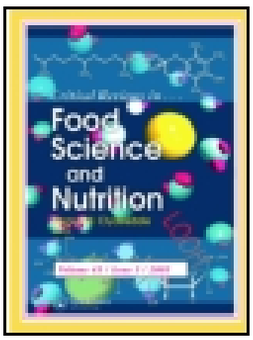

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Toxoplasma gondii infection and food consumption: A systematic review and meta-analysis of case-controlled studies

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ABSTRACT

Background: Toxoplasmosis is a zoonotic disease causing severe symptoms in pregnant women and immunocompromised individuals. On average, worldwide, around 30% of people are seropositive. The oral transmission route is of great significance and food, particularly meat, is an important transmission vehicle for *T. gondii*. However, the role of different food matrices is debated. *Objectives*: The aim of this review was to assess the risk of humans developing acute *T. gondii* infection via the foodborne route. *Study eligibility criteria*: Case-control studies including acute cases of *T. gondii* infection were included after literature searches, without time limits, in several databases. All studies estimating the risk of acquiring *T. gondii* infection after consumption of specific food categories were included. *Results*: Three risk factors proved to be significantly associated with acute *T. gondii* infection in humans: consumption of raw/undercooked meat, Odds Ratio (OR) 3.44 (1.29–9.16), consumption of raw/undercooked beef, OR 2.22 (1.57–3.12), and consumption of raw/undercooked sheep meat, OR 3.85 (1.85–8.00). Consumption of raw/undercooked pork, raw eggs, and unpasteurized milk proved to be non-significant risk factors. *Limitations*: Limitations in the present review and meta-analysis are due to the low number of case-control studies available for analysis and the lack of a search strategy targeting gray literature. *Conclusion*: Consumption of raw/undercooked beef and sheep meat are important risk factors for *T. gondii* infection. Their consumption should be avoided in order to prevent toxoplasmosis, particularly by those in at-risk categories, including pregnant women. The review protocol is registered in PROSPERO database (CRD42016043295).

KEYWORDS
Toxoplasma gondii
meat; beef; risk

Introduction

In 1965, when the story of toxoplasma research (Desmonts et al., 1965) met zoomotherapy (Lowy, 2010), the scientific community attained the first solid proof of meat's role in *T. gondii* transmission to humans. However, some aspects of the role of meat in human *T. gondii* infection remain unclear to this day.

Worldwide, *T. gondii* prevalences range up to about 30% (Flegr, 2013) and, according to disease burden indicators such as DALY (Disability Adjusted Life Years), this parasite ranks at the top of foodborne disease-causing agents (Havelaar et al., 2012; Torgerson and Mastroiacovo, 2013). *T. gondii* can cause abortions or severe fetal malformations when women acquire infection during pregnancy, but toxoplasmosis is also an important disease for immunocompromised individuals (Montoya and Liesenfeld, 2004). The impact of *T. gondii* in healthy individuals is still unclear but the parasite can encyst in human tissues with a potential for reactivation during strong immunosuppression events.

Felids hold a leading role in *T. gondii* epidemiology, as they are the only definitive host able to facilitate the sexual propagation of the parasite. Felids can spread millions of oocysts during primary infection, causing huge environmental contamination as, after sporulation, oocysts become infective for hosts accidentally ingesting contaminated products. Risk factors for oocyst ingestion are poor hygiene and consumption of contaminated water or vegetables.

However, the epidemiological importance of bradyzoites from tissue cysts is well known, and food is estimated to contribute to a proportion (between 42% and 61%) of all cases, depending on the geographical area (WHO, 2014). Acquisition of infection via the oral route is a fundamental event for *T. gondii* biology. The route is independent from the parasite's sexual reproduction, differentiating *T.gondii* from other closely related parasites such as *Neospora*, *Sarcocystis*, and *Hammondia*, and expediting the infection of almost all warm blooded animals (Su, 2003). The acquisition of this alternative transmission route probably explains the evolutionary success of *T. gondii*.

A third infective parasite stage is the tachyzoite, which can be transmitted by animal fluids. Milk is considered as a potential source of infection as, during acute animal infection, circulating tachyzoites can be transferred from blood to milk (Tenter, Heckeroth, and Weiss, 2000), but debate on this is still ongoing in the scientific community (Dehkordi et al., 2013; Dubey and Jones, 2014; Boughattas, 2015a). According to this premise, food plays a critical role in *T. gondii* transmission but the differential role of food sources, particularly within the meat category, has not been disclosed.

