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Toxoplasmosis – A Global Threat. Correlation of Latent Toxoplasmosis with Specific Disease Burden in a Set of 88 Countries

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Abstract

Background: Toxoplasmosis is becoming a global health hazard as it infects 30–50% of the world human population. Clinically, the life-long presence of the parasite in tissues of a majority of infected individuals is usually considered asymptomatic. However, a number of studies show that this 'asymptomatic infection' may also lead to development of other human pathologies.

Aims of the Study: The purpose of the study was to collect available geoepidemiological data on seroprevalence of toxoplasmosis and search for its relationship with mortality and disability rates in different countries.

Methods and Findings: Prevalence data published between 1995–2008 for women in child-bearing age were collected for 88 countries (29 European). The association between prevalence of toxoplasmosis and specific disease burden estimated with age-standardized Disability Adjusted Life Year (DALY) or with mortality, was calculated using General Linear Method with Gross Domestic Product per capita (GDP), geolatitude and humidity as covariates, and also using nonparametric partial Kendall correlation test with GDP as a covariate. The prevalence of toxoplasmosis correlated with specific disease burden in particular countries explaining 23% of variability in disease burden in Europe. The analyses revealed that for example, DALY of 23 of 128 analyzed diseases and disease categories on the WHO list showed correlations (18 positive, 5 negative) with prevalence of toxoplasmosis and another 12 diseases showed positive trends ($p<0.1$). For several obtained significant correlations between the seroprevalence of toxoplasmosis and specific diseases/clinical entities, possible pathophysiological, biochemical and molecular explanations are presented.

Conclusions: The seroprevalence of toxoplasmosis correlated with various disease burden. Statistical associations does not necessarily mean causality. The precautionary principle suggests however that possible role of toxoplasmosis as a triggering factor responsible for development of several clinical entities deserves much more attention and financial support both in everyday medical practice and future clinical research.

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Introduction

Toxoplasmosis, a disease caused by the obligate apicomplexan intracellular protozoan *Toxoplasma gondii*, is one of the world's most common parasites infecting most genera of warm-blooded animals (more than 30 species of birds and 300 species of mammals). It is the most prevalent infection in humans (estimated to be 30–50% of the world population), more than latent tuberculosis which infects about one-third of the human population (WHO, www.who.int/entity/tb/publications/2009/tbfactsheet_2009update_one_page.pdf, accessed July 2013). The definitive hosts are representatives of the felid (cat) family. Nicolle and Manceaux (1908) first observed the parasites in the blood and tissues of a North African rodent, *Ctenodactylus gondii*, and named it *Toxoplasma* (arclike form) *gondii* (after the rodent host) [1]. There are three infective stages of *T. gondii*: a) a rapidly dividing invasive tachyzoite; b) a slowly dividing bradyzoite in tissue cysts, which can persist inside human cells for protracted periods; and c) an environmental stage, the sporozoite, protected inside an oocyst. The oocysts, remarkably stable environmentally, are transmitted to other hosts through inadvertent ingestion.

Seroprevalence of toxoplasmosis

Seroprevalence is a measure of the accumulated exposure during a person's lifetime in a particular social setting. Most of the more than one third of the world's human population who are infected with *T. gondii* remain asymptomatic because the immune system usually keeps the parasite from causing illness. Chronic, usually lifelong, infection with *Toxoplasma* that is not accompanied with overt clinical symptoms of toxoplasmosis disease is termed latent toxoplasmosis while chronic infection associated with

continuous or recurrent clinical symptoms is termed chronic toxoplasmosis (this form of disease is relatively rare in Europe and Northern America). Worldwide seroprevalence of the parasite measured by specific anti-*Toxoplasma* IgG antibodies varies between 1% and 100% depending on the environmental and socioeconomic conditions, including eating habits and health-related practices [2–5], general level of hygiene, host susceptibility, geographical location (geolatitude) and humidity of the soil. The incidence of infection is higher in warmer and humid climates and increases with age [5]. The lowest seroprevalence (~1%) was found in some countries in the Far East and the highest (>90%) in some parts of European and South American countries. In the United States, the Centers for Disease Control and Prevention (CDC) reported an overall seroprevalence of 11% [National Health and Nutritional Examination Survey between 1999 and 2004]; another survey reported a higher number (22.5%) [6]. Nevertheless, toxoplasmosis is one of the leading causes of death attributed to foodborne illness [7]. In European countries, the prevalence ranges between 10% to 60%, and in some regions as high as 90% [8]. In one study, 84% of pregnant women had serum antibodies against the parasite [3]. Data from 88 countries are presented in Table 1; most of the published data on seroprevalence are in women of childbearing age and/or those who are pregnant.

In the majority of the human populations, the parasite seroprevalence increases with age, and may vary by gender [6,94]. Latitudinal variability in the geoseroprevalence of the parasite may be due to local rainy conditions (because oocysts live longer in humid conditions), and low altitude regions (especially at mid-latitudes); a north-south seroprevalence gradient has also been reported in animals [9,95,96].

The seroprevalence of toxoplasmosis is high in immunocompromised patients, such as those infected with human immunodeficiency virus (HIV), and transplant or cancer patients treated with immunosuppressive agents [5,97,98].

It may be pointed out that the different serological methods used to obtain prevalence data are not standardized, and vary in sensitivity, specificity, and predictive values. As a consequence, no two tests produce the same results in all cases, even when carried out in the same laboratory [5].

Genotypes and virulence of *T. gondii*

T. gondii strains are highly diverse but only a few lineages are widely spread. Different genotypes of the parasite show great diversity in pathogenicity and drug sensitivity. Some atypical strains have also been detected. In Europe, North America, and Africa, there are three dominant clonal lineages of *T. gondii* called type I (RH, GT1,CAST), type II (ME49, WIL, HART), and type III (VEG, MOO, SOU), as well as many atypical genotypes which differ in prevalence, virulence, migratory capacity within the host, and ability to convert to the bradyzoite cyst phase [99–101]. Different strains of the parasite induce different cytokine responses [102], thus triggering development of various clinical and biochemical disturbances in the host, including modulation of the host cell proteome [103,104]. Mice fed as few as 1 oocyst of *T. gondii* serotype I and several atypical strains died of acute toxoplasmosis within 21 days post inoculation, while some *T. gondii* type II, and III strains were less virulent [105]. In North America, the parasite serotype II and NE-II causes congenital toxoplasmosis, while prematurity and severity of disease at birth was associated with the coccidian NE-II serotype [106]. This serotype was also associated with rural residence, lower socioeconomic status and Hispanic ethnicity ($P<0.01$–0.001) [106]. A greater variety of genotypes are found in South America and Africa than in North America and Europe [107,108], suggesting that in these continents sexual replication of the parasite occurs more frequently than in any other part of the world [109]. This genetic divergence may contribute to the higher prevalence of seropositivity and ocular disease due to *T. gondii*, as exemplified by the higher prevalence of toxoplasmosis and *Toxoplasma*-induced eye disease in southern Brazil than in any other part of the world [110].

Transmission of *T. gondii*

Animals are infected by eating infected animals, by ingestion of or coming in contact with feces of an infected cat, or by transmission from mother to fetus. In humans, cats are the primary source of infection (contact with fecal material), but other pets may also be the secondary source of infection [3,111,112]. The seroprevalence of toxoplasmosis in the Arctic region proves that *T. gondii* can thrive in the absence of cats [113].

Contact with raw meat of infected animals, especially pork, is a more significant source of human infections in some countries, such as in Poland, where the majority of pigs, cattle and sheep (approximately 80%) test positive for *T. gondii* [8,114]. Transmission of the parasite can also occur by drinking municipal/well unboiled and unbottled water containing oocysts, exposure to contaminated soil, contaminated milk, exposure of children playing in sandpits, geophagia [115,116], eating raw or undercooked meat, especially venison [117] or rabbits [118], raw oysters, clams, or mussels [119], consumption of unwashed raw fruits and vegetables contaminated with the oocytes [117], blood transfusion [120–122], maternal-fetal passage of blood cells (including placental trophoblasts) [123,124], solid organ allografts [125,126], bone marrow transplantation [127], allogeneic stem cell transplantation [128], sputum [129], breast milk [130,131], and semen [132] (thus, probably the infection may be transmitted via both vaginal and oral sex, significantly more frequently from seropositive to passive sex partner than vice-versa ($P<0.001$) [133]). Poor hygiene, lower socioeconomic status and less education, as well as exposure to certain strains of *T. gondii* may also contribute to a higher rate of infection [134].

Cellular mechanism(s) of infection

T. gondii is remarkable in its ability to invade a wide variety of host cells. Invasion is an active process relying on parasite motility and the sequential secretion of proteins from secretory organelles, the micronemes, rhoptries, and the dense granules. *T. gondii* can invade and multiply inside any nucleated cell type including epithelial cells and blood leukocytes [135]. A preference to infect and multiply inside myeloid cells *in vitro* has also been reported [136], and several studies in mice indicate that the dendritic cells as well as monocytes/macrophages function as systemic parasite transporters ("Trojan horses") during infection [137–142]. The parasite can be transmitted from infected dendritic cells to NK cells [143], and thus, low levels of NK cells found in pregnant women may suggest transmission of the parasite [144]. Differential infectivity and division rate of intracellular tachyzoites in human peripheral blood leukocytes and other primary human cells *in vitro* has been demonstrated depending on the cell characteristics [136].

Clinical manifestations of toxoplasmosis

It is believed that the majority of immunocompetent individuals infected with *T. gondii* remain asymptomatic or have a subclinical course with minor symptoms [145]. It is nevertheless the most common food-borne parasitic infection requiring hospital treatment [146], and the third most common cause of hospitalization due to food-borne infection [147]. Both competent and immuno-

Table 1. Prevalence of latent toxoplasmosis in women of childbearing age in various countries.

Country	Prevalence (%)	Adj. Prevalence (%)	Reference	Period	No.
Albania	49	42	[10]	2004–2005	496
Argentina	60	53	[11]	2001	1007
Australia	23	16	[12]	2001	308
Austria	42	36	[13]	1997	4601
Bahrain	22	16	[14]	2005	3499
Bangladesh	38	38	[15]	1995–1996	286
Belgium	49	42	[16]	2004	16541
Benin	54	47	[17]	1993	211
Brazil	50	50	[18]	2012	2136
Burkina Faso	25	25	[19]	2006	336
Cameroon	77	70	[20]	1992	1014
Canada	20	17	[21]	2006	NA
Colombia	54	54	[22]	2006	630
Costa Rica	76	76	[23]	1996	1234
Croatia	29	24	[24]	2000	1109
Cuba	55	55	[25]	2004	526
Czech Republic	20	16	[26]	2007	1053
Congo	60	60	[27]	1990	2897
Denmark	28	20	[28]	1999	89873
Egypt	42	36	[29]	1995	62
Estonia	68.6	45	[30]	1999–2000	1277
Ethiopia	74	66	[31]	2012	1016
Finland	20	17	[32]	1989	16733
France	54	47	[33]	1995	13459
Gabon	71	71	[34]	1997	767
Germany	63	50	[35]	1999	4854
Greece	25	21	[36]	2004	5532
Grenada	57	50	[37]	2006	534
Hungary	45	39	[38]	2000	31759
Chile	39	33	[39]	1996	7536
China	11	11	[40]	2006	235
Iceland	13	8	[30]	1998	440
India	35	35	[41]	2003	180
Indonesia	53	46	[42]	2006	17735
Iran	39	33	[43]	2007	576
Iraq	49	42	[44]	2002	254
Ireland	34	25	[45]	2008	20252
Israel	21	17	[46]	1989	213
Italy	23	16	[47]	2004	3426
Jamaica	57	57	[48]	1986	1604
Japan	10	8	[49]	2011	4466
Jordan	47	40	[50]	2005	280
Kuwait	46	53	[51]	2002–2005	225
Lebanon	62	62	[52]	2010	232
Libya	45	34	[53]	2007	143
Lithuania	40	34	[54]	1991	NA
Macedonia	22	18	[55]	2005	NA
Madagascar	84	84	[56]	1992	599
Malaysia	49	42	[57]	2003	200
Mexico	49	49	[58]	2006	NA

Table 1. Cont.

Country	Prevalence (%)	Adj. Prevalence (%)	Reference	Period	No.
Montenegro	27	23	[55]	NA	NA
Morocco	51	44	[59]	2007	2456
Mozambique	19	13	[60]	2008	150
Nepal	55	55	[61]	1998	345
Netherlands	35	26	[62]	2004	7521
New Zealand	35	26	[63]	2004	500
Nigeria	78	71	[64]	1992	352
Norway	11	9	[65]	1993	35940
Pakistan	33	28	[66]	1997	105
Papua New Guinea	18	15	[67]	1990	197
Peru	39	33	[68]	NA	NA
Poland	40	34	[69]	2003	4916
Portugal	24	17	[70]	2011	401
Qatar	35	30	[71]	2005–2008	1857
South Korea	4	3	[72]	2000	NA
Romania	44	38	[73]	2008	184
Sao Tome and Principe	75	68	[74]	2007	499
Saudi Arabia	32	27	[75]	1991	921
Senegal	40	34	[76]	1993	353
Serbia	31	26	[55]	2007	765
Singapore	17	14	[77]	NA	120
Slovakia	22	18	[78]	2008	656
Slovenia	25	21	[79]	2002	21270
Spain	32	23	[80]	2004	16362
Sudan	42	36	[81]	2003	487
Sweden	18	13	[82]	2001	40978
Switzerland	35	26	[83]	2006	NA
Tanzania	35	35	[84]	1991	549
Thailand	13	11	[83]	2001	1200
Togo	75	68	[85]	1991	620
Trinidad and Tobago	43	43	[86]	2008	450
Tunisia	43	37	[87]	1996	2231
Turkey	54	47	[88]	2005	1149
United Arab Emirates	23	19	[89]	1997	1503
UK	9	6	[90]	2005	1897
USA	11	9	[91]	2007	NA
Venezuela	38	38	[92]	2006	446
Vietnam	11	9	[93]	2003	300

The second and third column show prevalence of toxoplasmosis and prevalence adjusted to a standard age of 22 years to account for variation in childbearing age in across countries (column 1) using the formula $Prevalence_{adj} = 1-(1-Prevalence)^{\wedge}(22/childbearing\ age)$ [9]. Column 5 shows year(s) when the study was performed and column 6 shows number of women in the sample. For Macedonia, the 2004 WHO data were not available therefore this 30th European country was not included in our data set.

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compromised persons can develop the disease, especially retinochoroiditis (ocular toxoplasmosis) [2,145,148]. In non-pregnant immunocompetent adults, acute disease may also lead to impaired eye sight [149,150]. For example, in the United States, one million new infections occur each year, which result in approximately 20 000 cases of retinal pathology [151]. Primary infection in pregnant women is a matter of great concern, since it can be transmitted to the fetus leading to spontaneous abortion or stillbirth. A newborn exposed to *T. gondii* in utero may develop congenital toxoplasmosis with major ocular and neurological consequences. In immunosuppressed (HIV, organ transplant or cancer) patients, the infection can lead to life-threatening cerebral toxoplasmosis [97,98,152].

