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2 3	Timing of pubertal growth and menarche in indigenous Qom girls of Argentina doi.org/10.1080/03014460.2018.1486455
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21	Abstract
22	Background: Pubertal timing is in part mediated by environmental factors, with greater
23	energy availability often associated with earlier or more rapid development. Many
24	indigenous populations are undergoing socioeconomic change that may affect pubertal
25	development and related health risks, necessitating fundamental longitudinal research
26	on growth and development in these populations.
27	Aim: We describe growth velocity and time to menarche among peri-urban indigenous
28	Qom (Toba) girls in Argentina.
29	Subjects and Methods: From 2011-2015, monthly anthropometrics and menstrual
30	status were collected from 61 Qom girls aged 7-14. Growth velocity curves were
31	generated using the 'Super-imposition by translation and rotation' (SITAR) method.
32	Median time to menarche was estimated by Kaplan-Meier survival analysis.
33	<b>Results:</b> Mean ages at peak height, weight, and BMI velocity were estimated at 10.8,
34	10.5, and 10.7 years, and median age at menarche at 11.6 years (95% CI 11.4 – 11.9).

35 At menarche, 45% of girls were overweight or obese and only one participant was

36 short-statured by international standards.

37 Conclusion: Qom participants in this study exhibit relatively fast pubertal development
38 as compared to other Latin American indigenous populations studied previously by
39 others. Genetic and environmental factors influencing body size, diet, and/or activity
40 levels should be investigated further in this population.

41 Keywords: puberty, growth and development, Latin America, indigenous health,
42 menarche

43

## 44 Introduction

45 The onset and pace of pubertal progression are flexibly attuned to environmental 46 conditions (Ellis, 2004; Ellison et al., 2012), with earlier maturation generally 47 associated with greater available energetic resources and more rapid growth during 48 childhood (Ellison, 1990, 2001). Earlier pubertal maturation in females has been 49 observed globally since the 20<sup>th</sup> century (Parent et al., 2003; Biro et al., 2012), and is a 50 growing public health concern, since earlier onset of menstruation and gains in 51 adiposity may increase later life risk of reproductive cancers, obesity, and other 52 metabolic diseases (Stoll, 1998; Stöckl et al., 2011; Akter et al., 2012; Glueck et al., 53 2013). In certain cultural contexts, earlier sexual maturation may also lead to earlier 54 sexual activity and increase risks of early adolescent pregnancy, sexually transmitted 55 diseases, sexual abuse, depression, or anxiety (Angold et al., 1999; Kaestle et al., 2005; 56 Boden et al., 2011).

57 Variation in pubertal development by socioeconomic class or ethnicity within
58 populations is of further interest, as such variation may both reflect underlying
59 differences in environmental quality or risk exposures, and predict later health

60 disparities. National surveys from Brazil, Argentina, and Colombia have shown that 61 earlier menarche is associated with higher income, better education, and greater 62 birthweight, height, and BMI (Orden et al., 2011; Castilho and Nucci, 2015; Jansen et 63 al., 2015). However, comparative research on pubertal development in Latin America 64 by ethnicity and genetic ancestry has been limited. Though Latin American indigenous 65 populations are generally economically marginalized, poverty may increase risks of 66 over- or undernutrition depending on the quality of diet and other local conditions 67 (Monteiro et al., 2004; Caballero, 2005), suggesting varying influences on pubertal development. For example, in the U.S. menarche generally occurs earlier among girls of 68 69 lower socioeconomic status (Obeidallah et al., 2000; Krieger et al., 2015), who also tend 70 have higher obesity risks (Drewnowski and Darmon, 2005; Frederick et al., 2014). In 71 contrast, a study in Chile found that Mapuche indigenous girls were shorter, heavier and 72 had later ages at menarche than their non-indigenous peers, with earlier menarche 73 across both groups associated with higher stature and SES, not greater weight or BMI 74 (Amigo et al., 2010, 2015, Ossa et al., 2010, 2012). 75 The Qom (Toba) are an indigenous population residing primarily in the 76 northeastern Gran Chaco region of Argentina. Most Qom live below the national 77 poverty level. However, mean height-for-age (HAZ) and BMI-for age z scores (BMIZ) 78 of Qom children aged 0 - 18.9 years are well within normal ranges of international and 79 national growth references (Alfonso-Durruty and Valeggia, 2016), and Qom adult 80 stature is among the highest of small-scale indigenous populations surveyed globally 81 (Walker et al., 2006). The prevalence of obesity and metabolic disorders in this 82 transitioning population has also been steadily increasing (Valeggia et al., 2010; 83 Lagranja et al., 2014a). Qom developmental trajectories may be either relatively slow or 84 fast, given that the Qom are an economically marginalized South American indigenous

population, but conversely relatively tall and well-nourished. In this descriptive study,
we analyse patterns of growth velocity, time to menarche, and additional measures of
nutritional status and pubertal development from a longitudinal study of pubertal Qom
females. We compare Qom pubertal trajectories to those of other sample populations
previously published, emphasizing Latin American and indigenous populations where
possible.