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/bfsn.

Oral exposure to *T. gondii* through food mainly depends on parasite prevalence and people's food consumption habits. *T. gondii* has been detected in different kinds of meats (Guo et al., 2015; Belluco et al., 2016), vegetables (Lass et al., 2012), and milk (Dehkordi et al., 2013). Whatever the food source is, consumption habits play a critical role, as *T. gondii* can be inactivated through cooking, freezing, and salting with appropriate parameters depending on product characteristics.

Epidemiological studies provide the opportunity to assess the risk associated with a particular food in the absence of Randomized Control Trials. Among observational studies, cohort and case-control study designs offer the opportunity to evaluate the causality associations.

In this systematic review, we mapped all relevant literature reporting the result of primary observational studies on food-related risk factors associated with *T. gondii* infection in the human population. We then narrowed the review question to case-control studies and, after appraising the quality of individual studies, we summed up the evidence using meta-analysis to estimate the risk of *T. gondii* infection associated with consumption of different foods.

Materials and methods

Selection of relevant studies

The review question was aimed at estimating the role of different foods (*E*) on *T. gondii* infection (*O*) in human population (*P*). We considered all studies published in peer reviewed journals in English, French, Italian, Spanish, and Portuguese. No time limits were imposed.

We searched multiple literature databases: PUBMED, Web of Science core collection – KCI-Korean Journal Database – Russian Science Citation Index – SCIELO Citation Index, and CAB Abstracts with the following search terms: (Toxoplasma OR Toxoplasmosis) AND risk factor.

The last date searched was 7 April 2016. To implement the search process, we used the final list of studies to carry out both a backward and a forward reference search using Google scholar as a search engine.

The review design is presented in Figure 1. Due to our inability to estimate the available number of case-control and cohort studies, we decided not to use study design as an eligibility criterion in the first screening but to code this item and to use it to narrow the review question in the second stage. The review protocol is registered in PROSPERO database (CRD42016043295).

Several criteria were used to select eligible studies beyond language restriction: (1) reported data had to belong to primary research; (2) cases had to belong to the human population; (3) cases had to be diagnosed with *T. gondii* infection; (4) food-related risk factors had to be considered. In the case of a poorly explicative abstract or in the case of doubt about the available data, the study was included and evaluated at full-text level.

Thereafter, 2 reviewers (SB, GS) screened all studies obtained via the initial literature search according to Title/Abstract and Full text, independently (parallel method). Disagreements were resolved through consensus. One reviewer (SB) collected data from relevant articles and a second reviewer (GS) checked the collected data against the original studies (sequential method). All studies were coded according to the previously chosen parameters and data were recorded. In the case of reviewer doubt about the reported data or in the absence of useful effect size, the study authors were contacted via e-mail.

Data were sought for the following variables: country, study year, population studied, case definition, case selection, selection of controls, exposure window, investigated risk factor, and outcome. Due to our study design, we used the Odds Ratio (OR) as the outcome.

The review process was carried out using EPPI-4 Reviewer software (Thomas, Brunton, and Graziosi, 2010).

Risk of bias in individual studies

Individual study quality was assessed using a score modified from the Newcastle–Ottawa Quality Assessment Scale for Case-Control Studies (Wells et al., 2006). Relevant confounders eligible for scoring were age and residency. Both statistical adjustment and matching by design were considered.

In addition to the Newcastle–Ottawa scale, we added 2 other relevant items: the inclusion of an exposure window (a time limitation) for exposure assessment purposes and the inclusion of only acute cases of infection. A recent case was defined as a patient with either: (1) a positive IgM test result following a negative test result; (2) IgM and IgG positivity; or (3) serological positivity and low avidity to IgG.

Synthesis of results

Meta-analyses were performed using the metafor package (Viechtbauer, 2010) of the statistical software R (R Core Team, 2012) through the interface developed in EPPI-4 Reviewer, and also directly without the interface.

A meta-analysis was run for each food-related risk factor considered, where the number of available studies was equal or higher than 3 and the risk factors investigated were suitable for aggregation.

Some included studies considered more than 1 risk factor, and thus, outcomes within the same studies are not independent. This has been considered in the statistical analysis where relevant.

