

1 **Physical and mental health status in *Toxoplasma*-infected women**  
2 **before and three years after they learn about their infection: The**  
3 **role of Rh factor**

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7 Health of *Toxoplasma*-infected women

8

9 Blanka Šebánková<sup>1</sup> and Jaroslav Flegr<sup>1,2\*</sup>

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14 <sup>1</sup> Division of Biology, Faculty of Science, Charles University in Prague, Vinicna 7, 128 44,  
15 Prague, Czech Republic

16 <sup>2</sup> National Institute of Mental Health, Klecany, 250 67, Czech Republic

17

18

19 \* Corresponding author. Address: Division of Biology, Faculty of Science, Charles University  
20 in Prague, Vinicna 7, 128 44, Prague, Czech Republic

21 tel: +(420) 221951821.

22 *E-mail address:* 1 ([J. Flegr](mailto:J.Flegr@cesnet.cz)) [flegr@cesnet.cz](mailto:flegr@cesnet.cz)

23

24 **Abstract**

25 Latent toxoplasmosis is known to be associated with specific changes in animal and human  
26 behavior and human personality. Many toxoplasmosis-associated shifts, such as an  
27 extroversion-introversion shift or a trust -suspicion shift, go in opposite directions in men and  
28 women. The stress coping hypothesis suggests that such behavioral effects of toxoplasmosis  
29 are side effects of chronic stress caused by lifelong parasitosis and associated health disorders.  
30 Several studies have searched for, and typically found, indices of impaired health in infected  
31 subjects. However, subjects were always aware of their toxoplasmosis status, which could  
32 influence obtained data and cause false-positive results of the studies. Here we searched for  
33 differences in physical and mental health status among 39 *Toxoplasma*-infected and 40  
34 *Toxoplasma*-free female university students who completed identical questionnaires (N-70,  
35 and anamnestic questionnaire), before and 3 years after they were informed of their  
36 toxoplasmosis status. Our results showed that infected women showed indices of poorer  
37 health status, not only after, but also before they were informed of their infection. In  
38 accordance with previously published data, these indices were more numerous and stronger in  
39 Rh-negative than in Rh-positive women. Present results suggest that observed indices of  
40 poorer health and symptoms of chronic stress in *Toxoplasma*-infected subjects are real. Due to  
41 its high (30%) prevalence, toxoplasmosis could represent an important factor for public  
42 health.

43

44 **Keywords:** CMV; IQ; I-S-T 2000 R; virus; cognitive functions; permutation tests.

45

## 46 1. Introduction

47 The prevalence of toxoplasmosis in the human population varies between 5-80% in various  
48 countries, depending on temperature, humidity, hygienic standards and kitchen habits (Tenter  
49 et al., 2000; Pappas et al., 2009). It is decreasing in many European countries and in Northern  
50 America, however, it is mostly increasing in the most populous countries in Eastern Asia, like  
51 China. *Toxoplasma gondii* reproduces sexually in the intestinal cells of its definitive host (any  
52 feline species, including domestic cats) and asexually in bodies of intermediate hosts (all  
53 warm blooded animals, including humans). In infected immunocompetent humans, a short  
54 phase of acute toxoplasmosis, which is accompanied by many nonspecific clinical symptoms  
55 including high body temperature, headache, swollen lymphatic nodes and fatigue,  
56 spontaneously proceeds into a lifelong latent phase. Latent toxoplasmosis is characterized by  
57 the presence of anamnestic IgG anti-*Toxoplasma* antibodies in serum and slowly dividing  
58 bradyzoites in tissue cysts localized mainly in immunoprivileged organs such as the brain,  
59 eye, and testes. Latent toxoplasmosis is usually considered harmless for infected  
60 immunocompetent subjects. However, many observations – typically anecdotal – suggest that  
61 it increases the risk of various disorders, for recent review see (Flegr et al., 2014).  
62 Psychiatrists performed systematic studies of the clinical effects of toxoplasmosis. They  
63 showed that toxoplasmosis likely strongly increases the risk of schizophrenia, bipolar  
64 disorder, obsessive-compulsive disorder, as well as epilepsy and migraines. For reviews see  
65 (Flegr, 2015; Sutterland et al., 2015).

66 Latent toxoplasmosis is also known to be accompanied by many specific changes in behavior  
67 and personality of infected animal and human hosts. *Toxoplasma* is transmitted from an  
68 intermediate to a definitive host by predation. Therefore, the behavioral changes observed in  
69 infected animals, like that of humans, are usually considered to be a feature of the adaptive  
70 manipulation of the parasite, intended to increase the probability of transmission of the  
71 dormant stages of *Toxoplasma* from intermediate to definitive host by trophic route. However,  
72 based on the nature of observed changes, especially based on the fact that many *Toxoplasma*-  
73 associated changes are in opposite directions in men and women (Flegr, 2010), it has been  
74 suggested that they are just nonspecific side-effects of mild but continuous stress induced by  
75 the parasitic disease (Lindová et al., 2010). It is known that men and women behaviorally  
76 cope with chronic stress in opposite ways. Stressed women express increased extroversion;  
77 they are more likely to seek and provide social support (Stone and Neale, 1984; Rosario et al.,  
78 1988; Carver et al., 1989), join with others (Hobfoll et al., 1994), and verbalize towards others  
79 or the self (Tamres et al., 2002). In contrast, stressed men express decreased extroversion, and  
80 seem to use more individualistic and antisocial (e.g., aggressive, hostile) forms of coping  
81 (Carver et al., 1989; Hobfoll et al., 1994).

82 Several studies have tried to test the stress coping hypothesis by searching for indices  
83 of chronic stress in subjects with the latent form of *Toxoplasma* infection. For example, an  
84 ecological study performed in 2014 showed that the prevalence of toxoplasmosis in particular  
85 countries largely explains the variability in mortality and morbidity associated with many  
86 diseases and disorders (Flegr et al., 2014) between countries. Recently, a large cross-sectional  
87 study performed on a nonclinical cohort of 1,500 internet users showed that *Toxoplasma*-  
88 infected subjects scored more poorly in 28 of 29 monitored health-related variables than

89 *Toxoplasma*-free subjects and reported significantly higher incidence of 77 of a list of 134  
90 disorders reported by at least 10 participants of the study (Flegr and Escudero, 2016). The  
91 main problem of the last study was that its participants self-reported their toxoplasmosis status  
92 and therefore knew whether or not they were infected. Therefore, it can be speculated that at  
93 least some of *Toxoplasma*-infected participants reported more health problems because of  
94 autosuggestion, as they believed that *Toxoplasma* could (or must) negatively influence their  
95 health.

