissive facial expressions such as a 'fear grimace' in response to the presence of a conspecific.
All analyses were conducted in R version 4.2.0 (R Core Team, 2022). We ran all models using the lme4 package (Bates et al., 2015). For all models, we calculated the variance inflation factor (VIF) for each covariate and found that VIFs for all covariates were below a value of 2.

Ethical Note

This research was conducted in accordance with The Association for the Study of Animal Behavior (ASAB) and The Animal Behavior Society (ABS) guidelines for the ethical treatment of animals, and all legal requirements of the countries in which the research took place, as well as institutional guidelines. The animals in this study are part of a well-studied population that have previously been habituated to human presence. Both behavioral observations and urine sample collection was done at a minimum distance of 1 meter from the animal(s). Urine was always collected opportunistically and field technicians waited until the animal had moved at least 1 meter away from the site of urination to safely collect the sample. This animal study was reviewed and approved by University of Puerto Rico, Institutional Animal Care and Use Committee (protocol number: A6850108).

Results

Both affiliation rate and agonism received were highly variable across the matched urine samples. For females, affiliation rate ranged from 0% to 48% of total focal behavioral scan time (mean 4%, standard deviation 8%), and for males, affiliation rate ranged from 0% to 89% of total focal behavioral scan time (mean 5%, standard deviation 12%). For females, agonism received ranged from 0 to 15 counts of agonistic behaviors received (mean 2.9, standard deviation 2.8), and for males, agonism received ranged from 0 to 12 counts of agonistic behaviors received (mean 2.1, standard deviation 2.1).

Female concentrations of both neopterin and suPAR had a higher mean and variance when compared to male concentrations. Female neopterin and suPAR concentrations each ranged across four orders of magnitude with mean concentrations of 238 ± 195 ng/mg creatinine for neopterin and 0.94 ± 2.36 ng/mg creatinine for suPAR. Among males, neopterin and suPAR concentrations each ranged across two orders of magnitude, with mean concentrations of 175 ± 130 ng/mg creatinine for neopterin and 0.39 ± 0.71 ng/mg creatinine for suPAR.

Affiliation

Among females, there was a significant negative association between neopterin concentrations and affiliation rate (β = -2.13, CI [-3.42, -0.84], p= 0.001, Table 1A), indicating that females that spent a higher proportion of their time over a 60-day period engaging in affiliative social behaviors have lower urinary neopterin concentrations. Additionally, there was a significant

negative interaction between affiliation and age in predicting female neopterin concentrations (β = -0.38, CI [-0.70, -0.06], p= 0.018, Table 1A). This interaction effect indicates that age modulated the relationship between affiliation and neopterin, wherein older females experienced a stronger effect of affiliative behavior reducing their neopterin concentrations when compared with younger females (Fig. 1). In contrast to females, among males, there was no association between neopterin and affiliation rate, and no interaction been affiliation rate and age in predicating neopterin concentrations (Table 1B). Overall, there was no association between affiliation rate and urinary suPAR concentrations in either males or females (Table 2).

Table 1 Model results from mixed-effect linear regressions predicting the influence of affiliation rate on log-transformed urinary neopterin concentrations for: (A) Females; and (B) Males. P-values < 0.05 are shown in bold.

Neopterin	**(A) Females**			**(B) Males**		
Predictors	Estimates	CI	p	Estimates	CI	P
Intercept	5.15	4.88 – 5.43	**<0.001**	4.97	4.76 – 5.18	**<0.001**
Affiliation rate	-2.13	-3.42 – -0.84	**0.001**	0.12	-1.12 – 1.37	0.847
Age	0.03	0.00 – 0.07	**0.033**	0.03	-0.01 – 0.07	0.128
Group [V]	0.00	-0.30 – 0.30	0.996	-0.15	-0.43 – 0.13	0.298
Rank [Low]	0.01	-0.31 – 0.34	0.931	-0.10	-0.43 – 0.24	0.561
Rank [Medium]	-0.13	-0.46 – 0.20	0.440	-0.15	-0.44 – 0.15	0.325
Affiliation:Age	-0.38	-0.70 – -0.06	**0.018**	0.17	-0.17 – 0.51	0.331
Random Effects						
σ^2	0.06			0.06		
τ_{00}	0.25 $_{\text{MonkeyID}}$			0.09 $_{\text{MonkeyID}}$		
	0.00 $_{\text{collectionYear}}$			0.00 $_{\text{collectionYear}}$		
ICC	0.06			0.03		
N	91 $_{\text{MonkeyID}}$			80 $_{\text{MonkeyID}}$		
	3 $_{\text{collectionYear}}$			3 $_{\text{collectionYear}}$		
Observations	500			349		

