

High resting metabolic rate among Amazonian forager-horticulturalists experiencing high pathogen burden

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Abstract

Objectives: Resting metabolic rate (RMR) reflects energetic costs of homeostasis and accounts for 60 to 75% of total energy expenditure (TEE). Lean mass and physical activity account for much RMR variability, but the impact of prolonged immune activation from infection on human RMR is unclear in naturalistic settings. We evaluate the effects of infection on mass-corrected RMR among Bolivian forager-horticulturalists, and assess whether RMR declines more slowly with age than in hygienic sedentary populations, as might be expected if older adults experience high pathogen burden.

Materials and Methods: RMR was measured by indirect calorimetry (Fitmate MED, Cosmed) in 1,300 adults aged 20 to 90 and TEE was measured using doubly labeled water ($n = 40$). Immune biomarkers, clinical diagnoses, and anthropometrics were collected by the Tsimane Health and Life History Project.

Results: Tsimane have higher RMR and TEE than people in sedentary industrialized populations. Tsimane RMR is 18 to 47% (women) and 22 to 40% (men) higher than expected using six standard prediction equations. Tsimane mass-corrected TEE is similarly elevated compared to Westerners. Elevated leukocytes and helminths are associated with excess RMR in multivariate regressions, and jointly result in a predicted excess RMR of 10 to 15%. After age 40, RMR declines by 69 kcal/decade ($p < .0001$). Controlling for lean mass and height accounts for 71% of age-related RMR decline, and adding indicators of infection minimally affects the age slope. The residual level of age-related decline from age 40 is 1.2% per decade.

Conclusion: High pathogen burden may lead to higher metabolic costs, which may be offset by smaller body mass or other energy-sparing mechanisms.

KEYWORDS

energetic expenditure, costs of infection, resting metabolic rate (RMR), Tsimane, maintenance costs, costs of infection, energetic expenditure, maintenance costs, resting metabolic rate, Tsimane

1 | INTRODUCTION

The size and allocation of an organism's daily energy budget reflects its evolved strategies for growth, reproduction, and maintenance, though trade-offs and integration of these functions across diverse environments in free-living organisms are poorly understood. In humans, roughly 60 to 75% of total energy expenditure (TEE, kcal/day) is spent on resting metabolic rate (RMR, kcal/day) (Manini, 2010; Speakman &

Selman, 2003). RMR reflects the energetic costs of maintaining homeostasis. The sum of estimated RMR, activity energy expenditure (FAO/WHO), and dietary-induced thermogenesis is a common means of estimating TEE. However, these RMR and TEE estimations may be inappropriate in non-Western settings. Direct studies of TEE and RMR in humans and other species suggest that individuals adapt to increased activity levels via behavioral and physiological energy-sparing mechanisms, reducing RMR, other nonmuscular activity, and TEE within

narrow ranges (Dugas et al., 2011; Heini et al., 1991; Pontzer, 2015). Further, standard RMR equations do not incorporate immune response and other maintenance costs that are commonly elevated outside of socioeconomically developed countries. The impact of prolonged immune activation from infection and enhanced baseline immunity on RMR in human populations facing high pathogenic burdens and energetic limitation is not currently known.

One set of vital metabolic challenges faced by all organisms including humans includes acute and chronic immune activation, and other maintenance functions that help tolerate or defend against pathogenic assault. Species such as primates with slow life histories specialize in energetically expensive specific defenses like cell-mediated and antibody-mediated immunity, rather than cheaper nonspecific defenses like inflammation (Lee, 2006). While maintenance of the immune system can be metabolically expensive, immune activation in particular is costly; a number of studies using avian and rodent models have quantified the energetic costs of infection or immune activation, while others have shown that energetic stress compromises certain immune function components (Frankenfield, Roth-Yousey, Compher, & Group, 1994; Lochmiller & Deerenberg, 2000; Nieman et al., 1990; Schmid-Hempel, 2003; Zuk & Stoehr, 2002). In humans, RMR increases by 8 to 14% in university students during an acute respiratory infection (Muehlenbein et al., 2010). RMR increases by 30% with sepsis (Carlssohn et al., 2011; Kreyman et al., 1993). Even vaccinations (e.g. typhoid fever) can raise RMR by 16% (Cooper et al., 1992). In humans and other species energetic costs of immune activation from infection or tissue injury may trigger "sickness behavior," a broad coordinated adaptive response to promote energy conservation and reallocation (Hart, 1988; Stieglitz et al., 2015b).

These estimates of acute immune response suggest that daily energy requirements vary depending on local pathogen burden, and all else equal may be higher in populations with chronically high pathogen load. Alternatively, such populations may adapt metabolically and/or behaviorally to chronic immune system activation and maintain TEE similar to that in other, less pathogenically burdened populations. Metabolic response to pathogens may also change with age, as maintenance becomes increasingly costly, and in response to other external pressures. Human metabolic adaptation and inherent energy allocation trade-offs may be less severe when more food is available (Pontzer et al., 2016). Similarly, the widely documented 1 to 2% per decade decline in adult RMR in industrialized populations (Elia et al., 2000; Fukagawa, Bandini, & Young, 1990; Manini, 2010; Van Pelt, Dinneno, Seals, & Jones, 2001; Vaughan, Zurlo, & Ravussin, 1991) may not generalize to preindustrial populations with higher pathogen burden. Such population-level differences in metabolic adaptation and age-related decline could contribute to differences in obesity, chronic disease, and premature mortality (Fabbri et al., 2015; Ruggiero & Ferrucci, 2006). To date, however, there have been few studies of human RMR in a free-living, energy-limited population with high rates of infectious morbidity. While RMR has been measured among Siberian Evenki, Keto, and Yakut (Katzmarzyk, Leonard, & Crawford, 1994; Snodgrass, Leonard, Tarskaia, & Schoeller, 2006), Bolivian Aymara (Kashiwazaki, Dejima, Orias-Rivera, & Coward, 1995; Kashiwazaki et al., 2009) and in low-

income countries (see Dugas et al., 2011), none of these studies have related RMR to indicators of infection or immune activation.

Here we estimate RMR among the Tsimane, a physically active population of forager-horticulturalists inhabiting a pathogen-rich environment in Amazonian Bolivia. We first assess the extent to which RMR measured by indirect calorimetry differs from RMR estimated from common prediction equations, and then test whether differences can be explained by a combination of environmental, anthropometric and health variables indicating infectious burden. We test whether indicators of infection are associated with higher RMR controlling for potential confounders, and then assess whether Tsimane RMR declines more slowly with age compared to hygienic, sedentary industrialized populations. We also measure TEE in a subset of our sample to examine the proportion of total daily energy requirement accounted for by RMR. By examining age-related changes in anthropometrics (e.g. fat and fat-free mass) and infection status, we test whether accounting for these conditions substantially attenuates the decline in Tsimane RMR with age.