91

## 92 Materials and Methods

93 Study population

94 The Qom of Argentina (referred to as "Toba" by neighbouring, but not related,

95 indigenous groups) were traditionally semi-nomadic hunter-gatherers, who resisted

96 Spanish colonization and Argentinian expansion policies until the late 1800s (Valeggia

97 and Tola, 2003). Since the 1930s, government policy and habitat degradation have

98 forced many Qom into peri-urban settlements. The total population today is around

99 70,000, with most Qom residing in the provinces of Chaco and Formosa, and in smaller

100 settlements around Santa Fe and Buenos Aires. This study was conducted with girls in

101 the peri-urban village of Namqom, a genetically homogenous Eastern Qom settlement

102 (pop. ~3000), located 11 km outside of the city of Formosa (pop 234,000), and

103 established in the early 1970s (Alfonso-Durruty and Valeggia, 2016).

104Namqom families subsist primarily on government subsidies, with additional105income generated from men's temporary wage labor and women's sales of artisanal106crafts. The typical diet in Namqom is high in carbohydrates and fat from staples like107*torta frita* (fried bread) (Lagranja et al., 2014b). Thirty-five and 45% of adults are

108 classified as obese and overweight, respectively (Lagranja et al., 2014a). In more rural

109 Qom communities BMI is positively associated with socioeconomic status (Valeggia et110 al., 2010), though this relationship may be reversed in peri-urban Namqom.

111 A health center in Namgom offers prenatal and child health care, and the 112 majority of births take place in a local city hospital. The incidence of pre-term births is 113 comparable to that of non-indigenous women in the area. The majority of infants are 114 within normal birth weight range (2500 - 4000 g), with 0-3% classified as low 115 birthweight and 10-12% as more than 4000g. In general infants are exclusively 116 breastfed until about four to six months of age and weaned when the mother gets 117 pregnant again, or the child weans him/herself (Valeggia and Ellison, 2003a; b; Olmedo 118 et al., 2014). Adolescent sexual activity, including prostitution, is not stigmatized but 119 may pose health risks. The average age at first birth is 16. Adolescent mothers usually 120 remain single and live at home, and it is common of them to foster away care of their 121 first born children to parents or other relatives (Valeggia and Tola, 2003).

122

# 123 Ethics approval and consent to participate

Participants and their caretakers were informed that the purpose of the study was to
examine pubertal development in the population. All girls and their adult caretakers
(usually the mother) provided verbal informed consent to participate. The research
protocol was approved by the internal review boards of both the University of
Pennsylvania (Protocol # 811200) and Yale University (HSC Protocol # 1406014104).
There were no ethics committees available to provide approval in the province of
Formosa, where the study took place.

131

#### 132 Data collection

133 Between 2011 – 2015, researchers affiliated with the Chaco Area Reproductive 134 Ecology (CARE) program followed a total of 61 self-identifying Qom girls between the 135 ages of 7 -14. This data was collected as part of a larger study to examine endocrine 136 correlates of female reproductive life history transitions. Subject recruitment: All 137 females aged 7-10 in Namqom were eligible for inclusion in the study and invited to 138 participate. As Qom families move frequently among kin residences and across 139 territories, participants were located and recruited into the study between 2011-2013 140 (Table 1). To our knowledge, there were no girls aged 7-10 living permanently in the 141 community during those years who were approached and excluded based on menarcheal 142 status, or who declined to participate. However, at the start of data collection in January 143 2011, four pre-menarcheal girls aged 12-13 requested to be part of the study and were 144 also included. To test if inclusion of these subjects biased results, we ran separate 145 survival analysis models of time to menarche both including and excluding these 146 subjects. The average age at first observation across all participants was  $9.4 \pm 1.2$  years 147 (range 7.3 – 13.4; IQR 8.4 – 10.9).