Table 2 Model results from mixed-effect linear regressions predicting the influence of affiliation rate on log-transformed urinary concentrations of suPAR for (A) Females, and (B) Males. P-values < 0.05 are shown in bold.

suPAR	**(A) Females**			**(B) Males**		
Predictors	Estimates	CI	p	Estimates	CI	p
Intercept	-1.41	-1.86 – -0.96	**<0.001**	-1.95	-2.55 – -1.35	**<0.001**
Affiliation	-1.13	-3.55 – 1.30	0.363	0.86	-1.80 – 3.51	0.526
Age	0.02	-0.03 – 0.07	0.479	0.01	-0.06 – 0.08	0.802
Group [V]	0.17	-0.35 – 0.70	0.518	-0.13	-0.77 – 0.52	0.699
Rank [Low]	-0.03	-0.58 – 0.52	0.913	0.30	-0.26 – 0.85	0.292

Rank [Medium]	-0.34	-0.93 – 0.25	0.260	0.05	-0.67 – 0.77	0.892
Affiliation:Age				-0.21	-3.52 – 3.11	0.902
Random Effects						
σ^2	0.19			0.45		
τ_{00}	0.33 $_{\text{MonkeyID}}$			0.20 $_{\text{MonkeyID}}$		
	0.02 $_{\text{collectionYear}}$			0.15 $_{\text{collectionYear}}$		
ICC	0.03			0.03		
N	82 $_{\text{MonkeyID}}$			79 $_{\text{MonkeyID}}$		
	3 $_{\text{collectionYear}}$			3 $_{\text{collectionYear}}$		
Observations	395			287		

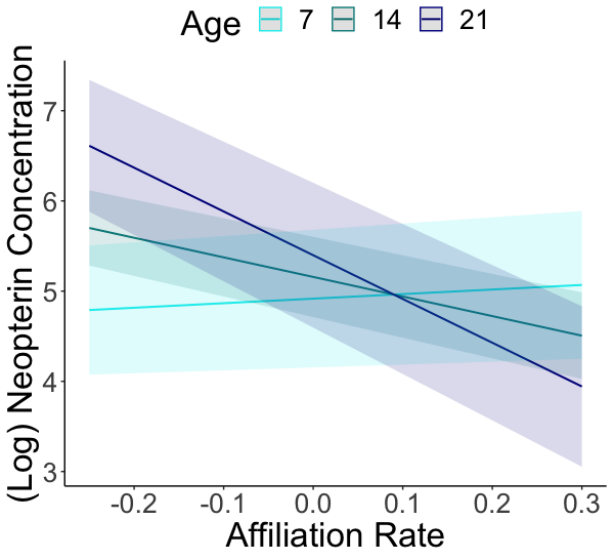

Fig. 1 The effect of affiliative behaviors in the past 60 days (affiliation rate) on log-transformed urinary neopterin concentrations (in ng/mg creatinine) in females. Rates of affiliative behavior were standardized by centering values at 0 and dividing by their standard deviation. Model predictions and 95% confidence intervals for the effect at distinct ages (7 years, 14 years, and 21 years) are shown.

In the additional model we ran to explore the associations between neopterin and each component of affiliation, there was no significant association between either grooming given or grooming received and neopterin (Table 3, Fig. 2A, 2B), but there was a significant negative association between huddling and neopterin concentrations (β = -6.92, CI [-10.12, -3.71], $p < 0.001$, Table 3, Fig. 2C). This suggests that the negative association between affiliation rate and neopterin is driven by huddling rather than grooming behavior. While there was no significant interaction between huddling and age or grooming received and age in predicting neopterin (Table 3, Fig. 2B, 2C), there was a significant interaction between grooming given and age in predicting neopterin (β = -0.54, CI [-0.96, -0.13], $p = 0.011$, Table 3, Fig. 3A). This suggests that

the interaction between affiliation rate and age is driven predominately by grooming given behavior.