2 | MATERIALS AND METHODS

2.1 | Study population

The Tsimane are forager-horticulturalists (population ~15,000) living in the Beni Department of the Bolivian Amazon, dispersed across 90+ villages ranging in size from 40 to 550 inhabitants. Many Tsimane are isolated from modern society and have not yet undergone an epidemiological and technological transition. Only two villages have any electricity (albeit intermittent), and there is no running water, sanitation, or waste management. Below we highlight relevant details about diet, physical activity, and infection.

Tsimane diet remains largely traditional, with 66% of calories derived from cultivated staples (plantains, rice, manioc, corn), 17% from wild game, 7% from freshwater fish, and 6% from fruits and nuts. Estimated dietary contributions from carbohydrates, protein and fat are 72%, 14%, and 14%, respectively (Martin et al., 2012). Less than 10% of calories come from market-derived foods. Obesity is rare in adulthood; Tsimane have 8 to 10 times lower levels of obesity than age-matched US peers (Gurven et al., 2009).

Tsimane are physically active throughout adulthood, spending roughly 5 to 6 h/day in moderate activity; male and female estimated physical activity levels (PALs), using a combination of accelerometry and heart rate, are 2.15 and 1.85, respectively (Gurven, Jaeggi, Kaplan, & Cummings, 2013). Tsimane living near the local town are not less active than Tsimane from other regions, perhaps because of the physical activity required for common wage labor options (e.g., logging, cash cropping). Men have higher PALs than women, although men's activity exhibits more seasonal and age-related variation. Older Tsimane adults remain active but generally engage in less physically demanding activities with age because of greater infirmity. This is especially apparent for men, as their PAL declines by 10 to 20% from the peak (achieved in the late 20s) to older adulthood (age 60+ years). Tsimane VO_{2max} matches that of other subsistence populations, and is higher than estimates from industrialized populations. Their VO_{2max} also declines

TABLE 1 Study sample description

Variable	Female		Male	
	20–39 (n = 236)	40+ (n = 415)	20–39 (n = 209)	40+ (n = 440)
RMR (kcal/d)	1,660 ± 320	1,632 ± 327	1,991 ± 341	1,986 ± 359
Age (yr)	31.2 ± 5.2	53.6 ± 11.4	31.9 ± 5	53 ± 10.5
Weight (kg)	57.5 ± 9.2	54.7 ± 9.5	62.4 ± 8	62.8 ± 8.8
Height (cm)	151.4 ± 6.3	150.4 ± 6.1	162.7 ± 6.4	161.5 ± 5.5
FFM (kg)	41.8 ± 4.6	39.8 ± 4.9	52.3 ± 6.1	50.4 ± 5.9
Body fat %	26.4 ± 7.6	26.5 ± 7.1	16 ± 5.1	19.1 ± 6.2
BMI (kg/m ²)	25.1 ± 3.7	24.2 ± 4.1	23.6 ± 2.8	24 ± 2.9
Hb (g/ml)	12.5 ± 1.2	13 ± 1.2	14 ± 1.2	13.9 ± 1.4
ESR (ml/mm)	28.9 ± 11.9	27.1 ± 13.8	22.2 ± 11.5	21.1 ± 13.3
WBC (x10 ³ cells/ μ L)	10.2 ± 2.7	9.4 ± 2.7	10.3 ± 3.1	9.5 ± 2.6
Clinical diagnoses				
Clinical helminths	0.06 ± 0.24	0.16 ± 0.37	0.02 ± 0.15	0.16 ± 0.37
Respiratory	0.17 ± 0.38	0.18 ± 0.38	0.16 ± 0.36	0.09 ± 0.29
Back pains	0.23 ± 0.42	0.29 ± 0.46	0.39 ± 0.49	0.39 ± 0.49
Gastrointestinal	0.26 ± 0.44	0.23 ± 0.42	0.19 ± 0.4	0.16 ± 0.37
All infection	0.55 ± 0.76	0.55 ± 0.73	0.36 ± 0.57	0.49 ± 0.66

Means ± SD shown for relevant variables.

more slowly than age-matched Canadians using a similar measurement method (Pisor, Gurven, Blackwell, Kaplan, & Yetish, 2013). Tsimane also show reduced vascular aging (e.g. low rates of hypertension), perhaps due to their relatively high level of physical activity (Gurven, Blackwell, Rodríguez, Stieglitz, & Kaplan, 2012a).

Tsimane are frequently diagnosed with an infection during annual clinical exams conducted by the Tsimane Health and Life History Project (THLHP) (respiratory: 20–30%, gastrointestinal: 10–30%, skin: 5%) (Gurven, Blackwell, Rodríguez, Stieglitz, & Kaplan, 2012b). Elevated levels of white blood cells (WBCs) (>10,000 cells/mm³) are 10 times more prevalent among Tsimane than in the U.S. WBCs also decline with age among Tsimane, particularly lymphocytes and eosinophils, suggesting increasing maintenance costs because older adults are not less likely to experience infection than younger adults (Gurven et al., 2009). Systemic immunity shows many indications of chronic activation from infection with helminths, with 70% of Tsimane infected at any given time (Blackwell et al., 2011, 2015, 2016; Blackwell, Martin, Kaplan, & Gurven, 2013); coinfection is not uncommon (Blackwell et al., 2013; Martin, Blackwell, Gurven, & Kaplan, 2013). Serum immunoglobulins are two orders of magnitude higher than among U.S. adults, especially for IgE (highly indicative of infection with helminths) (Blackwell et al., 2011). On average, 20% of WBCs are eosinophils, also indicative of intense parasitic infection, compared with the normal US reference range of <5%, with >90% of Tsimane adults in the clinically high range. Natural killer cells and B-cell counts are approximately twice as high as typical U.S. values (Blackwell et al., 2016). Tsimane also demonstrate higher levels of inflammation than those found in industrialized populations. C-reactive protein (CRP) is elevated in children, consistent with immune activation due to chronic exposure to acute infections, and increases with age (Gurven et al., 2009). Erythro-

cyte sedimentation rate (ESR) is also extremely high (Table 1), with mean levels of 27 mm/h for males and 37 for females, compared with US reference ranges of <15 and <20, respectively.