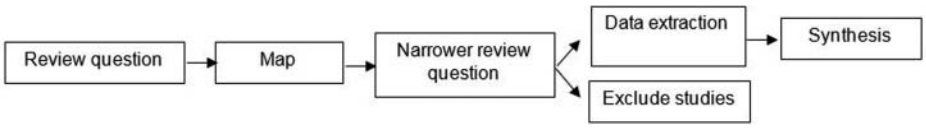

Figure 1. Review design.

All the other results were collected and discussed. The OR was selected as a relevant outcome and collected from primary studies according to adjustment for relevant confounders, if present. If an OR was calculated in the original study from a subpopulation (e.g., consumption of raw beef among people consuming raw meat), the OR was used to extrapolate the result to the entire population of respondents.

ORs from different studies were aggregated through a random-effects model, using restricted maximum likelihood (REML) as an estimator, which is considered approximately unbiased and relatively efficient. Knapp–Hartung adjustment was applied (Knapp and Hartung, 2003). Heterogeneity was assessed using the Q, T^2, and I^2 (Higgins and Thompson, 2002) parameters.

Risk of bias across studies

The potential for publication bias was assessed through the Trim and Fill method (Duval and Tweedie, 2000). Sensitivity analyses were performed for each meta-analysis, to evaluate the potential for studies exerting high influence on the model. Briefly, several parameters were examined: the externally studentized residuals, the DFFITS (DiFference in FIT, Standardized), the Cook's distance, the hat function, and the covariance ratio. Influence was defined according to metafor package criteria (absolute DFFITS value $> 3p[p/(k-p)]$, where p is the number of model coefficients and k is the number of studies *or* the lower tail area of a chi-square distribution with p degrees of freedom cut off by the Cook's distance being larger than 50% *or* hat value $> 3(p/k)$). In addition, studies were excluded one by one from the model to evaluate relevant changes in heterogeneity (T^2 and Q) and pooled estimate. A P-value < 0.05 was considered significant in the statistical meta-analysis (Viechtbauer, 2010).

Results

Study selection

A total of 2215 articles were retrieved according to the search criteria. In total, 285 full text articles were considered eligible for the initial review question and mapped particularly against study design. After narrowing the review question to include only case-control designs, 11 studies were retained and considered eligible for data extraction (Details are shown in Figure 2).

Study characteristics

All studies included after full-text screening were mapped against relevant characteristics to select criteria for narrowing the review question for meta-analytical purposes. The vast majority of studies mapped in our systematic review were carried out according to the cross-sectional design, and targeted pregnant women. Details are reported in Figure 3.

Study characteristics of the 11 case-control studies were collected in detail and are reported in Table 1. Briefly, publication year ranged from 1980 to 2014, and studies were carried out in Europe (6), South America (2), Asia (1), or in North America (1). The investigated populations comprised pregnant women (5) or the general population (4), whereas in 1 study, only

