

# Body height, body mass index, waist-hip ratio, fluctuating asymmetry and second to fourth digit ratio in subjects with latent toxoplasmosis

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## SUMMARY

Between 20% and 60% of the population of most countries are infected with the protozoan *Toxoplasma gondii*. Subjects with clinically asymptomatic life-long latent toxoplasmosis differ from those who are *Toxoplasma* free in several behavioural parameters. Case-control studies cannot decide whether these differences already existed before infection or whether they were induced by the presence of *Toxoplasma* in the brain of infected hosts. Here we searched for such morphological differences between *Toxoplasma*-infected and *Toxoplasma*-free subjects that could be induced by the parasite (body weight, body height, body mass index, waist-hip ratio), or could rather correlate with their natural resistance to parasitic infection (fluctuating asymmetry, 2D:4D ratio). We found *Toxoplasma*-infected men to be taller and *Toxoplasma*-infected men and women to have lower 2D:4D ratios previously reported to be associated with higher pre-natal testosterone levels. The 2D:4D ratio negatively correlated with the level of specific anti-*Toxoplasma* antibodies in *Toxoplasma*-free subjects. These results suggest that some of the observed differences between infected and non-infected subjects may have existed before infection and could be caused by the lower natural resistance to *Toxoplasma* infection in subjects with higher pre-natal testosterone levels.

Key words: human, (2D:4D), *Toxoplasma*, testosterone, immunity, resistance, immunocompetence handicap hypothesis.

## INTRODUCTION

Approximately 30% of people in the Czech Republic and about 20–60% of the population worldwide are infected with the protozoan parasite *Toxoplasma gondii*. Life-long latent toxoplasmosis is usually considered to pose no health threat to immunocompetent persons. However, *Toxoplasma*-infected and *Toxoplasma*-free subjects differ in several personality traits and certain psychomotor performance parameters (Flegr *et al.* 1996, 2002, 2003). Since some of these differences (e.g. psychomotor performance, personality traits Superego Strength in men and Affectothymia in women) increase with the duration of latent toxoplasmosis or with concentration of anti-*Toxoplasma* antibodies (personality trait Novelty Seeking) (Flegr, Kodym & Tolarova, 2000; Havlicek *et al.* 2001), they are likely to be induced by the presence of the parasite in the host organism. Other personality differences seem not to correlate with the duration of infection (e.g. personality trait Protension) (Flegr *et al.* 1996) and therefore

may have existed before infection, being linked to higher susceptibility of certain individuals to the infection. Individuals with higher fluctuating asymmetry (FA), i.e. with more pronounced random deviations from the right-left symmetry of the body, have been shown to be typically more prone to infections (Watson & Thornhill, 1994; Møller, 1996). Susceptibility to several infections also positively correlates with prenatal and adult testosterone levels (Zuk & McKean, 1996; Schuster & Schaub, 2001). The average testosterone level in humans and other mammalian species can be estimated on the basis of the 2D:4D ratio, i.e. the ratio between the lengths of the second and fourth digits (Manning, 2002). Individuals with a lower 2D:4D ratio (i.e. those with a relatively longer ring finger) were exposed to higher pre-natal testosterone levels (Manning *et al.* 1998). There is some evidence that the baseline pre-natal and post-natal testosterone levels are positively correlated (Sorenson, Meier & Campbell, 1993) but 2D:4D is not reliably correlated with adult testosterone levels (Neave *et al.* 2003). Manning (2002, pp. 95–99) has considered the evidence that links pre-natal testosterone, 2D:4D and compromised immune function, and has suggested that low 2D:4D (high pre-natal testosterone) is likely to be correlated with susceptibility to parasitic infections.

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The major aim of the present study was to search for differences in morphology between *Toxoplasma*-infected and *Toxoplasma*-free subjects that could be either indicative of health status (body weight, body height, body mass index, waist-hip ratio) or could correlate with natural resistance to parasitic infection (possibly fluctuating asymmetry, most likely the 2D:4D ratio). Human cytomegalovirus (CMV) was used as a control for non-specific effects of a neurotropic pathogen infection.

#### MATERIALS AND METHODS

##### *Study subjects*

Undergraduate biology students of the Faculty of Sciences, Charles University, Prague, were addressed during regular biology lectures and were invited to participate in the study on a voluntary basis. Two hundred and sixty-eight of the students (35%), 93 males and 175 females, mean age 21.2 years, s.d. = 1.85, were enrolled in the study after signing informed consent forms. They underwent anthropometric measurements and provided 2 ml of blood for serological testing. Both the probability of *Toxoplasma* infection and certain anthropometric parameters could correlate with the size of place of residence of the subjects, therefore, this variable must be controlled for in all statistical analyses. Reliable information on the size of place of residence was obtained from 262 study subjects, subsequently divided into 3 categories: those living in villages and small cities (<5 thousand population), those living in larger cities (5–100 thousand population) and those living in the Czech capital Prague (1.2 million population). The results of all analyses were virtually the same if the study subjects were divided into 4 categories (<5 thousand, 5–10 thousand, 10–100 thousand, >100 thousand). The recruitment of the study subjects and data handling were in accordance with Czech legislation in force.