96 The aim of the present study, was to search for possible indices of poorer physical and  
97 mental health status in a group of past and present female university students. These students  
98 voluntarily participated in behavioral studies at the Faculty of Science, Charles University,  
99 and approximately three years later, also participated in economic game experiments at the  
100 University of Economics, Prague. Most participants filled in two identical questionnaires (an  
101 anamnestic questionnaire monitoring physical and mental health status, and a standard N-70  
102 questionnaire monitoring seven potentially pathognomonic factors: anxiety, depression,  
103 obsession, hysteria, hypochondria, psychosomatic symptoms of vegetative lability, and  
104 psychasthenia) before and about three years after they were told whether they are  
105 *Toxoplasma*-infected or not. This experimental setup enables one to discriminate whether the  
106 *Toxoplasma*-infected subjects express the symptoms of impaired health because of the  
107 infection or because they know that they are infected and therefore believe that they should  
108 express (or report) such symptoms.

109

## 110 **2. Material and Methods**

### 111 **2.1. Participants**

112 Subjects were recruited from a pool of former biology students of the Faculty of Science,  
113 Charles University, Prague, who have voluntarily participated in various ethological studies  
114 over the past 20 years. All subjects were women who were tested for toxoplasmosis and  
115 rhesus (Rh) status between 2002-2013. These volunteers often take part in many studies, most  
116 of which are not related to *Toxoplasma* infection. Crucially, toxoplasmosis was not mentioned  
117 in the study recruitment invitation, and the experiments were run at the University of  
118 Economics—not the usual location for toxoplasmosis-related experiments. Moreover, the  
119 experimental games were primarily focused on the examination of the economic behavior of  
120 women (Lanchava et al., 2015). Therefore, it is unlikely that subjects suspected that the study  
121 was related to toxoplasmosis research. To achieve a balanced design and the highest possible  
122 power of the study, we invited all Rh-negative *Toxoplasma*-infected women in the pool (the  
123 rarest combination of the trait within the study), and also the same number of *Toxoplasma*-  
124 infected and *Toxoplasma*-free women. Therefore, the frequency of infected subjects and Rh-  
125 negative subjects did not correspond to their normal representation in the Czech population.  
126 All participants provided written informed consent. Subjects' recruitment and data handling  
127 were performed in compliance with the Czech legislation in force, and were approved by the  
128 Institutional Review Boards of the Faculty of Science, Charles University (No. 2014/21).

129

## 130 2.2. Questionnaires

131 At the beginning of the present study, the volunteers were asked to complete an anamnestic  
132 questionnaire as well as a N-70 questionnaire. Most participants completed these  
133 questionnaires at two different time points: before testing for toxoplasmosis, and then about 3  
134 years later at the beginning of the present study. In the anamnestic questionnaire, the  
135 participants rated their physical and mental health status by answering a panel of questions  
136 such as: “How often do you have allergies (or: non-allergic skin problems; digestive  
137 problems; common infectious diseases, such as flu; cardiovascular problems; orthopedic  
138 problems; neurological problems; headaches; other chronic or recurring pain; other chronic or  
139 recurring health problems; depression; other mental health problems; metabolic problems like  
140 diabetes; are you tired after returning from work/school; do you visit medical doctors (not  
141 dentists and not for prevention))?” using a 6-point Likert scale (0: never, 1: maximally once a  
142 year, 2: maximally once a month, 3: maximally once a week, 4: several times a week, 5: daily  
143 or several times daily). They were also asked how many times they used antibiotics in the past  
144 3 years (5 means 5 or more times), and how many times they spent more than a week in the  
145 hospital in the past 5 years. The new version of the questionnaire completed after 3 years also  
146 contained the question “At what age do you expect to die?”.

147 The N-70 is originally a Czech questionnaire constructed for the assessment of seven areas of  
148 psychiatric symptom clusters - anxiety, depression, obsession, hysteria, hypochondria,  
149 psychosomatic symptoms of vegetative lability, and psychasthenia (Vacíř, 1973). The English  
150 version of the questionnaire is available at (Flegr et al., 2012). Subjects are asked to answer  
151 70 questions using a 3-point agreement scale. Scores in each cluster range from 0–30. The  
152 total N-70 score is the sum for all 70 questions.

153

## 154 2.3. Serological tests

155 All testing for toxoplasmosis was performed at the National Reference Laboratory for  
156 Toxoplasmosis, National Institute of Public Health, Prague. The complement-fixation test  
157 (CFT), which determines the overall levels of IgM and IgG antibodies of particular  
158 specificity, and Enzyme-Linked Immunosorbent Assays (ELISA) (IgG ELISA: SEVAC,  
159 Prague) were used to detect *T. gondii* infection status of the subjects. ELISA assay cut-  
160 point values were established using positive and negative standards according to  
161 the manufacturer's instructions. In CFT, the titre of antibodies against *T. gondii* in sera was  
162 measured in dilutions between 1:4 and 1:1024. The subjects with CFT titres between 1:8 and  
163 1:128 were considered *T. gondii* infected. Only subjects with clearly positive or negative  
164 results of CFT and IgG ELISA tests were diagnosed as *T. gondii*-infected or *T. gondii*-free,  
165 whilst subjects with different results on these tests, or ambiguous results, were retested or  
166 excluded from the study.

167 A standard agglutination method was used for Rh factor examination. A constant  
168 amount of anti-D serum (human monoclonal antiD reagent; SeracloneH, Immucor Gamma  
169 Inc.) was added to a drop of blood on a white glass plate. Red cells of Rh-positive subjects  
170 were agglutinated within 2–5 minutes.

171

## 172 2.4. Data analysis

173 Statistica v. 10 was used for the statistical analysis. Differences in age were tested by a t-test.  
174 N-70 scores were analysed using an ANCOVA, with age as a confounding variable. Certain  
175 scores (obsession and, to a smaller extent, depression) had slightly asymmetric distributions;  
176 therefore, we repeated the analyses with nonparametric methods. However, results of the  
177 parametric and nonparametric analyses were qualitatively the same. Ordinal and binary data  
178 were analyzed by a partial Kendall's correlation test, which is used to measure the strength  
179 and significance of the association among binary, ordinal, or continuous data regardless of  
180 their distributions and allows for the control of one confounding variable – in this case, age  
181 (Siegel and Castellan, 1988). The Excel spreadsheet used to compute the partial Kendall tau  
182 and the significance for variables A (diseases) and B (*Toxoplasma* infection), once C (age)  
183 was controlled based on Kendall Tau's AB, AC, and BC- is available at:  
184 <http://web.natur.cuni.cz/flegr/programy.php>. The false discovery rate (preset to 0.1) was  
185 controlled with the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995). In  
186 contrast to the simple Bonferroni's correction, this procedure also takes into account the  
187 distribution of p values of performed multiple tests.