148 Subject follow-up: The original study design protocol called for researchers to 149 follow participants monthly until they reported menstruating three times or for six 150 months after menarche. The total number of observations per subject per year varied 151 due to age at initial observation, age at menarche, age at study exit, and intermittent 152 absences (Table 1). Age at menstruation was reported by 51/61 participants: three 153 participants had still not experienced menarche by the end of the study in 2015 (mean 154 age at last observation  $12.3 \pm 0.7$  years; mean number of observations  $37 \pm 4$ ); one 155 participant left the study at her mother's request at age 8.7 after five visits; six 156 participants moved away or were otherwise lost to follow up (mean age at last 157 observation 9.7  $\pm$  1.1 years; mean number of observations 12  $\pm$  13). The mean number 158 of observations per subject was  $24 \pm 11$  (range 2 - 46, IQR 16 - 29). Among participants 159 with known age at menarche, the mean number of pre- and post-menarcheal 160 observations per subject were  $20 \pm 4$  and  $4 \pm 3$ , respectively, and the mean age at last 161 observation was  $12.0 \pm 1.0$  (range 9.9 - 14.4).

162 Measurement protocols: Anthropometric measures and self-reported menstrual 163 status and Tanner breast stage were collected by researchers during monthly visits to the 164 participants' homes. Height was measured to the nearest centimeter using a portable 165 SECA 213 portable stadiometer. Chest, waist, and hip circumference were measured to 166 the nearest 0.5 cm using a portable tape measure. Weight (kg) and % body fat (via 167 electrical impedance) were recorded using TANITA ® body composition scale. Tricep 168 and subscapular skinfolds were measured in triplicate to the nearest mm using Lange 169 calipers. Participants were also given photographs of Tanner breast stages digitally 170 modified with darker skin images to reference, and asked to self-report their own stage 171 of development. However, in 39% of interviews, participants declined to report this 172 information. Maternal age at menarche and participants' birth weight, birth length, and 173 gestational age from birth records were collected at initial interviews if available.

174

## 175 Statistical analysis

176 All statistical analyses were run on R (ver. 3.4.1). Descriptive statistics were generated

177 for each of the following anthropometric measurements at initial observation and at age

178 of menarche: weight, height, BMI, % body fat, waist, hip, and chest circumference,

- 179 waist to hip ratio, and subscapular and triceps skinfold measurements. Triplicate
- 180 measures of subscapular and tricep skinfolds were averaged for each observation.
- 181 Height-for-age (HAZ) and BMI-for-age z-scores (BMIZ) were calculated using WHO
- 182 2007 growth standards (de Onis et al., 2007). HAZ and weight-for-age z scores (WAZ)

183 were also calculated based on Argentina LMS pediatric growth references (Lejarraga et 184 al., 2009). To account for intermittent missing self-reported Tanner breast stages, we 185 assigned a median breast stage score to each six-month period of observation for each 186 participant. Kaplan-Meier survival analysis was used to estimate median time to 187 menarche to incorporate both censored (n = 10) and non-censored participants (n = 51). 188 SITAR models of height, weight, and BMI velocity were generated using the 189 sitar package in R (Cole, 2017). The method has been previously used to model height 190 velocities of European and South American children (Cole et al., 2014; Blackwell et al., 191 2016b). As described in more detail elsewhere (Cole et al., 2010; Pizzi et al., 2014), the 192 SITAR method uses a shape invariant spline curve and a nonlinear random-effects 193 model to fit individual trajectories and estimate an average growth curve for a sample. 194 The model estimates three fixed and random effects ( $\alpha, \beta, \gamma$ ), referred to as *size, tempo*, 195 and *velocity*, which define how individual curves deviate from the mean (Cole et al., 196 2010). For each growth outcome, *size* is interpreted as a random intercept, with larger 197 values representing larger mean size than average (an upward shift of the curve). Tempo 198 adjusts for differences in the age at peak velocity (APV), with positive values indicative 199 of later maturation and negative values indicative of earlier maturation relative to the 200 mean (right or left shifts of the curve). *Velocity* adjusts for the duration of the growth 201 spurt, with positive values indicative of faster and negative values of slower growth 202 (stretching or shrinking the curve along the age scale). 203

To ensure model convergence, we constrained all observations to equivalent intervals by rounding each age at measurement in years to the nearest 1<sup>st</sup> decimal (e.g. 8.1, 8.2, 8.3). In the case of multiple measures per individual in an interval, only the first measure was retained. We eliminated from the sample any age intervals with fewer than five subjects per interval, and any subjects with fewer than three observations. The

resulting sample included 58 subjects ages 8.0 – 13.0, with 1174 height observations
and 1171 weight/BMI observations. Final models for height, weight, and BMI were all
fit with a five-degree polynomial curve.