Symptomatic infection with the parasite can be categorized into four groups: 1) cervical lymphadenopathy, headache, fever, sore throat, and myalgia, with possibility of splenomegaly and brief

erythematous (maculopapular) rash; 2) typhus-like exanthematous form with myocarditis, meningoencephalitis, atypical pneumonia and possibly death; 3) retinochoroiditis, which may be severe, requiring enucleation; and 4) central nervous system involvement [153]. In addition, several reports suggest that *T. gondii* infection may be responsible for additional wide range of symptoms, and development of several clinical entities (summarized in Table 2).

Some of the clinical manifestations of *T. gondii* infection may be as a result of extensive interaction of the pathogen with approximately 3000 host genes or proteins possibly because of frequent host/pathogen antigen homology that disrupts/creates/triggers host specific metabolic pathways, and finally contributes to the development of endophenotypes of different diseases [154]. The parasite and concomitant viral and/or bacterial infections scavenge important metabolites from host cells and/or donate other compounds to the host causing unwanted effects. In addition, *T. gondii*-derived autoantibodies also play an important role in the pathology associated with the parasite [154].

Association of seroprevalence of toxoplasmosis with other pathologies

Due to the fact that *T. gondii* infection is omnipresent and associated with development of many pathologies in humans and animals, including the disease burden of congenital toxoplasmosis, as represented by disability-adjusted life years (DALY) being the highest among all foodborne pathogens [149], the purpose of this work was to collectively evaluate available geoepidemiological data on the parasite worldwide national seroprevalence variations and their relationship with mortality and disability rates. In the analyses, gross domestic product (GDP) *per capita* as a covariate was used because earlier it was argued and demonstrated that culture-level correlations need to be controlled for regional socioeconomic parameters [9,215,322]. If possible (i.e. in multivariate GLM analyses), two potential confounding variables that could strongly influence both the survival of *Toxoplasma* oocysts in soil and a course of various diseases, namely the average latitude (proxy for temperature) and the average relative humidity of particular countries have also been included into the statistical models. In this study we found many positive and some negative associations between the prevalence of toxoplasmosis and various diseases burdens. The number and strength of these associations were much higher than could be expected by chance. Still, it must be emphasized that statistical association does not mean causality. Based on the finding of a statistical association between two phenomena, one cannot determine which of them is the cause and which is the effect – in other words, whether event A causes event B, or whether event B causes event A. Not only we are unable to determine whether event A causes B, or B causes A, but sometimes there is an (unknown) event C that causes both A and B. Therefore, all effects observed in the present exploratory study as well as all suggested biological or medical interpretations must be considered just as potential stimuli for the next, more focused research (search for unknown confounders and for independent evidence) that must follow.

Methods

Mortality and Burden of Diseases data

The data on disease burden, mortality and Disability Adjusted Life Year (DALY), were obtained from the table "Mortality and Burden of Diseases Estimates for WHO Member States in 2004" published by WHO [323] and available at: www.who.int/evidence/bod. The publication can be downloaded from the website: http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/index.html; accessed July 2013). Summary tables present the best estimates of WHO – based on the evidence available in mid-2008 – rather than from the official estimates of Member States. Methods and data sources are summarized in the Annexes of the "Global burden of disease: 2004 update" [323], and the methodology used is described in more details elsewhere [324]; also available at: http://www.dcp2.org/pubs/GBD; accessed July 2013.

The Disability Adjusted Life Year (DALY) has been defined [323] as "a health gap measure that extends the concept of potential years of life lost due to premature death and also to include equivalent years of 'healthy' life lost by virtue of being in a state of poor health or disability." Thus, the DALY combines in one measure the time lived with disability and the time lost due to premature mortality. One DALY can be thought of as one lost year of 'healthy' life, while the 'burden of disease' as a measure of the gap between current health status and an ideal situation where everyone lives into old age free of disease and disability. The method of calculation of age-standardized DALY has been described earlier [323].

Data collection for prevalence of toxoplasmosis

In the literature, most of toxoplasmosis prevalence (seroprevalence) data are available only for women in childbearing age. Therefore, all available data collected for this population were published mostly between 1995–2008; the final database was obtained from 88 countries (29 European). When more than one estimation of prevalence of toxoplasmosis was available for a particular country, we gave priority to multicenter studies performed between 1998–2004. When the studies published different prevalence data for various regions or different years we calculated an unweighted arithmetic mean. The obtained data were adjusted to a standard age 22 years to eliminate differences in prevalence caused by different childbearing ages in various countries [325] were kindly provided by Mudhakar Dama) using the formula:

$$\text{Prevalence}_{\text{adj}} = 1 - (1 - \text{Prevalence})^{(22/\text{child bearing age})} [9].$$

Statistical Methods

All statistical tests except partial Kendall correlation test were performed independently with SPSS 21 and Statistica 10.0. The association between seroprevalence of toxoplasmosis and specific disease burden estimated with age standardized DALY was calculated using nonparametric partial Kendall correlation test [326,327] with Gross Domestic Product per capita (GDP) as covariate. Because the results of similar analyses performed with the General Linear Model (GLM) method were qualitatively the same, GLM data were primarily interpreted in the Discussion section of present study. The GLM is more sensitive for the quality of data (e.g. to presence of outliers and non-Gaussian distribution of data, etc.), however, it enables to control for more than one covariate. In the present analysis, we controlled for GDP, geographical latitude and annual mean of relative humidity of particular countries using data available at http://data.worldbank.org/indicator/NY.GDP.PCAP.CD (accessed 10.12. 2013) and http://www.climatemps.com/ (accessed 2.4. 2013). No formal corrections for multiple tests were carried out, however, the fraction of significant results largely exceeded a theoretical value of 5 false positive results per 100 tests.

The medical importance of the association was expressed as regression coefficient 'B', the slope of the regression line. The

Table 2. Diseases and clinical entities associated with *T. gondii* infection.

Disease/Clinical entity	References
Congenital toxoplasmosis (encephalitis; chorioretinitis; neonatal mortality)	[100,149,155–158]
Psychosis; schizophrenia; bipolar disorder	[159–166]
Mood disorders; suicide; depression (?)	[167–174]
Obsessive-compulsive disorder	[175,176]
Attention/concentration deficit hyperactivity disorder	[175,177]
Anorexia	[178–181]
Autism spectrum disorders	[164,177,182–185]
Down's syndrome	[182,186–188]
Alzheimer's disease	[182,189–191]
Parkinson's disease	[192,193]
Migraine; other headaches	[194–197]
Idiopathic intracranial hypertension	[177,180,198]
Pseudotumor cerebri	[180,198]
Aseptic meningitis	[180,198]
Mollaret meningitis	[199]
Epilepsy	[200,201]
Aphasia and epilepsy (Landau-Kleffner syndrome)	[202]
Facial nerve palsy (Bell's palsy)	[203]
Hearing loss	[204,205]
Central diabetes insipidus; syndrome of inappropriate antidiuretic hormone secretion	[156,206–209]
Hypothalamo-pituitary dysfunction; panhypopituitarism	[209–211]
Brain tumors (meningioma; ependymoma; glioma)	[196,212–216]
Non-Hodgkin's lymphoma	[217,218]
Neoplasia	[216,219–221]
Melanoma	[216,222–226]
Breast cancer	[227]
Carcinoma of female genitalia, including cervical tissue	[228]
Chronic heart failure; myocarditis; arrhythmia	[229–231]
Inflammatory bowel disease	[232–234]
Ulcerative colitis	[232]
Crohn's disease	[232]
Celiac disease	[232,235]
Abdominal hernia	[233,236]
Hepatitis, including HCV infection	[237–246]
Granulomatous liver disease	[247,248]
Liver cirrhosis; granulomatous liver disease; impaired liver function	[242–244,249–253]
Primary biliary cirrhosis; biliary atresia; cholestatic disorders	[254–261]
Diabetes mellitus type 1 and 2	[189,262–264]
Goitre; iodine deficiency	[265–268]
Hashimoto's thyroiditis	[269]
Graves' disease; thyroid adenoma	[269–271]
Rheumatoid arthritis; Still's disease	[272–277]
Polymyositis	[231,278–283]
Systemic sclerosis	[277,284,285]
Systemic lupus erythematosus	[286]
Wegener's granulomatosis; other vasculitides	205; 215 [277,287]
Anti-phospholipid syndrome	[287]
Cryoglobulinemia	[287]

Table 2. Cont.

Disease/Clinical entity	References
Ocular toxoplasmosis (retinochorioiditis; uveitis; blurred vision; floaters; macular scars; nystagmus; strabismus; reduced visual acuity; blindness; scleritis; papillitis; retinal necrosis; vasculitis; retinal detachment; vitritis; congenital cataract; neuroretinitis; atrophic optic papilla; retinitis pigmentosa)	[225,288–291]
Glaucoma	[292,293]
Ovarian dysfunction	[294–296]
Uterine atrophy	[297]
Impaired reproductive function (*T. gondii* was present in testicles, epididymis, seminal vesicles, prostate gland in rams, and caused abnormalities in sperm motility, viability and concentration rates, weight of epididymis in rats, orchitis)	[255,296,298–300]
Nephrotic syndrome; lipoid nephrosis	[250,251,255,301–306]
Schönlein-Henoch purpura	[196,307,308]
Glomerulonephritis (various forms; including these with development of fibrosis); impaired kidney function	[250,251,301,305,306,309–312]
Atherosclerosis; obesity; cardiovascular deaths; all-cause mortality	[253,313–318]
Diverse abnormalities in aggregate personality; including aggressive behavior in animals and humans	[9,319–321]

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higher is the absolute value of B the greater is the positive or negative impact of the predictor variable (here prevalence of toxoplasmosis) on the dependent variable (here DALY or mortality). The strength of statistical association is expressed as Eta^2, which reflects the proportion of variance in the dependent variable (the DALY or mortality) associated with or accounted for by each of the main effects, interactions, and error in an ANOVA study (the prevalence of latent toxoplasmosis) [328] pp. 54–55, [329] pp. 317–319. The statistically significant results, i.e. the associations with p value <0.05 and trends, i.e. the associations with p value <0.1 (significant in one-sided but not in two-sided tests) were listed in the tables and in the main text.

Results and Discussion

Correlation of toxoplasmosis prevalence with GDP per capita, geolatitude and humidity

Fig. 1 suggests that the prevalence of toxoplasmosis correlates with GDP, and possibly also with latitude and humidity for the countries for which the information on toxoplasmosis prevalence is reported. For the whole set of countries ($n = 88$), the prevalence of toxoplasmosis correlated positively with GDP per capita (Spearman $R = -0.484$, $p<0.001$) and latitude (Spearman $R = -0.449$, $p<0.001$), and non-significantly positively correlated with the humidity (Spearman $R = 0.180$, $p = 0.093$) in the univariate nonparametric Spearman test. For European countries ($n = 29$) all three correlations were not significant ($p>0.151$) and for non-European countries ($n = 59$) the prevalence of toxoplasmosis correlated negatively with GDP per capita (Spearman $R = -0.382$, $p = 0.003$) and latitude (Spearman $R = -0.396$, $p<0.002$), and positively with humidity (Spearman $R = 0.308$, $p = 0.017$). The multivariate GLM analyses with GDP, latitude and humidity as independent variables showed negative correlation with GDP (all countries: $p = 0.006$, $Eta^2 = 0.085$; European: $p = 0.044$, $Eta^2 = 0.153$; non-European: $p = 0.022$, $Eta^2 = 0.092$). For the latitude and humidity, the results differed between European and non-European countries (latitude – all countries: $p = 0.014$, $Eta^2 = 0.070$; European: $p = 0.055$, $Eta^2 = 0.135$; non-European: $p = 0.073$, $Eta^2 = 0.057$; humidity – all countries: $p = 0.056$, $Eta^2 = 0.043$; European: $p = 0.037$, $Eta^2 = 0.162$; non-European: $p = 0.356$, $Eta^2 = 0.016$). These results suggest that the GDP, and possibly also the latitude and humidity, should be incorporated into the statistical models as covariates.

Correlation of toxoplasmosis prevalence with age-standardized DALY for diseases

The present study showed that prevalence of toxoplasmosis correlated with specific disease burden measured with age-standardized DALY or with specific mortality in particular countries (Fig. 2).

Because distribution of DALY and mortality for many diseases was not normal, the analysis of association of toxoplasmosis prevalence with disease burden was performed with two methods, nonparametric partial Kendall correlation test and GLM analysis.

Since, a nonparametric partial Kendall correlation test enables to control for one confounding variable, we controlled for the GDP per capita because this variable is known to be strongly correlated with the quality of health care and therefore with the burden associated with many diseases. The partial Kendall correlation test demonstrated that age standardized DALY of 57 of 128 diseases and disease categories on the WHO list showed significant correlation (53 positive and 4 negative) with prevalence of toxoplasmosis in all ($n = 88$) countries after the effect of GDP was controlled, and further 8 diseases showed such trends ($p<0.1$) (6 positive and 2), see Fig. 3. Similar analyses for 29 European countries showed 12 significant correlations (11 positive and 1 negative) and 11 trends (10 positive and 1 negative), and for 59 non-European countries test revealed 33 significant correlations (29 positive and 4 negative) and 10 trends (all positive), Fig 3.

GLM analyses with GDP, latitude and humidity as covariates showed that age standardized DALY of 23 of 128 diseases and disease categories on the WHO list had significant correlation (18 positive and 5 negative) with prevalence of toxoplasmosis in all ($n = 88$) countries after the effect of GDP was controlled, and further 12 diseases showed such trends ($p<0.1$) (all positive), Similar analyses for 29 European countries showed 32 significant correlations (29 positive and 3 negative) and 18 trends (16 positive and 2 negative), and for 59 non-European countries had 18 significant correlations (13 positive and 5 negative) and 13 trends (9 positive and 4 negative), Fig 4.