188 All raw data are available as the Supporting Information S1.

189

## 190 3. Results

191 The final set contained 14 Rh-negative and 26 Rh-positive *Toxoplasma*-free women  
192 and 13 Rh-negative and 26 Rh-positive *Toxoplasma*-infected women. Infected women were  
193 older than *Toxoplasma*-free women (24.6 vs. 23.0,  $t_{77}=-1.90$ ,  $p=0.06$ ). No significant effects  
194 of age ( $p=0.402$ ,  $\mu^2=0.01$ ), toxoplasmosis ( $p=0.206$ ,  $\mu^2=0.02$ ), and Rh factor ( $p=0.419$ ,  
195  $\mu^2=0.01$ ) were observed, but a significant effect of toxoplasmosis-Rh factor interaction  
196 ( $p=0.011$ ,  $\mu^2=0.08$ ) on total N-70 score was detected with an ANCOVA. The same analysis  
197 was performed separately on the seven N-70 traits, and showed significant effects of  
198 toxoplasmosis-Rh factor interaction on obsession ( $p=0.036$ ,  $\mu^2=0.06$ ), vegetative lability  
199 ( $p=0.032$ ,  $\mu^2=0.06$ ), and psychasthenia ( $p=0.008$ ,  $\mu^2=0.09$ ). The visual inspection of Figure 1  
200 suggests that the *Toxoplasma*-infected Rh-negative women had much higher N-70 traits,  
201 whilst *Toxoplasma*-infected Rh positive subjects had approximately the same or slightly lower  
202 N-70 traits than corresponding *Toxoplasma*-free controls.

203 The detailed examination of raw N-70 data showed that *Toxoplasma*-free women  
204 answered many questions of the N-70 questionnaire differently than *Toxoplasma*-infected  
205 women. Partial Kendall analyses, with age as a covariate, were performed on all 79 women,  
206 and showed that 13 of 70 observed differences remained significant after the correction for  
207 multiple tests. Separate analyses of 27 Rh-negative women and 52 Rh-positive women  
208 showed that the number of significant differences between *Toxoplasma*-infected women and  
209 *Toxoplasma*-free women was 32 of 70 and 12 of 70 in Rh-negative and Rh-positive women,  
210 respectively. While in Rh-negative women only 3 of 32 significant associations were  
211 negative, i.e., indicated better health status or wellbeing of *Toxoplasma*-infected women, in



212 Rh-positive subjects, 11 of 12 associations, significant after the correction for multiple tests,  
213 were negative (see Tab. 1).

214 The existence of a statistical association between two factors does not mean a causal  
215 relation between these factors. However, the existence of a causal relation can be supported  
216 when one or more Bradford-Hill criteria of causality are fulfilled. To search for such support,  
217 we tested the biological gradient of the effect of toxoplasmosis. This was achieved by  
218 studying the correlation between the concentration of anti-*Toxoplasma* antibodies and N-70  
219 factors in a subset of *Toxoplasma*-infected women. Fig. 2 and Table 2 show that the CFT titre  
220 of antibodies in *Toxoplasma*-infected women correlate with the total N-70 score, as well as  
221 with all seven N-70 factors in Rh factor-negative women but not in Rh factor-positive women.

222 Twenty (20) Rh-negative women (7 *Toxoplasma*-infected) and 31 Rh-positive women  
223 (11 *Toxoplasma*-infected) also completed the questionnaire 3 years earlier, before they knew  
224 whether or not they were infected. We repeated all analyses with this smaller data set. No  
225 effects of toxoplasmosis or toxoplasmosis-Rh factor interaction were significant after the  
226 correction for multiple tests, possibly due to the low number (7) of *Toxoplasma*-infected, Rh  
227 negative women, the results not shown. However, a more detailed analysis once again  
228 showed that many of the seventy N-70 questions were answered differently by the  
229 *Toxoplasma*-infected and *Toxoplasma*-free women (11 in the whole set, 5 in the subset of 20  
230 Rh-negative women and 6 in the subset of 31 Rh positive women; Benjamini-Hochberg  
231 correction for multiple tests), see Tab. 1. Fig. 3 shows that N-70 pathognomonic factors  
232 mostly decreased or stayed constant between the first and the second examination in Rh-  
233 positive *Toxoplasma*-infected and *Toxoplasma*-free women and in Rh-negative *Toxoplasma*-  
234 free women, but three factors (anxiety, depression, and psychasthenia) increased in Rh-  
235 negative *Toxoplasma*-infected women. The repeat measure ANCOVA with N-70 factors,  
236 measured before testing for toxoplasmosis and about 3 years later, showed that the time-  
237 toxoplasmosis-Rh interaction had a significant effect only on depression ( $p=0.027$ ,  $\mu^2=0.10$ ).

238 In the anamnestic questionnaire, the subjects rated their health status before testing for  
239 toxoplasmosis, and during N-70 testing 3 years later. Tab. 3 shows that infected Rh-negative  
240 as well as the Rh-positive women express several indices of impaired physical and mental  
241 health before, as well as after, obtaining the information about their toxoplasmosis status. For  
242 example, they estimated their probable age of survival to be lower than *Toxoplasma*-free  
243 women, reported more frequent hospitalizations in the past 5 years, and to have more serious  
244 or more frequent neurological problems.

245

#### 246 **4. Discussion**

247 The present study showed that *Toxoplasma*-infected women with Rh-negative  
248 phenotype expressed higher levels of certain potentially pathognomonic factors measured  
249 with the N-70 questionnaire, especially obsessiveness, vegetative lability, and psychasthenia.  
250 In the infected subjects, the level of these factors correlated positively with the concentration  
251 of anti-*Toxoplasma* antibodies in Rh-negative women but not in more numerous Rh-positive  
252 women. Both Rh-negative and Rh-positive women reported more serious and more frequent  
253 physical and mental health-related problems. Differences between *Toxoplasma*-infected and

254 *Toxoplasma*-free subjects in potentially pathognomonic factors and health-related variables  
255 were also observed in a subset of women who completed the N-70 and anamnestic  
256 questionnaires 3 years before the present study, i.e., during a time when they were not aware  
257 whether they were infected or not.