2.2 | Participants

Study participants were adults aged 20+ years (mean ± SD = 45.8 ± 13.9, range: 20–90) across 46 villages visiting the THLHP mobile (within-village) health clinic for medical consultation by project physicians. This clinic was also composed of laboratory technicians trained to analyze biomarkers of infection, and bilingual (Spanish-Tsimane) research assistants conducting interviews. THLHP participation rates are ~85% of the sampled population (random sampling for ages 20 to 39 and near-complete sampling for ages 40+). Figure 1 provides a flowchart describing the sampling and participant recruitment. Data collection occurred from January 2012 through November 2014, including 445 adults age 20 to 39 (53% female) and 855 adults age 40+ (48% female). Tsimane total fertility rate is 9.1 births, breastfeeding duration is 19.2 ± 7.3 months, and interbirth intervals are 30.7 ± 10.6 months (McAllister, Gurven, Kaplan, & Stieglitz, 2012; Veile, Martin, McAllister, & Gurven, 2014); we thus estimate that 62% and 29% of women age 20 to 39 years in our sample are breastfeeding or pregnant, respectively.

2.3 | Resting metabolic rate (RMR)

RMR was measured using the Fitmate MED indirect calorimetry system (Cosmed, Italy). The seated participant relaxed while wearing an RMR mask during an initial habituation phase (~5 min), which was followed by 10 min of continuous data acquisition. The Fitmate employs a turbine flowmeter for measuring ventilation and a galvanic fuel cell oxygen sensor for analyzing the fraction of oxygen in expired gases.

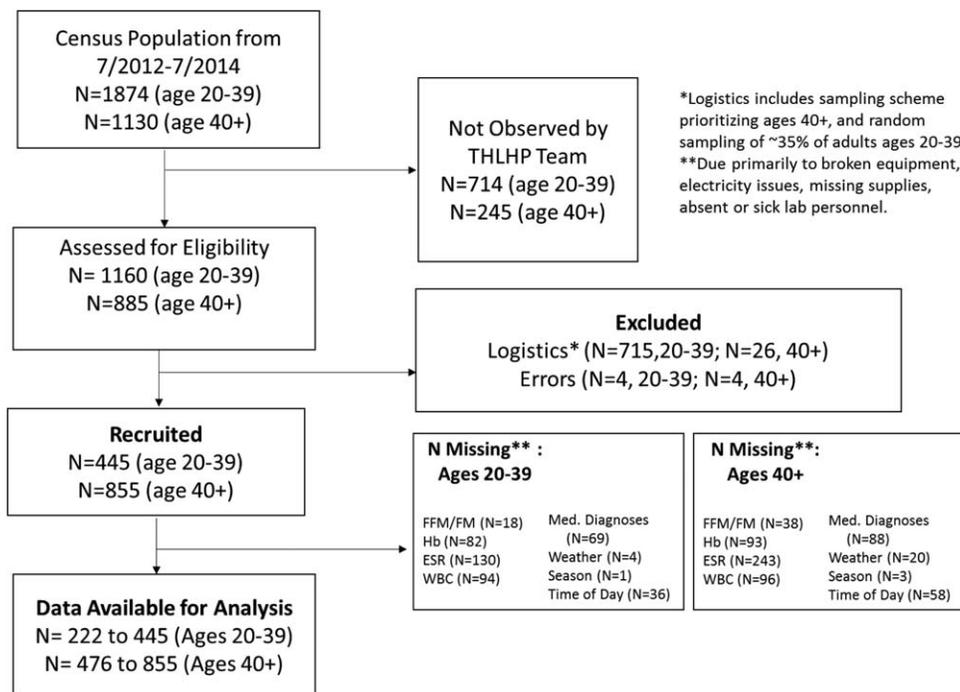


FIGURE 1 Flowchart of participant recruitment and sample.

Sensors measure humidity, temperature, and barometric pressure for use in internal calculations. The Fitmate uses standard metabolic formulas to calculate oxygen uptake. Fitmate monitors oxygen uptake (VO_2), ventilation (V_e), respiratory frequency (R_f), heart rate (HR), and fraction of O_2 expired (FeO_2). RMR (kcal/day) is estimated by a modified Weir equation: $RMR = [5.675 \times VO_2 + 1.593 \times VCO_2 - 21.7]$, where VO_2 is the volume of oxygen in the breath (ml/min), and VCO_2 is carbon dioxide output (ml/min) (Weir, 1949). VCO_2 is not measured directly but estimated assuming a fixed respiratory quotient (RQ) of 0.85, which has been shown to introduce little error in RMR estimation (Nieman, Austin, Chilcote, & Benezra, 2005; Nieman, Trone, & Austin, 2003). The Fitmate is portable, easy to use, and has been validated against the Douglas bag system (Nieman et al., 2006), and it shows very high inter- and intraday test-retest reliability for RMR measurement (Campbell et al., 2014).

Due to field conditions, a number of deviations from standard protocol were necessary. First, standard protocol requires 12 h of fasting, which we could not guarantee, especially as measurements were taken throughout the day during THLHP surveillance (3.1% of RMR assessments began <8 a.m., 61.4% between 8 a.m. and noon, 4.9% noon and 2 p.m., 26.2% 2 p.m. and 5 p.m., 4.4% >5 p.m.). 75.1% of participants reported having last eaten within 5 h, 3.9% between 5 and 10 h, and 20.9% 10+ h prior to RMR testing. Time of day and time since the patient last ate were thus used as controls in all analyses. Second, temperature varied across days, and maintaining a temperature-controlled setting was not possible. Daily ambient temperature, humidity, and precipitation were obtained from meteorological measures taken at the nearby San Borja airport (<http://www.wunderground.com/history/airport/SLRY>), and used as additional controls. Third, it was not possible to prevent physical activity during the 12 h prior to RMR assess-

ment. We also conservatively control for season (52.2% sampled in “dry” from May to August; 15.5% in “wet” from December to March; 32.3% in “other” during April and from September–November) because activity, pathogen burden, diet, and climate can vary throughout the year.

Estimated RMR was based on six standard prediction equations devised for settings where direct or indirect calorimetry is unavailable: Oxford (Henry, 2005), FAO (FAO/WHO/UNU, 1985), Cunningham (Cunningham, 1980), Harris-Benedict (Harris & Benedict, 1918), Mifflin-St. Jeor (Mifflin et al., 1990), and Owen Weight (Owen et al., 1986, 1987) equations. These all use age, sex, and anthropometric measures to estimate RMR, and a number of analyses have shown that different equations have varying degrees of accuracy depending on the age, ethnicity, physical fitness, body size, and composition of the study sample (Frankenfield et al., 2005). Anthropometric measures include weight and height (except for Owen, which uses only weight) in all but the Cunningham equation, which instead uses fat-free mass; its reliance on fat-free mass has led some researchers to argue that Cunningham is more relevant for active populations than the other equations (Carlssohn, Scharhag-Rosenberger, Cassel, & Mayer, 2011; De Lorenzo, Bertini, Candeloro, & Piccinelli, 1999). The Oxford equations were developed due to oversampling of Italians and undersampling of people from the tropics in formulation of the FAO equations, and tend to generate lower RMR estimates than the other equations (Henry, 2005).

