Physiology & Behavior 119 (2013) 110–114

Contents lists available at SciVerse ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Serum testosterone levels in males are not associated with entrepreneurial behavior in two independent observational studies

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HIGHLIGHTS

- Current research into the relationship between testosterone and self-employment is limited.
- We investigated this relationship using two large, independent, population-based, observational studies.
- Measures of serum bioactive as well as total testosterone were not associated with self-employment.

ARTICLE INFO

Article history:
Received 8 March 2013
Accepted 4 June 2013
Available online 12 June 2013

Keywords:
Entrepreneurship
Self-employment
Serum testosterone
Free testosterone
Non-sex hormone-binding globulin-bound testosterone
Sex hormone-binding globulin

ABSTRACT

Previous research has suggested a positive association between testosterone (T) and entrepreneurial behavior in males. However, this evidence was found in a study with a small sample size and has not been replicated. In the present study, we aimed to verify this association using two large, independent, population-based samples of males. We tested the association of T with entrepreneurial behavior, operationalized as self-employment, using data from the Rotterdam Study ($N = 587$) and the Study of Health in Pomerania ($N = 1697$). Total testosterone (TT) and sex hormone-binding globulin (SHBG) were measured in the serum. Free testosterone (FT), non-SHBG-bound T (non-SHBG-T), and the TT/SHBG ratio were calculated and used as measures of bioactive serum T, in addition to TT adjusted for SHBG. Using logistic regression models, we found no significant associations between any of the serum T measures and self-employment in either of the samples. To our knowledge, this is the first large-scale study on the relationship between serum T and entrepreneurial behavior.

1. Introduction

Entrepreneurial behavior is an important element and a driving force behind dynamic changes in modern economies [1]. Empirical evidence suggests that important economic stimuli ensue from entrepreneurship [2–4]. Thus, understanding the motivations underlying entrepreneurial behavior is highly relevant. Individual socio-demographic characteristics such as age, sex, and educational attainment have traditionally been a major research focus [5], but recently, increased testosterone (T) levels have been suggested to be a biological predisposing factor for entrepreneurial behavior.

Specifically, White et al. [6] observed that many of the features that characterize entrepreneurs correlate with T. For example, risk-taking behavior is a much-debated feature of entrepreneurship [7,8] and has been shown to be associated with T [9–14]. Based on such relationships, White et al. [6] argued that higher T levels may induce entrepreneurial behavior, and these authors developed a theoretical basis for this relationship by drawing upon evolutionary psychology theory. They hypothesized that individuals with higher T levels are more likely to engage in new venture

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0031-9384/$ – see front matter
http://dx.doi.org/10.1016/j.physbeh.2013.06.003

creation, the authors' measure of entrepreneurship, and that this relationship is partially mediated by an individual's risk propensity. White et al. [6] found evidence for their hypothesis using a salivary T measure in a sample of 110 male North American MBA students. However, this study was limited by a small sample size and has not been replicated. Although there is some evidence to suggest that the 2D:4D digit ratio, a hypothesized proxy for prenatal and adult T levels [15,16], and entrepreneurial behavior are associated [17–19], there is contradictory evidence about the validity of this digit ratio as a proxy for T (see Ref. [20] for the most recent discussion). The precise role of T in entrepreneurial behavior therefore remains unknown.

Thus, the aim of our study was to evaluate the relationship between entrepreneurship, operationalized as self-employment, in a much larger sample of males than previously used. In particular, we utilized two large, independent, population-based samples of males and measured their serum T levels, in contrast to the salivary T measure used by White et al. [6]. In the serum, T is mainly bound to sex hormone-binding globulin (SHBG) and albumin, leaving only a small fraction of T unbound or free. By binding to T, SHBG prohibits T from diffusing from the bloodstream into target tissue cells and performing its biological function. Hence, free testosterone (FT) is generally regarded as bioactive. It is unclear if albumin-bound T is also bioactive [21,22]. In our analyses, we used FT and non-SHBG-bound T (albumin-bound and free) as measures of bioactive T, in addition to the total T (TT)/SHBG ratio and TT adjusted for SHBG. Our measures are similar to the salivary T measure used by White et al. [6] because salivary T reflects the part of serum T that is free [23]. For completeness, we also tested for an association between TT and self-employment. Based on previous findings, we hypothesized that there is a positive association between the serum T measures and self-employment.