258 Poorer health status of *Toxoplasma*-infected subjects was observed in many case-  
259 controlled studies – for a review see (Flegr et al., 2014). A recent study performed on a large  
260 nonclinical cohort of 1,486 volunteers showed that *Toxoplasma*-infected subjects scored more  
261 poorly in 28 of 29 health-related variables, including number of stays in the hospital, number  
262 of doctors visits, frequency of being tired, and seriousness or frequency of allergic,  
263 neurological and mental health problems. In contrast to previous studies, here we  
264 demonstrated the existence of toxoplasmosis-related effects before the subjects were informed  
265 of whether they are *Toxoplasma*-infected or not. This means that the observed effects could  
266 not be the result of autosuggestion based on the subjects' belief that toxoplasmosis has a  
267 negative effect on their health. The only factor that significantly increased in Rh-negative,  
268 *Toxoplasma*-infected women was depression, i.e., the factor that was not significantly higher  
269 in *Toxoplasma*-infected than in *Toxoplasma*-free Rh-negative women during the second N-70  
270 testing. Our conclusion – that impaired physical and mental health status, not autosuggestion,  
271 was responsible for higher N-70 factors – was also supported by the fact that *Toxoplasma*-  
272 infected women had the same level of hypochondria as the *Toxoplasma*-free women. The  
273 negative effects of toxoplasmosis on human health were also demonstrated in a recent  
274 ecological study (Flegr et al., 2014). The prevalence of toxoplasmosis in 88 countries  
275 correlated positively with specific disease burden for 23 of 128 studied disorders. The effects  
276 of toxoplasmosis on public health was relatively large. For example, the differences in  
277 prevalence of toxoplasmosis explained 23 % of inter country variability in total disease  
278 burden in Europe (Flegr et al., 2014).

279 At the same time, the present results concerning factors in women measured with the  
280 N-70 questionnaire contrasted with results of a similar study performed on male soldiers who  
281 went through the entrance examinations for (well-paid) participation in international military  
282 missions. The authors of the study suggested that the *Toxoplasma*-infected subjects were  
283 objectively motivated to mask their negative and accentuate their positive characteristics. It is,  
284 however, also possible that toxoplasmosis had an opposite effect on these pathognomonic  
285 factors in men and women as it has been already demonstrated for many personality factors  
286 and behavioral patterns (Lindová et al., 2006; Lindová et al., 2010; Flegr et al., 2011).

287 Both the present and previous studies show a much stronger effect of toxoplasmosis  
288 on Rh-negative than Rh-positive subjects. In the present study, we observed significantly  
289 higher N-70 factors in *Toxoplasma*-infected Rh-negative women and slightly (not  
290 significantly) lower N-70 factors (i.e., better physical and mental health) in *Toxoplasma*-  
291 infected Rh-positive women. Detailed analyses of the N-70 questionnaire responses of  
292 *Toxoplasma*-infected and *Toxoplasma*-free Rh-positive women showed that 11 of 12  
293 significant differences indicated better physical or mental health of infected subjects. Such  
294 paradoxical (positive) effects of *Toxoplasma* infection have been previously reported to exist.  
295 The case control study performed on 500 blood donors showed that *Toxoplasma*-infected Rh-



296 positive heterozygotes showed better psychomotor performance – namely, shorter reaction  
297 times – than *Toxoplasma*-free Rh-positive heterozygotes. At the same time, psychomotor  
298 performance of infected Rh-positive homozygotes and especially of infected Rh-negative  
299 homozygotes was much poorer than that of corresponding controls (Novotná et al., 2008). It  
300 has been shown that toxoplasmosis has various effects on human physiology and some of  
301 these effects, such as increase of testosterone (Flegr et al., 2008a; Flegr et al., 2008b) or  
302 partial immunosuppression (Flegr and Stríž, 2011), could have a positive impact on human  
303 performance and health in certain situations. It must be remembered that our population of  
304 Rh-positive women represents a mixture of homozygotes and heterozygotes. At the same  
305 time, current data suggests that protective effects of Rh factor positivity are fully expressed  
306 only in the Rh-positive heterozygotes (Novotná et al., 2008; Flegr, 2016). Therefore, future  
307 studies should be performed on DNA genotyped populations.

308 A combination of results of observational studies performed on humans, and  
309 especially experimental studies performed on animals, suggests (but of course does not prove)  
310 that toxoplasmosis is the cause rather than the effect of impaired physical and mental health of  
311 infected hosts. The present study showed that the level of N-70 pathognomonic factors  
312 correlated with the level of anti-*Toxoplasma* antibodies measured with CFT. This test  
313 measured the concentration of specific IgM and of certain subclasses of IgG antibodies  
314 reacting with various *Toxoplasma* antigens. It has been shown that the intensity of the CFT  
315 signal decreases with time from the infection and could be therefore used as a proxy of the  
316 duration of latent toxoplasmosis. The intensity of many toxoplasmosis-associated changes,  
317 such as personality factor changes (Flegr et al., 2000) or the impairment of reaction times  
318 (Havlíček et al., 2001), are negatively correlated with the concentration of anti-*Toxoplasma*  
319 antibodies measured with CFT. It has been shown that CFT titres are probably a better proxy  
320 for the duration of the infection than the concentration of IgG measured with enzyme-linked  
321 immunosorbent assay (Kodym et al., 2007) but worse than – now rarely used – indirect  
322 immunofluorescence assay (Kaňková et al., 2007). The existence of a negative correlation is  
323 mostly considered to be indirect evidence for models suggesting that given toxoplasmosis-  
324 associated changes represent slow cumulative effects of latent infection. In contrast, a positive  
325 correlation between the concentration of antibodies and the changes suggests that the  
326 observed effects represent transient vanishing effects of acute toxoplasmosis. Such positive  
327 correlations were observed, for example, for the probability of traffic accidents (Flegr et al.,  
328 2009) and predisposition to gestational diabetes mellitus (Kaňková et al., 2015), and now  
329 additionally for N-70 factors.