211 Prior to assembling the database used in this study, raw data points were visually 212 inspected. Biologically implausible measures (monthly deviations of > 2 cm or > 5 kg 213 from previous or subsequent measures) were checked against written records and 214 amended, or removed in extreme cases. For the SITAR models, we examined additional 215 outliers within individual trajectories using custom package functions. Removal of 216 weight and BMI outliers substantially reduced the sample, resulting in an altered weight 217 velocity curve and non-convergence of the BMI velocity model. Since errors appeared 218 randomly distributed across subjects, and there was a high number of discrete data 219 points per subject, we ultimately elected not to remove flagged outliers from the final 220 models. Growth velocities calculated over measurement increments of < 0.85 years are 221 more affected by seasonal shifts and measurement error (Tanner and Davies, 1985). 222 However, SITAR growth models for Qom girls did not converge when the dataset was 223 reduced to measurements taken every 3 or 6 months, likely due to the resulting small 224 sample size. Removal of one subject observed to be an extreme outlier for weight (mean 225 84.7  $\pm$  11.4 kg) and BMI (mean 37.0  $\pm$  2.8) resulted in biomodal growth velocity 226 distributions or nonconvergence of models. In general, the SITAR models were highly 227 sensitive to any data reduction. A model of fat velocity, with % body fat measured from 228 bioelectrical impedance, also failed to converge. Velocity curves and estimates for peak 229 velocity and age at peak velocity were generated from *sitar* package custom commands. 230 Datasets and R code used to generate analyses are publically available on figshare 231 (https://doi.org/10.6084/m9.figshare.4757164.v2).

#### 233 Results

234 Eighty percent of Qom girls with known age at menarche (40/51) experienced menarche 235 before age 12. The median time to menarche estimated by survival analysis for censored 236 and non-censored subjects was 11.6 years (95% CI 11.4 – 11.9) (Fig.1), which was 237 largely concordant with mean and median ages from girls with known age at menarche 238 (Table 2). Median time to menarche was slightly decreased by removing the four pre-239 menarcheal subjects who were aged 12-13 at first observation from the survival analysis 240 (11.4, 95% CI 11.3 – 11.8). There are no standard cut-offs for defining early menarche, 241 with researchers varyingly using population cut-offs of < 11 to < 12 years (Ibáñez et 242 al., 2006; Stöckl et al., 2011; Akter et al., 2012; Glueck et al., 2013). We estimate that 243 77% (66 – 89% 95% CI) of Qom girls are still premenarchal at age 11, and only 31% 244 (21-47%) at age 12. (Figure 1). For subjects' mothers with available data (n = 48), their 245 average age of menarche reported by recall was  $12.81 \pm 1.08$ , suggesting a secular trend 246 towards earlier pubertal development. Participants and their mothers' reported ages at 247 menarche were weakly correlated (Pearson's r = 0.337, 95% CI = 0.041 - 0.579; p =248 0.027).

249 Precocious the larche is frequently diagnosed if breast development is observed 250 before age 8, ideally confirmed by palpation in a supine position (Kaplowitz and Bloch, 251 2015). We lack appropriate diagnoses for precocious the larche based on these criteria, 252 and only two subjects observed at age seven ever self-reported breast stage, both 253 reporting stage I development. Across all participants observed from ages 7-9 (n = 57), 254 in 59% of monthly observations (226/381) participants reported Tanner Stage I breast 255 development, 36% (138/381) reported Stage II, and 5% (17/381) reported Stage III-V. 256 Among subjects reporting menarche, 7% (3/51) reported Stage I breast development in

the month of menarche, 64% (29/51) Stage II, 27% Stage III (12/51), and 2% (1/51)
Stage IV.