2. Materials and methods

2.1. Participants

All of the participants provided written informed consent, and the study was approved by the medical ethics committee of the Erasmus Medical Center and the local Ethics Committee of the University of Greifswald.

We used cross-sectional data from two population-based cohorts: the Rotterdam Study (RS) and the Study of Health in Pomerania (SHIP). The RS is a large, population-based cohort study of the elderly that has been ongoing since 1990 in the city of Rotterdam in the Netherlands [24,25]. From 1990 to 1993, 10,215 inhabitants aged 55 and over from the Ommoord district were invited to participate, and 7983 (response 78%) took part in the baseline examination, including 3105 males. In addition to the original cohort used here (RS-I), there are two other cohorts included in the Rotterdam Study (RS-II and RS-III), but T was not measured in these cohorts. We excluded those participants who used sex hormones (ATC code G03), testosterone 5a-reductase inhibitors (ATC code G04CB), sex hormone antagonists (ATC code L02B), or anabolic steroids (ATC code A14A) because of the effects of these drugs on the serum T level. Males with missing data on hormone levels, self-employment, or covariates were also excluded, leaving 589 males from the RS in our sample.

The SHIP is a population-based cohort study ongoing in West Pomerania, a region in northeastern Germany [26]. A two-stage cluster sampling method was adopted from the WHO MONICA Project (Augsburg, Germany) to select a sample of 7008 individuals from the entire population of 212,157 people living in the area using the population registration offices, where all German inhabitants are registered. Individuals without German citizenship and those who did not reside in the study area were excluded. The final sample comprised 4308 participants at baseline (response 69%), including 2116 males. We excluded users of sex hormones (ATC code G03), testosterone 5a-reductase inhibitors (ATC code G04CB), sex hormone antagonists (ATC code L02B), or anabolic steroids (ATC code A14A). After excluding males with missing data on self-employment, hormone levels, or covariates, 1697 males from the SHIP were available for the analyses.

2.2. Hormone measurements

The serum TT and sex hormone-binding globulin (SHBG) levels were measured using coated tube (T) or double antibody (SHBG) radioimmunoassays (Diagnostic Systems Laboratories, Inc., Webster, TX) in the RS and using competitive chemiluminescent enzyme immunoassays (Siemens Immulite 2500 Total Testosterone, ref. L5KTW, lot 110; Immulite 2550 SHBG ref. L5KSH, lot 119; Siemens Healthcare Medical Diagnostics, Bad Nauheim, Germany) in the SHIP. Further details have been described previously [27–29].

As measures of bioactive T, we used FT, non-SHBG-bound T (non-SHBG-T), the TT/SHBG ratio, and TT adjusted for SHBG. Serum FT and non-SHBG-T levels were calculated according to the method of Södergard et al. [30], using previously described equations [31] assuming a fixed albumin level of 40 g/l.

2.3. Self-employment and covariate measures

At baseline, participants from the RS were interviewed at home and asked for their complete work-life histories. The participants' occupations and employment status (employed, self-employed, or a collaborating family member) for each occupation were recorded. Based on this information, we were able to identify individuals who were self-employed at some point during their working careers and individuals who had not been self-employed. Individuals who had never had a job and individuals with an incomplete work-life history except those who were classified as self-employed at least once were excluded from our study. The rationale for excluding these individuals is that individuals with incomplete work-life histories could have been self-employed at least once in the past, which would make it impossible to interpret the coefficient for self-employment.