### 330 **Limitations**

331 The main limitation of the present study is that its participants were tested for toxoplasmosis  
332 several years before the current study. Toxoplasmosis is a life-long infection and, therefore,  
333 women with positive results of the serological test stay infected for their entire lives.  
334 However, at least some originally *Toxoplasma*-free women could have acquired the infection  
335 in the years that passed between the diagnosis and the start of the present study. Monte Carlo  
336 model-based analysis showed that the presence of such false negative subjects in the study  
337 population could easily result in Type 2 error, i.e., failure to detect existing effects of

338 toxoplasmosis, but could not result in false positive results of a study – in the detection of  
339 non-existing effects (Flegr and Horáček, 2017).

### 340 **Conclusions**

341 Our results support the notion that many behavioral effects of toxoplasmosis represent side-  
342 effects of mild but long-term impaired health status rather than a product of adaptive parasitic  
343 manipulation aimed to increase the chances for the transmission of *Toxoplasma* from  
344 intermediate to definitive hosts. The results also suggest that toxoplasmosis likely has a  
345 serious impact on subjectively perceived physical and mental health. Toxoplasmosis affects  
346 about one third of the human population worldwide and therefore its global impact on public  
347 health may be important. No method of treatment of latent toxoplasmosis and no vaccine that  
348 could protect humans against the infection are currently available. The results that slowly  
349 accumulated over the past 15 years strongly suggest that such methods and vaccines should be  
350 intensively searched for.

351

### 352 **Authors' contribution**

353 JF designed the study and performed the analyses. BŠ collected and preprocessed the  
354 data. Both authors contributed to and have approved the final manuscript.

355

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363

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460 Table 1 Differences between responses of *Toxoplasma*-infected and *Toxoplasma*-free women  
 461 to 70 N-70 questions

Question	New examination			Old examination		
	All (N=79)	Rh- (N=27)	Rh+ (N=52)	All (N=51)	Rh- (N=20)	Rh+ (N=31)
Do you feel anxious when your superior calls you and you don't know why?	-0.044	<b>0.224</b>	<b>-0.203</b>	0.037	<b>0.404</b>	-0.193
Do you experience uncomfortable inner tension such as if something bad is going to happen?	-0.051	0.141	-0.146	-0.030	0.139	-0.136
In demanding situations, do you feel butterflies in your belly or chest; do you need to go to the toilet more often?	-0.064	0.061	-0.127	<b>-0.208</b>	-0.183	-0.229
Do you suffer from stage fright?	-0.012	-0.007	-0.012	<b>-0.231</b>	-0.328	-0.178
Do you suffer from fear that is unproportional to the situation from which it originates?	-0.150	-0.115	-0.177	-0.174	-0.112	-0.240
Do you feel like vomiting when expecting trouble?	<b>-0.222</b>	-0.054	<b>-0.316</b>	0.023	0.006	0.018
Do you comfort eat when you are sad or worried more than other people?	0.068	0.113	0.046	-0.084	-0.199	-0.024
Do you suffer from indeterminate fear despite having no reason for such worries?	0.141	0.209	0.115	0.157	0.298	0.056
Do you feel unpleasant thumping of your heart when confronted with a distressing situation?	-0.134	<b>0.218</b>	<b>-0.300</b>	-0.065	-0.088	-0.054
Do you suffer from any agitated states when you cannot hold still, you must keep moving or do something without purpose, e. g. chain smoking?	0.094	<b>0.295</b>	-0.047	-0.042	-0.106	0.008
Have you been lately easily depressed?	0.020	<b>0.375</b>	-0.185	-0.031	-0.091	0.011
Do you ever feel like you have lost your ability to have fun, revel, or look joyfully to the future?	0.130	<b>0.312</b>	0.037	-0.011	0.045	-0.042
Do you think that you are an unhappy person?	-0.011	0.017	-0.026	-0.124	-0.213	-0.065
Do you have problems controlling tears in harming situations?	0.080	-0.129	0.165	0.013	-0.318	0.213
Do you have black thoughts; are you unable to get rid of them?	0.072	<b>0.408</b>	-0.085	<b>0.230</b>	0.164	<b>0.277</b>
Do you feel that your interest in things that you were earlier interested in has decreased because of sad moods?	0.108	<b>0.341</b>	0.011	0.081	0.064	0.094
Does sadness or joyless mood decrease your working performance?	0.019	<b>0.249</b>	-0.076	0.010	0.101	-0.043
Do you have problems to get asleep in the evening because you are unable to get rid of	<b>-0.155</b>	-0.069	<b>-0.203</b>	-0.155	-0.073	-0.221

distressing thoughts?						
Do you feel that your friends avoid you though you haven't done them anything bad?	0.116	<b>0.259</b>	0.055	<b>-0.254</b>	-0.274	<b>-0.262</b>
Have you been experiencing suicidal thoughts lately?	-0.010	0.023	-0.024	-0.165	-0.302	-0.058
Do you often have thoughts about you suffering from some severe illness or the possibility of acquiring one?	0.014	0.204	-0.086	0.116	0.274	0.026
Do you suffer from irrational fear in closed spaces?	<b>0.237</b>	<b>0.425</b>	0.121	0.178	<b>0.419</b>	0.068
Do you have strong fear of heights, are you afraid of fall or – when high above – is something inside tempting you to jump down?	0.119	<b>0.482</b>	-0.083	0.144	0.356	0.010
Do you suffer from strong anxiety in crowded places?	<b>-0.230</b>	<b>-0.262</b>	<b>-0.226</b>	-0.153	-0.103	-0.188
Do you suffer from an uneasy feeling that you forgot some of your domestic tasks (such as closing windows, locking doors, switching off lights)?	-0.009	0.138	-0.066	0.148	0.117	0.182
Do you often have nonsensical ideas such as to count windows, to walk only on specific cobblestones, or to say inappropriate words in stressful situations?	-0.133	-0.077	-0.155	0.010	0.112	-0.031
Do you often have inappropriate thoughts that you don't agree with and that are difficult to get rid of?	<b>0.193</b>	<b>0.367</b>	0.115	-0.077	-0.327	0.064
Do you often have to double check your previous tasks to get calm and to be reassured that you did them right?	-0.047	-0.032	-0.050	-0.122	-0.048	-0.171
Do you get severely out of balance when your daily habits are disturbed?	<b>-0.157</b>	-0.031	<b>-0.231</b>	<b>0.203</b>	<b>0.430</b>	0.062
Do you think that you are a perfectionist? Do you hate when something is done imprecisely or if there is not absolute order around you?	<b>-0.221</b>	-0.132	<b>-0.265</b>	-0.018	0.167	-0.141
Do you feel like fainting when you are strongly keyed up?	-0.052	-0.181	-0.005	0.135	0.072	0.169
Do you feel good when you are the center of attention?	-0.095	-0.124	-0.084	0.131	-0.149	<b>0.282</b>
Do you feel pins and needles or loss of sensitivity in some places when you are strongly keyed up?	-0.108	-0.138	-0.097	-0.066	-0.181	-0.019
Do you have problems to control your limbs because of strong excitement?	-0.020	0.144	-0.117	0.013	0.054	-0.020