Table 3 Model results from a mixed-effect linear regression predicting the influence of three types of affiliation (Giving grooming, receiving grooming, and huddling) on log-transformed urinary neopterin concentrations for females. P-values < 0.05 are shown in bold.

Neopterin Concentration	**Females**		
Predictors	Estimates	CI	P
Intercept	5.17	4.91 – 5.42	**<0.001**
Age	0.04	0.01 – 0.07	**0.021**
Groom Give	-1.54	-3.55 – 0.48	0.135
Groom Receive	-0.62	-2.66 – 1.42	0.550
Huddling	-6.92	-10.12 – -3.71	**<0.001**
Group [V]	0.01	-0.28 – 0.30	0.958
Rank [Low]	0.02	-0.29 – 0.34	0.897
Rank [Medium]	-0.14	-0.46 – 0.18	0.393
Groom Give:Age	-0.54	-0.96 – -0.13	**0.011**
Groom Receive:Age	-0.33	-0.95 – 0.29	0.291
Huddle:Age	0.06	-0.76 – 0.88	0.883
Random Effects			
σ^2	0.06		
$\tau_{00\ MonkeyID}$	0.20		
$\tau_{00\ collectionYear}$	0.00		
$N_{\ MonkeyID}$	91		
$N_{\ collectionYear}$	3		
Observations	500		

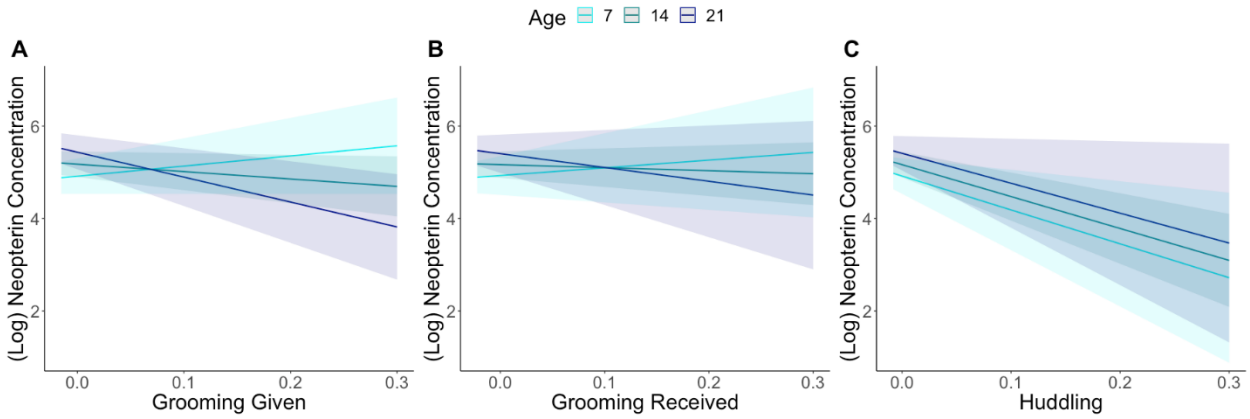

Fig. 2 The effect of three types of affiliative behavior on (log-transformed) urinary neopterin concentrations (in ng/mg creatinine) in females. Rates of each type of affiliative behavior were standardized by centering values at 0 and dividing by their standard deviation. Model predictions and 95% confidence intervals for the effects at distinct ages (7 years, 14 years, and 21 years) are

shown. (A) There was a significant interaction between age and grooming given, with older individuals experiencing a more negative relationship between grooming given and neopterin. (B) There was no effect of grooming received on neopterin levels and no difference between ages. (C) There was a significantly negative effect of huddling behavior on neopterin, and this effect did not differ across ages.