##### *Anthropometry*

The following anthropometric parameters were measured double blind to the enrollee's *Toxoplasma*-infection status on the right and left sides using a sliding caliper and a spreading caliper with a resolution of 0.5 mm: ear length, ear width, ear insertion height, wrist breadth, hand breadth, hand length (on the ventral surface of the hand from the basal crease to the tip of the third digit), lengths of all fingers (the ventral surface of digits 1 to 5, from the basal crease of the digit to the tip), elbow breadth (bicipital breadth of the humerus), knee breadth (bicipital breadth of the femur) and ankle breadth. An anthropometer (measuring to the nearest 0.5 cm), a personal scale (weighing to the nearest 0.1 kg) and a flexible metric tape (measuring to the nearest

0.1 cm) were used for basic anthropometric measurements (body height, body weight, minimum waist circumference, hip circumference). Martin-Saller's method (Martin & Saller, 1957) was used for measurement of all parameters but the hand length and finger lengths measured using the method of Knussmann (1988). All measurements were made by the same person (M.H.). The fluctuating asymmetry for each trait was calculated as the absolute difference between the right and left sides divided by the average of the right and left sides. The total fluctuating asymmetry for each subject was obtained by averaging the asymmetries of all 15 traits, see Table 1.

##### *Immunological tests for toxoplasmosis and CMV*

Specific anti-*Toxoplasma* IgG and IgM antibody concentrations were determined by ELISA (IgG: SEVAC, Prague, IgM: TestLine, Brno), optimized for early detection of acute toxoplasmosis (Pokorný *et al.* 1989), and complement fixation test (CFT) (SEVAC, Prague) which is more sensitive and therefore more suitable for the detection of old *T. gondii* infections (Warren & Sabin, 1942). Titres of antibodies to *Toxoplasma* in sera were measured at dilutions between 1:8 and 1:1024. The subjects testing IgM negative by ELISA (positivity index <0.9) and having CFT titres higher than 1:8 were considered latent-toxoplasmosis positive. Specific anti-Cytomegalovirus (CMV) IgG antibodies were measured by quantitative ELISA (ETI-CYTOK-G plus, DiaSorin). Antibody concentration was expressed in arbitrary units (AU). Individuals with AU <40 were considered seronegative for CMV.

##### *Statistical analysis*

The Statistica<sup>®</sup> v.6.0 general linear models module was used for all statistical testing i.e. for log-linear analyses, ANCOVA and multiple linear regression. The results of testing of ANCOVA assumptions, namely the normality of data distribution, normality of residuals and homogeneity of variances, were non-significant for all studied models.

#### RESULTS

Twenty-nine (16.6%) out of 175 females and 20 (21%) out of 93 males were *Toxoplasma*-infected. The difference in prevalence of toxoplasmosis between females and males was not significant ( $\chi^2 = 0.75$ , D.F. = 1,  $P = 0.39$ , log-linear analysis, factors: toxoplasmosis, gender, place of residence). The only significant interaction in the model was the association between toxoplasmosis and size of place of residence ( $\chi^2 = 6.62$ , D.F. = 2,  $P = 0.037$ ). The prevalence rates of toxoplasmosis were 31.8% among 44 residents of villages and small cities, 18.8%

Table 1. Differences in anthropometric parameters between *Toxoplasma*-free and *Toxoplasma*-infected subjects, and between men and women

(*P* and *F* values show the results of GLM analysis with factors age, body weight, body height, size of place of residence, gender and toxoplasmosis. *P* for difference between *Toxoplasma*-infected and *Toxoplasma*-free subjects of the whole study set, mean for *Toxoplasma*-infected subjects, mean for *Toxoplasma*-free subjects, *P* for women, *P* for men, *P* for difference between men and women, *F* for difference between men and women, mean for women and mean for men are given in columns 2–9, respectively. Measured distances: ear length (superaurale-subaurale), ear breadth (praeaurale-postaurale), ear insertion height (otobasion superius-otobasion inferius), forehead breadth (tragion-glabella), wrist breadth (supracarpale ulnare scu-supracarpale radiale scr), hand breadth (metacarpale radiale-metacarpale ulnare), hand length (ventral surface of the hand, from the basal crease to the tip of the third digit), finger length (ventral surface of digits 1 to 5, from the basal crease of the digit to the tip), elbow breadth (biepicondylar breadth of the humerus), knee breadth (biepicondylar breadth of the femur), ankle breadth (bimalleolar breadth). Significant *P* values are printed in bold and significant after Bonferroni's correction are labelled with **b**. The traits significantly correlated with concentration of anti-*Toxoplasma* antibodies are labelled with \* ( $P < 0.05$ ) and \*\*\* ( $P < 0.001$ ). Except the ear insertion height, all other correlations were positive.)