2.4 | Total energy expenditure (TEE)

TEE (kcal/day) was measured in a subset ($n = 40$, 44% male; mean \pm SD age: 48.6 ± 14.2) using the doubly labeled water method (Speakman, 1997). After providing a baseline urine sample, subjects ingested

114 g (males) or 79 g (females) of water enriched to 6% $^2\text{H}_2\text{O}$ and 10% H_2^{18}O . Six urine samples were collected over the subsequent 12 days, and sent frozen to the Pontzer Lab (Hunter College, New York) for determination of isotope concentrations (^2H and ^{18}O) via cavity ring down spectrometry (L2120i, Picarro Inc., Santa Clara CA). Isotope dilution spaces and elimination rates were calculated via the slope-intercept method and used to calculate the mean rate of carbon dioxide production using Eq. 17.15 in Speakman (1997). Carbon dioxide production was converted to TEE using the modified Weir equation, assuming a respiratory quotient of 0.93, following dietary macronutrient estimates described in Martin et al. (2012). Isotope dilution was also used to determine fat-free mass for these subjects.

Physical activity was measured by accelerometry counts based on a 3-day sample with an Actigraph GT3X accelerometer (Actigraph LLC, Pensacola, FL) in a subset of participants ($n = 28$) in order to assess the relative impact of physical activity on TEE (see Gurven et al., 2013 for additional details).

2.5 | Anthropometrics and biomarkers of infection

Height and weight were measured during medical exams using a Seca 213 portable stadiometer and Tanita scale (BF680). The scale also recorded body fat percentage by bioelectric impedance, which was used to calculate fat-free mass (FFM) and fat mass based on proprietary prediction equations. The TEE subsample permits a validation of the Tanita-based anthropometric measures. Correlations between Tanita-based and isotope dilution methods for FFM, fat mass and weight are 0.91, 0.74, and 0.91, respectively (all p 's $< .0001$).

In-field blood analysis of fasting venous samples using the QBC Diagnostics dry hematology system (Drucker Diagnostics Inc., Port Matilda, PA) provided estimates of hemoglobin (Hb) and WBC. ESR was measured via the Westergren method (Westergren, 1957). THLHP project physicians diagnosed illnesses and trauma presented by patients with the aid of bilingual Tsimane assistants. Diagnoses from the International Classification of Disease (ICD-10) are grouped into several categories, including respiratory ailments, back pain, and intestinal helminths. The latter category was based on having clinical symptoms of intestinal infection, and supplemented by laboratory confirmation from fecal samples analyzed by direct microscopy when possible (30.1% of cases) (Blackwell et al., 2013).

2.6 | Ethics

Informed consent was obtained for all protocols from the Tsimane government that represents Tsimane interests and oversees research projects, from village officials for each participating village, and from all study participants. Consent procedures and protocols were approved by the University of California, Santa Barbara and University of New Mexico Institutional Review Boards.

2.7 | Statistical analyses

Multiple linear regressions of RMR and TEE were performed using SAS 9.3. Stepwise regressions using Akaike's Information Criterion (AIC)-

based stop criterion were used to determine best-fit models. Comparative analyses of RMR and TEE were performed by ordinary least squares (OLS) regression using 185 indirect calorimetry studies compiled by Dugas et al. (2011). To assess age changes in RMR, a series of regression models were conducted on adults age 40+, although some data were missing resulting in varying sample sizes (see Figure 1). Controlling for age and sex, cases with missing data had only slightly lower RMR (est = -42.6 , $p = .065$, $\beta = -0.05$). Nonetheless, analyses were run on several datasets created to insure that missing data did not skew results. These four datasets include: (a) list wise deletion ($n = 471$); (b) raw data ($n = 471-855$); (c) imputed data using stochastic regression ($n = 855$); and (d) multiple imputations using Markov Chain Monte Carlo (MCMC) ($n = 855$).

3 | RESULTS

Mean \pm SD RMR for men and women age 20+ is $1,988 \pm 353$ and $1,642 \pm 325$ kcals/day, respectively (Table 1). Men have higher RMR than women at all ages; RMR plateaus from ages 20 to 39, then declines with age thereafter (Figure 2). TEE for men and women is $3,065 \pm 422$ and $2,186 \pm 366$ kcals/day, respectively. The proportion of TEE that is RMR is higher in women ($\beta = -0.33$, $p = .05$) and by age ($\beta = 0.31$, $p = .07$, $n = 32$); predicted RMR/TEE from ages 20 to 80 is 63.7 to 78.6% for women and 56.3 to 71.1% for men.

3.1 | TEE and RMR

We examine whether RMR is associated with TEE, and whether the association is independent of FFM and physical activity. RMR is highly correlated with TEE (Pearson $r = 0.63$; $p < .0001$, $df = 36$). Mean \pm SD ratio of RMR/TEE is 0.71 ± 0.12 for women (range: 0.56–0.90), and 0.64 ± 0.10 for men (range: 0.49–0.85), well within the range observed in other populations. FFM alone accounts for 73% of the variance in TEE ($p < .0001$, $df = 36$, est = 52.4 ± 5.3). No other demographic or anthropometric variables (sex, age, height, fat mass, total body mass) are significantly associated with TEE in multiple regression including FFM (all other p 's $> .10$). RMR remains positively associated with TEE after controlling for accelerometer-based estimates of calories expended per hour of physical activity (RMR: $\beta = 0.56$, $p < .001$; activity: $\beta = 0.37$, $p = .019$; Adj $R^2 = 0.57$), but its magnitude and significance are reduced after controlling for FFM (RMR: $\beta = 0.18$, $p = .150$; FFM: $\beta = 0.70$, $p < .0001$; activity: $\beta = 0.19$, $p = .076$; Adj $R^2 = 0.81$).

3.2 | Do Tsimane have elevated RMR and TEE?