259 For participants with available data, most were born within normal birthweight 260 ranges, though 5% (3/58) would be classified as low birthweight (< 2.5 kg) and 9% 261 (5/58) as macrosomic (> 4 kg). For subjects with known gestational ages, 23% (9/39) 262 were classified as preterm at < 37 weeks. At initial observations, 26% of participants 263 were overweight and 8% were obese, with only 7% classified as short-statured (Table 264 3). By menarche, the percentage of short-statured girls slightly decreased while 265 percentages of obese and overweight girls slightly increased (Table 3). Mean HAZ 266 scores at menarche were well within normal ranges as calculated by either WHO 267 standards or Argentina growth references (Table 2). 268 There have been limited studies to determine cut-offs for abdominal obesity 269 based on waist circumference or waist/height ratios in children, and cut-off values may 270 vary with age and ethnicity (Lear et al., 2010; Lewitt et al., 2012; Magalhães et al., 271 2014). Waist circumference cut-offs of  $\geq$  70.1 and  $\geq$  69.9 cm have been recommended 272 for Mexican girls aged 8-9 and 10 year-old, respectively (Gomez-Diaz et al., 2005), and 273 65.1 - 69.1 cm for mixed-ethnicity Chinese girls aged 7 - 18 (Yan et al., 2008). Waist-274 height ratio cut-offs of > 0.44 and > 0.43 cm have been recommended for Brazilian 275 girls aged 8 and 9 (Sant'Anna et al., 2010), and 0.475 - 0.50 for Chinese, Spanish, and 276 Italian children up to age 18 (Yan et al., 2007; Maffeis et al., 2008; Marrodán et al., 277 2013). Conservatively, we applied cut-off values of  $\geq$ 70 cm for waist circumference and 278  $\geq$  0.50 for waist/height ratio as potentially indicative of abdominal obesity. At first 279 observation (n = 61), 11% of participants had a waist circumference of  $\geq$ 70 cm and 25% 280 had a waist/height ratio  $\geq 0.50$ . For participants reporting menarche (n = 51), the 281 prevalence was 43% and 25%, respectively, at month of menarche. Waist/height ratio at

282 first observation was not associated with age at menarche after adjusting for age at first

observation (Est. = -2.2, 95% CI = -7.21 - 2.28; p = 0.381).

284 As estimated by SITAR models, mean age at peak velocity and mean peak 285 velocity were estimated at 10.8 years and 9.4 cm/years for height, and 10.5 years and 286 8.5 kg/year for weight. Mean age at BMI velocity was estimated at 10.7 years. Velocity 287 and distance curves for each growth measure are shown in Figures 2a-c. The models 288 explained 98.8%, 99.1, and 97.8% of variance in height, weight, and BMI, respectively. 289 Random effects for size and tempo were positively correlated in models of height 290 (0.63), weight (0.61), and BMI velocity (0.60), indicating that later maturation is 291 associated with greater average body size. Growth velocity was more strongly 292 correlated with size and tempo in models of weight (size/tempo 0.62/0.80) and BMI 293 (0.58/0.56) than in models of height (0.14/0.32).

294

283

# 295 Discussion

296 There have been relatively few longitudinal studies on growth and menarcheal 297 onset in indigenous populations, limiting knowledge of normative variation in pubertal 298 development globally. Pubertal development among the Qom girls observed here 299 appears relatively accelerated when compared to available published estimates of 300 growth velocity in indigenous and non-indigenous populations. To our knowledge, only 301 two studies have used similar methods—i.e. SITAR curves or pseudo-velocity curves 302 from median LMS values—to characterize pubertal growth in indigenous populations. 303 These were conducted with neotropical horticulturalist populations, the Tsimane of 304 Bolivia and the Shuar of Ecuador. For both height and weight, mean peak velocities are 305 greater and mean ages of peak velocity are earlier in Qom as compared to Tsimane 306 females (height: 8.2 cm/yr, 11.3 years; 6.5 kg/yr, 12.0 years) (Blackwell et al., 2016b).

307	Comparatively, Shuar females exhibited a slightly earlier mean age of peak height
308	velocity (10.2 years), but later mean age at peak weight velocity (12.1 years) and
309	substantially lower velocities for height and weight (5.4 cm/yr, 2.2 kg/yr, 12.1 years)
310	(Urlacher et al., 2015).