	<i>P</i> toxoplasmosis	Mean Toxo-infect.	Mean Toxo-free	<i>P</i> Toxo women	<i>P</i> Toxo men	<i>P</i> gender	<i>F</i> gender	Mean women	Mean men
Ear length right	0.538	6.10	6.02	0.760	0.237	<b>0.007b</b>	7.51	5.90	6.29
Ear length left	0.321	6.16	6.06	0.984	0.122	<b>0.023</b>	5.23	5.94	6.33
Ear breadth right*	0.781	3.23	3.21	0.977	0.846	<b>0.004b</b>	8.62	3.12	3.38
Ear breadth left	<b>0.037</b>	3.36	3.24	0.067	0.334	<b>0.002b</b>	9.96	3.17	3.43
Ear insertion height right*	0.155	5.22	5.10	0.131	0.521	0.757	0.096	5.06	5.24
Ear insertion height left	0.193	5.22	5.11	0.150	0.420	0.307	1.048	5.05	5.29
Forehead breadth right	<b>0.002</b>	12.54	12.28	0.106	<b>0.012</b>	<b>0.000b</b>	39.94	12.02	12.91
Forehead breadth left	<b>0.001b</b>	12.63	12.34	0.147	<b>0.003</b>	<b>0.000b</b>	30.19	12.10	12.95
Wrist breadth right	<b>0.011</b>	5.38	5.24	0.066	0.143	<b>0.000b</b>	67.50	5.03	5.71
Wrist breadth left	<b>0.047</b>	5.31	5.19	0.326	0.189	<b>0.000b</b>	49.27	4.97	5.65
Hand breadth right	0.085	7.82	7.67	0.065	0.996	<b>0.000b</b>	96.40	7.36	8.34
Hand breadth left	<b>0.031</b>	7.74	7.56	<b>0.029</b>	0.782	<b>0.000b</b>	107.77	7.26	8.23
Hand length right	<b>0.032</b>	18.09	17.77	0.065	0.366	<b>0.000b</b>	33.78	17.18	19.05
Hand length left*	<b>0.019</b>	18.14	17.80	0.066	0.304	<b>0.000b</b>	33.00	17.21	19.08
Finger length I right	0.131	6.00	5.88	0.285	0.379	<b>0.000b</b>	40.80	5.63	6.41
Finger length I left	0.418	5.92	5.84	0.538	0.690	<b>0.000b</b>	55.45	5.58	6.38
Finger length II right	<b>0.014</b>	7.13	6.95	<b>0.027</b>	0.243	<b>0.004b</b>	8.47	6.75	7.41
Finger length II left	0.214	7.07	6.95	0.214	0.855	<b>0.000b</b>	16.83	6.71	7.45
Finger length III right	<b>0.001b</b>	7.87	7.63	<b>0.016</b>	<b>0.042</b>	<b>0.000b</b>	13.22	7.40	8.18
Finger length III left*	<b>0.011</b>	7.85	7.65	<b>0.050</b>	0.195	<b>0.001b</b>	11.10	7.41	8.19
Finger length IV right*	<b>0.003</b>	7.29	7.08	<b>0.024</b>	0.064	<b>0.000b</b>	18.87	6.85	7.63
Finger length IV left***	<b>0.005</b>	7.29	7.08	<b>0.047</b>	0.058	<b>0.000b</b>	16.76	6.85	7.61
Finger length V right	<b>0.010</b>	5.94	5.76	<b>0.041</b>	0.133	<b>0.000b</b>	33.04	5.54	6.28
Finger length V left	<b>0.005</b>	5.95	5.76	<b>0.021</b>	0.108	<b>0.000b</b>	36.20	5.53	6.30
Elbow breadth right	0.204	6.53	6.43	0.051	0.671	<b>0.000b</b>	105.39	6.12	7.05
Elbow breadth left	0.747	6.48	6.42	0.511	0.633	<b>0.000b</b>	113.40	6.11	7.04
Knee breadth right	0.613	9.24	9.16	<b>0.044</b>	0.163	<b>0.000b</b>	64.41	8.80	9.89
Knee breadth left	0.412	9.21	9.11	0.081	0.538	<b>0.000b</b>	65.63	8.76	9.82
Ankle breadth right	<b>0.015</b>	6.91	6.74	0.152	<b>0.030</b>	<b>0.000b</b>	46.43	6.51	7.26
Ankle breadth left	<b>0.046</b>	6.72	6.57	0.128	0.122	<b>0.000b</b>	26.66	6.36	7.06