Do you feel that you can't stop yourself when you are upset despite unconsciously feeling that you are acting wrongly?	0.023	0.120	-0.006	-0.059	0.184	-0.236
Are you ever unable to talk as if your tongue is numb in unpleasant situations?	<b>-0.171</b>	-0.081	<b>-0.223</b>	-0.188	-0.134	-0.224
Do you like dramatic situations when you have a chance to show off?	-0.114	-0.020	-0.166	-0.122	0.099	-0.227
Do you have spasms in your limbs during conflict situations?	-0.071	0.160	-0.151	0.094	0.000	0.120
Do you ever feel that you have tendencies to sham and pretend?	-0.095	0.125	<b>-0.218</b>	0.078	0.224	-0.046
Do you ever deceive other people to achieve your own goals?	-0.121	-0.126	-0.115	<b>0.210</b>	0.043	<b>0.341</b>
Do you often feel ill?	0.004	0.191	-0.097	0.151	0.125	0.160
Do you obsess over health problems?	0.050	<b>0.238</b>	-0.040	-0.007	0.289	-0.214
Do you often visit a physician even with minor problems?	0.008	-0.201	0.115	0.084	0.072	0.089
Do you check your body temperature, pulse, face in mirror etc. when feeling sick?	0.047	0.086	0.019	<b>0.206</b>	<b>0.532</b>	-0.005
Do you try to educate yourself when diagnosed with a health problem (by reading popular medical articles or books)?	0.048	-0.135	0.144	-0.082	0.029	-0.166
Do you suffer from unpleasant stabbing pain in heart area when you are at rest?	-0.076	<b>-0.281</b>	0.030	-0.150	0.178	<b>-0.330</b>
Do you suffer from indigestion?	0.027	0.126	-0.024	0.012	0.018	0.003
Do you have diarrhea or constipation?	0.019	0.132	-0.049	-0.073	-0.122	-0.048
Do you ever suffer from a general feeling of pain or discomfort in your muscles or joints?	<b>0.191</b>	<b>0.381</b>	0.108	-0.026	0.278	-0.241
Do you confide your problems to your acquaintances and/or friends?	0.042	<b>0.219</b>	-0.043	<b>0.230</b>	<b>0.481</b>	0.105
Do you suffer from full body excess sweating or sweating of your hands and/or feet?	<b>-0.174</b>	<b>-0.270</b>	-0.122	<b>-0.210</b>	-0.249	-0.191
Do you suffer from headaches?	0.044	<b>0.229</b>	-0.064	0.136	0.244	0.050
Do you feel like your heart sometimes skips a beat?	0.130	<b>0.333</b>	0.027	0.020	0.241	-0.099
Does your heart flutter or start to race easily in demanding situations?	-0.001	<b>0.304</b>	-0.162	0.076	0.216	-0.026
Do you blush easily?	0.053	0.181	-0.009	0.138	0.142	0.153
Do you always feel cold?	<b>0.282</b>	<b>0.335</b>	<b>0.263</b>	0.113	0.161	0.114
Do you feel that you have difficulties with breathing even when relaxing?	0.086	<b>0.281</b>	-0.016	0.140	0.091	0.168
Do you suffer from vertigo or dizziness?	-0.130	-0.081	-0.174	0.048	-0.148	0.162

Do you feel like vomiting when you see something disgusting or if you hear someone talking about detestable things?	0.112	0.125	0.106	<b>0.228</b>	0.260	0.211
Do you feel nauseous before common dental or medical interventions and minor surgical procedures?	0.143	<b>0.330</b>	0.053	<b>0.206</b>	0.261	0.162
Do you suffer from inner disquiet, tension, or restlessness?	0.046	<b>0.556</b>	-0.131	0.046	0.212	-0.035
Do you think that your memory isn't as good as it was?	-0.041	<b>0.352</b>	<b>-0.204</b>	-0.106	0.166	<b>-0.264</b>
Do you think that you are less tolerant to noise and rush in your surroundings lately?	0.068	<b>0.228</b>	-0.008	0.017	0.030	0.010
Do you feel weariness and exhaustion that doesn't correspond with your working load?	0.075	0.180	0.022	-0.095	-0.004	-0.156
Do you feel very weak (like after suffering long-term illness)?	<b>0.210</b>	<b>0.344</b>	0.134	-0.046	0.179	-0.210
Do you feel that your sexual appetite is diminishing, do you have problems in sexual intercourse that you didn't have before?	-0.030	<b>0.224</b>	-0.171	0.129	0.182	0.110
Do you have a short fuse, do nonessential things that get you out of balance?	-0.142	0.084	<b>-0.247</b>	-0.002	0.071	-0.040
Do you feel that you don't work as effectively as before and that your performance is worsening despite all your efforts?	0.127	<b>0.517</b>	-0.096	-0.092	0.021	-0.162
Do you tire more quickly than before?	<b>0.164</b>	<b>0.486</b>	-0.017	0.034	0.136	-0.028
Do you sleep badly; do you wake up feeling that sleep didn't refresh you?	0.114	<b>0.230</b>	0.049	-0.112	0.046	-0.211

462

463 The table shows the results (partial Taus) of a partial Kendall correlation with age of a subject  
 464 as a covariate between binary variable toxoplasmosis and ordinal variables showing intensity  
 465 of particular problems (coded as 1, 2, 3) examined by 70 questions of the N-70 questionnaire.  
 466 Positive Tau means that infected women reported more serious problems. Results that are  
 467 significant after the correction for multiple tests with Benjamini-Hochberg procedure are  
 468 printed in bolt.

