Challenging the Inevitability of Age Related Prostate Enlargement: Low Levels of Benign Prostatic Hyperplasia among Bolivian Amerindians

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Introduction

In Western industrialized populations, the majority of men experience prostate enlargement with age. Autopsy data indicate that at least 40% of men in their 50s, and 90% of men in their 80s experience clinical benign prostatic hyperplasia (BPH) (Berry et al. 1984; Oesterling 1995). Although the relationship between BPH and prostate cancer is equivocal, BPH nonetheless has important health consequences. It can diminish urethral size leading to dysuria, nocturia, incontinence and incomplete urination, with approximately 40% of US men requiring medical treatment for BPH in their lifetime (Oesterling 1995), at an inflation-adjusted estimated cost of more than $7.45 billion per year in the United States (Graversen et al. 1989; Oesterling 1995). Thought to be an inevitable effect of aging in many industrialized populations, evidence suggests that BPH occurs in all cultures and ethnic groups (Oesterling 1995). Clinical cutoffs for prostate volumes above 20 mL are often used as diagnosis for BPH, and men with prostate volumes larger than 30 mL often report more symptoms and worse outcomes (Garraway et al. 1991; Oesterling 1995). This study is the first to examine BPH in a non-Western subsistence population, the Tsimane forager-horticulturalists of the Bolivian Amazon.

The Tsimane (population ~11,000) live in villages of approximately 30-500 people in the jungles of lowland Bolivia, relying on hunting, fishing, and gathering, and small-scale horticulture for subsistence. The Tsimane face higher levels of parasite and pathogen exposure than individuals in the US (McDade et al. 2005; Gurven et al. 2009) as demonstrated by high levels of C-Reactive protein, erythrocyte sedimentation rates, leukocyte and immunoglobulin levels, and other biomarkers of infection (McDade et al. 2005; Gurven et al. 2008; Gurven et al. 2009). Two-thirds of Tsimane adults present with signs of intestinal parasites, with one-third reporting symptoms of respiratory illness (Gurven et al. 2009). Though the Tsimane suffer from high levels of infectious disease and parasitism, the prevalence of obesity is eight times lower among the Tsimane, and there is little evidence of heart disease, hypertension, metabolic syndrome, or other diseases associated with aging in industrialized populations (Gurven et al. 2009; Gurven et al. 2012); thus understanding the prevalence of BHP with age in this population is of special interest.

While the etiology of BPH is still debated, permissive links between androgens and BPH are well characterized, with evidence that higher levels of testosterone and dihydrotestosterone (DHT) are associated with larger prostate sizes (Berry et al. 1984; Partin et al. 1991). The Tsimane and other subsistence populations experiencing energetic constraints and pathogenic stress face a trade-off between investing in survival, or reproductively beneficial, but metabolically costly and immunosuppressive testosterone (Folstad and Karter 1992; Muehlenbein and Bribiescas 2005). These populations show lower levels of testosterone across all adult ages as compared with men in industrialized nations (Bribiescas 1996; Ellison et al. 2002; Trumble et al. 2012), as well a slower and shallower rate of change with age (Ellison et al. 2002), or no association between testosterone and age (Trumble et al. 2012). Preliminary reports suggest that salivary testosterone is approximately 30% lower among Tsimane men, controlling for age and BMI (Trumble et al. 2012), see figure 2 B.

With low absolute levels of testosterone across the lifespan, the Tsimane experience significantly lower levels of cumulative testosterone exposure then men in industrialized

populations, which is thought to be one of the most important causes of BPH and prostate cancer (Ross and Henderson 1994; Alvarado 2010). A recent meta-analysis of prostate cancer finds evidence that men in urban populations thought to experience higher cumulative androgen exposure experience significantly higher levels of prostate cancer (Alvarado 2010). Thus we hypothesize that that Tsimane, with significantly lower cumulative androgen exposure will present with smaller prostates than men in industrialized populations, and experience significantly lower levels of BPH across the lifespan.

Methods

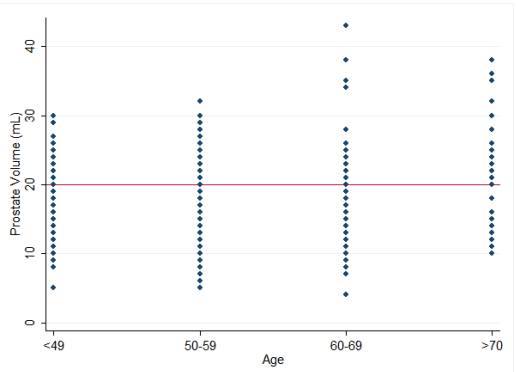
Abdominal ultrasounds on 350 Tsimane men were conducted as a part of the medical evaluations completed by the Tsimane Health and Life History Project. A medical doctor measured prostate size with a Mindray M7 Diagnostic Ultrasound System; prostate volume (mL) was calculated using the standard formula for an ellipsoid, multiplying the longitudinal, transverse, and posterior measures by 0.52. A subset of specimens was also evaluated by a radiologist; with inter-rater agreement greater than 87%. Prostate volume measured from abdominal ultrasound is highly correlated with gold-standard trans-rectal ultrasounds, and is significantly less invasive (Prassopoulos et al. 1996). The men in this sample ranged in age from 28 to 89 years, with a mean age of 57.7 (SD=11.9).