among 101 residents of middle-size cities, and 13.7% among 117 residents of the capital Prague; for 6 subjects the residence address was not available. Anthropometrical data were available for 157 females and 85 males. The females had a significantly higher body mass index (BMI) (22.27 g/cm<sup>2</sup>) than males (20.91 g/cm<sup>2</sup>) ( $F_{1,249} = 17.49$ ,  $P = 0.000$ , GLM, factors: age, place of residence, toxoplasmosis, gender) and a significantly lower waist-hip ratio (WHR) (0.729) than males (0.821) ( $F_{1,227} = 285.3$ ,  $P = 0.000$ , GLM, factors: age, place of residence, toxoplasmosis, gender, WHR). The difference in fluctuating asymmetry (FA) between females and males was not significant (0.0243 and 0.0251, respectively)

( $F_{1,225} = 1.66$ ,  $P = 0.199$ , GLM, factors: age, place of residence, toxoplasmosis, gender, FA). The 2D:4D ratio for the right hand was significantly higher in females (0.986) compared to males (0.972) ( $F_{1,229} = 8.7$ ,  $P = 0.0035$ , GLM, factors: age, place of residence, toxoplasmosis, gender), while the difference between females and males for the left hand (0.981 and 0.979, respectively) was not significant ( $F_{1,229} = 1.2$ ,  $P = 0.314$ ). As expected (Wilson, 1983; Manning, 2002), the 2D:4D ratio for the right but not the left hand negatively correlated with another testosterone-dependent morphological trait, the WHR (right hand: beta = -0.17,  $F_{1,232} = 3.4$ ,  $P = 0.034$ , left hand: beta = 0.02,  $F_{1,232} = 0.0$ ,  $P = 0.42$ ,

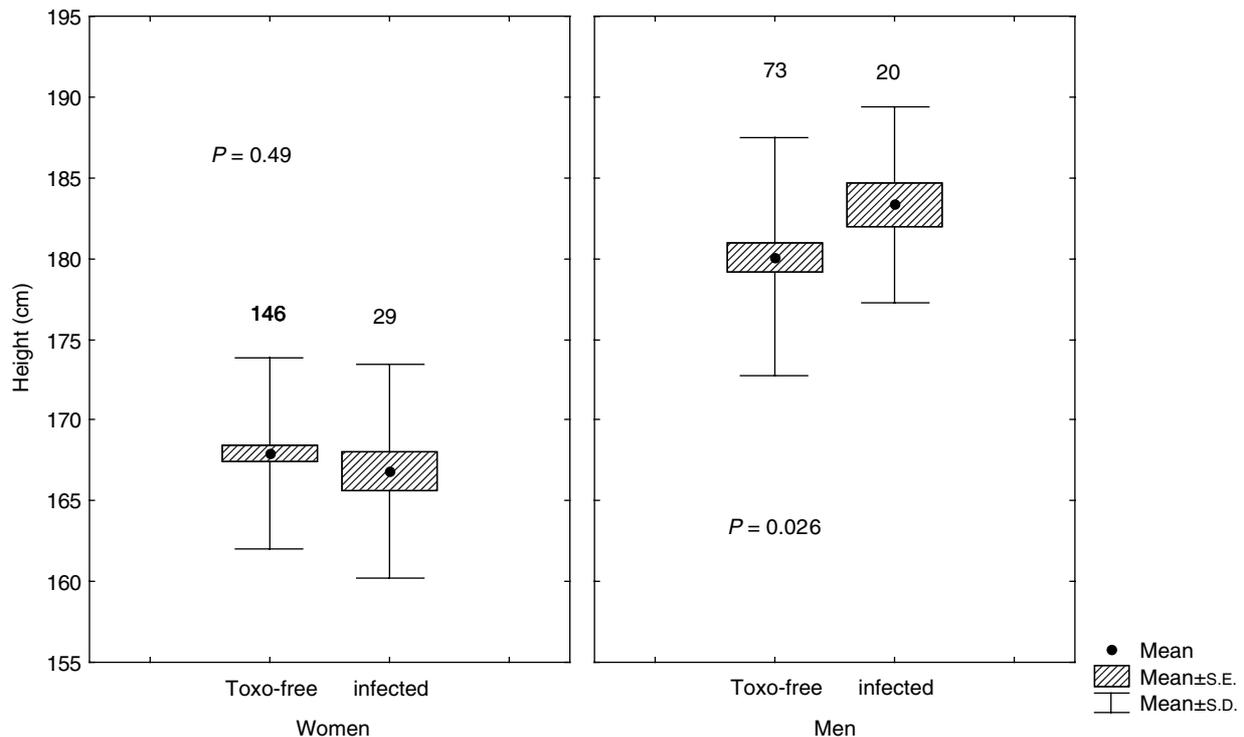


Fig. 1. Differences in height between *Toxoplasma*-free and *Toxoplasma*-infected women and men. The figures indicate the numbers of study subjects in particular categories. The *P* values are given for separate GLM analyses for men and women, with factors age and size of place of residence.