Agonism Received

Among females, there was a significant positive association between neopterin and agonism received ($\beta = 0.04$, CI [0.00, 0.08], p= 0.031, Table 4A), indicating that females who experienced more instances of agonism over a 60-day period had higher urinary neopterin concentrations. There was no interaction between agonism received and age in predicting female neopterin concentrations (Table 4A). Among males, there was no association between neopterin and agonism received, and no interaction been agonism received and age in predicating neopterin (Table 4B). Overall, there was no association between agonism received and urinary concentrations of suPAR in either males or females (Table 5).

Table 4 Model results from mixed-effect linear regressions predicting the influence of agonism received on log-transformed urinary neopterin concentrations for (A) Females, and (B) Males. P-values < 0.05 are shown in bold.

Neopterin Concentration	**(A) Females**			**(B) Males**		
Predictors	Estimates	CI	p	Estimates	CI	p
Intercept	5.13	4.88 – 5.38	**<0.001**	5.00	4.79 – 5.21	**<0.001**
Agonism	0.04	0.00 – 0.08	**0.031**	0.03	-0.02 – 0.09	0.186
Age	0.04	0.01 – 0.07	**0.011**	0.01	-0.02 – 0.05	0.469
Group [V]	0.09	-0.21 – 0.39	0.554	-0.05	-0.33 – 0.22	0.697
Rank [Low]	-0.07	-0.36 – 0.23	0.653	-0.09	-0.42 – 0.24	0.579
Rank [Medium]	-0.12	-0.44 – 0.20	0.459	-0.22	-0.51 – 0.07	0.140
Agonism:Age	-0.00	-0.01 – 0.01	0.777	0.01	-0.01 – 0.02	0.269
Random Effects						
σ^2	0.84			0.77		
τ_{00}	0.14 $_{\text{MonkeyID}}$			0.10 $_{\text{MonkeyID}}$		
	0.00 $_{\text{collectionYear}}$			0.00 $_{\text{collectionYear}}$		
ICC	0.15			0.12		
N	89 $_{\text{MonkeyID}}$			82 $_{\text{MonkeyID}}$		
	2 $_{\text{collectionYear}}$			2 $_{\text{collectionYear}}$		
Observations	476			357		

Table 5 Model results from mixed-effect linear regressions predicting the influence of antagonism on log-transformed urinary concentrations of suPAR for (A) Females, and (B) Males. P-values < 0.05 are shown in bold.

suPAR	**(A) Females**			**(B) Males**		
Predictors	Estimates	CI	p	Estimates	CI	p
Intercept	-1.44	-1.96 – -0.91	**<0.001**	-2.04	-2.55 – -1.52	**<0.001**
Antagonism	0.05	-0.03 – 0.12	0.208	0.09	-0.02 – 0.19	0.107
Age	0.04	-0.02 – 0.09	0.169	0.01	-0.06 – 0.07	0.880
Group [V]	0.34	-0.20 – 0.88	0.212	0.04	-0.46 – 0.55	0.870
Rank [Low]	-0.03	-0.58 – 0.52	0.917	-0.26	-0.88 – 0.36	0.410
Rank [Medium]	-0.14	-0.73 – 0.45	0.647	0.14	-0.39 – 0.67	0.602
Antagonism:Age	-0.01	-0.02 – 0.00	0.167	0.01	-0.02 – 0.04	0.605
Random Effects						
σ^2	2.78			2.86		
τ_{00}	0.35 $_{\text{MonkeyID}}$			0.14 $_{\text{MonkeyID}}$		
	0.05 $_{\text{collectionYear}}$			0.08 $_{\text{collectionYear}}$		
ICC	0.13			0.07		
N	87 $_{\text{MonkeyID}}$			78 $_{\text{MonkeyID}}$		
	2 $_{\text{collectionYear}}$			2 $_{\text{collectionYear}}$		
Observations	378			292		