In the SHIP, participants were asked about their current or last occupational status using questionnaires. We coded individuals as self-employed if they reported that they were farmers with more than 10 hectares of property (2.5% of the self-employed), university graduates with a liberal profession, e.g., physician, lawyer, or tax accountant (8.6% of the self-employed), or self-employed in business, craft, or the tertiary sector (88.9% of the self-employed). The self-employment rate was lower in the SHIP than in the RS, in agreement with the fact that the SHIP is located in the former German Democratic Republic, where self-employment was systematically discouraged [32].

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. In the RS, weight and height were measured during the research facility visit while participants were wearing indoor clothing and no shoes. SHIP participants were wearing lightweight clothing and no shoes during height and weight measurements. Current smoking status was assessed using a computerized questionnaire during the home interview in the RS and using computer-assisted personal interviews in the SHIP. To harmonize educational attainment measures across the RS and the SHIP, we first transformed the study-specific measures to an internationally comparable measure of educational attainment according to UNESCO's International Standard Classification of Education (ISCED) scale [33]. The ISCED levels were then converted to US years of schooling equivalents.

2.4. Statistical analyses

Categorical data are reported as percentages, and continuous data are represented as the mean together with the standard deviation. Differences between groups were tested using Pearson's χ^2 tests for categorical data and *t*-tests for continuous data.

We used logistic regression models to investigate the association between self-employment and serum T measures. These models were adjusted for age, age^2, and educational attainment because age has been shown to exhibit an inverted U-shaped relationship with entrepreneurship [34] and because of the positive effect of education on entrepreneurship [35]. We also controlled for BMI, current smoking, and time of blood sampling, as these are well-known confounders of serum T [36–39]. All regression analyses were performed separately for the RS and SHIP samples, after a Chow test discouraged data pooling ($p < 0.001$ for all models).

We performed the following sensitivity analyses. First, we used the multivariable fractional polynomial (MFP) algorithm to test for non-linear effects of serum T measures [40] and to avoid categorization [41,42]. Second, we performed all regression analyses in a subset of 743 males from the SHIP who were younger than 60 years and were part- or full-time (non-)self-employed at the time of the hormone measurements to ensure that T could not have been influenced by other factors in the period between the self-employment period and when the blood samples for hormone measurements were taken. p-values smaller than 0.05 were considered significant. All statistical analyses were performed using Stata version 12.1 (Stata Corporation, College Station, TX, USA).

3. Results

The descriptive statistics for the participating males from the RS and the SHIP are reported in Table 1. The self-employment rate in the RS was higher than in the SHIP, and males from the RS were on average older than males from the SHIP. Educational attainment was higher in the SHIP than in the RS. BMI was lower in the RS than in the SHIP, and a larger percentage of males in the SHIP were smokers than in the RS. The serum TT, SHBG, FT, and non-SHBG-T levels were all lower in the RS than in the SHIP, although the TT/SHBG ratio was similar between the two studies. The differences between the RS and SHIP were all significant except for the difference in the TT/SHBG ratio. The mean serum TT, FT, and non-SHBG-T levels did not significantly differ between self-employed and non-self-employed males in the RS or the SHIP (Fig. 1; $p > 0.05$ for all comparisons).

The logistic regression results indicated that none of the serum T measures were associated with self-employment in either of the samples (Table 2). Sensitivity analyses using MFP models did not provide evidence for a non-linear association between serum T measures and self-employment. Finally, analyses in a subset of males from the SHIP who were (non-)self-employed at the time of hormone measurement did not reveal associations between serum T measures and self-employment ($p > 0.05$ for all serum T measures).

Table 1
Characteristics of the participants from the Rotterdam study (RS) and the Study of Health in Pomerania (SHIP).