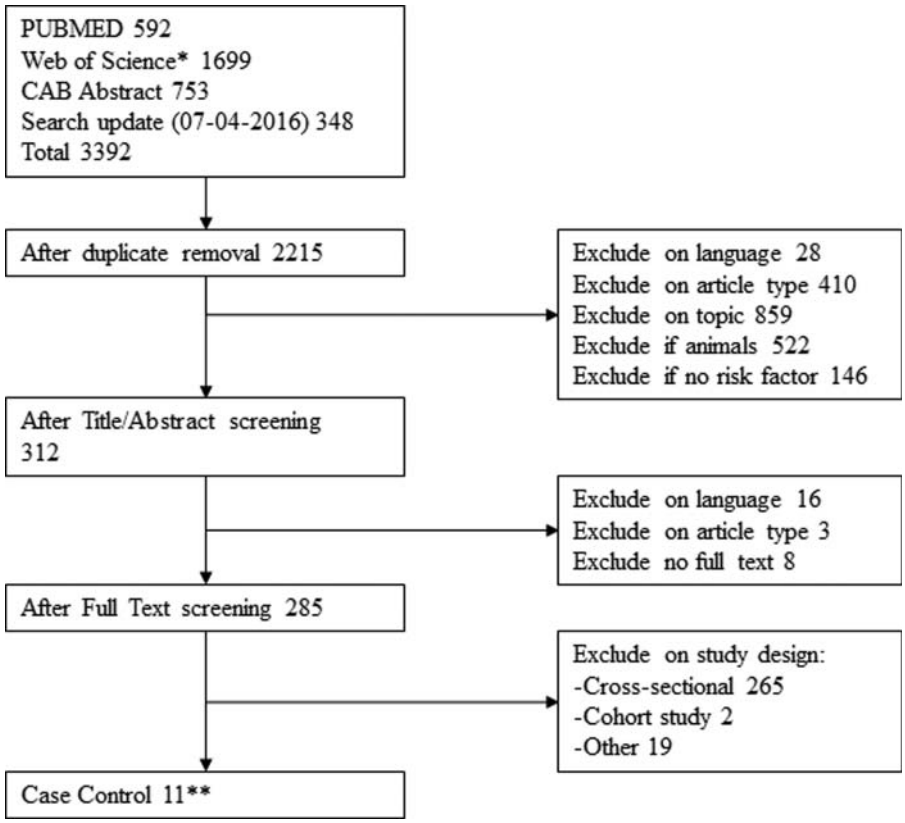

Figure 2. PRISMA diagram showing the detailed results of the study selection process. *Web of Science allowed the search to be conducted in multiple databases as specified in the Materials and Methods section. **Two studies were considered eligible but did not report results which could be included.

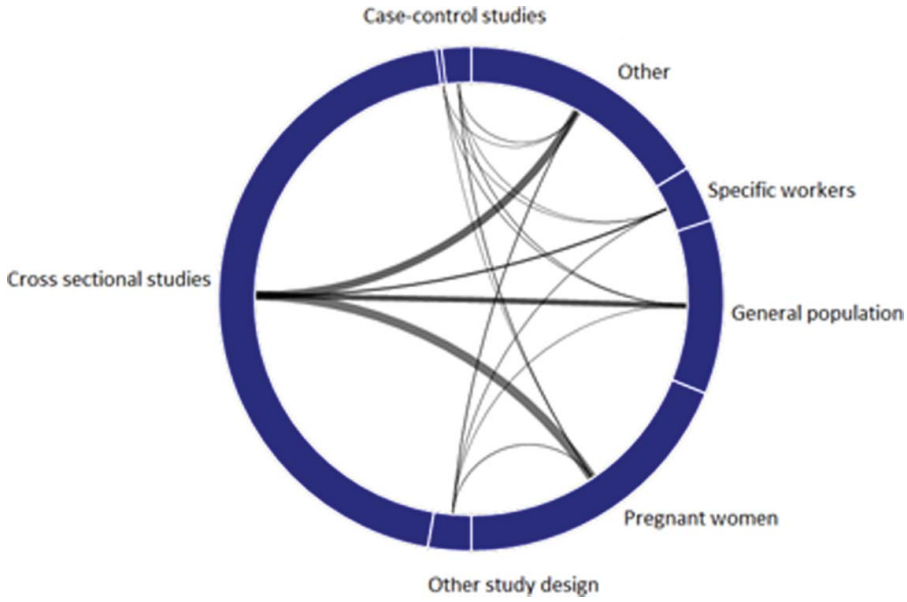

Figure 3. Circular relation diagram showing the results of mapping as regards study design and population. The thickness of the connection line is proportional to the number of studies.

mothers of newborns diagnosed with *T. gondii* were selected as the target population. Cases were always confirmed through serology and in general, all positive subjects were recruited.

Several food-related risk factors were included in the exposure assessment design of the selected studies beyond the 6 food categories included in meta-analyses. A full list is reported in Table 5.

Risk of bias within studies

The Newcastle–Ottawa scale was used to evaluate the potential for bias within each included study. The case definition was of no concern, as all studies were based on serological findings. As regards case selection in general and due to the low number of acute cases identified, all positive subjects giving consensus were included. However, in 1 study (Kapperud et al., 1996) the number of cases was increased by 22 individuals from sporadic testing. Controls were selected within the same community as the cases, with 2 exceptions (Carellos et al., 2014; Chiang et al., 2014), where controls were selected from previous programs or from the general population. In particular, the study of Carellos et al. (2014) has a major limitation, as controls were not serologically tested to exclude *T. gondii* antibodies, whereas they were in all the other studies. Different matching strategies were applied and most studies matched cases and controls according to age and/or residency. Details are reported in Table 2 and Table 4.

Assessments of exposure were always carried out through questionnaire or interview but blinding was never reported. In 1 case, there is no detail about how exposure was assessed (Bobić et al., 2007). As regards the non-respondent rate, it was generally reported in the included studies.