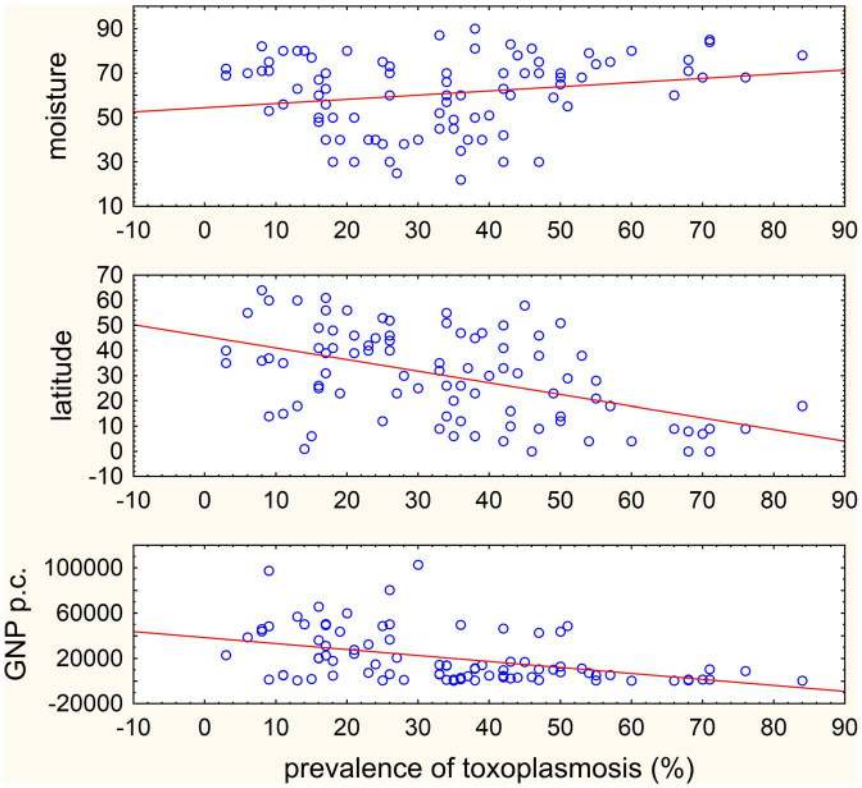

Figure 1. Correlation between prevalence of toxoplasmosis humidity, geolatitude and GDP per capita in all 88 countries. The GDP (1000 $), latitude (°) and relative humidity (%) data are shown only for the region or locality for which latent toxoplasmosis prevalence information (%) is reported.
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Correlation of toxoplasmosis prevalence with disease mortality

Partial Kendal correlation tests also showed that mortalities from 31 of 111 diseases and disease (WHO) categories with nonzero mortality had significant correlation (29 positive and 2 negative) with prevalence of toxoplasmosis in 88 countries after the effect of GNP was controlled, and further 6 diseases showed such trends ($p<0.1$) (5 positive and 2 negative), see Fig. 3. Similar analyses performed for 29 European countries demonstrated 6 significant correlations (all positive), and 11 trends (all positive) (here only 90 diseases had the mortality data necessary for analysis), and for 59 non-European countries showed 16 significant correlations (14 positive and 2 negative) and 8 trends (7 positive and 1 negative) (109 diseases had enough data for the analysis) (Fig. 3).

GLM analyses also showed that mortalities of 12 out of 111 diseases and disease categories (for 17 diseases the mortality data were available for less than 3 countries) revealed significant correlation (11 positive and 1 negative) with prevalence of toxoplasmosis in 88 countries after the effects of GDP, latitude humidity were controlled, and further 11 diseases showed such trends (10 positive and 1 negative), see Fig. 4. Similar analyses performed for 29 European countries showed 11 significant correlations (all positive) and 13 trends (all positive), and for 59 non-European countries had 11 significant correlations (8 positive and 3 negative) and 8 trends (7 positive and 1 negative), Fig. 4.

Several explanations may be put forward for positive correlation between prevalence of latent toxoplasmosis and the DALY or the morbidity from a particular disease: a) *T. gondii* infection may increase the risk of development of some diseases, b) certain diseases may increase the risk of acquiring toxoplasmosis, or c) some unknown factor(s) may increase both the risk of triggering certain diseases and *Toxoplasma* infection. Similarly, there are several possible explanations for the observed negative correlations: a) infection with the parasite can increase resistance/tolerance of the infected host to a certain disease by modulating its innate and/or acquired cellular/humoral immunity. For example, suppression of cellular immunity observed in *in vivo* as well as *in vitro* systems can make the host more sensitive to infection by certain pathogens, and at the same time protect it against development of some autoimmune diseases. On the other hand, chronic inflammation loci in tissues/organs can be responsible for inducing health problems, including development of certain tumors [214,215], and at the same time activation of the host immune system can make local tissue environment unfavorable for growing, proliferation and persistence of certain infectious agents. For example, toxoplasmosis increases dopamine levels in the brain tissue, which can protect the host against symptoms of certain diseases, e.g. Parkinson's disease, and at the same time it can increase the risk for development of other pathologies, such as schizophrenia [330,331].

In the present GLM analyses, three potential confounding factors, the GDP *per capita* (which strongly correlates with quality of health services and hygienic standards), the geolatitude (which strongly correlates with temperature and quantity and quality of sunlight) and humidity which influences survival of *Toxoplasma* oocysts in soil), were controlled. However, many other factors, such as cultural habits, can also influence the risk of *Toxoplasma* infection, and/or other infections as well. It has been, for example, suggested that toxoplasmosis could be a sexually transmitted

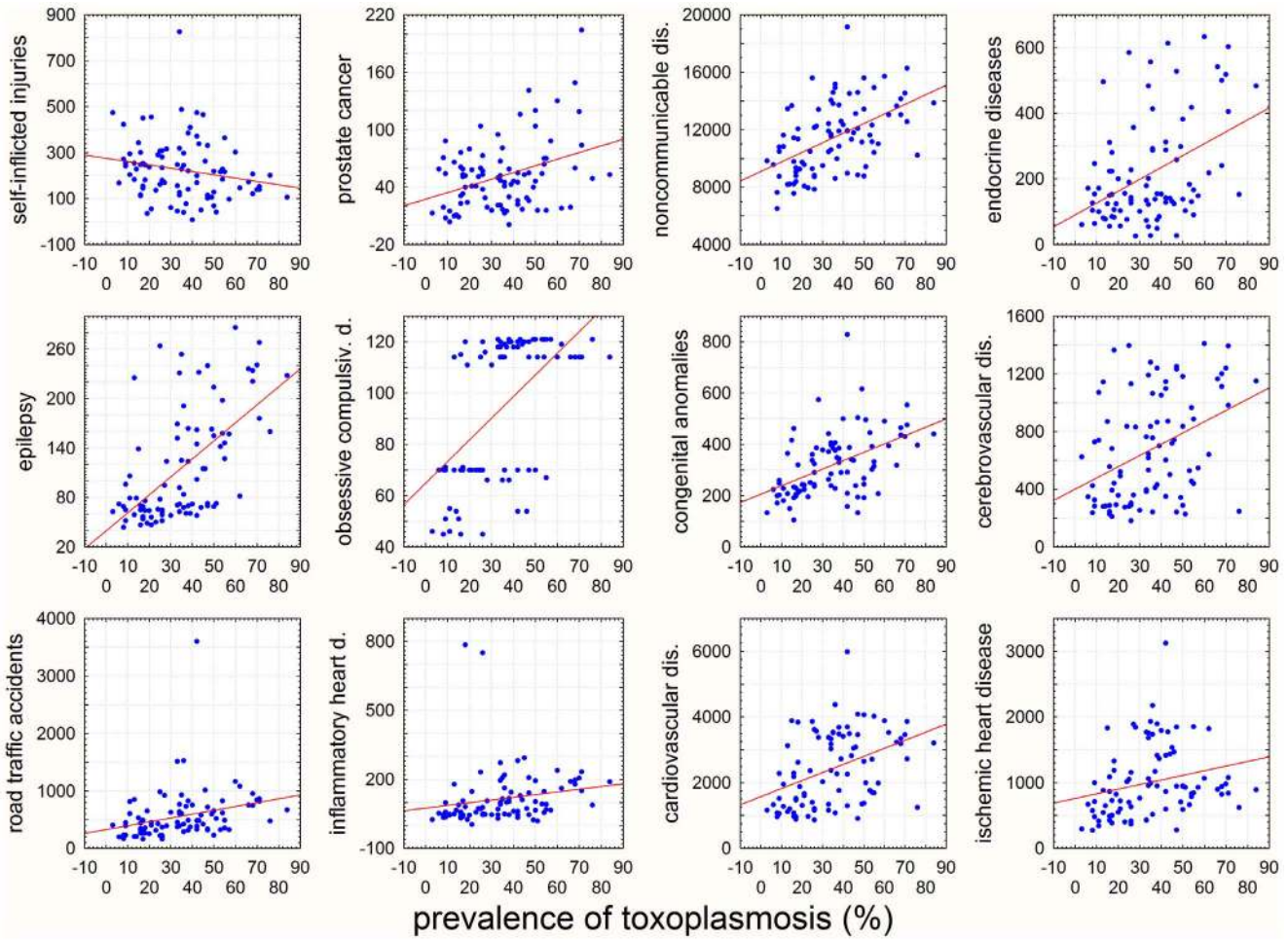

Figure 2. Correlation of prevalence of toxoplasmosis with various disease-attributed DALY for 88 WHO-member countries. The x-axes show prevalence of toxoplasmosis (%) in women of childbearing age and y-axes the number years of 'healthy' life lost by virtue of being in a state of poor health or disability due to particular disease per 100,000 inhabitants in 2004.
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disease (STD) transferred from men to women with semen/ejaculate [331,332]. This could explain the observed positive correlation between the prevalence of latent toxoplasmosis and DALY for several STDs. Finally, it is to be noted that the incidence of a certain disease can be decreased by an increased risk of death due to another concomitant disease.

In the next part of discussion, comments are made on the results obtained for particular diseases, mainly the results of GLM tests as the partial Kendall correlation tests can control for one confounding variable only and the regression coefficient (B-value) has more straightforward interpretation than Kendall Tau. We have concentrated on the age-standardized DALY data because only a subset of disease could result in the death of patients under normal conditions. The strength of correlation is usually estimated by Eta^2, which reflects fraction of variability of dependent variable that can be explained by an independent variable (here, by the prevalence of toxoplasmosis). The clinical relevance of a particular association is however better reflected by the regression coefficient B, which shows an increase of a dependent variable (here, the age standardized DALY expressed in years of life lost due to premature death per 100 000 inhabitants) that corresponds to the increase of an independent variable per one unit (here, the increase of prevalence of toxoplasmosis by 1%). Therefore, the B-value reflects not only the strength of the correlation but also the incidence of particular disease.

Association of seroprevalence of toxoplasmosis with specific diseases in all 88 countries

All disease burden. Prevalence of toxoplasmosis explained about 23% of between-countries variability in mortality and age-standardized DALY in Europe (mortality: $B = 3.538$, $Eta^2 = 0.229$, $p = 0.024$; DALY: $B = 68.18$, $Eta^2 = 0.227$, $p = 0.014$). This association was not significant for non-European countries (mortality: $B = 3.37$, $Eta^2 = 0.026$, $p = 0.239$; DALY: $B = 92.49$, $Eta^2 = 0.030$, $p = 0.204$) or for all 88 countries (mortality: $B = 3.78$, $Eta^2 = 0.031$, $p = 0.104$; DALY: $B = 98.287$, $Eta^2 = 0.034$, $p = 0.093$). Both communicable and noncommunicable diseases were responsible for the observed association in Europe, however, for communicative infection was significant only for DALY (mortality: $B = 0.024$, $Eta^2 = 0.007$, $p = 0.878$; DALY: $B = 11.44$, $Eta^2 = 0.166$, $p = 0.039$).

Noncommunicable diseases. The highest regression coefficient ($B = 26.33$, $p = 0.019$) was found for the entire category of noncommunicable diseases. In this case, a difference of 1% in the prevalence of toxoplasmosis corresponded to a difference of 26.33