GLM, one-tailed tests, factors: age, place of residence, gender, toxoplasmosis, WHR).

*Toxoplasma*-infected and *Toxoplasma*-free subjects did not differ in BMI (21.25 g/cm<sup>2</sup> posit. vs 21.47 g/cm<sup>2</sup> negat.,  $F_{1,249}=0.03$ ,  $P=0.857$ , GLM, factors: age, place of residence, gender, toxoplasmosis), WHR (0.772 posit. vs 0.759 negat.,  $F_{1,227}=0.75$ ,  $P=0.387$ , GLM, factors: age, place of residence, gender, toxoplasmosis) or FA ( $F_{1,225}=0.349$ ,  $P=0.555$ , GLM, factors: age, place of residence, gender, toxoplasmosis). A significant *toxoplasmosis-gender* interaction, however, existed with respect to body height ( $F_{1,249}=6.4$ ,  $P=0.012$ , GLM, factors: age, place of residence, gender, toxoplasmosis), as shown in Fig. 1. Infected men had higher body height, another trait expected to correlate positively with testosterone levels (Heald *et al.* 2003). A nearly significant 3-way interaction *size of place of residence-toxoplasmosis-gender* was found with respect to BMI ( $F_{2,249}=3.0$ ,  $P=0.052$ , GLM, factors: age, place of residence, gender, toxoplasmosis), see Fig. 2. *Toxoplasma*-infected subjects had a lower 2D:4D ratio for the left hand (0.972 vs 0.984,  $F_{1,229}=5.3$ ,  $P=0.022$ , GLM, factors: age, place of residence, toxoplasmosis). At the same time, they did not differ in the 2D:4D ratio for the right hand (0.977 vs 0.982,  $F_{1,228}=0.6$ ,  $P=0.46$ ). In separate analyses, the *Toxoplasma*-infected and *Toxoplasma*-free females did not differ in the 2D:4D ratio for the left hand (0.977 vs 0.985,  $F_{1,150}=2.1$ ,  $P=0.15$ ), the difference

in males being significant (0.966 vs 0.974,  $F_{1,78}=4.3$ ,  $P=0.041$ ), as can be seen in Fig. 3.

A lower 2D:4D ratio can be primarily ascribed either to a relatively shorter index finger or to a relatively longer ring finger. Raw anthropometrical data presented in Table 1 show that *Toxoplasma*-infected in comparison with *Toxoplasma*-free subjects as well as males in comparison with females had longer digits (mainly on the right hand). However, the difference was very small for the index finger of the left hand, which resulted in a decreased 2D:4D ratio for the left hand of *Toxoplasma*-infected subjects.

After removing the effects of confounding variables age, body weight, size of place of residence, and gender, the 2D:4D ratio and several other traits (Table 1) correlated with the concentration of anti-*Toxoplasma* antibodies in the sera of the study subjects. The correlation was stronger for the right hand and *Toxoplasma*-free subjects (right hand:  $\beta=-0.16$ ,  $F_{1,189}=5.1$ ,  $P=0.025$ , left hand:  $\beta=-0.14$ ,  $F_{1,189}=3.8$ ,  $P=0.052$ ) compared to *Toxoplasma*-infected subjects (right hand:  $\beta=-0.26$ ,  $F_{1,39}=3.9$ ,  $P=0.075$ , left hand:  $\beta=-0.034$ ,  $F_{1,39}=0.04$ ,  $P=0.836$ ), Fig. 4. Neither a difference in prevalence of infection between low and high 2D:4D ratio subjects (right hand:  $F_{1,184}=0.5$ ,  $P=0.461$ , left hand:  $F_{1,184}=1.0$ ,  $P=0.309$ ), nor correlation between the 2D:4D ratio and level of specific IgG (right hand:  $\beta=-0.04$ ,  $F_{1,202}=0.0$ ,  $P=0.937$ , left