469

470 Table 2 Correlation between concentration of anti-*Toxoplasma* antibodies and N-70 factors

	New examination				Old examination			
	Rh negative (N=13)		Rh positive (N=26)		Rh negative (N=7)		Rh positive (N=11)	
	Tau	p	Tau	p	Tau	p	Tau	p
anxita	<b>0.527</b>	<b>0.012</b>	0.153	0.272	0.532	0.093	0.215	0.357
depression	<b>0.433</b>	<b>0.039</b>	0.028	0.843	0.168	0.596	0.107	0.646
obsession	<b>0.481</b>	<b>0.022</b>	0.104	0.456	<b>0.802</b>	<b>0.011</b>	0.324	0.165
histeria	<b>0.585</b>	<b>0.005</b>	0.189	0.176	0.363	0.253	0.335	0.151
hypochondria	<b>0.517</b>	<b>0.014</b>	0.154	0.271	0.432	0.173	0.253	0.280
vegetative lability	<b>0.508</b>	<b>0.016</b>	-0.076	0.587	0.276	0.384	0.171	0.465
psychasteny	<b>0.427</b>	<b>0.042</b>	-0.026	0.854	0.491	0.121	0.191	0.413

471

472 Partial Tau correlations (age controlled) that are significant after the correction for multiple  
 473 tests are printed in bolt.

474 Table 3 Differences in health related variables between *Toxoplasma*-infected and  
 475 *Toxoplasma*-free women

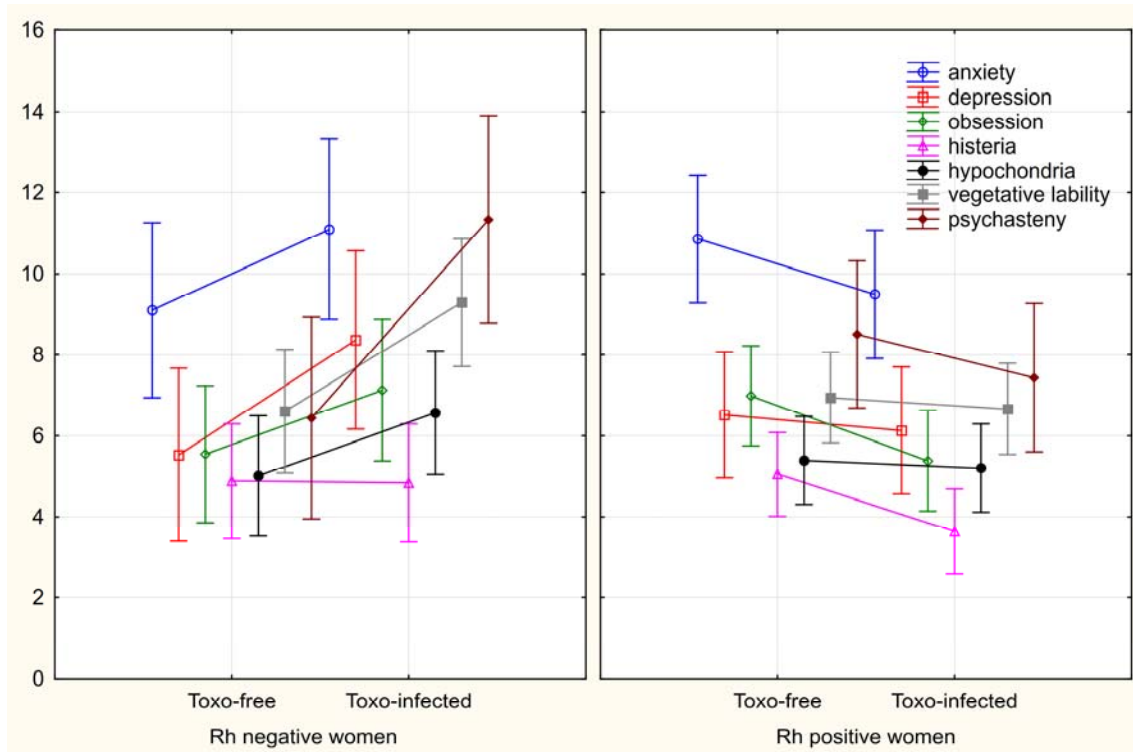
476

	New examination			Old examination		
	All (N=79)	Rh- (N=27)	Rh+(N=52)	All (N=51)	Rh- (N=20)	Rh+ (N=31)
allergic problems	0.05	<b>0.23</b>	-0.06	0.14	0.21	0.12
dermatologic problems	-0.09	0.01	-0.16	0.01	0.03	-0.02
digestive organs problems	0.05	0.03	0.07	0.09	0.14	0.05
metabolic problems	-0.02	-0.18	0.05	0.09	-0.15	0.21
infectious dis. problems	-0.06	-0.01	-0.09	-0.10	-0.10	-0.11
cardiovascular problems	0.07	0.00	0.09	-0.17	0.00	-0.21
orthopedic problems	-0.03	0.07	-0.10	0.00	0.03	-0.10
neurological problems	0.13	<b>0.23</b>	0.09	<b>0.25</b>	0.26	<b>0.26</b>
headache	-0.01	0.20	-0.11	-0.03	-0.02	-0.09
other chronic pain	-0.08	0.16	<b>-0.18</b>	0.15	0.07	0.20
other chronic problems	0.04	0.06	0.03	0.15	-0.05	<b>0.26</b>
depression	0.10	<b>0.23</b>	0.02	-0.03	0.06	-0.06
other psychiatric problems	-0.06	<b>0.23</b>	<b>-0.21</b>	-0.12	-0.12	-0.12
tired after work	0.06	<b>0.29</b>	-0.06	-0.02	0.14	-0.18
antibiotics per year	0.14	0.19	0.13	0.03	0.02	0.04
doctors' visits per year	0.08	0.04	0.10	0.16	-0.06	<b>0.37</b>
spending week in hospital	<b>0.27</b>	<b>0.38</b>	<b>0.21</b>	<b>0.28</b>	0.04	<b>0.53</b>
life self-expectancy	<b>-0.24</b>	<b>-0.29</b>	<b>-0.24</b>	nd.	nd.	nd.

477

478 Partial Tau correlations (age controlled) that are significant after the correction for multiple  
 479 tests are printed in bolt. For more details concerning particular health-related variables, see  
 480 Materials and methods.