	mortality All			mortality Europe			mortality no Europe			DALY All			DALY Europe			DALY no Europe		
	N	Tau	p	N	Tau	p	N	Tau	p	N	Tau	p	N	Tau	p	N	Tau	p
All Causes	88	0.1714	0.0181	29	0.1429	0.2763	59	0.1444	0.1061	88	0.2182	0.0029	29	0.1499	0.2535	59	0.1925	0.0312
Communicable, maternal, perinatal and nutritional conditions	88	0.1477	0.0416	29	0.0742	0.5722	59	0.1128	0.2068	88	0.1949	0.0072	29	0.2347	0.0738	59	0.1429	0.1098
A. Infectious and parasitic diseases	88	0.1444	0.0463	29	0.2257	0.0857	59	0.0889	0.3199	88	0.1905	0.0086	29	0.2805	0.0327	59	0.1422	0.1117
1. Tuberculosis	87	0.0803	0.2710	29	0.0780	0.5525	58	0.0160	0.8594	88	0.0514	0.4780	29	0.2016	0.1246	59	-0.0197	0.8256
2. STDs excluding HIV	60	-0.0016	0.9856	11			49	-0.0441	0.6548	88	0.2620	0.0002	29	0.1593	0.2252	59	0.2067	0.0207
a. Syphilis	45	-0.1978	0.0555	2			43	-0.1354	0.2006	85	0.1911	0.0096	29	0.0785	0.5499	56	0.1011	0.2713
b. Chlamydia	13	-0.0811	0.6997	0			13	-0.0339	0.8719	88	0.2540	0.0004	29	0.2223	0.0905	59	0.1492	0.0949
c. Gonorrhoea	6	-0.4453	0.2096	0			6	-0.4077	0.2506	88	0.3029	0.0000	29	0.2350	0.0734	59	0.2777	0.0019
3. HIV/AIDS	85	0.1376	0.0623	28	0.2490	0.0630	57	0.0931	0.3062	88	0.1439	0.0471	29	0.0926	0.4806	59	0.1306	0.1440
4. Diarrhoeal diseases	82	0.1478	0.0494	23	0.0679	0.6503	59	0.1278	0.1526	88	0.1625	0.0250	29	0.1978	0.1320	59	0.1223	0.1712
5. Childhood-cluster diseases	60	0.0693	0.4337	9	-0.4247	0.1109	51	0.0812	0.4004	88	0.1517	0.0363	29	0.2325	0.0766	59	0.1168	0.1913
a. Pertussis	35	0.0938	0.4281	1			34	0.1169	0.3311	88	0.1232	0.0892	29	0.2178	0.0972	59	0.1292	0.1483
b. Poliomyelitis	18	-0.1847	0.2843	6	0.2941	0.4072	12			20	0.1754	0.2795	4			16	0.1151	0.5340
c. Diphtheria	20	0.5506	0.0007	1			19	0.5564	0.0009	23	0.1901	0.2041	1			22	0.2665	0.1083
d. Measles	31	0.1499	0.2360	0			31	0.1658	0.1901	36	0.1843	0.1137	4			32	0.1637	0.1879
e. Tetanus	42	-0.1114	0.2987	1			41	-0.0793	0.4650	43	-0.2129	0.0442	0			43	-0.1505	0.1550
6. Meningitis	87	0.2303	0.0016	29	0.1488	0.2571	58	0.1613	0.0737	88	0.2160	0.0029	29	0.2093	0.1110	59	0.1674	0.0611
7. Hepatitis B (g)	84	0.0241	0.7454	25	0.1012	0.4781	59	-0.0862	0.3346	86	0.0232	0.7514	27	0.0718	0.5994	59	-0.0798	0.3721
Hepatitis C (g)	75	0.0400	0.6117	22	0.1102	0.4730	53	-0.0957	0.3117	77	0.0374	0.6304	24	0.0934	0.5226	53	-0.1016	0.2829
8. Malaria	33	0.0620	0.6119	1			32	0.0787	0.5267	42	0.0431	0.6878	4			38	0.1478	0.1914
9. Tropical-cluster diseases	38	-0.0439	0.6982	2			36	-0.0347	0.7661	51	0.0730	0.4495	2			49	0.0842	0.3932
a. Trypanosomiasis	14	-0.2781	0.1660	0			14	-0.2717	0.1759	14	-0.2467	0.2190	0			14	-0.2430	0.2260
b. Chagas disease	6	-0.1229	0.7291	0			6	-0.1253	0.7241	8	0.0970	0.7368	0			8	0.0627	0.8279
c. Schistosomiasis	20	-0.2048	0.2067	0			20	-0.1495	0.3567	33	-0.1128	0.3563	0			33	-0.0628	0.6075
d. Leishmaniasis	27	-0.0292	0.8307	2			25	-0.0173	0.9036	35	-0.0822	0.4873	2			33	-0.0678	0.5791
e. lymphatic filariasis	3			1			2			27	0.1281	0.3485	0			27	0.1686	0.2173
f. Onchocerciasis	0			0			0			10	0.6949	0.0052	0			10	0.6712	0.0069
10. Leprosy	28	-0.1600	0.2322	0			28	-0.1553	0.2462	36	-0.1582	0.1747	0			36	-0.1284	0.2705
11. Dengue	16	-0.1038	0.5750	0			16	-0.1122	0.5446	21	-0.1216	0.4408	0			21	-0.1363	0.3874
12. Japanese encephalitis	9	0.0734	0.7829	0			9	0.1234	0.6433	10	0.1734	0.4853	0			10	0.2380	0.3421
13. Trachoma	1			0			1			22	0.1396	0.3633	0			22	0.1517	0.3231
14. Intestinal nematode infections	15	-0.4449	0.0208	1			14	-0.4089	0.0417	47	-0.0318	0.7528	1			46	-0.0058	0.9545
a. Ascariasis	7	0.1443	0.6491	0			7	0.1238	0.6962	43	-0.1365	0.1972	0			43	-0.0948	0.3702
b. Trichuriasis	4			0			4			42	-0.3164	0.0032	0			42	-0.2777	0.0096
c. Hookworm disease	1			0			1			43	-0.2846	0.0072	0			43	-0.2431	0.0216
B. Respiratory infections	88	0.1080	0.1363	29	-0.0694	0.5970	59	0.0914	0.3065	88	0.1668	0.0214	29	0.0617	0.6383	59	0.1292	0.1482
1. Lower respiratory infections	88	0.1090	0.1327	29	-0.0492	0.7080	59	0.0936	0.2949	88	0.1609	0.0264	29	0.0593	0.6516	59	0.1247	0.1630
2. Upper respiratory infections	66	0.0217	0.7963	18	0.3162	0.0669	48	-0.0970	0.3307	88	0.0837	0.2482	29	0.0932	0.4776	59	0.0313	0.7260
3. Otitis media	31	0.1349	0.2864	4	0.6940	0.1572	27	0.1179	0.3883	88	0.1941	0.0074	29	0.1041	0.4281	59	0.1797	0.0444
C. Maternal conditions	74	0.1008	0.2039	19	0.2391	0.1526	55	0.0615	0.5075	88	0.2027	0.0052	29	0.2153	0.1011	59	0.1806	0.0433
D. Perinatal conditions (h)	87	0.2083	0.0043	29	0.1912	0.1453	58	0.1847	0.0406	88	0.2119	0.0035	29	0.1605	0.2215	59	0.1875	0.0359
1. Prematurity and low birth weight	87	0.2011	0.0058	29	0.0969	0.4604	58	0.2101	0.0198	88	0.2053	0.0046	29	0.0860	0.5123	59	0.2185	0.0145
2. Birth asphyxia and birth trauma	87	0.1688	0.0206	29	0.1169	0.3733	58	0.1301	0.1491	88	0.1848	0.0108	29	0.0715	0.5862	59	0.1660	0.0633
3. Neonatal infections and other conditions (i)	87	0.1879	0.0100	29	0.1830	0.1633	58	0.1642	0.0687	88	0.1954	0.0070	29	0.1597	0.2239	59	0.1681	0.0599
E. Nutritional deficiencies	86	0.1707	0.0200	28	0.1886	0.1591	58	0.1228	0.1734	88	0.1305	0.0719	29	0.1912	0.1453	59	0.0553	0.5362
1. Protein-energy malnutrition	74	0.1703	0.0318	19	0.2308	0.1674	55	0.1543	0.0962	81	0.1033	0.1724	23	0.1024	0.4937	58	0.0555	0.5381
2. Iodine deficiency	17	0.2293	0.1989	0			17	0.2152	0.2281	60	-0.0096	0.9139	17	0.2070	0.2461	43	-0.0795	0.4527
3. Vitamin A deficiency	24	-0.2384	0.1026	1			23	-0.1833	0.2207	26	-0.1869	0.1806	0			26	-0.1426	0.3069
4. Iron-deficiency anaemia	81	0.1736	0.0218	23	0.1467	0.3269	58	0.0986	0.2740	88	0.0940	0.1948	29	0.1284	0.3282	59	0.0202	0.8214
Noncommunicable diseases	88	0.1639	0.0238	29	0.1420	0.2794	59	0.1587	0.0759	88	0.2067	0.0044	29	0.1193	0.3637	59	0.2004	0.0250
A. Malignant neoplasms	88	-0.0281	0.6986	29	0.0883	0.5015	59	0.0339	0.7042	88	-0.0243	0.7371	29	0.1228	0.3497	59	0.0121	0.8921
1. Mouth and oropharynx cancers	88	0.0538	0.4576	29	0.3417	0.0093	59	-0.0058	0.9487	88	0.0587	0.4184	29	0.3238	0.0137	59	0.0152	0.8647
2. Oesophagus cancer	88	-0.0169	0.8159	29	0.1372	0.2962	59	-0.0576	0.5193	88	-0.0234	0.7467	29	0.1179	0.3691	59	-0.0765	0.3922
3. Stomach cancer	88	-0.0140	0.8466	29	0.0656	0.6173	59	0.0137	0.8783	88	0.0028	0.9691	29	0.1121	0.3933	59	0.0234	0.7931
4. Colon and rectum cancers	88	-0.0908	0.2105	29	0.0078	0.9529	59	-0.0336	0.7072	88	-0.0848	0.2421	29	-0.0309	0.8140	59	-0.0205	0.8185
5. Liver cancer	88	-0.0810	0.2637	29	0.0629	0.6321	59	-0.1153	0.1971	88	-0.0916	0.2062	29	0.0809	0.5376	59	-0.1222	0.1717
6. Pancreas cancer	88	-0.0083	0.9087	29	0.1015	0.4395	59	0.1547	0.0835	88	-0.0246	0.7349	29	0.1208	0.3576	59	0.1021	0.2531
7. Trachea, bronchus, lung cancers	88	-0.1439	0.0472	29	0.1357	0.3015	59	-0.1254	0.1606	88	-0.1037	0.1524	29	0.1945	0.1385	59	-0.0896	0.3162
8. Melanoma and other skin cancers	87	-0.0035	0.9618	29	-0.0857	0.5166	58	0.1750	0.0523	87	-0.0106	0.8840	29	-0.0303	0.8172	58	0.1710	0.0579
9. Breast cancer	88	0.1532	0.0346	29	0.2661	0.0427	59	0.2191	0.0142	88	0.1063	0.1424	29	0.2305	0.0792	59	0.1484	0.0969
10. Cervix uteri cancer	88	0.1684	0.0202	29	0.1262	0.3366	59	0.2034	0.0242	88	0.1716	0.0179	29	0.1444	0.2715	59	0.2089	0.0194
11. Corpus uteri cancer	88	0.0180	0.8043	29	-0.0152	0.9076	59	0.0932	0.2969	88	-0.0384	0.5967	29	-0.0921	0.4829	59	0.0232	0.7951
12. Ovary cancer	88	0.0372	0.6078	29	0.0723	0.5818	59	0.1265	0.1569	88	0.0075	0.9181	29	0.0366	0.7806	59	0.0979	0.2733
13. Prostate cancer	88	0.2502	0.0006	29	-0.1415	0.2813	59	0.3368	0.0002	88	0.2089	0.0040	29	-0.2019	0.1242	59	0.3305	0.0002
14. Bladder cancer	88	-0.0545	0.4517	29	0.0894	0.4961	59	-0.0808	0.3662	88	-0.0667	0.3575	29	0.0559	0.6704	59	-0.0683	0.4451
15. Lymphomas, multiple myeloma	88	0.1400	0.0534	29	0.0468	0.7213	59	0.1927	0.0310	88	0.1980	0.0063	29	0.0895	0.4955	59	0.2080	0.0199
16. Leukaemia	88	0.0879	0.2254	29	0.2986	0.0230	59	0.0725	0.4173	88	0.1037	0.1524	29	0.2907	0.0268	59	0.0661	0.4593
B. Other neoplasms	85	0.1954	0.0081	28	0.0691	0.6059	57	0.2437	0.0074	85	0.2275	0.0020	28	0.0981	0.4636	57	0.2566	0.0048
C. Diabetes mellitus	88	0.1937	0.0075	29	0.1363	0.2991	59	0.1780	0.0464	88	0.1786	0.0137	29	0.0697	0.5956	59	0.1377	0.1234
D. Endocrine disorders	87	0.1517	0.0374	29	0.2009	0.1261	58	0.1075	0.2334	87	0.1831	0.0120	29	0.1295	0.3240	58	0.1911	0.0341
E. Neuropsychiatric conditions	88	-0.0187	0.7969	29	0.0652	0.6194	59	-0.0490	0.5832	88	0.0379	0.6013	29	0.0771	0.5570	59	0.0618	0.4892
1. Unipolar depressive disorders	50	-0.0632	0.5173	15	0.3207	0.0956	35	-0.1999	0.0911	88	0.0324	0.6545	29	0.1109	0.3982	59	0.0169	0.8502
2. Bipolar disorder	5	0.1386	0.7343	4	0.1442	0.7688	1			88	0.2068	0.0043	29	0.2147	0.1020	59	0.1498	0.0938
3. Schizophrenia	69	0.1009	0.2201	25	0.2547	0.0743	44	0.0639	0.5407	88	0.0863	0.2339	29	0.2558	0.0518	59	-0.1017	0.2551
4. Epilepsy	87	0.2022	0.0056	29	0.2184	0.0963	58	0.2080	0.0223	88	0.3081	0.0000	29	0.1278	0.3305	59	0.3452	0.0001
5. Alcohol use disorders	82	0.0369	0.6233	28	0.2684	0.0450	54	0.0046	0.9611	88	-0.0744	0.3046	29	0.0584	0.6566	59	-0.0287	0.7485
6. Alzheimer and other dementias	87	-0.0903	0.2158	29	-0.0822	0.5315	58	-0.1000	0.2677	88	-0.1334	0.0657	29	-0.1548	0.2385	59	-0.0935	0.2957
7. Parkinson disease	85	-0.0589	0.4248	29	0.0184	0.8885	56	-0.0443	0.6299	88	-0.0823	0.2559	29	0.0590	0.6530	59	-0.0358	0.6892
8. Multiple sclerosis	80	-0.1001	0.1888	29	0.0157	0.9048	51	0.0051	0.9582	88	-0.1033	0.1543	29	-0.1024	0.4356	59	-0.0190	0.8314
9. Drug use disorders	76	-0.0903	0.2484	27	-0.0136	0.9205	49	-0.1274	0.1965	88	-0.0701	0.3336	29	-0.1557	0.2356	59	-0.0384	0.6674
10. Post-traumatic stress disorder	1			1			0			88	-0.1800	0.0130	29	0.0707	0.5901	59	-0.1882	0.0352
11. Obsessive-compulsive disorder	0			0			0			88	0.3482	0.0000	29	0.2592	0.0484	59	0.3933	0.0000
12. Panic disorder	0			0			0			88	0.0044	0.9518	29	0.2578	0.0496	59	-0.0941	0.2922
13. Insomnia (primary)	0			0			0			88	-0.0498	0.4923	29	-0.2165	0.0992	59	0.0924	0.3014
14. Migraine	0			0			0			88	-0.1096	0.1304	29	-0.1333	0.3101	59	-0.0737	0.4095
F. Sense organ diseases	34	0.0475	0.6931	3	[illegible]	0.0681	31	0.0117	0.9266	88	0.1482	0.0409	29	0.3193	0.0150	59	0.0221	0.8046
1. Glaucoma	1			1			0			88	0.2921	0.0001	29	0.3023	0.0213	59	0.2584	0.0046
2. Cataracts	0			0			0			88	0.1681	0.0204	29	0.1540	0.2408	59	0.1000	0.2634
3. Refractive errors	0			0			0			88	0.0969	0.1813	29	-0.2892	0.0276	59	0.0495	0.5798
4. Hearing loss, adult onset	0			0			0			88	0.0243	0.7373	29	0.1568	0.2325	59	-0.0447	0.6170
5. Macular degeneration and other (j)	34	0.0505	0.6744	3	[illegible]	0.0681	31	0.0117	0.9266	88	0.1566	0.0308	29	-0.0020	0.9877	59	0.1020	0.2536
G. Cardiovascular diseases	88	0.1274	0.0788	29	0.0959	0.4651	59	0.1037	0.2458	88	0.1357	0.0612	29	0.0557	0.6713	59	0.1202	0.1786
1. Rheumatic heart disease	87	0.0320	0.6608	28	0.2056	0.1247	59	-0.0427	0.6330	87	0.1163	0.1108	28	0.1382	0.3021	59	0.0572	0.5219
2. Hypertensive heart disease	88	0.1906	0.0085	29	0.1945	0.1385	59	0.1366	0.1263	88	0.2005	0.0057	29	0.2042	0.1198	59	0.1427	0.1104
3. Ischaemic heart disease	88	0.1208	0.0955	29	0.0506	0.7001	59	0.0844	0.3449	88	0.1191	0.1004	29	0.0667	0.6113	59	0.0715	0.4240
4. Cerebrovascular disease	88	0.0510	0.4814	29	0.0004	0.9976	59	0.0937	0.2947	88	0.0790	0.2760	29	0.0359	0.7844	59	0.1585	0.0762
5. Inflammatory heart diseases (k)	88	0.2030	0.0056	29	0.3273	0.0127	59	0.1936	0.0303	88	0.1829	0.0116	29	0.1289	0.3261	59	0.2306	0.0099
H. Respiratory diseases	88	0.0767	0.2899	29	-0.0153	0.9071	59	0.0501	0.5752	88	0.0984	0.1745	29	-0.1240	0.3449	59	0.1147	0.1994
1. Chronic obstructive pulmonary disease	88	0.0347	0.6324	29	0.0075	0.9546	59	0.0015	0.9869	88	0.0203	0.7793	29	-0.0931	0.4782	59	-0.0141	0.8748
2. Asthma	88	0.1772	0.0145	29	0.2425	0.0648	59	0.1347	0.1317	88	0.2076	0.0042	29	-0.0668	0.6111	59	0.2948	0.0010
I. Digestive diseases	88	0.1861	0.0103	29	0.1639	0.2119	59	0.1717	0.0547	88	0.1681	0.0204	29	0.1613	0.2192	59	0.1612	0.0713
1. Peptic ulcer disease	88	0.0719	0.3211	29	-0.0993	0.4496	59	0.1051	0.2396	88	0.0517	0.4759	29	-0.1095	0.4044	59	0.1023	0.2523
2. Cirrhosis of the liver	87	0.0236	0.7460	28	0.2286	0.0878	59	-0.0272	0.7610	87	0.0226	0.7562	28	0.2354	0.0787	59	-0.0299	0.7378
3. Appendicitis	80	0.0981	0.1976	26	-0.0223	0.8729	54	0.0559	0.5508	88	0.1892	0.0090	29	0.0504	0.7011	59	0.2218	0.0133
J. Genitourinary diseases	88	0.0895	0.2170	29	-0.0520	0.6923	59	0.0498	0.5773	88	0.1422	0.0498	29	0.0218	0.8681	59	0.1263	0.1576
1. Nephritis and nephrosis	88	0.0889	0.2198	29	0.0339	0.7962	59	0.0426	0.6339	88	0.1372	0.0584	29	0.1045	0.4263	59	0.1151	0.1979
2. Benign prostatic hypertrophy	83	0.1159	0.1208	26	0.2088	0.1348	57	0.0048	0.9581	88	0.2402	0.0009	29	0.0849	0.5178	59	0.2271	0.0110
K. Skin diseases	84	0.0806	0.2777	27	0.0681	0.6182	57	0.0320	0.7249	88	0.2510	0.0005	29	0.3018	0.0216	59	0.2183	0.0146
L. Musculoskeletal diseases	88	0.1004	0.1658	29	0.0266	0.8393	59	0.1198	0.1802	88	0.1047	0.1485	29	0.1016	0.4391	59	0.1088	0.2235
1. Rheumatoid arthritis	82	0.0075	0.9209	26	-0.1276	0.3609	56	0.0356	0.6982	88	0.0395	0.5860	29	0.0878	0.5037	59	0.1081	0.2266
2. Osteoarthritis	58	0.0467	0.6043	17	-0.0547	0.7593	41	0.0640	0.5558	88	0.0652	0.3684	29	0.0763	0.5611	59	0.0617	0.4900
M. Congenital anomalies	88	0.2344	0.0012	29	0.1706	0.1939	59	0.2156	0.0160	88	0.2922	0.0001	29	0.2069	0.1151	59	0.2746	0.0021
N. Oral conditions	32	0.1768	0.1551	7	0.3233	0.3073	25	0.1347	0.3451	88	0.2281	0.0016	29	0.2011	0.1256	59	0.2341	0.0088
1. Dental caries	1			1			0			88	0.1598	0.0275	29	0.2592	0.0484	59	0.1887	0.0348
2. Periodontal disease	0			0			0			88	0.3125	0.0000	29	0.2592	0.0484	59	0.3069	0.0006
3. Edentulism	0			0			0			88	0.2755	0.0001	29	0.3337	0.0110	59	0.2538	0.0045
Injuries	88	0.1276	0.0784	29	0.1203	0.3594	59	0.1008	0.2594	88	0.1895	0.0089	29	0.1176	0.3703	59	0.1800	0.0440
A. Unintentional injuries	88	0.1107	0.1267	29	0.0812	0.5362	59	0.0581	0.5153	88	0.1349	0.0627	29	0.0849	0.5177	59	0.0878	0.3260
1. Road traffic accidents	88	0.1476	0.0417	29	0.1143	0.3840	59	0.1187	0.1841	88	0.1640	0.0237	29	0.0990	0.4509	59	0.1252	0.1612
2. Poisonings	87	-0.0622	0.3936	29	-0.1073	0.4137	58	-0.0673	0.4557	88	-0.0568	0.4330	29	-0.1133	0.3881	59	-0.0361	0.6861
3. Falls	88	-0.0266	0.7141	29	0.0199	0.8796	59	-0.0501	0.5751	88	-0.0626	0.3878	29	0.1181	0.3683	59	-0.1187	0.1842
4. Fires	86	0.1168	0.1113	29	-0.0130	0.9209	57	0.0902	0.3216	88	0.1298	0.0733	29	0.0784	0.5502	59	0.1021	0.2533
5. Drownings	88	0.0781	0.2811	29	0.0321	0.8071	59	-0.0190	0.8319	88	0.1090	0.1326	29	0.0301	0.8187	59	0.0222	0.8041
6. Other unintentional injuries	88	0.1177	0.1043	29	0.0344	0.7935	59	0.0949	0.2882	88	0.1517	0.0364	29	0.1107	0.3990	59	0.1321	0.1395
B. Intentional injuries	88	0.0697	0.3365	29	0.2238	0.0883	59	0.0544	0.5427	88	0.1445	0.0462	29	0.2305	0.0792	59	0.1447	0.1055
1. Self-inflicted injuries	88	-0.1207	0.0959	29	0.2629	0.0453	59	-0.1834	0.0401	88	-0.1349	0.0628	29	0.2218	0.0912	59	-0.1979	0.0268
2. Violence	88	0.2182	0.0026	29	-0.0268	0.8384	59	0.2534	0.0046	88	0.2443	0.0008	29	0.0653	0.6192	59	0.2781	0.0020
3. War	30	0.2652	0.0395	8	-0.0213	0.9411	22	0.3333	0.0350	82	0.1588	0.0347	28	0.1987	0.1378	54	0.1607	0.0862