Tsimane measured RMR is 18 to 47% higher in women and 22 to 40% higher in men than BMR estimated using the six standard prediction equations (Supporting Information Table S1), including Oxford (Henry, 2005), FAO (FAO/WHO/UNU 1985), Cunningham (Cunningham, 1980), Harris-Benedict (Harris & Benedict, 1918), Mifflin-St. Jeor (Mifflin et al., 1990), and Owen Weight (Owen et al., 1986, 1987) equations. Pearson correlations between measured and estimated RMR range from 0.32 to 0.41. Even the most accurate prediction

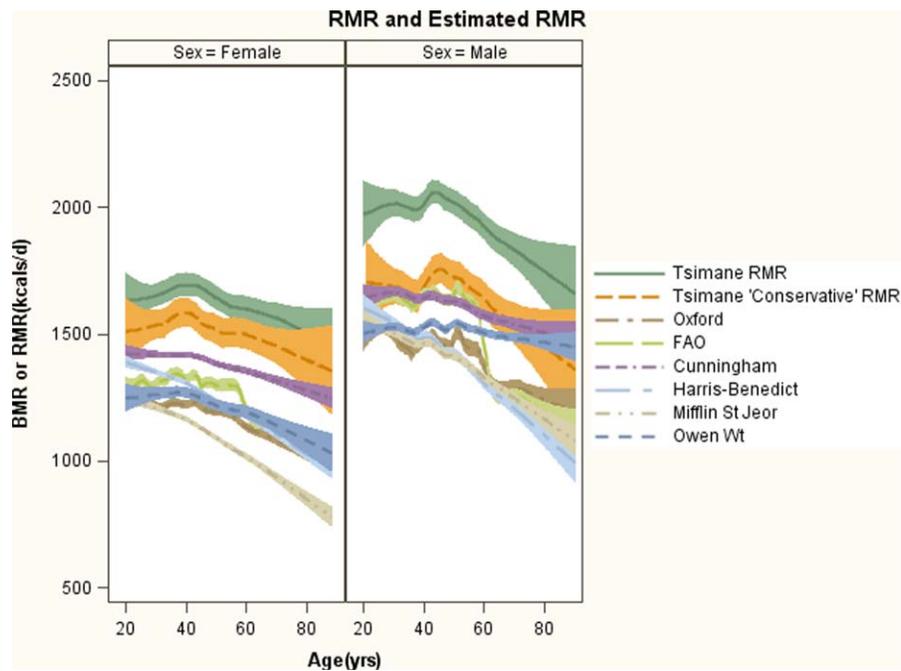


FIGURE 2 Measured and estimated RMR by age and sex. Estimations based on six prediction equations that have been widely applied to different populations. Tsimane “conservative” RMR is a loess spline of adjusted raw data, using average regression coefficients of excess RMR across the six equations, correcting for season, time since last meal, time of day and precipitation. Mean \pm SD “conservative” RMR is $1,678 \pm 354$ for men and $1,526 \pm 322$ for women.

(Cunningham) underestimates RMR by 253 kcal/day in women and 365 kcal/day in men (Supporting Information Table S1). RMR is only 55 ($n = 65$) and 82 ($n = 77$) kcal/day lower in women and men, respectively, after conservatively eliminating samples within 5 h of eating, during mid-day and afternoon from noon to 5 p.m. and during dry season months; these lower RMR measures remain 14 to 42% higher (in women) and 17 to 35% higher (in men) than expected based on the five prediction equations.

Tsimane RMR is high relative to other studies where RMR is similarly measured by indirect calorimetry. Using energetic and anthropometric data from a recent meta-analysis, we compare Tsimane RMR with samples from “high” and “low” socioeconomic development as assessed by the Human Development Index (HDI) (Dugas et al., 2011). We find that Tsimane women’s RMR is higher than 11/11 of low or middle HDI samples, and 71/79 (90%) high HDI samples; men’s RMR is higher than 9/9 of low HDI samples, and 46/48 (96%) high HDI samples. Most strikingly, Tsimane RMR is higher by 482 kcal ($p < .0001$) than RMR in 31 countries from 150 samples, after controlling for sex, mean age, body mass, and physical activity (PAL) (generalized linear model, $n = 148$, Adj $R^2 = 0.88$) (Supporting Information Table S2, Figure 3).

Tsimane TEE is also high relative to other populations (Supporting Information Table S3). Tsimane TEE is 284 kcal/day higher relative to other populations ($\beta = 0.06$, $p = .10$) when controlling for weight, age, and sex. When PAL is included in the models as an additional covariate, the Tsimane “excess” TEE reduces to 177 kcal/day (Supporting Information Table S3: Model 3). If RMR is added instead of PAL to the mod-

els, the Tsimane no longer appear different than other populations ($p = .88$) (Supporting Information Table S3: Model 2).

3.3 | Predictors of excess RMR

We first assess whether groups of variables summarizing anthropometric status, weather conditions at time of study, and medical diagnoses predict “excess” RMR, i.e. the deviation of measured RMR from its estimation based on the most conservative prediction equation (Cunningham), after controlling for age, sex, season, time of day, and time last eaten. Being taller, and having greater fat mass but lower weight are associated with having excess RMR (Table 2: Model 1). Lower daily average temperature, mean humidity, and precipitation are also associated with excess RMR (Table 2: Model 2). Lastly, excess RMR is higher among those with clinical symptoms of intestinal helminth infection, greater immune activation as indicated by elevated WBCs, high hemoglobin and back pains (Table 2: Model 3). In all models, men have greater excess RMR, and excess RMR is greatest in the dry season.

Stepwise regression with AIC stop criterion to yield a best-fit model starting with all variables, suggests that variables from all three macro-categories are associated with excess RMR (Table 2: Model 4; Supporting Information Table S4). Having recently eaten (std $\beta = 0.19$ – 0.21), being male ($\beta = 0.11$ – 0.29), taller ($\beta = 0.08$ – 0.17), fatter ($\beta = 0.09$ – 0.14), and older ($\beta = 0.07$ – 0.19) have moderate to large effect sizes for excess RMR, but these are not consistently statistically significant in all best-fit models based on the five prediction equations (Supporting Information Table S4). We use average regression coefficients