	RS ($N = 589$)		SHIP ($N = 1697$)		p for difference
Self-employed (%)	12.4		4.8		<0.001
Age (years)	68.29	(7.63)	50.68	(16.56)	<0.001
Educational attainment (US years of schooling)	11.47	(3.82)	13.56	(3.79)	<0.001
Body mass index (kg/m^2)	25.81	(2.94)	27.64	(4.09)	<0.001
Current smoker (%)	28.9		34.2		0.017
TT (nmol/L)	11.36	(3.93)	16.76	(6.01)	<0.001
SHBG (nmol/L)	35.9	(14.42)	51.6	(25.6)	<0.001
FT (nmol/L)	0.27	(0.11)	0.34	(0.11)	<0.001
Non-SHBG-T (nmol/L)	6.66	(2.6)	8.36	(2.81)	<0.001
TT/SHBG ratio	0.37	(0.24)	0.37	(0.16)	0.984

TT: total testosterone; SHBG: sex hormone-binding globulin; FT: free testosterone; non-SHBG-T: non-SHBG-bound testosterone. Categorical data are presented as percentages, and continuous data are presented as the mean (standard deviation). p-values were calculated using Pearson's χ^2 tests for categorical data and t-tests for continuous data.

4. Discussion

To our knowledge, this is the first large-scale investigation of the suggested association between T and entrepreneurial behavior based on serum T measures. We observed no association between any of the serum T measures and self-employment in two large, independent, population-based samples of males. Several sensitivity analyses were conducted to confirm the robustness of our results. First, we verified that T did not have a non-linear effect on self-employment. Second, in a subset of males from the SHIP who were younger than 60 years and part- or full-time (non-)self-employed at the time the blood for hormone measurements was collected, no significant associations were found. These findings confirm that the association was not masked by the fact that a substantial proportion of the participants in our study were elderly males in which we tried to associate T—which could have been influenced by many other causes over time—to occupational choices that happened much earlier in their lives.

Our findings contradict earlier evidence of a positive and significant relationship between salivary T levels and entrepreneurial behavior [6]. There are at least four reasons to explain these divergent results. First, White et al. [6] operationalized entrepreneurship as being involved full-time in new venture creation, whereas we defined entrepreneurship as being self-employed at least once during the working career, the most frequently used measure of entrepreneurial behavior in the economics literature [34]. The different definition used by White et al. [6] may imply that T merely plays a role in the initial phases of starting a new business and is irrelevant to being self-employed. However, new venture creation and self-employment are strongly correlated ($\rho > 0.7$ [43]), and we would thus expect, at least to a certain extent, an association between T and self-employment.

Second, it is known that measurements of T in saliva, as used by White et al. [6], can be influenced by sample handling, leakage of blood (plasma) into the saliva, and the storage conditions of archived samples [44], challenging the validity of these measurements.

Third, the strongly selected study sample of White et al. [6], comprising North American MBA students, is very different from the Dutch and German population-based samples used in the present study. The non-replication may be an effect of this heterogeneity, meaning that the effects of T may differ depending on the environment.

Fourth, it is well known that non-replication is especially pronounced in studies with small sample sizes because such studies are underpowered [45]. Our calculations indicate that the sample of White et al. [6] was seriously underpowered to find a true effect of T on entrepreneurial behavior. For example, if we adopt a 5% significance level and assume that, similar to the sample of White et al. [6], 28% of the individuals in a population are involved full-time in new venture creation, then the smallest detectable odds ratio with 80% power in a sample of $N = 110$ is approximately 1.9. However, White et al. ([6], Table 4, column 5) estimated that the odds ratio of T (in pg/ml) for being engaged full-time in new venture creation is approximately 1.03 ($e^{0.03}$). If we assume that this odds ratio is an unbiased estimate of the population odds ratio, then they would have needed approximately 45,000 participants to achieve 80% power to detect such an effect. Therefore, the original association is more likely to be due to chance than to a true difference. The replication of the original association in an independently obtained sample would have increased the probability that the initial findings were true [46].