Figure 3. Correlation of mortality and Disability Adjusted Life Year (DALY) with prevalence of toxoplasmosis for all 88 WHO member countries (29 European and 59 non-European countries). The correlations were estimated with partial Kendall correlation test with GDP per capita as covariate. Positive Kendall Taus (red) correspond to positive and negative Taus (blue) to negative correlations. Significant results ($p<0.05$) are labeled with yellow and trends ($p<0.10$) with green colors.
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DALY per 100,000 inhabitants. The prevalence of toxoplasmosis explained 6.4% of between countries variability in DALY.

Cardiovascular diseases. The second highest regression coefficient ($B = 12.49$, $p = 0.026$, $Eta^2 = 0.058$) was observed for cardiovascular diseases. However, prevalence of toxoplasmosis explained about 15% of variability in mortality attributed to cardiovascular diseases in European countries subset ($B = 18.23$, $p = 0.048$, $Eta^2 = 0.153$). Also, in the European countries, the difference in prevalence of toxoplasmosis explained about 17% of variability of ischemic heart disease ($B = 8.59$, $p = 0.039$, $Eta^2 = 0.166$). Stronger correlations between prevalence of toxoplasmosis and heart disease, especially inflammatory heart disease, were revealed with nonparametric partial Kendall test (comparing the data in tables shown in Fig. 3 and 4). One may suggest that the non-Gaussian distributions of dependent variables, e.g. a bimodal distribution for cerebrovascular and cardiovascular disease and highly skewed distribution for hypertensive, rheumatic and inflammatory heart diseases (results not shown), were responsible for the false negative results of the GLM tests.

Theoretically, the inability to control for more than one confounding variable (here, the latitude and annual precipitation) in the distribution-robust nonparametric tests could be responsible for the false positive results of the partial Kendall test. However, the present data do not support this explanation. Fig. 1 shows that the latitude correlates negatively and the humidity positively with the prevalence of toxoplasmosis. The Kendall correlation test showed, for example, the positive association between hypertensive heart disease and prevalence of toxoplasmosis (DALY: $p = 0.06$; mortality: $p = 0.008$), while GLM demonstrated lack of such association (DALY: $p = 0.345$; mortality: $p = 0.282$). The negative association between prevalence of toxoplasmosis and latitude (see above) could explain the positive correlation between the disease burden for hypertensive heart disease and prevalence of toxoplasmosis, because the disease burden for hypertensive heart disease correlated negatively with the latitude (DALY: $B = -3.846$, $Eta^2 = 0.139$, $p<0.001$), but also negatively with humidity ($B = -2.145$, $Eta^2 = 0.059$, $p = 0.024$), which is in contradiction to the explanation). However, the negative correlation between prevalence of toxoplasmosis and latitude could not explain the positive correlation between prevalence of toxoplasmosis and the inflammatory heart disease (DALY: $p = 0.012$, mortality: $p = 0.006$), because inflammatory heart disease correlated positively with latitude ($B = 0.749$, $Eta^2 = 0.010$, $p = 0.362$), and negatively with humidity ($B = -1.392$, $Eta^2 = 0.041$, $p = 0.060$). This contradicts the notion that the correlations with the latitude or humidity could be responsible for the association between toxoplasmosis and cardiovascular diseases detected with the partial Kendall correlation tests.

Perinatal conditions. The third highest regression coefficient ($B = 9.66$) was demonstrated for this category, but, it explained only 3.3% of the variability making the correlation non-significant ($p = 0.097$). The important components of this category were prematurity and low birth weight ($B = 3.43$; $Eta^2 = 0.053$; $p = 0.034$). Published data suggest that early development of embryos in mothers with latent toxoplasmosis was slower, although, the birth weight of newborns was approximately the same as those of infection-free mothers [26]. These studies were performed in Czech Republic, a developed European country, with low frequency of virulent *T. gondii* strains. It is possible that the effect of toxoplasmosis on development of embryos is qualitatively different in other parts of the world. It is indicative that the association between prevalence of toxoplasmosis and DALY for prematurity and low birth weight is much weaker for the European countries ($B = 0.320$; $Eta^2 = 0.004$; $p = 0.761$) than for others. Once again, the correlation of DALY for perinatal conditions with prevalence of toxoplasmosis detected with nonparametric tests were stronger than those detected with GLM. Here, however, the correlation observed in Kendall test (in which the GDP but not the latitude and humidity was controlled) can be explained by correlation of both prevalence of toxoplasmosis and the DALY for perinatal conditions, controlling for the latitude, because the latter correlation is negative and relatively strong (and significant).

Congenital abnormalities. The regression coefficient was only medium ($B = 2.613$; $Eta^2 = 0.133$; $p<0.001$). The correlation was significant for the 88 countries, however, it was non-significant for the European countries ($B = 1.970$; $Eta^2 = 0.137$; $p = 0.062$). Interestingly, more than 55 years ago, it was observed that children with Down syndrome had a much higher probability of having mothers with latent toxoplasmosis (84%) than normal children (32%) [333]; the probability of having fathers with latent toxoplasmosis did not differ between children with and without this disorder. Recently, it has been suggested that Down syndrome may be caused by congenital *T. gondii* infection [182], Table 2. This hypothesis is supported by the finding that *T. gondii* has a specific protein transporter exposed at the parasite surface, with high affinity for folic acid, which is responsible for the acquisition and salvaging of exogenous folate compounds [187], thus leading to folate deficiency in the host. The transport of folic acid across the parasite plasma membrane was found to be rapid, biphasic, bidirectional, specific, and concentration- and temperature-dependent, and methotrexate, an antifolate, was found to be internalized by the protozoan pathogen to the mitochondrion [187]. In addition, it has been demonstrated that simultaneous dietary restriction of folic acid and infection with *T. gondii* induces DNA damage in peripheral blood cells of infected mice [186]. Furthermore, *T. gondii* infection was also associated with nutritional deficiencies of iron and iodine [266,334,335], which may lead to have adverse effect on the growth and development of the fetus.

Principally different explanation of the observed association suggest results of three studies on the influence of toxoplasmosis on secondary sex ratio and on the rate of prenatal and early postnatal development of children of infected mothers, These results indicate that latent toxoplasmosis could protect the embryos with less serious developmental disturbances against spontaneous abortion [26,336–338]. It is possible that such beneficial activity of the parasite could translate into positive correlation between prevalence of toxoplasmosis and incidence and severity of congenital abnormalities.

Lymphatic filariasis. The regression coefficient was medium ($B = 4.534$; $Eta^2 = 0.140$, $p = 0.072$). This disease occurs in 27 countries of our data set and therefore the highly non-Gaussian distribution of DALY (and mortalities) makes the results of GLM analysis not fully credible. The nonparametric test showed no significant association between filariasis and toxoplasmosis. How-