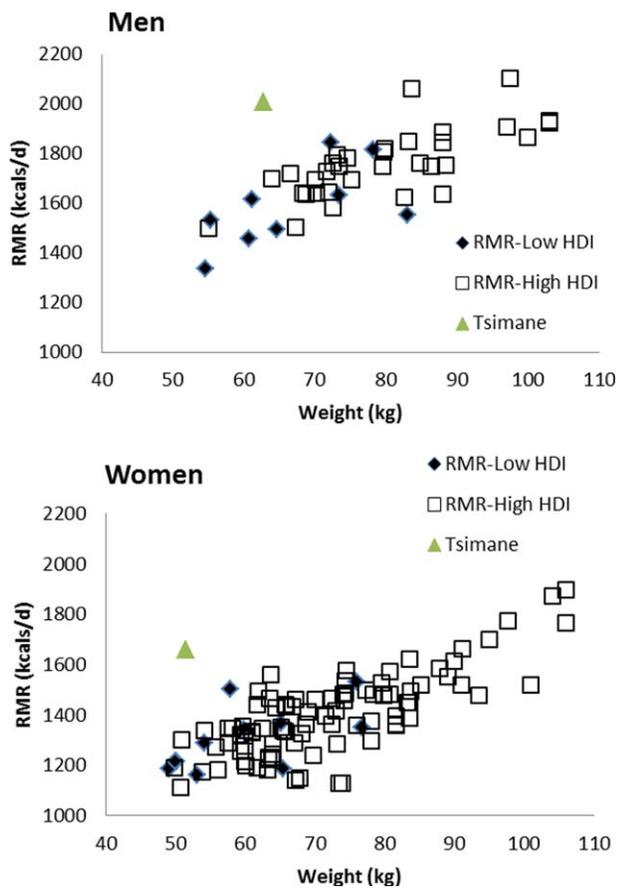


FIGURE 3 RMR in comparative perspective for adults. Comparative data from Dugas et al. (2011): Appendix. RMR is shown separately for developing (low or middle Human Development Index (HDI) populations, solid diamonds) and developed societies (high HDI, blue squares). Green triangle represents Tsimane.

from the full models of sex-specific excess RMR to derive a “conservative” estimate of RMR by subtracting the effects of season, time of day, time since last meal and precipitation from an individual’s measured RMR, and then construct a loess smooth of “conservative” RMR in Figure 2. “Conservative” RMR is substantially lower than measured RMR, especially in men, where values overlap in late adulthood with predicted RMR based on the Cunningham equation.

Elevated WBCs ($\beta = 0.08\text{--}0.10$), intestinal helminths ($\beta = 0.11\text{--}0.13$), and greater back pain ($\beta = 0.07\text{--}0.09$) were consistently associated with excess RMR across all six best-fit models. Based on the full regression models in Supporting Information Table S4, an adult diagnosed with helminths and marked WBC elevation (additional 3.0×10^6 cell/ μL) can expect to have excess RMR of 143 to 168 kcal/day, depending on the prediction equation used. This amount reflects increases of 10 to 12% and 11 to 15% above predicted mean RMR in men and women, respectively, which are independent of other covariates. No interactions between anthropometric variables and WBC count, helminths or ESR are significant when added to the best fit models. The best fit models retained a number of the control variables: recent eating is associated with excess RMR of 140 to 160 kcal/day, dry season sampling with 105 to 129 kcal/day, and mid-day sampling

with 117 to 136 excess RMR kcal/day. Despite the size and number of significant effects, our best-fit models explain only 9 to 19% of the variance in excess RMR, depending on which estimation equation is used as the baseline (Supporting Information Table S4).

Women’s lactation (proxied by having an infant <18 months) is associated with 223 kcal/day higher RMR ($p = .025$) when controlling for age, time of day, last eaten, ambient temperature, precipitation, and season. However, the effect of lactational status is reduced to 170 kcal/day ($p = 0.067$) in models that include anthropometric variables, and loses significance when additionally controlling for indicators of infection or immune activation (est = 129, $p = .225$). Because of this confounding with other variables, lactation did not appear in any of the best-fit models. Pregnancy was not significant in any of the models of RMR. Rather than being unimportant variables, we instead suspect that there is too little variation in pregnancy or lactation status among Tsimane women age 20 to 39 as 91% of women are either pregnant or breastfeeding. Unfortunately we do not have data on pregnancy trimester nor on breastfeeding intensity to obtain more fine-grained results.

3.4 | RMR decline with age

RMR changes minimally from ages 20 to 39, but then declines starting by age 40 years (Figure 2). We test the extent to which this age decline diminishes after controlling for other time-varying factors that are associated with RMR. Supporting Information Figures S1 and S2 show the age profiles of anthropometric and biomedical variables for men and women. FFM, height, weight, and WBC count decline with age in both sexes. Fat mass tends to decline after age 50 in women; fat mass and body fat percentage tend to increase with age in men. Serum hemoglobin tends to increase with age in women, but decreases with age in men. ESR shows a greater increase in men than women, though it remains higher in women overall.

We add covariates in a stepwise fashion to regression models of RMR on age for adults aged 40+ years and examine the change in the age slope (Table 3, Supporting Information Tables S6–S8). The baseline model controlling for sex shows a 69 kcal/decade decline in RMR ($p < .0001$). Adding controls for ambient weather, time of day, and time since last eaten reduces the baseline age slope by 9%. It reduces further by 71% after considering FFM and height. Consideration of biomedical variables slightly improves overall model fit in Models 5 to 9 and reduces statistical significance of the age effect, but does not substantially alter its magnitude (range: 67–89% below baseline age effect). A stepwise regression model with AIC stop criterion using all the variables of Model 9 in Table 3 shows an age effect that is 68% below the baseline estimate. This level of decline is about 1.2% per decade from an initial 1,826 kcal/day average from ages 20 to 39. Overall, at least two-thirds of the decline in RMR with age is due to changes in other aspects of phenotypic condition indicating nutritional and health status. Results vary only minimally when not restricting the dataset to non-missing cases (Supporting Information Table S6) or when imputing missing data using two different methods (Supporting Information Tables S7 and S8).