Our results do not necessarily rule out an influence of T on entrepreneurial behavior. For example, along the same line serum T has been suggested to be associated with social rank in rhesus macaques [47]. Our largest sample had 80% power to detect odds ratios larger than 1.4, which is equivalent to an odds ratio of approximately 1.9 for being engaged in new venture creation given the correlation

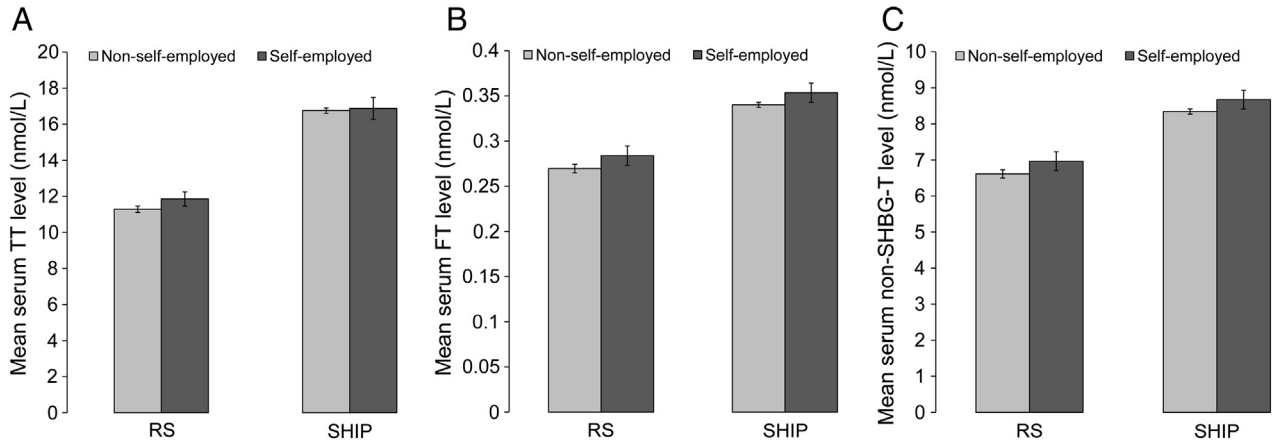

Fig. 1. Mean serum testosterone measures by self-employment status for participants from the Rotterdam study (RS) and the Study of Health in Pomerania (SHIP). The figure shows the mean serum levels of total testosterone (TT; panel A), free testosterone (FT; panel B), and non-SHBG-bound testosterone (non-SHBG-T; panel C) by self-employment status for participants from the RS and the SHIP. The errors bars indicate the standard error of the mean. The mean serum TT, FT, and non-SHBG-T levels did not significantly differ between self-employed and non-self-employed participants from the RS or the SHIP ($p > 0.05$ for all comparisons).

with self-employment. Therefore, we cannot exclude the existence of an effect of T on entrepreneurial behavior with a smaller effect size. Larger samples will be needed in future studies to draw definitive conclusions regarding the potential association between T and entrepreneurial behavior. However, we believe that the practical utility of such an effort will be very small. If we assume that our estimates of the regression coefficients are the true population parameters, then the odds ratio of FT (in pg/ml as in White et al. [6]) for being at least once self-employed is almost one.

The cross-sectional nature of our study does not allow causal inferences to be drawn. Additionally, there may have been omitted variables, selection bias, reverse causality, or measurement error, which could have led to endogeneity for T and subsequently the inconsistent estimation of the logistic regression model parameters. In such cases, Mendelian Randomization is an attractive approach to tackle the endogeneity problem and allows the inference of causal relationships with cross-sectional data [48,49]. Statistically, Mendelian Randomization is the use of instrumental variables (IV) regression using genes as instruments [50]. We considered performing a Mendelian Randomization analysis but found that the only candidate instrument for our serum T measures that is currently available, single nucleotide polymorphism (SNP) rs5934505 on chromosome X [51], was correlated with self-employment. This implies that we cannot rule out that this SNP influences self-employment via different channels than through levels of serum T, for example, due to pleiotropic effects, which will invalidate the Mendelian Randomization analysis. The other two SNPs identified in the genome-wide association study of T were only associated with TT [51] and therefore could not be used as instruments for measures of bioactive T.