	mortality All			mortality Europe			mortality no Europe			DALY All			DALY Europe			DALY no Europe		
	B	p	eta	B	p	eta	B	p	eta	B	p	eta	B	p	eta	B	p	eta
All Causes	3.7771	0.1043	0.0315	3.5381	0.0242	0.2292	3.3696	0.2388	0.0256	98.2868	0.0933	0.0336	68.1836	0.0138	0.2271	82.4934	0.2044	0.0297
Communicable, maternal, perinatal and nutritional conditions	1.7077	0.2734	0.0144	0.0244	0.8779	0.0066	1.5937	0.4216	0.0120	68.5588	0.1968	0.0200	11.4396	0.0390	0.1657	55.4942	0.3364	0.0171
A. Infectious and parasitic diseases	0.9296	0.3945	0.0087	0.0850	0.2137	0.0031	0.7731	0.5801	0.0057	28.9996	0.3455	0.0107	3.2596	0.0934	0.1128	24.8763	0.5266	0.0075
1. Tuberculosis	0.0319	0.8483	0.0004	0.0546	0.0836	0.0137	-0.0127	0.9534	0.0001	1.5491	0.6634	0.0023	1.1972	0.1114	0.1022	0.6049	0.8948	0.0003
2. STDs excluding HIV	0.0515	0.2628	0.0227				0.0589	0.2495	0.0300	1.6270	0.0635	0.0409	0.4127	0.0170	0.2152	1.6985	0.1330	0.0413
a. Syphilis	0.0408	0.3187	0.0249				0.0419	0.3211	0.0259	0.5714	0.2858	0.0142	0.0083	0.3797	0.0323	0.6667	0.3482	0.0173
b. Chlamydia	0.0130	0.2082	0.1898				0.0130	0.2082	0.1898	0.2811	0.0465	0.0469	0.2288	0.0187	0.2095	0.2873	0.0974	0.0501
c. Gonorrhoea	-0.0029	0.7951	0.1000				-0.0029	0.7951	0.1000	0.5206	0.0192	0.0643	0.1755	0.0175	0.2135	0.5486	0.0494	0.0696
3. HIV/AIDS	0.1548	0.8021	0.0008	-0.0190	0.4213	0.0816	0.0926	0.9091	0.0003	2.5659	0.8685	0.0003	0.1555	0.8686	0.0012	-0.6344	0.9753	0.0000
4. Diarrhoeal diseases	0.3638	0.1066	0.0335	0.0440	0.0470	0.2633	0.3675	0.1850	0.0323	8.2548	0.1196	0.0289	0.7436	0.1583	0.0812	8.3240	0.2068	0.0293
5. Childhood-cluster diseases	0.1604	0.0687	0.0590	-0.0013	0.5657	0.0026	0.1854	0.0610	0.0742	4.2372	0.0411	0.0493	0.0469	0.2508	0.0545	4.8506	0.0820	0.0550
a. Pertussis	0.1000	0.0042	0.2420			0.0000	0.1051	0.0023	0.2789	1.8101	0.0031	0.1003	0.0427	0.2995	0.0448	2.0629	0.0107	0.1147
b. Poliomyelitis	0.0000	0.9718	0.0001	0.0015	0.7043	0.0101				0.0101	0.5766	0.0213				0.0103	0.6522	0.0191
c. Diphtheria	0.0021	0.0107	0.3612				0.0020	0.0187	0.3354	0.0577	0.0218	0.2594				0.0588	0.0234	0.2672
d. Measles	0.1281	0.1566	0.0757				0.1281	0.1566	0.0757	4.2237	0.1368	0.0700				4.2298	0.1610	0.0714
e. Tetanus	0.0181	0.3335	0.0253				0.0183	0.3317	0.0262	0.5917	0.3174	0.0263				0.5917	0.3174	0.0263
6. Meningitis	0.0524	0.1414	0.0262	0.0100	0.0536	0.0665	0.0455	0.3297	0.0179	1.5636	0.1123	0.0301	0.3930	0.0494	0.1515	1.5934	0.2139	0.0285
7. Hepatitis B (g)	0.0006	0.9703	0.0000	-0.0051	0.4136	0.0988	-0.0012	0.9501	0.0001	-0.0302	0.8918	0.0002	-0.0628	0.3659	0.0373	-0.0574	0.8309	0.0009
Hepatitis C (g)	0.0084	0.3573	0.0121	0.0074	0.4425	0.0020	0.0090	0.4168	0.0138	0.1159	0.3500	0.0121	0.0550	0.6149	0.0136	0.1524	0.3247	0.0202
8. Malaria	0.3504	0.3943	0.0260				0.2620	0.3531	0.0320	8.8242	0.3477	0.0239				3.4856	0.7270	0.0037
9. Tropical-cluster diseases	0.0694	0.4912	0.0145				0.0719	0.4964	0.0151	5.0931	0.0931	0.0601				5.2011	0.0969	0.0614
a. Trypanosomiasis	-0.1768	0.3982	0.0804				-0.1768	0.3982	0.0804	-4.3655	0.4069	0.0776				-4.3655	0.4069	0.0776
b. Chagas disease	0.0160	0.8852	0.0322				0.0160	0.8852	0.0322	0.4138	0.6045	0.0998				0.4138	0.6045	0.0998
c. Schistosomiasis	-0.0260	0.7185	0.0089				-0.0260	0.7185	0.0089	0.0332	0.9777	0.0000				0.0332	0.9777	0.0000
d. Leishmaniasis	-0.0065	0.6271	0.0109				-0.0066	0.6459	0.0108	0.0106	0.9816	0.0000				0.0147	0.9752	0.0000
e. lymphatic filariasis										[illegible]	0.0716	0.1400				[illegible]	0.0716	0.1400
f. Onchocerciasis										[illegible]	0.1796	0.3273				[illegible]	0.1796	0.3273
10. Leprosy	-0.0017	0.6563	0.0088				-0.0017	0.6563	0.0088	-0.0229	0.4782	0.0163				-0.0229	0.4782	0.0163
11. Dengue	-0.0136	0.1582	0.1725				-0.0136	0.1582	0.1725	-0.4092	0.1070	0.1542				-0.4092	0.1070	0.1542
12. Japanese encephalitis	0.0012	0.8260	0.0136				0.0012	0.8260	0.0136	0.0684	0.7564	0.0210				0.0684	0.7564	0.0210
13. Trachoma										1.5982	0.3933	0.0432				1.5982	0.3933	0.0432
14. Intestinal nematode infections	-0.0063	0.0694	0.2925				-0.0067	0.0613	0.3366	-0.2123	0.6886	0.0039				-0.2147	0.6913	0.0039
a. Ascariasis	0.0020	0.4086	0.3498				0.0020	0.4086	0.3498	0.4385	0.3377	0.0242				0.4385	0.3377	0.0242
b. Trichuriasis										-0.2820	0.0002	0.3203				-0.2820	0.0002	0.3203
c. Hookworm disease										-0.2868	0.0360	0.1106				-0.2868	0.0360	0.1106
B. Respiratory infections	0.4111	0.2234	0.0178	-0.1405	0.2740	0.0628	0.4341	0.3154	0.0187	12.2522	0.0968	0.0329	1.1350	0.4764	0.0213	12.7612	0.1803	0.0330
1. Lower respiratory infections	0.4070	0.2226	0.0179	-0.1379	0.2864	0.0980	0.4294	0.3148	0.0187	12.0880	0.0968	0.0329	1.0894	0.4940	0.0197	12.5997	0.1803	0.0330
2. Upper respiratory infections	0.0006	0.9645	0.0000	-0.0451	0.4920	0.0349	0.0011	0.9026	0.0004	0.1244	0.3361	0.0112	0.0032	0.9866	0.0000	0.1229	0.4436	0.0109
3. Otitis media	0.0026	0.2015	0.0620				0.0027	0.1645	0.0859	0.0389	0.1280	0.0277	0.0376	0.0857	0.1180	0.0382	0.2148	0.0284
C. Maternal conditions	0.0928	0.2849	0.0166	0.0137	0.0285	0.2969	0.1007	0.3515	0.0174	3.2808	0.1548	0.0242	1.4993	0.0367	0.1695	3.3582	0.2684	0.0226
D. Perinatal conditions (h)	0.2379	0.0711	0.0392	0.0635	0.2040	0.2117	0.2597	0.1167	0.0458	8.6605	0.0601	0.0419	1.8796	0.3076	0.0433	10.7477	0.0922	0.0516
1. Prematurity and low birth weight	0.0893	0.0358	0.0526	0.0146	0.6229	0.2131	0.1028	0.0520	0.0694	3.4280	0.0342	0.0529	0.3198	0.7601	0.0040	3.8761	0.0489	0.0699
2. Birth asphyxia and birth trauma	0.0616	0.0990	0.0328	0.0097	0.5300	0.0970	0.0679	0.1499	0.0387	3.1157	0.0693	0.0392	0.3065	0.6161	0.0106	3.5294	0.0936	0.0512
3. Neonatal infections and other conditions (i)	0.0873	0.1327	0.0274	0.0389	0.1483	0.0355	0.0894	0.2262	0.0275	3.1233	0.1204	0.0288	1.2595	0.1555	0.0822	3.2494	0.2011	0.0301
E. Nutritional deficiencies	0.0528	0.4456	0.0072	0.0092	0.2841	0.0925	0.0541	0.5589	0.0065	2.3693	0.3116	0.0123	3.6768	0.0405	0.1635	1.7522	0.5598	0.0063
1. Protein-energy malnutrition	0.0020	0.9408	0.0001	0.0084	0.2700	0.0707	-0.0089	0.7985	0.0013	0.4079	0.7096	0.0018	0.8859	0.1735	0.1004	0.0245	0.9857	0.0000
2. Iodine deficiency	0.0179	0.0891	0.2219				0.0179	0.0891	0.2219	0.4946	0.5026	0.0082	1.6908	0.4552	0.0473	0.2686	0.7376	0.0030
3. Vitamin A deficiency	0.0195	0.5008	0.0242				0.0179	0.5498	0.0202	0.1559	0.8118	0.0028				0.1559	0.8118	0.0028
4. Iron-deficiency anaemia	0.0385	0.3623	0.0109	0.0008	0.8519	0.0649	0.0435	0.4256	0.0120	0.9156	0.3885	0.0090	0.5209	0.0774	0.1242	0.8943	0.5279	0.0074
Noncommunicable diseases	[illegible]	0.0284	0.0566	2.9025	0.0322	0.2626	1.6347	0.0947	0.0509	26.3257	0.0195	0.0640	40.5477	0.0250	0.1923	24.9489	0.0593	0.0643
A. Malignant neoplasms	-0.0314	0.8655	0.0003	0.2563	0.4534	0.0009	-0.1519	0.4451	0.0108	0.2537	0.9044	0.0002	4.3191	0.2445	0.0560	-1.1121	0.6360	0.0042
1. Mouth and oropharynx cancers	-0.0327	0.2671	0.0148	0.0708	0.0596	0.0100	-0.0596	0.1169	0.0449	-0.1858	0.5415	0.0045	1.0139	0.0684	0.1317	-0.4988	0.1773	0.0335
2. Oesophagus cancer	0.0413	0.3135	0.0122	-0.0180	0.4878	0.2187	0.0451	0.4046	0.0129	0.3134	0.3543	0.0103	-0.0538	0.8260	0.0021	0.3028	0.4966	0.0086
3. Stomach cancer	-0.0638	0.1751	0.0220	0.0200	0.6467	0.0239	-0.0749	0.2291	0.0267	-0.4879	0.2276	0.0175	0.2941	0.5228	0.0172	-0.5843	0.2674	0.0227
4. Colon and rectum cancers	-0.0284	0.4354	0.0073	-0.0113	0.8935	0.0032	-0.0376	0.2529	0.0241	-0.2711	0.4139	0.0081	-0.3853	0.6113	0.0109	-0.2999	0.3445	0.0166
5. Liver cancer	-0.1768	0.0106	0.0760	-0.0079	0.7664	0.0010	-0.2187	0.0200	0.0963	-1.8311	0.0076	0.0826	-0.0697	0.7976	0.0028	-2.2762	0.0143	0.1060
6. Pancreas cancer	0.0088	0.4851	0.0059	0.0186	0.3281	0.0026	0.0063	0.6451	0.0040	0.0516	0.6561	0.0024	0.2463	0.1864	0.0716	0.0100	0.9344	0.0001
7. Trachea, bronchus, lung cancers	-0.0844	0.1505	0.0247	0.1506	0.2321	0.0177	-0.1276	0.0381	0.0773	-0.2579	0.6528	0.0024	2.3543	0.0589	0.1408	-0.7516	0.1762	0.0336
8. Melanoma and other skin cancers	0.0093	0.3659	0.0100	-0.0037	0.8094	0.0707	0.0135	0.2740	0.0225	0.0846	0.3949	0.0088	-0.0075	0.9683	0.0001	0.1098	0.3174	0.0189
9. Breast cancer	0.0636	0.0186	0.0649	0.0431	0.2272	0.0183	0.0571	0.0877	0.0530	0.6397	0.0607	0.0417	0.5028	0.2600	0.0526	0.5741	0.1884	0.0318
10. Cervix uteri cancer	0.0409	0.0957	0.0331	0.0417	0.0769	0.0357	0.0380	0.2192	0.0278	0.4148	0.1315	0.0272	0.7235	0.0837	0.1194	0.3370	0.3075	0.0193
11. Corpus uteri cancer	0.0062	0.4174	0.0079	-0.0074	0.3613	0.0026	0.0081	0.4067	0.0128	0.0378	0.7005	0.0018	-0.1758	0.1824	0.0729	0.0688	0.5725	0.0059
12. Ovary cancer	0.0060	0.3816	0.0092	0.0082	0.4826	0.0715	0.0031	0.6709	0.0034	0.0608	0.4686	0.0063	0.1464	0.3391	0.0381	0.0234	0.7853	0.0014
13. Prostate cancer	0.1264	0.0023	0.1062	-0.0274	0.2151	0.0308	0.1495	0.0048	0.1379	0.6676	0.0045	0.0932	-0.2345	0.1333	0.0914	0.8199	0.0063	0.1300
14. Bladder cancer	-0.0033	0.8572	0.0004	0.0130	0.4782	0.0129	-0.0109	0.6374	0.0041	0.0036	0.9834	0.0000	0.0842	0.5657	0.0139	-0.0540	0.8093	0.0011
15. Lymphomas, multiple myeloma	0.0390	0.0525	0.0445	-0.0032	0.8628	0.1448	0.0439	0.0948	0.0508	0.5774	0.0612	0.0416	0.1862	0.3806	0.0322	0.6336	0.1157	0.0452
16. Leukaemia	0.0206	0.0677	0.0397	0.0252	0.0898	0.0120	0.0176	0.2311	0.0264	0.2349	0.3757	0.0095	0.4448	0.0168	0.2157	0.1953	0.5796	0.0057
B. Other neoplasms	0.0494	0.0087	0.0829	0.0325	0.3617	0.0110	0.0537	0.0159	0.1067	0.5752	0.0188	0.0670	0.3223	0.3685	0.0353	0.6528	0.0312	0.0862
C. Diabetes mellitus	0.1510	0.1879	0.0208	-0.0012	0.9902	0.0049	0.1977	0.1958	0.0308	0.4897	0.6893	0.0019	0.1889	0.8086	0.0025	0.9215	0.5659	0.0061
D. Endocrine disorders	0.0482	0.1580	0.0242	0.0331	0.1335	0.1317	0.0432	0.3235	0.0184	2.1176	0.0278	0.0576	1.3130	0.2339	0.0585	2.0176	0.1047	0.0489
E. Neuropsychiatric conditions	0.0610	0.3377	0.0111	0.0888	0.5292	0.0111	0.0422	0.5260	0.0075	1.0422	0.7363	0.0014	10.1181	0.0283	0.1849	0.0855	0.9828	0.0000
1. Unipolar depressive disorders	-0.0008	0.6664	0.0042	0.0126	0.0293	0.2839	-0.0028	0.1575	0.0655	0.0550	0.9683	0.0000	3.5948	0.2574	0.0531	-0.4108	0.7997	0.0012
2. Bipolar disorder	-0.0002	0.0000	0.0000							0.1225	0.1051	0.0313	0.1950	0.0125	0.2332	0.1337	0.1275	0.0425
3. Schizophrenia	0.0007	0.7539	0.0015	0.0095	0.0151	0.2270	-0.0021	0.4715	0.0134	-0.2212	0.2492	0.0160	0.4198	0.1412	0.0880	-0.2517	0.2649	0.0230
4. Epilepsy	0.0441	0.0101	0.0780	0.0379	0.0042	0.0461	0.0416	0.0530	0.0688	0.9726	0.0012	0.1198	0.8160	0.0248	0.1930	0.9668	0.0075	0.1249
5. Alcohol use disorders	0.0164	0.0907	0.0367	0.0791	0.0190	0.0087	0.0015	0.8323	0.0009	-1.6077	0.3372	0.0111	[illegible]	0.0733	0.1275	-2.8454	0.0983	0.0498
6. Alzheimer and other dementias	-0.0212	0.5877	0.0036	-0.0880	0.4523	0.0001	-0.0099	0.7925	0.0013	-0.5279	0.0439	0.0480	-1.0631	0.0535	0.1466	-0.5010	0.0902	0.0522
7. Parkinson disease	0.0020	0.7116	0.0017	-0.0038	0.7963	0.0002	0.0030	0.6052	0.0053	0.1144	0.4363	0.0073	0.1684	0.3869	0.0313	0.1427	0.4527	0.0105
8. Multiple sclerosis	0.0044	0.1027	0.0351	0.0089	0.3182	0.0576	0.0038	0.0129	0.1270	0.0131	0.6662	0.0023	-0.0636	0.4142	0.0280	0.0163	0.5166	0.0078
9. Drug use disorders	0.0016	0.9284	0.0001	0.0018	0.9021	0.1360	-0.0041	0.8523	0.0008	-0.3966	0.6698	0.0022	-2.6199	0.0622	0.1375	-0.0197	0.9864	0.0000
10. Post-traumatic stress disorder										-0.0504	0.0435	0.0482	0.0132	0.2481	0.0552	-0.0656	0.0525	0.0678
11. Obsessive-compulsive disorder										0.8361	0.0000	0.2866	0.6813	0.0180	0.2117	0.9245	0.0000	0.3586
12. Panic disorder										-0.0161	0.3625	0.0100	0.1008	0.0158	0.2196	-0.0312	0.0973	0.0501
13. Insomnia (primary)										0.1069	0.3391	0.0110	-0.2408	0.0151	0.2219	0.1355	0.3292	0.0176
14. Migraine										-0.4009	0.2219	0.0179	-1.7202	0.0170	0.2151	-0.3874	0.2069	0.0293
F. Sense organ diseases	0.0017	0.6756	0.0061				0.0009	0.8187	0.0021	1.7605	0.5463	0.0044	1.6905	0.0043	0.2930	1.7461	0.6169	0.0047
1. Glaucoma										0.9148	0.0122	0.0733	0.3581	0.0058	0.2761	0.9859	0.0310	0.0833
2. Cataracts										2.4438	0.1141	0.0298	0.8097	0.0626	0.1371	2.7069	0.1509	0.0378
3. Refractive errors										-1.4228	0.1138	0.0299	-0.3481	0.0051	0.2837	-1.6686	0.1542	0.0372
4. Hearing loss, adult onset										-0.2995	0.7224	0.0015	0.9017	0.0898	0.1152	-0.4692	0.6541	0.0037
5. Macular degeneration and other (j)	0.0014	0.7246	0.0043				0.0009	0.8187	0.0021	0.1329	0.5906	0.0035	-0.0219	0.6727	0.0076	0.2002	0.5073	0.0082
G. Cardiovascular diseases	1.3929	0.0177	0.0659	2.3663	0.0479	0.3136	1.3442	0.0442	0.0729	12.8880	0.0261	0.0582	18.2348	0.0483	0.1528	12.5438	0.0622	0.0629
1. Rheumatic heart disease	-0.0252	0.1854	0.0213	0.0191	0.1185	0.0002	-0.0334	0.1733	0.0341	-0.0775	0.7979	0.0008	0.2216	0.1217	0.1009	-0.1270	0.7376	0.0021
2. Hypertensive heart disease	0.1536	0.2816	0.0140	0.2367	0.2170	0.0433	0.1670	0.3505	0.0162	0.9381	0.3452	0.0107	1.5398	0.2113	0.0643	0.9809	0.4324	0.0115
3. Ischaemic heart disease	0.5415	0.1171	0.0293	1.2428	0.0613	0.0890	0.4887	0.2060	0.0295	4.2219	0.1779	0.0218	8.5948	0.0389	0.1659	4.3269	0.2801	0.0216
4. Cerebrovascular disease	0.1451	0.4992	0.0055	0.5615	0.2226	0.2880	0.0904	0.7135	0.0025	2.2476	0.2212	0.0180	3.7057	0.2986	0.0449	2.1292	0.3266	0.0178
5. Inflammatory heart diseases (k)	0.0290	0.8187	0.0006	-0.1011	0.8500	0.1129	0.1044	0.0058	0.1327	0.8581	0.2683	0.0147	0.7655	0.7977	0.0028	1.1746	0.0082	0.1225
H. Respiratory diseases	-0.0426	0.7849	0.0009	-0.1069	0.4427	0.0167	-0.0601	0.7466	0.0020	1.4969	0.4052	0.0084	-4.7545	0.1022	0.1074	2.4447	0.2350	0.0260
1. Chronic obstructive pulmonary disease	-0.1892	0.1324	0.0271	-0.0542	0.6055	0.0295	-0.2365	0.1260	0.0428	-1.1375	0.3776	0.0094	-1.1238	0.6159	0.0106	-1.2359	0.4222	0.0120
2. Asthma	0.0634	0.0638	0.0408	0.0489	0.0784	0.1390	0.0646	0.1496	0.0381	1.2899	0.0137	0.0711	-1.5714	0.1248	0.0954	1.8791	0.0024	0.1582
I. Digestive diseases	0.1676	0.0667	0.0399	0.2242	0.2158	0.0001	0.1315	0.1997	0.0303	2.8064	0.0786	0.0368	2.8591	0.3669	0.0340	2.3013	0.2088	0.0291
1. Peptic ulcer disease	-0.0045	0.7787	0.0010	-0.0091	0.6263	0.0112	-0.0055	0.7861	0.0014	0.1208	0.6788	0.0021	-0.0766	0.7689	0.0037	0.1190	0.7469	0.0019
2. Cirrhosis of the liver	0.0103	0.8616	0.0004	0.3141	0.0326	0.0494	-0.0496	0.4661	0.0099	0.0794	0.9270	0.0001	[illegible]	0.0265	0.1964	-0.9426	0.3000	0.0199
3. Appendicitis	-0.0011	0.3960	0.0096	-0.0003	0.8074	0.0015	-0.0015	0.3449	0.0182	0.0190	0.2796	0.0141	0.0046	0.7670	0.0037	0.0203	0.3747	0.0146
J. Genitourinary diseases	0.0101	0.8534	0.0004	-0.0370	0.3938	0.0066	0.0214	0.7472	0.0019	0.8141	0.2649	0.0150	-0.0556	0.9195	0.0004	1.0364	0.2331	0.0262
1. Nephritis and nephrosis	0.0268	0.5933	0.0035	-0.0147	0.6901	0.0380	0.0373	0.5465	0.0068	0.5341	0.2974	0.0131	0.0462	0.9244	0.0004	0.6426	0.3016	0.0197
2. Benign prostatic hypertrophy	-0.0003	0.9318	0.0001	0.0076	0.3004	0.2142	-0.0017	0.6806	0.0033	0.2136	0.0451	0.0475	0.0619	0.1652	0.0787	0.2841	0.0184	0.0987
K. Skin diseases	-0.0190	0.2187	0.0191	0.0014	0.8637	0.1839	-0.0478	0.2616	0.0242	0.1673	0.4684	0.0064	0.5447	0.0117	0.2367	0.0732	0.7920	0.0013
L. Musculoskeletal diseases	0.0133	0.3021	0.0128	0.0022	0.8868	0.0116	0.0134	0.4182	0.0122	-0.6084	0.3046	0.0127	3.3735	0.0290	0.1835	-1.1330	0.0347	0.0799
1. Rheumatoid arthritis	-0.0020	0.3197	0.0129	-0.0018	0.6428	0.0111	-0.0020	0.4295	0.0123	0.2843	0.0999	0.0323	0.7716	0.0157	0.2197	0.2609	0.1914	0.0314
2. Osteoarthritis	0.0023	0.2680	0.0231	0.0008	0.7819	0.0218	0.0025	0.3575	0.0236	-0.1368	0.7616	0.0011	2.4572	0.0393	0.1652	-0.5199	0.1551	0.0371
M. Congenital anomalies	0.0462	0.0044	0.0937	0.0337	0.1326	0.0971	0.0525	0.0091	0.1193	2.6133	0.0006	0.1332	1.9705	0.0623	0.1374	2.9118	0.0018	0.1662
N. Oral conditions	0.0013	0.3059	0.0388	0.0024	0.3732	0.4638	0.0016	0.3054	0.0524	0.4519	0.2513	0.0158	0.4009	0.0184	0.2104	0.6492	0.1825	0.0327
1. Dental caries										0.2578	0.3008	0.0129	0.1908	0.0180	0.2117	0.3817	0.2200	0.0277
2. Periodontal disease										0.0157	0.0359	0.0520	0.0136	0.0180	0.2117	0.0166	0.0958	0.0505
3. Edentulism										0.1603	0.3057	0.0126	0.1807	0.0144	0.2246	0.2329	0.2282	0.0268
Injuries	0.2437	0.5277	0.0048	0.6104	0.0843	0.0240	0.1415	0.7765	0.0015	13.4044	0.3564	0.0103	16.2040	0.0970	0.1106	12.0527	0.5264	0.0075
A. Unintentional injuries	0.1561	0.3678	0.0098	0.4615	0.0595	0.0176	0.0881	0.6751	0.0033	6.7480	0.3301	0.0114	12.7638	0.0605	0.1392	5.5146	0.5463	0.0068
1. Road traffic accidents	0.1048	0.2556	0.0155	0.0248	0.6616	0.0096	0.1150	0.3285	0.0177	3.0179	0.2672	0.0148	0.6997	0.6669	0.0078	3.2209	0.3564	0.0158
2. Poisonings	0.0137	0.6008	0.0034	0.1344	0.0891	0.0485	-0.0047	0.8284	0.0009	0.5055	0.3726	0.0096	3.0508	0.0863	0.1176	0.1232	0.7885	0.0013
3. Falls	-0.0155	0.4587	0.0066	0.0482	0.4668	0.0129	-0.0305	0.1373	0.0404	-0.1795	0.8159	0.0007	1.5874	0.1294	0.0932	-0.4908	0.6208	0.0046
4. Fires	0.0067	0.7431	0.0013	0.0471	0.0493	0.0094	-0.0058	0.8180	0.0010	0.4978	0.4555	0.0067	1.1948	0.0163	0.2177	0.3437	0.6842	0.0031
5. Drownings	-0.0031	0.8630	0.0004	0.0428	0.1336	0.0052	-0.0132	0.5545	0.0065	0.0297	0.9489	0.0000	1.0277	0.1190	0.0982	-0.1969	0.7314	0.0022
6. Other unintentional injuries	0.0396	0.5623	0.0041	0.1607	0.0599	0.0086	0.0124	0.8882	0.0004	2.8842	0.3206	0.0119	[illegible]	0.0651	0.1347	2.3210	0.5390	0.0070
B. Intentional injuries	0.1288	0.5890	0.0035	0.1493	0.3892	0.0164	0.1053	0.7398	0.0021	6.6566	0.4446	0.0071	3.4329	0.4850	0.0205	6.7395	0.5625	0.0062
1. Self-inflicted injuries	-0.0563	0.1397	0.0261	0.2010	0.0574	0.0000	-0.1075	0.0046	0.1394	-1.1442	0.1656	0.0230	4.0504	0.0651	0.1347	-2.1569	0.0122	0.1107
2. Violence	0.0787	0.2725	0.0145	0.0502	0.0973	0.0565	0.0769	0.4176	0.0122	3.8079	0.2101	0.0189	1.9518	0.0875	0.1168	3.8827	0.3279	0.0177
3. War	0.3959	0.5483	0.0146	-0.8593	0.1951	0.3399	0.6251	0.4357	0.0361	3.7000	0.6267	0.0031	-2.6990	0.4497	0.0251	4.7208	0.6498	0.0042