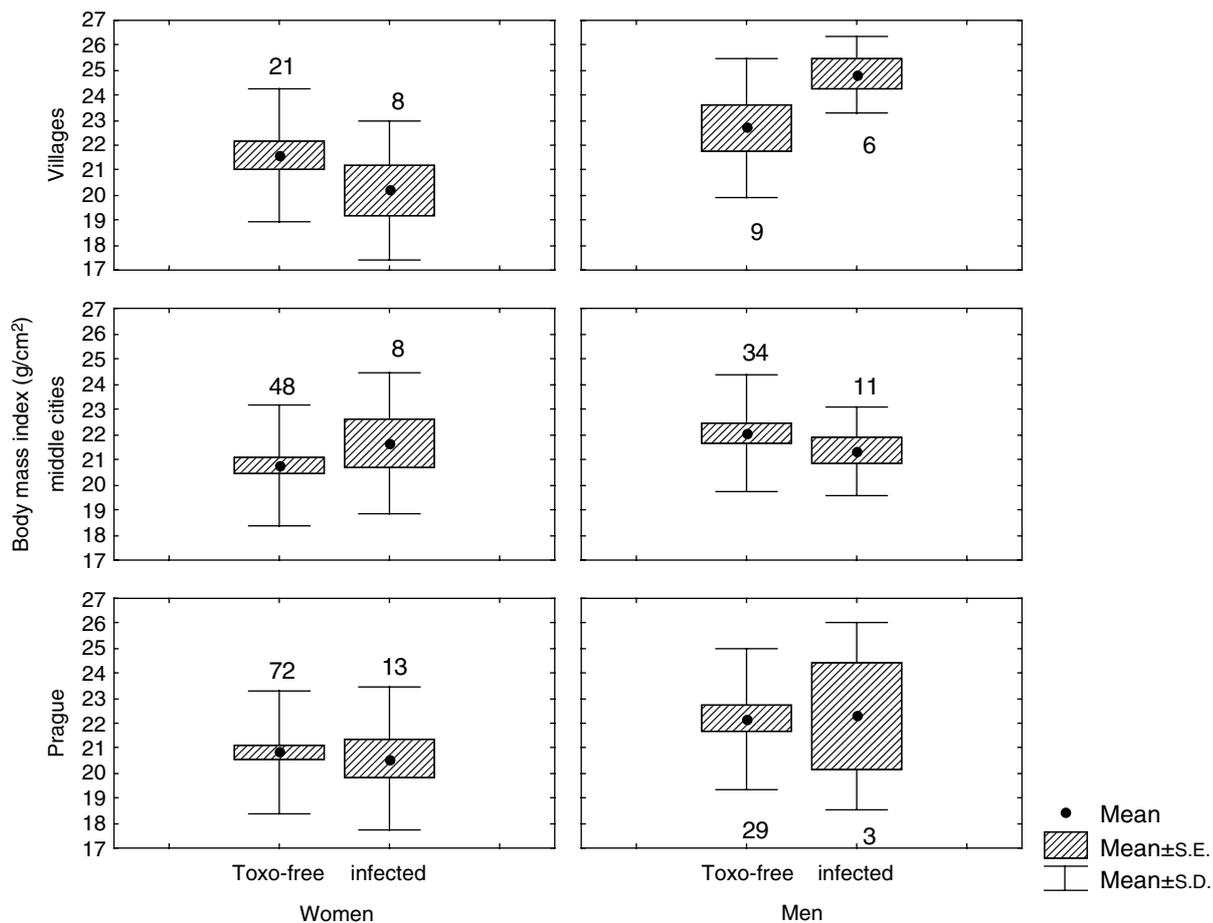


Fig. 2. Differences in body mass index between *Toxoplasma*-free and *Toxoplasma*-infected women and men. The figures indicate the numbers of study subjects in particular categories. The results of *post hoc* tests of differences of BMI between *Toxoplasma*-free and *Toxoplasma*-infected subjects for 6 particular categories were not significant.

hand:  $\beta = -0.04$ ,  $F_{1,202} = 0.3$ ,  $P = 0.608$ ) was observed for another common pathogen, the human cytomegalovirus (with the prevalence rates of 60.9% and 65.5% in females and males, respectively).

#### DISCUSSION

We have the following results. After all potential confounders (age, size of place of residence, and gender) were controlled for, *Toxoplasma*-infected and *Toxoplasma*-free subjects had similar BMI and FA. *Toxoplasma*-infected subjects had lower 2D:4D ratios for the left hand, longer fingers, and longer or wider ears, forehead, hands and legs. Several anatomical parameters including the 2D:4D ratio correlated with the level of anti-*Toxoplasma* antibodies which was also true of *Toxoplasma*-free subjects. However, such correlation was not found for specific anti-cytomegalovirus antibodies. Therefore, higher levels of anti-*Toxoplasma* antibodies in low 2D:4D ratio subjects seem to reflect stronger (already cleared) infection rather than higher levels of all antibodies (stronger humoral immunity) and resulting stronger cross-reactivity with anti-*Toxoplasma* antibodies in serological tests.