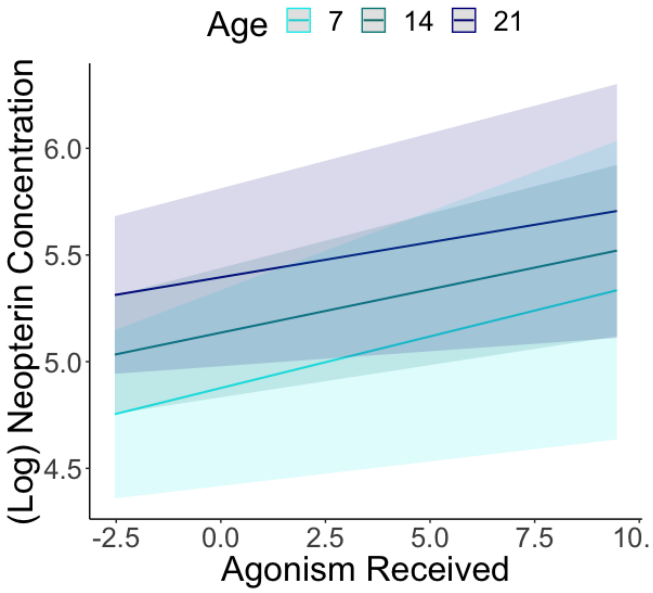

Fig. 3 The effect of agonism received in the past 60 days on log-transformed urinary neopterin concentrations (in ng/mg creatinine) in females. Counts of agonism received were standardized

by centering values at 0 and dividing by their standard deviation. Model predictions and 95% confidence intervals for the effects at distinct ages (7 years, 14 years, and 21 years) are shown.

In the additional model we ran to explore the associations between neopterin and each component of agonism we found that while there was a positive effect estimate for each of the three subcategories of agonism, all of these effects were highly non-significant (Table 6, Fig.4). This suggests that the positive association between agonism received and neopterin concentrations in females is driven cumulatively by all three types of agonistic behaviors.

Table 6. Model results from a mixed-effect linear regression predicting the influence of three types of agonism (severe agonism received, mild agonism received, and submissive behaviors) on log-transformed urinary concentrations of neopterin for females. P-values < 0.05 are shown in bold.

Neopterin Concentration		**Females**	
Predictors	Estimates	CI	P
Intercept	5.13	4.88 – 5.38	**<0.001**
Severe Agonism	0.03	-0.09 – 0.14	0.660
Mild Agonism	0.02	-0.17 – 0.20	0.846
Submissive	0.04	-0.00 – 0.09	0.070
Age	0.04	0.01 – 0.06	**0.011**
Group [V]	0.09	-0.21 – 0.39	0.558
Rank [Low]	-0.07	-0.37 – 0.23	0.644
Rank [Medium]	-0.12	-0.43 – 0.20	0.468
Random Effects			
σ^2	0.84		
$\tau_{00\ MonkeyID}$	0.14		
$\tau_{00\ collectionYear}$	0.00		
ICC	0.14		
$N_{MonkeyID}$	89		
$N_{collectionYear}$	2		
Observations	476		