311 Differences in pubertal growth between the Qom and these indigenous 312 populations are expected due to substantial intra-and inter-population environmental 313 and genetic variation. For example, the Tsimane and the Shuar are characterized by 314 short adult stature, a high prevalence of childhood stunting and infectious diseases, and 315 relatively low prevalence of overweight/obesity (Godoy et al., 2006; Blackwell et al., 316 2010, 2016a; Liebert et al., 2013; Rosinger et al., 2013; Urlacher et al., 2016). In 317 contrast, the average height of Qom adults are among the highest documented for 318 indigenous groups globally (Walker et al., 2006), and 35% and 45% of Qom adults are 319 obese and overweight, respectively (Lagranja et al., 2014a). 320 Estimated peak height velocity for these participants is also earlier as compared 321 to estimates of 11.5 - 12.1 years published in seminal studies of American and 322 European girls observed from the 1960s – 1990s (Tanner, 1989; Abbassi, 1998; 323 Granados et al., 2015). The SITAR method was recently applied to a study of English 324 girls measured in the 1970s (Cole et al., 2014), and estimated age at peak height 325 velocity and peak velocity in those subjects at 11.9 years and 7.6 cm/year, respectively. 326 In an early study of pubertal growth in North American children, early maturation was 327 noted to coincide with greater peak height velocity (Tanner and Davies, 1985). In Qom 328 girls, the estimated age at peak weight velocity preceded age at peak height velocity by 329 ~ four months, whereas elsewhere peak height velocity has been reported to precede 330 peak weight velocity by about six months elsewhere (Rogol et al., 2000). Average peak 331 height velocity of Qom girls also preceded average age at menarche by approximately

9.6 months, whereas an average difference of about one year between these events was
estimated for English girls measured in the 1970s (Cole et al., 2014). The growth
differences observed in these comparisons may reflect local genetic and obesogenic
conditions, but also general secular trends operating across disparate observation
periods.

337 At ~11.5 years, menarche also occurs on average about 6 months to 2 years 338 earlier in these Qom girls than as reported in recent studies for girls in the U.S., Europe, 339 and Latin America, including Argentina (Ossa et al., 2010; Orden et al., 2011; Torres et 340 al., 2011; Currie et al., 2012; Cabrera et al., 2014; Castilho and Nucci, 2015; Jansen et 341 al., 2015; Krieger et al., 2015), and may reflect the influence of obesogenic conditions 342 as observed elsewhere. For example, average ages of menarche around 11.5 years or 343 earlier have been observed and associated with excess weight and/or body fat in girls 344 from the Brazilian Amazon (Barcellos Gemelli et al., 2016), Yucatán, México (Datta 345 Banik et al., 2015), Italy (Rigon et al., 2010), and Argentina (Figueroa Sobrero et al., 346 2016). Similarly, a comparative study of pubertal development in children from Bolivia 347 (Takana and Esse ejja ethnicities) and Senegal (Tokolor, Wolof, and Serer ethnicities), 348 all of whom lived in rural, tropical environments, found that the characteristically "short 349 and plump" Bolivian girls had much earlier ages of menarche (median 12.9 years) than 350 the characteristically "tall and thin" Senagalese girls (median 15.9 years) (Benefice et 351 al., 2011). Average ages of menarche around 11.5 years have also been associated with 352 relative affluence in specific demographic groups within populations—e.g.: Saudi 353 Arabian girls attending private schools (Shaik et al., 2015), and Mexican girls born after 354 1990 (Marván et al., 2016). Finally, while Mapuche girls in Chile experience menarche 355 2-4 months later on average than non-indigenous neighbouring girls (Amigo et al., 356 2010, 2012; Ossa et al., 2012), among the Mapuche themselves, researchers have

observed a secular trend in decreasing age at menarche since the 1960s (Ossa et al.,
2010), and earlier menarche in association with obesity and higher socioeconomic status
(Amigo et al., 2012).

360 Qom environmental and genetic conditions influencing infant and childhood 361 growth patterns may influence relatively accelerated pubertal development. The present 362 study suggests a picture of sufficient to excess nutrition in later childhood, as at first 363 observations 24% of participants were overweight, 8% were obese, and only 7% were 364 short-statured. A previous survey showed that mean HAZ in Qom children increased in 365 each successive age group following infancy, while mean WAZ was u-shaped (with a 366 nadir during ages 3-6), and mean BMIZ was lower in each age group following infancy, 367 levelling off after age 11. Mean BMIZ in infants (0-2.9 years) of both sexes and across 368 all regions was  $1.64 \pm 1.18$ , which is notable because Qom infants are exclusively breastfed for about six months and breastfed for about 2-3 years. Mean HAZ was also 369 370 significantly higher among more rural Western Qom than among peri-urban Eastern 371 Qom (Alfonso-Durruty and Valeggia, 2016), suggesting a wider underlying genetic 372 influence.