It is generally supposed that the 2D:4D ratio is more or less stable after 2 years of age (Manning *et al.* 1998; Phelps, 2004). The pre-natal testosterone level is considered the most important non-genetic factor influencing this ratio (Manning *et al.* 1998). Lower 2D:4D ratios are found in males compared to females as well as in patients with congenital adrenal hyperplasia, a condition characterized by overproduction of pre-natal androgens (Okten, Kalyoncu & Yaris, 2002; Brown *et al.* 2004). In normal men and women the 2D:4D ratio correlates with several testosterone-associated traits, including fecundity and fertility (Manning *et al.* 1998, 2000), WHR (Manning, Trivers & Singh, 1999), assertiveness and male physical aggression (Wilson, 1983; Manning, 2002). As the genital and limb development is influenced by the same Hox gene complexes (Herault *et al.* 1997; Peichel, Prabhakaran & Vogt, 1997), the authors suggest that the timing of Hox gene expression could be responsible for the correlation between the testosterone level and the 2D:4D ratio (Manning *et al.* 1998). In view of extensive short-term and long-term fluctuations in testosterone levels, the 2D:4D ratio could in fact be a better predictor of the *in utero* testosterone level than the

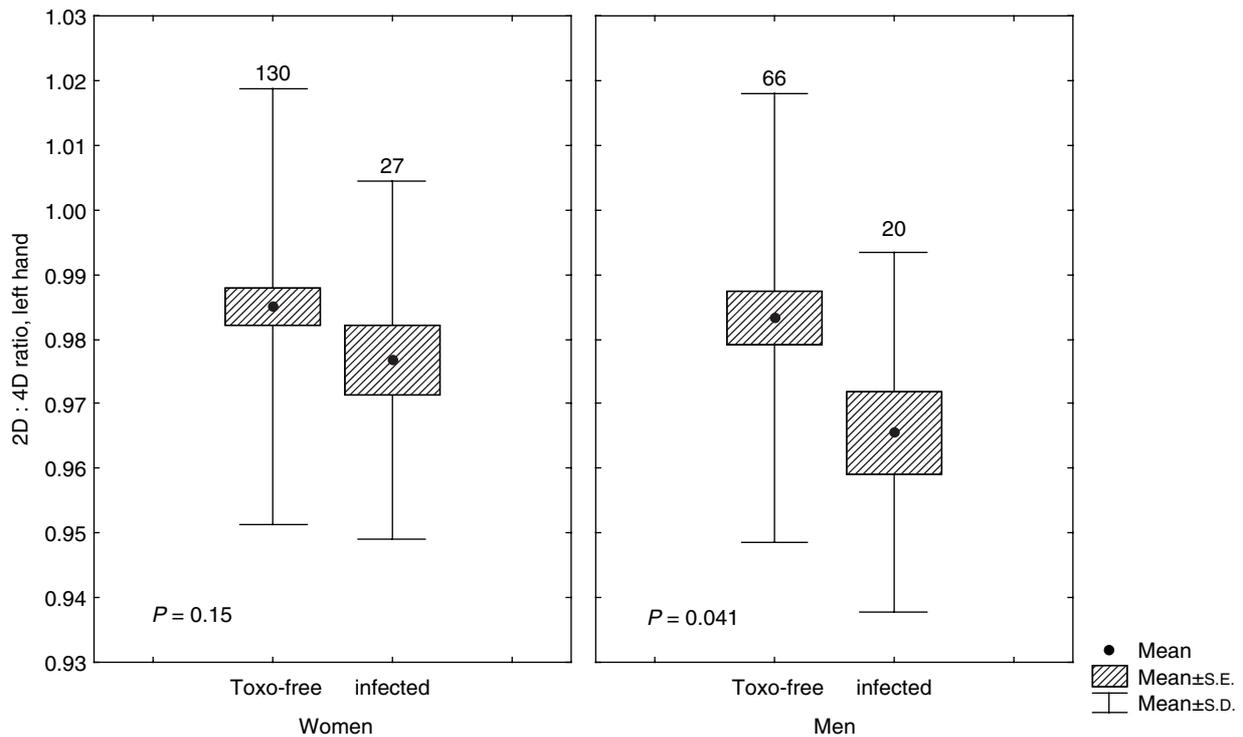


Fig. 3. Differences in 2D : 4D ratio for the left hand between *Toxoplasma*-free and *Toxoplasma*-infected women and men. The figures indicate the numbers of study subjects in particular categories. The *P* values are given for separate GLM analyses for men and women.