Figure 4. Correlation of mortality and Disability Adjusted Life Year (DALY) with prevalence of toxoplasmosis for all 88 WHO member countries (29 European and 59 non-European countries). The correlations were estimated with General Linear Model with GDP per capita, latitude humidity, as covariates. Positive B (red) correspond to positive, and negative B (blue) to negative correlations. Significant results ($p<0.05$) are labeled with yellow and trends ($p<0.10$) with green colors.
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ever, possible relationship between toxoplasmosis and filariasis could theoretically be explained by the fact that *T. gondii* usually disseminates via lymphatic system in the infected patients, who usually have symptomatic lymphadenopathy. In addition, possible interactions exist between toxoplasmosis-associated changes in the host lymphatic system and a progressive clinical picture of lymphatic filariasis (Table 2). Filariasis may therefore represent another co-morbidity of the host infected with *T. gondii*.

Measles. The regression coefficient was medium ($B = 4.124$; $Eta^2 = 0.070$; $p = 0.137$), and the correlation was not significant. A possible association, if it really exists, is difficult to rationalize, however, latent cerebral toxoplasmosis could influence susceptibility to measles because of changes in the immune status of the children (Table 2) [339,340] caused by the parasite or measles-mumps-rubella (MMR) vaccination.

Asthma. The regression coefficient B was 1.290 ($Eta^2 = 0.071$, $p = 0.014$). An opposite direction association was observed for European ($B = -1.571$, $Eta^2 = 0.096$, $p = 0.124$) and non-European ($B = 1.879$, $Eta^2 = 0.158$, $p = 0.002$) countries. We have no explanation for the positive association, but, the negative association between *T. gondii* infection and asthma could be, at least partially, explained by the anti-inflammatory effect of histamine produced in excess in asthmatic patients, since, asthma is a chronic inflammatory disorder associated with an increased number of T_H2 (T helper type 2) cells producing anti-inflammatory cytokines and decreased number of T_H1 (T helper type 1) cells generating pro-inflammatory cytokines. Histamine modulates the cytokine T_H1/T_H2 balance because it enhances secretion of T_H2 cytokines, such as IL-4, IL-5, IL-10, and IL-13, and inhibits production of T_H1 interleukins (IL-2, IFN-γ, and monokine IL-12) [341], thus exerting beneficial anti-inflammatory effects.

Epilepsy. Epilepsy had a small regression coefficient ($B = 0.972$; $Eta^2 = 0.112$, $p = 0.001$), but the correlation was highly significant. This association was observed both in European ($B = 0.816$, $Eta^2 = 0.193$, $p = 0.025$) and non-European countries ($B = 0.967$, $Eta^2 = 0.125$, $p = 0.007$). The association between latent toxoplasmosis and cryptic epilepsy has already been suggested to exist on the basis of the case control studies – for example, see Ref. [342,343] Table 2.

Leukemia. Surprisingly, there was a strong association between toxoplasmosis and DALY for leukemia in European countries ($B = 0.445$, $Eta^2 = 0.216$, $p = 0.017$) explaining about 22% of variability in DALY. In a small study performed in 15 patients with leukemia, 10 (66.7%) individuals had increased serum IgG, and 2 also had increased IgM antibodies to *T. gondii* [219]. It is known that tachyzoites of *T. gondii* use a "Trojan horse" strategy to penetrate various tissues and organs of the infected host. They even transform the phenotype of infected white cells by, for example, increasing migratory activity of the infected dendritic cells [344] and by inhibiting apoptotic activity of the infected cells [345–349]. It is also possible that the increased risk of various forms of cancer, including leukemia, could be as a result of infection with *T. gondii*, which may cause a nonspecific chronic local inflammation.