373 We have previously proposed that Qom growth patterns—i.e. decreasing mean 374 BMIZ and increasing mean HAZ after infancy-may reflect an evolutionarily selected strategy (Alfonso-Durruty and Valeggia 2016). Life-history theory posits that somatic 375 376 energy expenditure at key phases of the life course may be shaped by selection to 377 maximize survival or reproduction through differential energy allocation. Energy trade-378 offs can occur between investment in growth, reproduction, or maintenance, but also 379 within those individual categories, for example between linear growth and adiposity. 380 Preferential investment in adiposity (maintenance) relatively to linear growth during 381 infancy may buffer against energy losses related to infectious disease and nutritional

scarcity, and therefore may be common strategy in risky environments (Ellison 2001;
Walker et al., 2006). Conversely, the observed gains in linear height during childhood
and adolescence—which result in larger adult body size relative to other small-scale
populations (Walker et al., 2006)—may reflect energetic adaptations to the Chacoan
ecology and/or relaxed selection pressures from infectious disease burdens post-infancy.

388 Limitations and Future Directions

389 A strength of our study is the longitudinal design with multiple, discrete measurements 390 per subject. Longitudinal research on growth and development in indigenous 391 populations in particular has been limited. While participants in this study represented 392 all available female subjects in the study village at the time, the study design is 393 unbalanced due to participants entering and exiting the study at different ages, rather 394 than according to set observational windows. Analysis of pubertal development 395 according to Tanner stages was not possible because of cultural sensitivity issues, which 396 limited data collection to self-reported breast development, with participants frequently 397 declining to report this information. Finally, though recall bias for age at menarche was 398 minimized through monthly visits, we cannot rule out inaccurate self-reporting.

399 Analysis of causal factors associated with variation in pubertal growth is beyond 400 the scope of this dataset. While shorter gestational age, low birth weight, and more rapid 401 postnatal catch-up growth have been associated with earlier pubertal maturation 402 (Wehkalampi et al., 2011; Addo et al., 2014), we lacked sufficient data to investigate 403 these relationships among our participants. Similarly, while over a third of participants 404 in our study were overweight or obese at initial observations, additional longitudinal 405 research beginning in mid-childhood would be necessary to assess whether the patterns 406 of pubertal development observed here are reflective of age at pubertal onset, the pace

407 of pubertal development, or both. Ongoing research stemming from this study will
408 investigate the relationship between growth velocity and concordant changes in
409 metabolic, reproductive, and immunological urinary biomarkers, which may provide
410 more insight into cumulative energetic influences on pubertal development.

411 Additional longitudinal research would be necessary to assess differences in 412 pubertal maturation between Qom and more affluent non-Qom residents of Formosa. If 413 pubertal development among the Qom does indeed occur relatively earlier, the pattern 414 may be more analogous to that observed in the U.S., in which lower SES and minority 415 groups tend to have earlier ages at menarche but also greater BMI and earlier skeletal 416 maturation (Bogin, 1999; Obeidallah et al., 2000; Kelly et al., 2014). In this case, future 417 research should also explore local patterns of pubertal development in relation to 418 variation in diet, activity, early growth trajectories, and exposure to endocrine 419 disrupting chemicals or specific dietary components. Such research may help determine 420 to what extent early pubertal development in the Qom may be genetic or owing to 421 modifiable socioeconomic and cultural factors. Finally, while early adolescent sexual 422 activity and pregnancy among Qom girls are common and culturally accepted, 423 additional research may examine if differences in pubertal trajectories within the 424 population influence variation in subsequent sexual activity, timing of first births, or 425 later life metabolic or reproductive health risks.

426

# 427 Conclusions

We have described pubertal growth and age at menarche in a sample of indigenousQom girls from a peri-urban village in Formosa, Argentina. Mean ages at peak height

430 velocity (10.8 years) and menarche (11.6 years) of participants were relatively early

431 compared to estimates reported in several other studies of girls in Latin America, U.S.,

432 and Europe. Accelerated pubertal development in these girls may reflect local energetic 433 factors—including a high carbohydrate-high fat diet and sedentarism—and population specific growth patterns, characterized by marked adiposity in infancy and gains in 434 435 linear height in later childhood. However, additional research on diet, activity, growth, 436 and environmental exposures in a wider Qom sample and other local non-indigenous 437 populations is needed to both confirm this pattern and illuminate possible causal 438 relationships. This study underscores the importance of conducting longitudinal studies 439 with diverse populations to better understand current global secular trends and variation 440 in pubertal development.

441

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464	
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741 742 743 Table 1. Number of participants entering and exiting study and total observed per study

year.