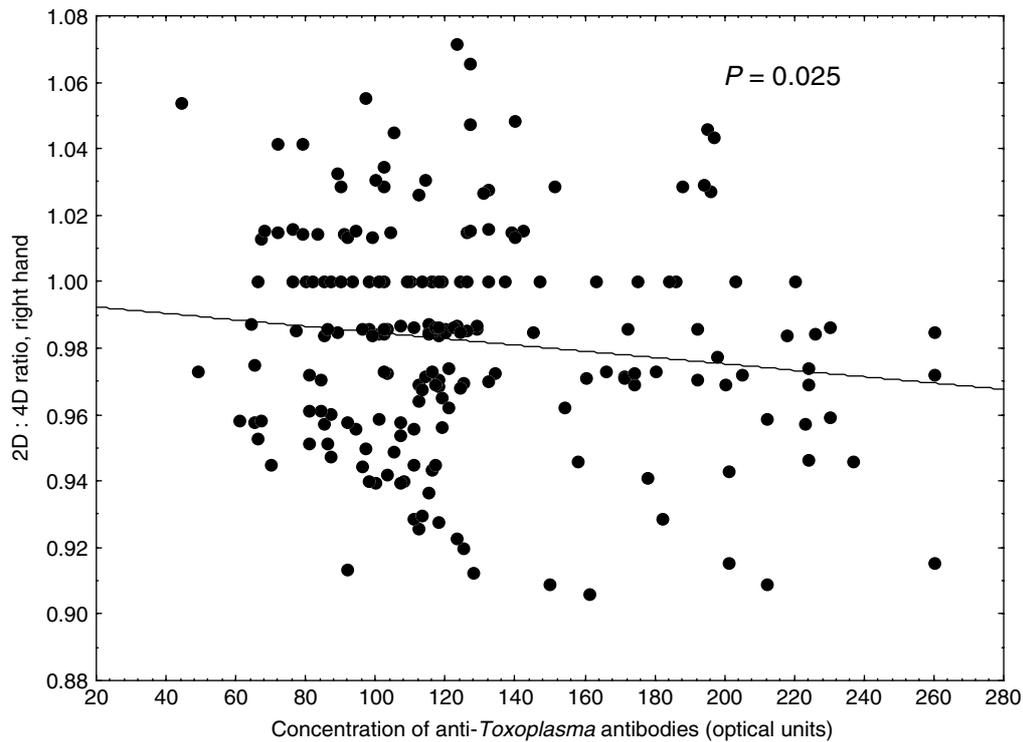


Fig. 4. Correlation between the concentration of specific anti-*Toxoplasma* antibodies and 2D : 4D ratio for the right hand in *Toxoplasma*-free subjects.

result of a single direct measurement of its concentration (Shirtcliff, Granger & Likos, 2002; Dermitzakis *et al.* 2003).

The average oestrogen level correlates negatively with cellular immunity and positively with humoral

immunity while the testosterone level correlates negatively with both cellular and humoral immunity (Roberts, Walker & Alexander, 2001; Schuster & Schaub, 2001). The immunocompetence handicap hypothesis (Folstad & Karter, 1992) suggests that

because of a negative influence of testosterone on the immunocompetence of an individual, the testosterone-dependent secondary sexual characters can be used as honest signals of male genetic quality. Females can safely choose the best mates according to their expression of the secondary sexual characters because the low-quality males with strongly expressed secondary sexual characters have a higher probability to be eliminated from the population by infectious diseases. Students of the handicap hypothesis have found the expected negative correlation between the immunocompetence of an individual and the testosterone level in different intraspecies studies (Barnard, Behnke & Sewell, 1994; Zuk, Johnsen & MacLarty, 1995; Poiani, Goldsmith & Evans, 2000; Buchanan, Evans & Goldsmith, 2003).

The lower 2D:4D ratios observed in subjects with either latent toxoplasmosis or higher levels of anamnestic anti-*Toxoplasma* antibodies may be ascribed to higher pre-natal testosterone levels and resulting lower immunity against *Toxoplasma* infection. Higher pre-natal testosterone levels may also be responsible for the observed higher prevalence of toxoplasmosis in men compared to women (21% vs 16.6%) and some of the reported differences in personality traits (Flegr *et al.* 1996). According to our knowledge, higher prevalence of toxoplasmosis in low 2D:4D ratio subjects as well as the negative correlation between the level of anti-*Toxoplasma* antibodies and 2D:4D ratio seem to be the first indirect evidence for lower anti-*Toxoplasma* immunity in humans with higher pre-natal testosterone levels. The results also suggest that at least some of the reported behavioural differences between *Toxoplasma*-infected and *Toxoplasma*-free subjects, namely the changes that do not increase during the infection, e.g. Protension in men, can be ascribed to higher testosterone levels in *Toxoplasma*-infected subjects rather than to manipulation by the parasite.

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