Synthesis of results

Eleven studies were eligible for meta-analysis, although of these, 2 studies did not have eligible data for inclusion. One study reported data from multivariate analysis accounting for different risk factors (Jones et al., 2009), but our e-mail request to be supplied with univariate data garnered no response. The other study reported only 1 risk factor relevant for inclusion, but due to the low number of exposed people did not estimate the OR for such risk (Lopez-Castillo, Diaz-Ramirez, and Gomez-Marin, 2005).

Additional data and explanations were obtained by e-mail for 2 studies (Bobić et al., 2007, 2010).

Three food consumption risk factors were significantly associated with *T. gondii* infection: raw/undercooked meat, OR 3.44 (1.29–9.16) (Figure 4), raw/undercooked beef, OR 2.22 (1.57–3.12) (Figure 5), and raw/undercooked sheep meat, OR 3.85 (1.85–8.00) (Figure 6). No heterogeneity was observed according to I^2 statistics in the cases of beef and sheep meat consumption, confirming the agreement among the results of individual studies. A high heterogeneity of 73% was observed within the category raw meat consumption, producing a more uncertain result as the prediction interval (0.47–25.20) had the potential to generate non-significant results.

Consumption of raw/undercooked pork (Figure 7), raw milk (Figure 8), and raw eggs (Figure 9) were not significantly associated with *T. gondii* infection. In the case of raw eggs, slightly different risk factors were considered in the studies included in our meta-analysis: eating raw eggs (Kapperud et al., 1996; Baril et al., 1999), eating eggs with soft yolk (Carellos et al., 2014), and frequent consumption of soft-boiled eggs (Stray-Pedersen and Lorentzen-Styr, 1980). Details of individual study results are shown in Figure 4, while details of our meta-analysis results are reported in Table 3.

Publication bias analysis was carried out to account for potentially missing studies. Results should be interpreted cautiously due to the low k of different meta-analyses. Publication bias was observed in the raw meat analysis, with a potential loss of statistical significance, in the raw beef analysis, suggesting underestimation of the real OR, and more interestingly in the pork analysis, where, according to the Trim and Fill test, missing studies could lead to the acquisition of statistical significance.

Table 1. Relevant information collected from relevant papers.

Authors	Country	Study Year	P	Case Definition	Case Number and Selection	Control Number and Selection	EW
Baril et al. , 1999	France	1995	PW	Seroconversion Negative test to specific IgG and IgM followed by a positive test	80 All positives Giving consensus	80 Non-random Matched	1
Bobić et al., 2007	Serbia	2001–2005	PW	IgG and IgM positivity	53 All positives	53 Non-random Matched	NS
Bobić et al., 2010	Serbia	2004–2008	GP	IgG and IgM positivity IgG avidity low	35 All positives	35 Non-random Matched	NS
Carellos et al., 2014	Brazil	2006–2007 cases, 2011 controls	M	Clinical and serological on newborns	175 All positives	278 Random (stratified per municipalities).	9
Chiang et al., 2014	Taiwan	2008–2013	GP	IgG and IgM positivity IgG avidity low or PCR positive in blood or body fluids	30 All positives (from surveillance)	224 Random (from blood donors)	NS
Cook et al., 2000	Italy, Switzerland, Denmark, Norway, Belgium	1994–1995	PW	Negative test to specific IgG and IgM followed by a positive test or IgG and IgM positivity, IgG avidity low, or IgA positive	252 All positives	852 Random (next 4 women negative for Toxoplasma)	4
Jones et al., 2006	Brazil	2003–2004	GP	IgG and IgM positivity	All positives Patients from an ophthalmology clinic	Non-random (next patient which was seronegative)	12
Jones et al., 2009	USA	2002–2007	GP	IgG and IgM positivity, IgG avidity low, or IgA positive	All positives >18 years, infection within 6 months	Random (among *T. gondii* seronegative tested in the laboratory)	12
Kapperud et al., 1996	Norway	1992–1994	PW	Seroconversion OR dye test > 300 IU/ml and specific IgM	All positive to specific program + positives from sporadic testing	Non-random Matched	4
Lopez-Castillo et al. 2005	Colombia	2004–2005	PW	IgG and IgM or IgA positivity or newborn with *T. gondii*	Not described	Non-random Matched	9
Stray-Pedersen and Lorentzen-Styr, 1980	Norway	NS	PW	Negative test to specific IgG and IgM followed by a positive test or IgM detection	Random (specified)	Randomization non-described	NS

P, population investigated, PW, pregnant women, GP, general population; M = mothers of positive newborns; NS, not specified; EW, exposure window (months).