Study Year	Recruited		Exited Study	Total Followed/Yr
	n		n	n
2011		41	2	41
2012	2	16	10	55
2013	5	4	22	49
2014	Ļ		15	27
2015	i		12	12

among participants with know	n age at menarc.	ne(n = 51  out of)	i or original participants).
	Range	Mean $\pm$ SD	Median (IQR)
Age (yrs)	9.6 - 13.8	$11.5\pm0.9$	11.3 (10.9 - 11.9)
Height (cm)	136 – 157	$146.7\pm6.7$	147 (143 – 151)
Weight (kg)	29.3 - 100.7	$44.5 \pm 11.2$	41.2 (38.1 - 46.9)
BMI $(kg/m^2)$	15.6 - 40.9	$20.6\pm4.3$	20.0 (17.9 – 21.5)
HAZ (WHO) <sup>a</sup>	-2.34 - 2.49	$-0.12 \pm 1.05$	-0.11 (-0.71 – 0.33)
HAZ (Argentina) <sup>b</sup>	-0.89 - 3.61	$0.89 \pm 1.00$	0.84 (0.33 – 1.29)
WAZ (Argentina) <sup>b</sup>	-1.71 – 4.73	$1.02 \pm 1.25$	1.16 (0.31 – 1.50)
BMIZ (WHO) <sup>a</sup>	-1.98 - 4.64	$0.83 \pm 1.22$	0.93 (0.22 - 1.45)
Body fat %	13 - 52	$20.6\pm6.9$	25 (22 - 30)
Waist circ. (cm)	59 - 112	$70.0\pm8.8$	69 (64 – 73)
Hip circ. (cm)	68 - 118	$78.3\pm8.3$	76 (73 – 82)
Chest circ. (cm)	60 - 119	$78.5\pm8.6$	76.5 (75 – 119)
Bicep circ. (cm)	17 - 37	$23.1\pm3.2$	23 (21 – 25)
Waist/height ratio	0.39 - 0.71	$0.48\pm0.05$	0.48(0.44 - 0.50)
Waist/hip ratio	0.79 - 0.97	$0.89\pm0.04$	0.89(0.87 - 0.92)
Subscapular skinfold (mm)	6.7 - 28.3	$14.5\pm4.9$	13.5 (11.0 - 16.8)
Tricep skinfold (mm)	6.7 - 25.0	$13.3\pm4.7$	12.0 (10.0 - 25.0)

Table 2. Descriptive statistics of nutritional & developmental markers at menarche, among participants with known age at menarche (n = 51 out of 61 original participants). 

<sup>a</sup>WHO 2007 standards were used to calculate height-for-age (HAZ) and BMI-for-age (BMIZ) z scores. <sup>b</sup>Argentina 2009 pediatric growth references used to calculate HAZ and weight-for-age z scores (WAZ). 

752 Table 3. Prevalence of thinness, overweight, obese, and short stature among

52	participa	nts at first	observation	(n = 61)	) and at first re	port of menarche	(n = 51).
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	First observation	At menarche	
BMIZ cut-off			
Thinness (< - 2 SD)	2 (3%)	0 (0%)	
Overweight (> 1 SD)	16 (26%)	17 (33%)	
Obese $(> 2 \text{ SD})$	5 (8%)	6 (12%)	
HAZ < -2SD	4 (7%)	1 (2%)	

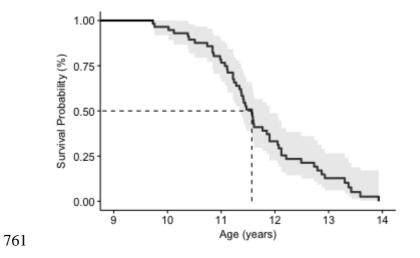
BMIZ, HAZ, and cut-offs calculated from WHO (2007) standards and guidelines.

## **Figure Captions**

757 Figure 1. Age at menarche survival curve for Qom girls estimated from 61 subjects (n

758 events = 51, n censored subjects = 10). The graph depicts the Kaplan-Meier survival

- function (black line) with 95% of confidence interval (grey band), and median survival
- 760 (dashed horizontal and vertical lines)



762

763 Figure 2 A-C. SITAR models of age at peak growth velocity, APGV (black dashed

line), and peak velocity, PV (solid grey line), for (A) height (APGV = 10.8 years, PV =

765 9.4 cm/year), (B) weight (APGV = 10.5 years, PV = 8.5 kg/year, and (C) BMI (APGV

- 766 = 10.7 years). Models were estimated from 1174 and 1171 observations, respectively,
- for height and weight/BMI from 58 Qom girls ages 8 13.