481 Fig. 1 Differences between *Toxoplasma*-infected and *Toxoplasma*-free women in seven N-70  
482 factors



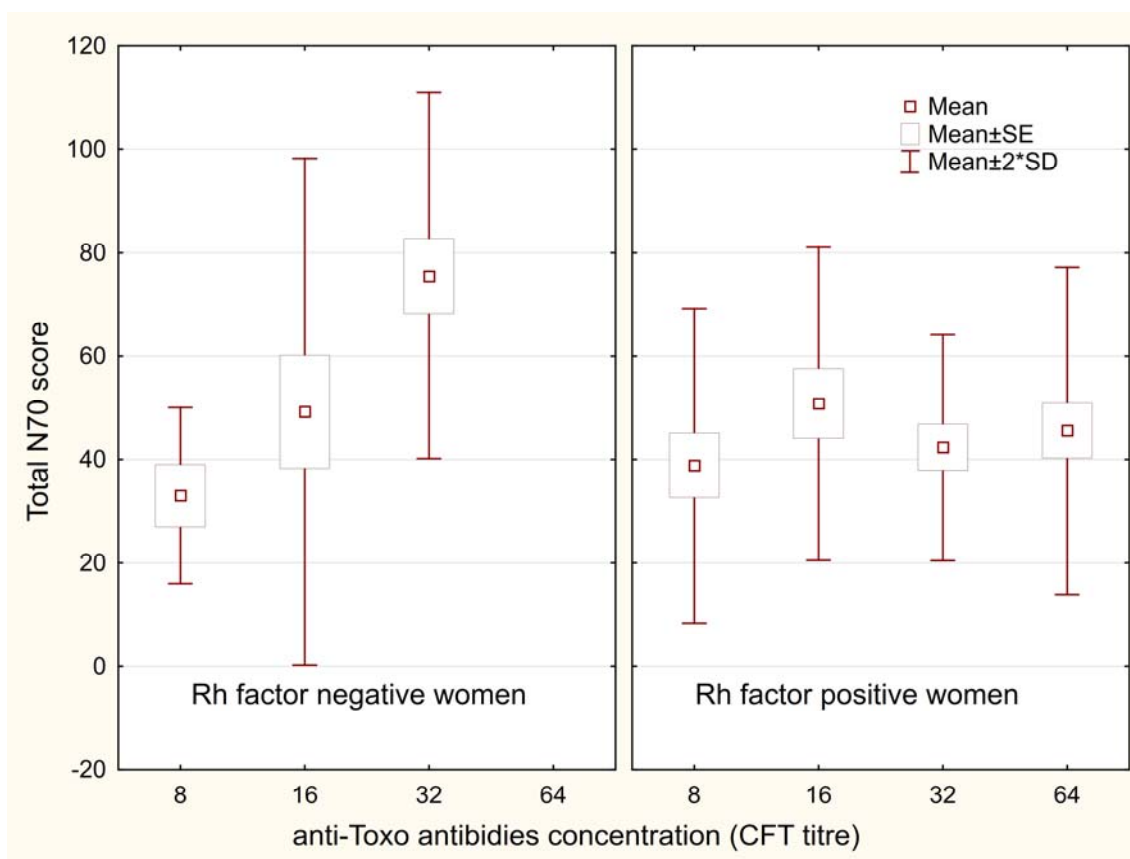
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484

485 The spreads show 95% C.I.

486

487 Fig. 2 Correlation between N-70 score and anti-*Toxoplasma* antibodies concentration



488

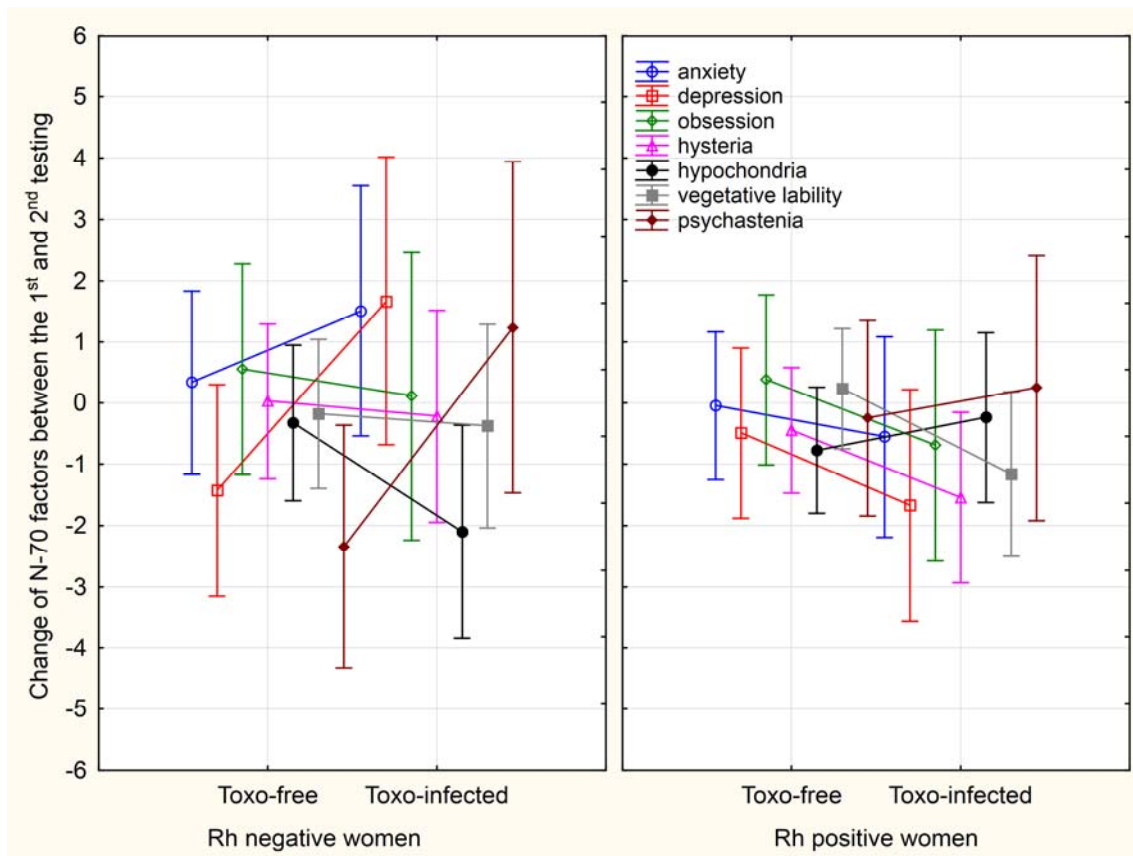
489

490 The boxes indicate the mean  $\pm$  standard error, and spreads indicate the mean  $\pm 2 \times$  standard  
491 deviation.

492



493 Fig. 3. Changes in N-70 factors between the first and second testing



494

495 The spreads show 95% C.I.

496