TABLE 2 Predictors of “excess” RMR

Parameter	Model 1: anthropom (n = 1,155)			Model 2: weather (n = 1,139)			Model 3: medical (n = 702)			Model 4: full (n = 691)		
	Est.	β	p	Est.	β	p	Est.	β	p	Est.	β	p
Intercept	-697.1	0.00	.0053	693.5	0.00	<.0001	-280.5	0.00	.0508	-927.9	0.00	.0017
Sex (1 = male)	188.1	0.29	<.0001	115.6	0.18	<.0001	108.9	0.17	<.0001	178.3	0.28	<.0001
Age (yrs)	-1.2	-0.05	.0933									
Time												
<8:00 vs. 8–12 p.m.	88.4	0.05	.087	81.6	0.04	.1241				62.9	0.03	.3342
12–2 p.m. vs. 8–12 p.m.	60.2	0.04	.1661	68.1	0.04	.1306				123.3	0.09	.0178
2–5 p.m. vs. 8–12 p.m.	63.3	0.09	.0026	53.5	0.07	.014				58.8	0.08	.0311
>5 p.m. vs. 8–12 p.m.	39.0	0.02	.4516	-31.7	-0.02	.4914				40.5	0.03	.5074
Hrs ago ate												
0–4 vs. 5–9	89.1	0.11	.0954				134.3	0.17	.0161	146.6	0.19	.0257
10+ vs. 5–9	132.5	0.16	.0179				115.9	0.14	.0547	128.4	0.15	.0598
Season												
Dry vs. wet	128.8	0.20	<.0001	110.7	0.17	.0002	136.7	0.21	.0002	122.0	0.19	.0007
Other vs. wet	76.9	0.11	.0061	40.8	0.06	.1721	77.2	0.12	.0347	85.4	0.13	.0162
Fat-free mass (kg)										-8.7	-0.20	.0002
Fat mass (kg)	22.7	0.42	<.0001							12.7	0.24	<.0001
Height (cm)	6.4	0.16	.0002							6.5	0.17	.0017
Weight (kg)	-9.2	-0.27	<.0001									.
Mean daily temp (°C)				-5.3	-0.11	.0006						
Mean daily humidity (%)				-2.1	-0.07	.0153						
Daily Precipitation (mm)				-89.7	-0.05	.1123				-144.2	-0.08	.0294
Hemoglobin (mg/l)							16.0	0.07	.098			
WBC ($\times 10^3$ cells/ μ l)							8.8	0.08	.0363	10.1	0.09	.0142
Helminths (1 = yes)							150.5	0.14	.0002	131.3	0.13	.0008
Back pains (1 = yes)							47.5	0.07	.0547	50.7	0.08	.0347
Model fit	Adj $R^2 = 0.1322$			Adj $R^2 = 0.1139$			Adj $R^2 = 0.1040$			Adj $R^2 = 0.1732$		

Note. Excess is defined as measured RMR - estimated RMR from Cunningham prediction equation. Models consider variables on anthropometrics, weather, infection/medical status, with age, sex, time since eaten, and time of day as controls. Each model employs stepwise selection method with AIC selection criterion. Additional variables in the models that were excluded from the stepwise selection include fat-free mass, fever, giardia (1 = yes), respiratory ailment (1 = yes), gastrointestinal ailment (1 = yes). “est.” refers to unstandardized parameter estimate; β is the standardized regression coefficient.

4 | DISCUSSION

Tsimane RMR is much higher than predicted by standard equations that rely only on age and anthropometric measures. Standard equations are often poor predictors of RMR in select samples, such as professional athletes. For example, Harris-Benedict and Cunningham equations have grossly underestimated RMR in male heavyweight endurance athletes (Carlssohn et al., 2011). Prediction equations underestimated RMR in male rowers and canoeists by 133 to 202 kcals/day (Carlssohn et al., 2011). FAO equation overestimated RMR in a Vietnamese sample by 7 to 14% (Nhung et al., 2005). The closest predictions with the Cunningham equation still underestimated Tsimane RMR by over 250 kcals/day. However, no prediction equation can fit all individuals and situations (Wang, Heshka, Zhang, Boozer, & Heymsfield, 2001). While FFM often accounts for the majority (~50–80%) of intrapopulation variation in daily RMR, a high level of intraspecies variation in RMR not explained by

differences in FFM, age and sex suggests the importance of other processes (Henry, 2000; Weiss, Cappola, Varadhan, & Fried, 2012).

One source of additional variation in RMR that we isolated was the high burden of pathogens in a tropical environment. The high RMR is surprising given that RMR is expected to be lower in tropical climates with higher mean temperatures (Froehle, 2008; Leonard, Snodgrass, & Sorenson, 2005). The costs of immune activation can be substantial: Tsimane adults with clinical symptoms of intestinal helminth infection have excess RMR of 116 to 138 kcals/day (Supporting Information Table S4). Elevated WBC counts are 10 times more prevalent among Tsimane than Americans; Tsimane WBCs are 2,600 cells/ μ L higher on average than U.S. levels among adults age 18 to 49 (Blackwell et al., 2016), which in our model adds 23 to 28 excess RMR kcals/day. These findings build upon results from studies in Western populations showing RMR increases with infection (Muehlenbein, Hirschtick, Bonner, & Swartz, 2010). However, the role of infection on energy balance and

TABLE 3 Rate of RMR decline with age for adults age 40+

Model	Parameter estimate: AGE	Std. error	Pr > t	β	% Reduced from Model 1	% Decline per Decade	Adj R ²	Controlling for:
1	-6.85	1.05	<.0001	-0.194	-	3.7	0.246	Sex
2	-6.25	1.08	<.0001	-0.178	8.7	3.4	0.269	+ Time since last ate, time of day, mean ambient temperature that day, mean precipitation that day
3	-2.30	1.12	0.0405	-0.066	66.4	1.3	0.350	+ FFM
4	-1.96	1.12	0.0822	-0.056	71.4	1.1	0.355	+ ht
5	-0.89	1.22	0.4674	-0.025	87.0	0.5	0.353	+ Hb
6	-0.74	1.40	0.5977	-0.021	89.2	0.4	0.351	+ ESR, WBC
7	-2.08	1.44	0.1486	-0.060	69.6	1.1	0.367	+ helminth
8	-2.29	1.45	0.1151	-0.066	66.6	1.3	0.368	+ fever
9	-2.28	1.45	0.1161	-0.066	66.7	1.2	0.368	+ Respiratory, giardia, back pains
Step	-2.18	1.44	0.1311	-0.063	68.1	1.2	0.367	+ Sex, FFM, ht, Hb, WBC, helminths, respiratory infection, precipitation, time since last eaten

Note. Effects of adding additional covariates to regression models on the rate of RMR decline with age. Model 1 is the baseline model controlling only for age. "Step" model is a stepwise regression with AIC stop criterion starting with all variables from Model 9.

maintenance costs in community-dwelling populations is still underappreciated. It has been estimated that quiescent WBCs require approximately 382 kcals/day, whereas activated WBCs responding to an infection require an additional 36 to 118 kcals/day from glucose, glutamine, ketone bodies, and fatty acid sources (Straub, Cutolo, Buttgeriet, & Pongratz, 2010). Chronic inflammation due to chronic infection and/or repeated acute infections often induces an "energy appeal reaction" (i.e. redirection of energy-rich fuels from stores to activated immune cells) to fuel sustained immune activation, resulting in elevated RMR via hypothalamic-pituitary-adrenal axis and sympathetic nervous system-directed activity.