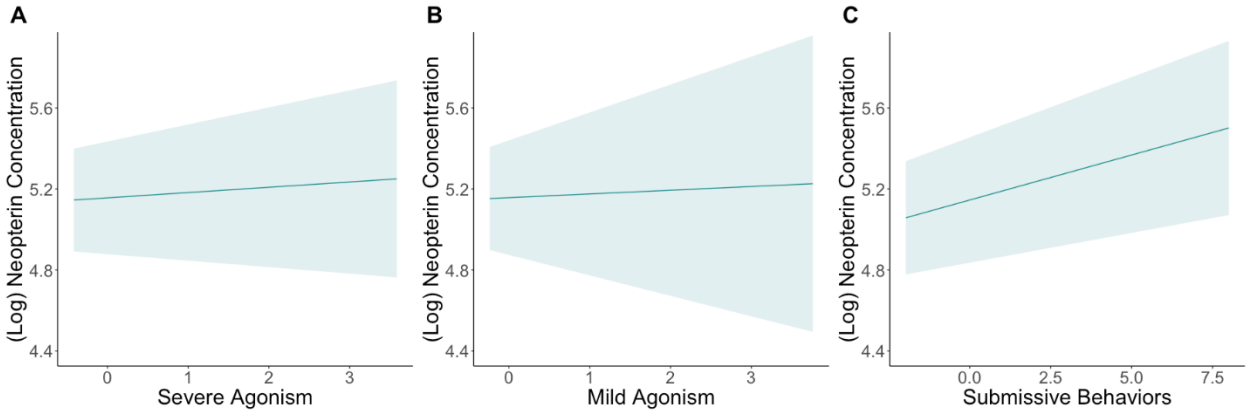

Fig. 4 The effects of the three categories of agonism, including (A) severe agonism received, (B) mild agonism received, and (C) submissive behaviors, experienced in the past 60-days on log-transformed urinary neopterin concentrations (in ng/mg creatinine) in females. For each category, counts of agonism were standardized by centering values at 0 and dividing by their standard deviation. Model predictions and 95% confidence intervals are shown.

Discussion

In this study we found that the social environment is associated with urinary neopterin concentrations in female rhesus macaques living in the free ranging population of Cayo Santiago, Puerto Rico, in a way that recapitulates the associations between social environment and proinflammatory immune activation commonly observed in human populations (Eisenberger et al., 2017; K. J. Smith et al., 2020; Uchino, 2006). Specifically, in females, experiencing affiliative behavior was associated with lower neopterin concentrations, while experiencing agonistic behavior was associated with higher neopterin concentrations. Importantly, these findings indicate that immune activity is a potential mediator of the relationship between social environment and fitness previously observed in this population of rhesus macaques (Brent et al., 2013, 2017a; Ellis et al., 2019). Additionally, we found that age modulated the association between affiliation and neopterin, with older females experiencing a greater reduction in neopterin with a highly affiliative social environment. Below we discuss the potential proximate and ultimate mechanisms driving these associations between social environment and neopterin, as well as discuss the potential reasons for why we did not find such an effect of social environment on suPAR, or any effects of social environment among males.

The association between social environment and neopterin we found in female rhesus macaques mirrors the general trends seen in human populations (Eisenberger et al., 2017; K. J. Smith et al., 2020; Uchino, 2006), indicating that the proximate and ultimate mechanisms driving the associations between social environment and immune activation might be conserved across primates. The functioning of the immune system is highly interconnected to the functioning of the HPA axis, providing the physiological infrastructure through which neuroendocrine responses to social experiences can have direct consequences on the activation of the immune system (Dunn, 2007). The opposite directionality is also possible, wherein individuals who are sick and consequently have highly activated immune systems will change their own social behavior, perhaps leading to less affiliative social interactions, and receiving more agonistic social interactions (Devlin et al., 2021). However, given that in this study we measured social

environment in the 60 days preceding the measure of neopterin, rather than the proceeding days, and given that the social environment we measured is primarily driven by the behavior of social partners rather than the individual measured, it is more likely that the directionality of the effect is from the social environment affecting neopterin concentrations, rather than the other way around.

In addition to the direct effects of sociality-linked HPA axis activation driving the association between social environment and neopterin, the association may also be driven by indirect effects of the social environment on neopterin. One potential indirect effect of the social environment on immune activity is through social support and agonism received relating to injury risk. A higher incidence of experiencing agonistic behavior is likely to relate directly to injury risk, which is likely to increase immune activity and consequently neopterin concentrations. Conversely, a higher incidence of experiencing affiliative behavior is likely to reduce injury risk through the increase in social support. Indeed, in this population females that have more affiliative partners have lower likelihood of being physically injured (Pavez-Fox et al., 2022). Consequently, both an increase of physical injuries associated with experiencing agonism as well as a decrease in physical injuries associated with experiencing affiliation are likely mechanistic links between social environment and neopterin concentration in this population.