Results

Prostate volumes ranged from 4 to 43 mL, with a mean volume of 17.4 mL (SD= 6.2). Prostate volume increased slightly with age (β=0.08, p=0.006) see figure 1 A & B. The prevalence of BPH was also associated with age (β= 0.03, p=0.002), see table 1. There was no association between body mass index (BMI) and prostate size (p=0.701), nor were men with BMI scores above the median more likely to experience BPH, controlling for age (p=0.620).

Figure 1: A) Prostate Size (mL) by age for 350 Tsimane men (categorical). The line at 20 mL indicates BPH diagnosis. B) Prostate Size (mL) by age for 350 Tsimane men with a linear fit (continous).

A



B

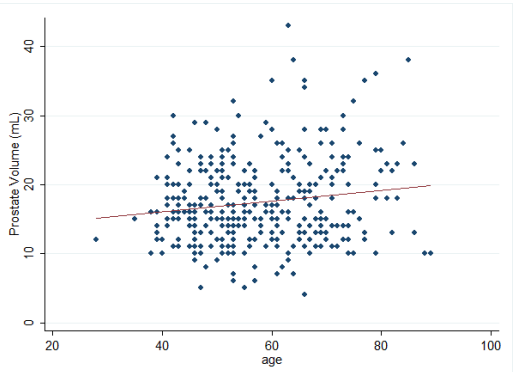


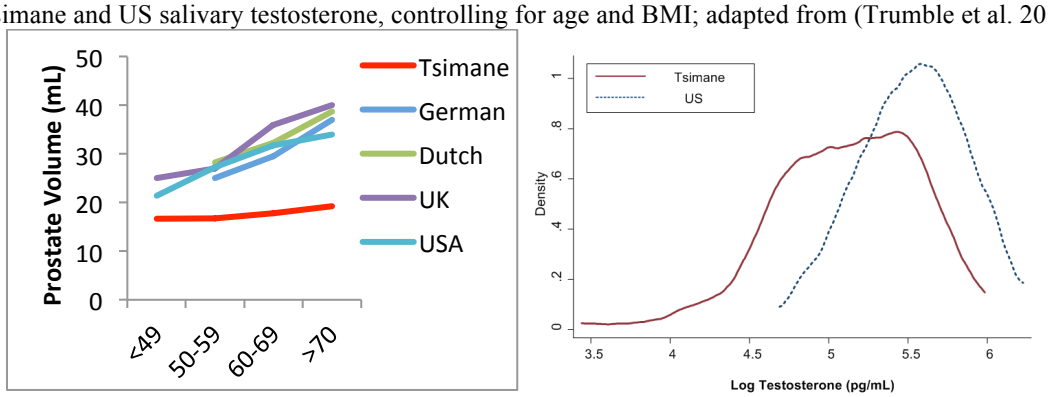
Table 1: Number and percentage of Tsimane men with evidence of Benign Prostate Hyperplasia (prostate volume >20 mL and >30 mL) by age category (n=350).

	<49	**50s**	**60s**	**>70s**
Normal	81 **(81.0%)**	74 **(75.5%)**	64 **(72.7%)**	37 **(57.8%)**
BPH>20 mL	19 **(19.0%)**	24 **(24.5%)**	24 **(27.3%)**	27 **(42.2%)**
BPH >30 mL	1 **(1.0%)**	2 **(2.0%)**	6 **(6.8%)**	6 **(9.5%)**

Compared to 1,240 German men (Berges and Oelke 2011), 3,924 Dutch men (Blanker et al. 2000), 472 Scottish Men (Collins et al. 1993), 631 US men (Rhodes et al. 1999), the Tsimane

have significantly smaller prostate volumes (t=9.9, p<0.001), and a shallower rate of change with age (see figure 2).

Figure 2: A) Comparison of Tsimane Prostate volume (mL) to other studies. B) Comparison of the distribution of Tsimane and US salivary testosterone, controlling for age and BMI; adapted from (Trumble et al. 2012).



Conclusions and Next Steps

These results provide evidence that men in subsistence populations have significantly lower levels of prostate enlargement and clinical BPH compared to men in industrialized populations. While clinically relevant BPH is common in 90% of men in their 80s in industrialized populations, the Tsimane experience less than half this level of BPH.

In the complete manuscript, individual total testosterone, free testosterone, sex hormone binding globulin, engrained-2 protein (EN2), and prostate specific antigen (PSA) levels will be compared with prostate size to form a better understanding of male prostate and aging in subsistence population facing pressures similar to those faced throughout human evolution. Additional emphasis will be placed on lifestyle differences between the Tsimane and industrialized populations with regards to obesity, physical activity, alcoholism, and other factors associated with BPH. This manuscript challenges the notion that BPH is an inevitable part of the male ageing process, suggesting that clinically relevant prostate enlargement would not have been the norm throughout human evolution, and may be a byproduct of industrialized living conditions.

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