Cancer of the mouth/oropharynx. The regression coefficient was small ($B = 1.014$; $Eta^2 = 0.132$, $p = 0.067$) and the correlation was non-significant (positive for European but negative for non-European countries). A typical symptom of acute toxoplasmosis is tonsillitis. Thus, it is possible that tonsillitis leading to the development of local chronic inflammation may result in inducing precancerous changes in predisposed individuals. Association of prevalence of toxoplasmosis with cancer of the larynx in men and women, and lung cancer in men (but not with cancer of oropharynx), has been reported [214]. In addition, one cannot exclude that frequent oral sex could, at least in part, affect this correlation, since, the parasite has been found in the semen and ejaculate of both animals and humans infected with *T. gondii* [331,332], see also Table 2.

Prostate cancer. Prostate cancer had a B of 0.667 ($Eta^2 = 0.093$, $p = 0.005$). An association in opposite direction was observed for European ($B = -0.235$, $Eta^2 = 0.091$, $p = 0.133$) and non-European ($B = 0.820$, $Eta^2 = 0.130$, $p = 0.006$) countries. Benign prostate hypertrophy had a B of 0.214, ($Eta^2 = 0.482$, $p = 0.045$) and this association was positive but non-significant for non-European countries ($B = 0.062$, $Eta^2 = 0.079$, $p = 0.165$) and positive and significant ($B = 0.284$, $Eta^2 = 0.098$, $p = 0.018$) for European countries. It is possible that the increased incidence of prostate cancer and hypertrophy could be related to the increased concentration of testosterone as observed in *Toxoplasma*-infected male rats [350] and men [351,352]. Histopathologic studies of the reproductive system in male sheep experimentally infected with the parasite showed inflammatory process in the prostate gland and seminal vesicles strongly suggestive of *Toxoplasma* infection [300] (Table 2). Thus, persistent chronic inflammation caused by the parasite also must be taken into account in the development of prostate cancer, although perhaps having different clinical courses in European versus non-European countries.

Obsessive compulsive disorder. Obsessive compulsive disorder (OCD) had a B value of 0.836, but the prevalence of toxoplasmosis explained 28.7% of total variability in DALY ($p < 0.001$). For European countries the association was weaker ($B = 0.681$, $Eta^2 = 0.212$, $p = 0.018$), but for non-European countries, it was nearly two times higher ($B = 0.925$, $Eta^2 = 0.358$, $p < 0.001$). The association between latent toxoplasmosis and OCD has already been suggested to exist on the basis of results of a case-control study [176], in which the authors found 47.6% seroprevalence of toxoplasmosis among OCD patients ($n = 42$) and only 19% prevalence in controls ($n = 100$). Both neurotransmitters, dopamine and serotonin, are expected to play an important role in OCD. It is possible that either an increased concentration of dopamine, synthesized by two enzymes encoded in *T. gondii* genome, and a decreased level of serotonin, the metabolite of tryptophan degradation – the part of the host defense against parasitic infection – could be important etiologic factors in the development of OCD. Incidentally, OCD is not an uncommon disease (incidence of about 3%) and is probably associated with an increased risk of suicide [353–356]. It can be speculated that an association between toxoplasmosis and OCD could, in part, be responsible for the increased risk of suicides reported in *Toxoplasma*-infected individuals. It is possible that the nearly twice stronger relationship between toxoplasmosis and OCD in European ($Eta^2 = 0.202$) than in non-European ($Eta^2 = 0.360$) countries could somehow be related with the negative, not positive, relationship between the prevalence of toxoplasmosis and incidence of suicides in non-European countries observed in our study, see below.

Endocrine disorders. A regression coefficient (B) of 2.118 was observed for the category of 'endocrine disorders'. The prevalence of toxoplasmosis explained about 5.8% of total variability ($p = 0.028$) and non-significant trends were observed for both European and non-European countries. The positive and negative associations between toxoplasmosis and testosterone concentration were observed for men and women, respectively. However, our unpublished data suggest that toxoplasmosis could also play a role in the production of thyroid hormones. This finding is supported by recent literature data demonstrating the prevalence of anti-*Toxoplasma* IgG antibodies in patients with thyroid autoimmunity [277,357] as well as in many other autoimmune diseases, as compared with controls (Table 2). The autoantibody burden has also been demonstrated even in non-autoimmune individuals during infections [358]. Patients with autoimmune diseases frequently present neurologic manifestations [359], and this may further support the significant prevalence of toxoplasmosis in patients with endocrine disorders, because central nervous system is the most immunoprivileged organ for *T. gondii* dissemination and settlement in the host. Fetal [360] and maternal microchimerism, acting as a "Trojan horse" in dissemination of the parasite, could play an important role in endocrine and other health disorders [361].

Sexually transmitted diseases (STDs). A regression coefficient (B) of 1.63 was observed for the general category of 'sexually transmitted diseases except AIDS'. Prevalence of toxoplasmosis explained 4.1% of variability ($p = 0.063$). The association was stronger in European countries ($B = 0.413$, $Eta^2 = 0.215$, $p = 0.017$) than in non-European countries ($B = 1.699$, $Eta^2 = 0.041$, $p = 0.133$). Similar effects were observed for gonorrhea ($B = 0.175$, $Eta^2 = 0.213$, $p = 0.018$) and chlamydia ($B = 0.229$, $Eta^2 = 0.209$, $p = 0.019$) in Europe, but were different for non-European countries for gonorrhoea ($B = 0.549$, $Eta^2 = 0.069$, $p = 0.049$) and chlamydia ($B = 0.287$, $Eta^2 = 0.050$, $p = 0.097$). We believe that the correlation of both prevalence of toxoplasmosis and STD with other factor(s), such as a risky sexual behavior (promiscuity and frequent unprotected sex) is responsible for the observed positive association between prevalence of toxoplasmosis and age/controlled DALY for STDs. It has been suggested by other investigators [332] that *Toxoplasma* is frequently transmitted by ejaculate in several animal species. An indirect evidence exists that the same could also occur in humans [331]. Practicing oral sex or even kissing may also be another important route of wide dissemination of the parasite among sexual partners, in addition to intercourse.

Pertussis. Pertussis had a regression coefficient (B) of 1.81. Prevalence of toxoplasmosis explained 10% of variability in DALY ($p = 0.003$). This correlation could, at least in part, be rationalized by the findings that in some instances immunization could shorten the incubation period of certain diseases or convert a latent infection/inflammation into clinically active disease. The necessary precondition for such an occurrence is the presence of latent infection or asymptomatic bacterial/viral/parasitic colonization [362].

It has been reported that some infants and young children develop various urinary tract diseases, such as acute renal failure, nephrotic syndrome, or pyelonephritis, after the injection of the whole-cell DTP vaccine [363]. Administration of DTP vaccine caused dose-, and time-dependent biological changes in animals, including increased hepatic mRNA expression for several cytokines, marked inhibition of liver CYP450 enzymes activity, induction of IFN-γ, and enhanced NOS mRNA expression [364,365]. In addition, a significant increase in toxoplasma-cysts was observed in brain tissues of mice exposed to both *T. gondii* infection and methylmercury (thimerosal, a vaccine preservative) versus the parasite alone [366]. Thus, it seems that a concomitant use of strong lipopolysaccharide antigen (a component of the whole-cell pertussis) and thimerosal exerted serious synergistic adverse health effects when given to individuals with latent central nervous system *T. gondii* infection [184,340]. It is not clear, however, whether the incidence of pertussis correlates with intensity of DPT vaccination.

Childhood cluster diseases. The regression coefficient was high ($B = 4.24$), and it explained 4.9% of variability ($p = 0.041$). The high regression coefficient is not surprising because, for example, respiratory tract diseases are the most frequent cause of hospitalization and death in children and *T. gondii* infection is extensively prevalent worldwide [148,367].

There are many predisposing, provocative, facilitating, and other factors, such as chronic hypoxia, viral infections/bacterial toxins, inflammatory states, biochemical disorders, and genetic abnormalities that are the most likely triggers of development of respiratory tract diseases, including sudden infant death syndrome [368]. For example, exposure of children to cigarette smoke (second-hand) increased their susceptibility to viral and bacterial infections because children who died of sudden infant death syndrome had markedly higher concentration of cotinine (a metabolite of nicotine) in their lung tissue and pericardial fluid than in controls [369,370]. Thus, negative effects of latent toxoplasmosis on children's physiology, including function of the immune system, may markedly affect clinical course of diseases in children and might significantly affect disease severity and mortality.

Suicides. Latent toxoplasmosis was found to be associated with an increased risk of attempted suicides [161,170,171,371]. The results of earlier correlation studies performed for 17–20 European countries [172,173] were confirmed by the present study, wherein a positive trend was observed for the 29 European countries ($B = 4.05$, $p = 0.065$, $Eta^2 = 0.135$), but, this correlation could not be detected for the entire 88 countries. In fact, a negative correlation between risk of suicide and prevalence of latent toxoplasmosis was found for the 59 non-European countries ($B = -2.157$, $p = 0.012$, $Eta^2 = 0.11$). We have no explanation for this qualitative difference between European and non-European countries. However, the existence of positive correlation between the prevalence of latent toxoplasmosis and violence [174] was confirmed by partial Kendall correlation for all countries ($Tau = 0.244$, $p = 0.001$) and non-European countries ($Tau = 0.276$, $p = 0.002$), but not for European countries ($Tau = 0.065$, $p = 0.619$), the GLM method showed just a trend for European countries (see tables shown in Fig. 3 and Fig. 4).

Traffic accidents. On the basis of four published case-control studies, a positive correlation was expected between the burden of traffic accidents and prevalence of latent toxoplasmosis. However, this correlation was significant in nonparametric tests (mortality: $Tau = 0.148$, $p = 0.042$; DALY: $Tau = 0.164$, $p = 0.023$). Weak correlation in other tests may be caused by the fact that the traffic accident rates depend on many confounding variables, including the number of vehicles in circulation, length of the road network, mean number of kilometers (miles) travelled by one inhabitant per year, driver behavior (alcohol/drug use, sleep deprivation, etc.), etc. Probably, much stronger correlations would be detected when these variables would be included into the models. Interestingly, the strongest association of latent toxoplasmosis and traffic accidents was found for RhD negative drivers [372], while the RhD positive subjects, especially RhD positive heterozygotes seem to be relatively protected against impairment of reaction times [373,374] as well as against traffic accidents [372]

(the RhD refers to "Rhesus factor" with immunogenic D antigen, while RhAG indicates no Rh antigens on red blood cell membranes). The lack or deficiency of RhAG proteins in the host red blood cell membrane and an impaired function of aquaporin P1 and P4 water/gas channels in the central nervous system could be associated with various degrees of brain hypoxia [339], thus affecting usual driving performance possibly in synergy with the effects of toxoplasmosis on reaction times and ability of long-term concentration [373−375]. Since RhD negative individuals are rare in African and Asian populations [376], an association between traffic accidents and prevalence of toxoplasmosis can be expected mainly in countries inhabited by Caucasians.

Limitations of the study

It is possible that some of the toxoplasmosis prevalence data are inaccurate, as there are no published national survey data of latent toxoplasmosis carried out systematically. In addition, surveys performed in a relatively small, and ethnically and sociologically homogeneous population, such as in the Czech Republic, demonstrate that seroprevalence of toxoplasmosis varies considerably in different regions of the country. Therefore, it is difficult to estimate the average prevalence of this clinical entity in women of child-bearing age in a particular country on the basis of one or two studies performed in one hospital or even in one city. Furthermore, it is important to point out that the different serological methods used to obtain toxoplasmosis seroprevalence data are not standardized, and vary in sensitivity, specificity, and predictive values. As a consequence, no two tests produce the same results in all cases, even when carried out in the same laboratory [5].

For the present study, probably most of available data for the period 1995–2008 were collected, and published information for period prior to 1995 was also considered. To maximally avoid possible subjective bias, we completed our data set on January 2013 and did not change it after starting the analyses despite of the fact that data for other four countries appeared during 2013. To further decrease the risk of subjectivity in selection of countries, we included available data for all countries; our data set contained the prevalence of toxoplasmosis in 88 countries, which represented the largest ever data set analyzed in all toxoplasmosis correlation studies. To increase the reliability of our results, we confirmed the results of parametric GLM analysis with the nonparametric Kendall test, which is less sensitive to contamination of data with few incorrect values. It may be noted that lack of precision in the prevalence data increases the risk of false negative but not false positive results of correlation.

The existence of a factor correlating with both the prevalence of latent toxoplasmosis and the disease burden can lead to a false positive value in correlation studies. We controlled for one potential confounding variable (GDP) in partial Kendall test and for three potential confounding variables (GDP, latitude and humidity) in GLM tests. It is possible that some unknown factor(s), such as hygienic or eating habits, could influence both the prevalence of latent toxoplasmosis and incidence or morbidity of certain diseases. Existence of such factor(s) could be revealed by confirming present analyses with another set of countries. In the present study, data from all 88 countries were analyzed, and also separately for the European and non-European countries. It is important to repeat the correlation studies based upon independent data sets (if available) for particular regions (such as in France) or various states (such as in USA).

It is quite probable that the incidence of particular diseases reflects better the prevalence of latent toxoplasmosis in an unknown past, rather than the present prevalence. In many countries, the prevalence of latent toxoplasmosis in young women is changing: in some cases it is increasing (China, Korea and Mexico) and in some it is decreasing (most of European countries and USA). The prevalence of latent toxoplasmosis in a general population (the parameter which probably better correlates with disease burden) is more stable because it reflects past rather than present epidemiological situation in particular countries. Still, our lack of knowledge of optimal interval between toxoplasmosis survey and disease burden surveys increases the risk of false negative results of the obtained correlation studies.

Conclusions

The present results suggest that the prevalence of latent toxoplasmosis in particular countries correlated (mostly positively) with various disease burden measured with age standardized Disability Adjusted Life Years or with age standardized mortality. It must be emphasized that no epidemiological study and especially no correlation (ecological) study can prove existence of causal relation between the two factors. At the same time, results of such studies could indicate which hypothesis should be tested in the future. It is highly probable that some of the observed correlations represent "false correlations" – either the Type 1 errors of used statistical tests or the expression of existence of unknown factor(s) that correlates with both the risk of latent toxoplasmosis and incidence (or severity) of particular disease. However, it is also highly probable that at least some of the observed correlations do occur because toxoplasmosis is, up to now rarely suspected, etiological agent of particular diseases. Existence of some correlations could be expected to happen on the basis of our present knowledge for certain diseases (for example, epilepsy, obsessive compulsive disorder, congenital abnormalities). Some of the obtained correlations may be regarded as rather surprising and should therefore be studied in more detail in the future. In the opinion of the authors, slowly emerging important role of latent toxoplasmosis in etiology of several clinical entities deserves much more attention and financial support in future clinical research.

Author Contributions

Conceived and designed the experiments: JF. Analyzed the data: JF. Contributed reagents/materials/analysis tools: JF. Wrote the paper: JF JP ZI. Data collection: MS.

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