With sustained immune activation, a number of co-morbid conditions can result from prolonged energetic allocation to immune defenses, including sickness behavior, cachexia, osteopenia, dyslipidemia, and anemia (Straub et al., 2010). These energy allocation decisions are regulated by circadian rhythms of interacting neuroendocrine and immune systems, which help coordinate the storage and utilization of energy throughout the day (Straub et al., 2010). Sickness behavior is common with a proinflammatory state, and is associated with more sedentary behavior (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). Depressed affect has been associated with higher inflammatory cytokines and reduced physical activity in Tsimane (Stieglitz et al., 2015b). Consistent with these and other associations of prolonged immune investment, osteopenia (Stieglitz et al., 2015a), low HDL, LDL, and total cholesterol (Gurven et al., 2009) and anemia are prevalent conditions among Tsimane. Despite their relatively active lifestyle and traditional diet, Tsimane bone mineral status, HDL, LDL, and total cholesterol are substantially lower than among age-matched U.S. peers. One hypothesis to be tested in future work is that these conditions may represent consequences of high RMR due to diversion of energy to maintain sustained immune responses.

High RMR in older age has been identified as an indication that greater energetic investment is needed to repair damage and

maintain functional homeostasis. The expectation in "healthy aging" is that RMR should decline with age, due to lower FFM and physical activity, but also after considering the effects of changing body composition and fat composition (Luhmann, Edelmann-Schafer, & Neuhauser-Berthold, 2010). Several organs decrease in mass at later ages, as do the metabolic rates of some tissues. These changes with age may be the result of tradeoffs meant to fuel other maintenance functions. If aging involves increasing costs of maintaining homeostasis, higher RMR should be associated with increasing multisystem dysregulation, physical frailty, and cachexia-like muscle loss due to insufficient energy to meet the high metabolic needs of muscle homeostasis (Ruggiero & Ferrucci, 2006; Straub et al., 2010). Some evidence is consistent with the idea that high RMR in older adults is associated with health deterioration. Older U.S. adults from the Baltimore Longitudinal Study of Aging (BLSA) with no functional limitations or medical conditions had 109 kcals/day lower RMR than those suffering from chronic conditions and comorbidities (Schrack, Knuth, Simonsick, & Ferrucci, 2014). Other studies show positive associations between RMR, morbidity and mortality (Ruggiero et al., 2008), leading some to label RMR a "candidate biomarker of global health status" (Ruggiero & Ferrucci, 2006; Schrack et al., 2014). We found that RMR makes up a greater proportion of TEE with age and for women (whereas in the same limited sample, activity-based expenditure did not vary with age ($p = .73$)), consistent with greater metabolic needs at later ages and lower relative energy available for other allocations. RMR declined with age among Tsimane over age 40 at a similar rate as in other populations, but most of this cross-sectional age effect was reduced after controlling for variation in anthropometric and health status. Additionally accounting for variation in hemoglobin levels eliminated the age effect altogether (Table 3). The lack of a robust age decline in RMR could suggest a higher level of frailty and morbidity among older Tsimane adults relative to other populations.

5 | STUDY LIMITATIONS

Field conditions limited our ability to obtain RMR measures in a completely standardized manner that is temperature controlled with participants abstaining from food and activity for 12 h. In the current study, we show that field conditions were responsible for some of the excess RMR as would be expected; time of sampling and recency of food consumption combined account for a maximum of up to 297 excess RMR kcals/day (Supporting Information Table S4). But on average, we conservatively estimate that these effects account for at most 26 to 46% of the excess RMR in women and 54 to 85% in men (Figure 2, Supporting Information Table S1). We also do not report estimates of diet-induced thermogenesis, which are likely to be greater in diets high in protein and carbohydrate, and lower in fat (Westerterp, Wilson, & Rolland, 1999). Additionally, RMR is about ~70 kcals/day higher in a seated rather than supine testing position (Compher, Frankenfield, Keim, Roth-Yousey, & Group, 2006; Levine, Schleusner, & Jensen, 2000). Despite these limitations, “resting state” can be difficult to define, and minimal metabolism will be sensitive to many other factors, including menstrual cycle, wakefulness and nervousness (Ruggiero & Ferrucci, 2006). Our data on breast feeding are limited, and the estimated cost of lactation reported here (223 kcal/day) is lower than previous estimates (Butte & King, 2005). Similarly, our pregnancy status data are limited and show no significant increase in RMR while other studies in well-nourished populations report a 90 to 470 kcal/day increase in RMR depending on trimester (Butte, Hopkinson, Mehta, Moon, & Smith, 1999). Under energy-limited conditions, BMR has been observed to slightly decrease or change only minimally during pregnancy as an energy-sparing strategy, along with lowering activity expenditure or increasing dietary intake (Jasienska, 2009; Lawrence, Coward, Lawrence, Cole, & Whitehead, 1987; Poppitt, Prentice, Goldberg, & Whitehead, 1994). Another possibility is that we were unable to find an effect because there was not a large enough sample of individuals who were not pregnant or lactating (only 9% of women aged 20–39 years). Additionally these women may have underlying pathologies impeding their reproductive state, and thus may not be comparable. Lastly, the cross-sectional design limits causal inference about age changes in RMR.

6 | CONCLUSION

Tsimane RMR is high in comparison with other human populations, even after adjusting for body mass and other covariates. These results are confirmed by DLW analyses showing that high Tsimane RMR is consistent with their higher mass- and age-adjusted TEE. Tsimane TEE is similar to that of other populations when controlling for their higher RMR. Bolivian highland agropastoralists show similar TEE and lean body mass as Tsimane, but lower RMR and higher PAL (Kashiwazaki et al., 1995, 2009). Our findings are consistent with TEE being constrained within a relatively narrow range (Pontzer, 2015), whereas, given their physically active lifestyle, an additive, unconstrained model of energy expenditure would predict even higher Tsimane TEE than we document here. If greater immune surveillance and activation require higher resting energetic expenditure in

a high pathogen tropical environment, we should expect reduced allocations towards other activities and physiological processes in populations like the Tsimane, including physical activity and cognitive performance (Ezeamama et al., 2005; Gurven et al., 2013; Trumble et al., 2015). It is noteworthy that energetic limitations do not appear to shunt energy away from reproductive effort, given the high fertility, short interbirth intervals, early menarche and intensive breastfeeding patterns observed among Tsimane (McAllister et al., 2012; Veile et al., 2014). Future studies of the patterning and causes of RMR variation with age in different populations should help provide important insights about the changing maintenance costs affecting senescence.

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M.G. conceptualized the study and wrote the paper; M.G. and H.K. designed the study; H.P., B.T., J.S., G.Y., and A.B. revised the paper. H.K. and M.G. are co-directors of The Tsimane Health and Life History Project (THLHP), under which all data were collected. G.Y. and D.C. trained field personnel and along with THLHP staff collected RMR and DLW data. H.P. analyzed DLW samples. B.T. supervised field lab operations. B.B., A.B., B.T., and J.S. organized the datasets, M.G. and B.T. conducted statistical analyses, and had final responsibility for content.

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