The relationship between affiliation and neopterin in females was modulated by age, with older females experiencing a greater reduction in neopterin concentration when they experienced a highly affiliative social environment when compared to younger females. One possible driver for this age interaction effect is simply that older females have, on average, higher neopterin concentrations (Cooper, Watowich, et al., 2022), and so the extent to which any environmental trigger, including social environment, can act to reduce neopterin values is going to be greater in magnitude. However, at the highest rates of affiliation experienced in the population, the model in our study predicted that a 21-year-old female would have lower neopterin concentrations than a 7-year-old female (Fig. 1), which indicates that the effect of age is not being solely driven by the magnitude of absolute change in neopterin values being greater for older females. Another possible driver of the age-specific effect of affiliation on neopterin is that females' experience of affiliative relationships changes as they get older. In both human and nonhuman primates, individuals tend to become more selective with age in the social relationships that they do maintain, but these relationships are of a higher quality (Lang & Carstensen, 1994; Rosati et al., 2020). This age-related social selectivity has been shown to occur in females in this population (Siracusa et al., 2022), and so it's possible that the age-affiliation interaction we found in predicting neopterin concentration is evidence that these older females are conferring greater physiological benefits of friendship due to their increased social selectivity. Interestingly, the age interaction effect was driven by grooming behavior (both grooming given and grooming received), and age did not interact with huddling behavior in predicting neopterin concentration. This indicates that the effect of grooming behavior specifically, both giving and receiving, may change with age in a way that has an observable effect on physiology.

In contrast to neopterin, we did not find any association between urinary suPAR concentrations and social environment. This highlights that, while both neopterin and suPAR are general markers of proinflammatory immune activation (Capuron et al., 2014; Thunø et al., 2009), they are only moderately correlated with one another (Cooper, Watowich, et al., 2022; Nyamweya et

al., 2012; Tahar et al., 2016), and each can reflect distinct physiological processes. In contrast to human populations, in which suPAR concentrations have moderate to high within-individual repeatability (Haupt et al., 2019; Schenk et al., n.d.), suPAR concentrations in rhesus macaques have low repeatability (Cooper, Watowich, et al., 2022), indicating that individual suPAR concentrations can vary greatly within an individual over time. This difference in the within-individual variance of suPAR concentrations between humans and rhesus macaques may explain why human studies have identified a link between suPAR and social environment (Matthews et al., 2024; Rasmussen et al., 2019), while our study of rhesus macaques did not. It's possible that suPAR is too stochastic in rhesus macaques to reflect changes in systemic inflammation as a consequence of behavior experienced over the scale of weeks. For example, if suPAR concentrations respond more acutely to day-to-day fluctuations in the social environment, then we might not be capable of observing effects on the timescale of the present study. It is also possible that the limited duration of focal behavioral observations per individual sample impacted our ability to detect what may be small associations between social environment and suPAR concentrations.

While we found effects of both affiliative and agonistic social environments on female neopterin, we found no association between social environment in males. Rhesus macaques are a species with female philopatry, and while males typically move between social groups multiple times in their lives, females will typically spend their entire lifetime within a single social group (Maestripieri, 2010). This gives females more time to develop strong social bonds with their groupmates when compared to males (Kapsalis & Berman, 1996; Maestripieri, 2012). This difference in the permanence of social partners might be why we see an effect of the affiliation on female neopterin concentrations, but not on male neopterin concentrations. While female rhesus macaques are generally believed to engage more often in both affiliative and agonistic social behaviors when compared to males (Brent et al., 2017b), we did not find this sex difference in behavioral frequency in the present dataset. Consequently, the associations between social environment and neopterin concentration found in females, but not males, cannot solely be explained by a sex difference in the frequency of experiencing social interactions.

Our study demonstrates that it is possible to recapitulate findings in humans and captive animals that both an affiliative and an agonistic social environment can observably modulate proinflammatory immune activity in a nonhuman primate living under naturalistic conditions. This is, to our knowledge, the first study that demonstrates that proinflammatory immune activity is a potential link between the social environment and fitness in a population under naturalistic conditions. However, it’s also important to note that that high levels of inflammation is not necessarily synonymous with lower fitness, and the relationship between inflammation and fitness can vary greatly depending on environmental context (McDade, 2023). The relationship between inflammation and more direct proxies of fitness, such as survival and reproduction, requires further study in rhesus macaques living under naturalistic conditions. The effects of social environment on neopterin observed in this population are likely driven by multiple co-occurring mechanisms, including the effect of the social environment on HPA axis regulation as well as the association between social environment and injury risk.

Data Availability

All relevant data files as well as the complete annotated R code used in the analysis of this study are available via dryad using this link: https://datadryad.org/stash/share/FDWPVfl7h49evlhaRE2MmMQh4599YCp5XZPJm-gLHNk

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