Table 2
Association between serum testosterone measures and self-employment in the Rotterdam study (RS) and the Study of Health in Pomerania (SHIP).

Sample	Serum T measure	β	(95% CI)	p-value
RS	TT	0.045	(−0.018, 0.109)	0.163
	FT	1.479	(−0.905, 3.863)	0.224
	Non-SHBG-T	0.060	(−0.037, 0.157)	0.224
	TT/SHBG ratio	0.227	(−0.749, 1.204)	0.648
	TT adjusted for SHBG	0.048	(−0.017, 0.113)	0.146
SHIP	TT	0.011	(−0.030, 0.053)	0.602
	FT	0.762	(−1.583, 3.108)	0.524
	Non-SHBG-T	0.031	(−0.065, 0.127)	0.524
	TT/SHBG ratio	0.447	(−1.269, 2.162)	0.610
	TT adjusted for SHBG	0.019	(−0.034, 0.072)	0.486

TT: total testosterone; SHBG: sex hormone-binding globulin; FT: free testosterone; non-SHBG-T: non-SHBG-bound testosterone. All models were adjusted for age, age^2, educational attainment, time of blood sampling, body mass index, and current smoking status.

Another limitation of our study is the different age ranges in the RS and SHIP. Whereas the RS participants were aged over 55 years at baseline and had data on their complete working-life history, the age range of the SHIP participants was 20 to 80 years, implying a right-censored self-employment status. Furthermore, our data included only male participants, and a role of T in females cannot be ruled out a priori. We restricted our analyses to males because the original association was based on results from a male-only sample. Furthermore, T levels were unavailable for females in the SHIP and were available only for postmenopausal females in the RS.

In conclusion, using two large, independent, population-based samples of males, we did not find evidence to support the hypothesis that T is associated with entrepreneurial behavior and thereby failed to replicate findings from a previous study. Future research in adequately powered, independent samples using, preferably, methods that allow causal inference will be needed to draw definitive conclusions about the role of T in entrepreneurial behavior.

Acknowledgments

We would like to thank Najiba Lahlou (Département de Biologie Hormonale, CHU Cochin, Paris) for her helpful comments and suggestions. We are very grateful to the participants and staff from the Rotterdam Study, the participating general practitioners and the pharmacists. The Rotterdam Study is funded by the Erasmus Medical Center and Erasmus University, Rotterdam; the Netherlands Organization for the Health Research and Development (ZonMw); the Research Institute for Diseases in the Elderly (RIDE); the Ministry of Education, Culture and Science; the Ministry of Health, Welfare and Sport; the European Commission (DG XII); and the Municipality of Rotterdam. The contributions to data collection made by the field workers, the study physicians, the ultrasound technicians, the interviewers, and the computer assistants from the Study of Health in Pomerania (SHIP) are gratefully acknowledged. SHIP is part of the Community Medicine Research net (www.community-medicine.de) and the Greifswald Approach to Individualized Medicine (GANI_MED) consortium (www.gani-med.de) of the University Medicine Greifswald, Germany, which are funded by the Federal Ministry of Education and Research (BMBF 01ZZ9603, 01ZZ0103 and 03IS2061A), the Ministry of Cultural Affairs, and the Social Ministry of the Federal State of Mecklenburg-West Pomerania. The University of Greifswald is a member of the 'Center of Knowledge Interchange' program of the Siemens AG and the Caché Campus program of the InterSystems GmbH. The funders had no role in study design, data collection, analysis and interpretation of data, preparation of the manuscript, or decision to publish.

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