Table 2. Ottawa–Newcastle checklist details for each relevant study with items added for quality assessment purpose.

	Baril	Bobić	Bobić	Carellos	Chiang	Cook	Jones	Jones	Kapperud	Lopez-Castillo	Stray-Pedersen
	1999	2007	2010	2014	2014	2000	2006	2009	1996	2005	1980
SELECTION											
(1) Independent case definition											
(2) Representativeness of the cases											
(3) Selection of controls											
(4) Definition of controls (no history of disease)											
COMPARABILITY											
(1) Comparability of cases and controls											
(a) Study controls for age*											
(b) Study controls for residency*											
EXPOSURE											
(1)Blinded ascertainment of exposure											
(2) Same method of ascertainment for cases and controls											
(3) Same non-response rate											
ADDITIONAL ITEMS FOR QUALITY EVALUATION											
Is the exposure window specified?											
Are selected case acutes?											
Quality SCORE	8	6	7	4	6	9	8	8	8	9	8

Sensitivity analyses were performed for meta-analyses involving raw meat and raw beef as other meta-analyses included only a limited number of studies. No individual study influenced the model according to the statistical parameter evaluated. The multicentric study of Cook et al. (2000) contributed heavily to the result of our meta-analysis when it was included, but the high appraised methodological quality of this study makes the introduction of potential biases unlikely. Meta-analysis on raw/undercooked beef was conducted both with and without the study by Carellos et al. (2014) due to methodological concerns we observed in that study. When the study was not included, the resultant OR 2.10 (1.21–3.64) did not significantly differ from the OR obtained when meta-analysis was conducted on all studies.

Other results

Results not included in our meta-analyses comprised the multivariate model of Jones et al. (2009) and individual ORs from relevant but sporadic food-related risk factors investigated in the studies.

The results from the multivariate model identified several risk factors which increased the risk of *T. gondii* infections. These were: eating raw ground beef, eating rare lamb, eating locally produced cured, dried, or smoked meat, and drinking unpasteurized goat milk (Jones et al., 2009).

All other relevant but sporadic risk factors, which were not included in our meta-analysis, are available in Table 5. In some cases, different risk factors from different studies looked to be classifiable in a common category, but due to heterogeneity in the definitions of these factors, we finally judged them as not suitable for aggregation.

Cook et al. (2000) found a significant association between *T. gondii* infection and consumption of dry or cured meat and salami more than once a week, whereas this association was not found in the other study (Stray-Pedersen and Lorentzen-Styr, 1980). Several eating habits were investigated by Cook et al. (2000), and participant's preference for raw/rare beef was significantly associated with an increased risk of *T. gondii* infection, similarly to actual consumption of this kind of meat. Among hygienic habits, only infrequent knife washing was significantly associated with infection (Kapperud et al., 1996), whereas none of the other 8 risk factors similarly associated with the potential for cross-contamination were significant. Meat consumption and meat consumption frequency were never associated with an increased risk

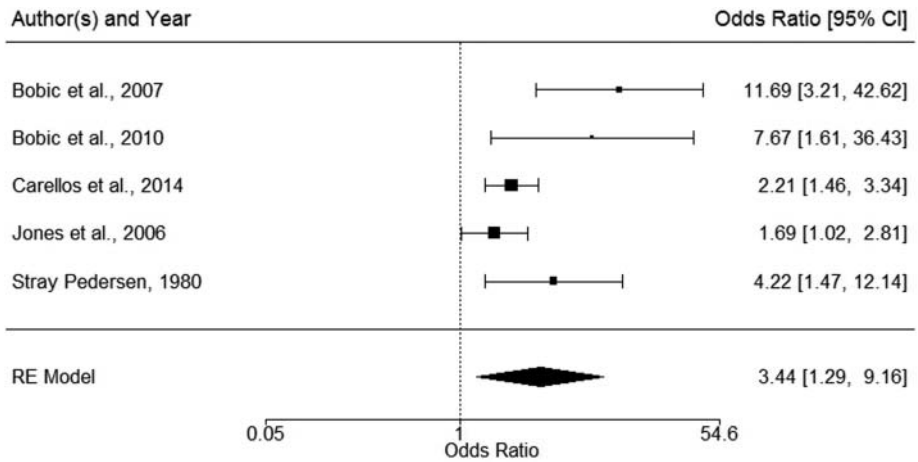

Figure 4. Forest plot of studies investigating the consumption of raw/undercooked meat as a risk factor for *T. gondii* infection in humans.

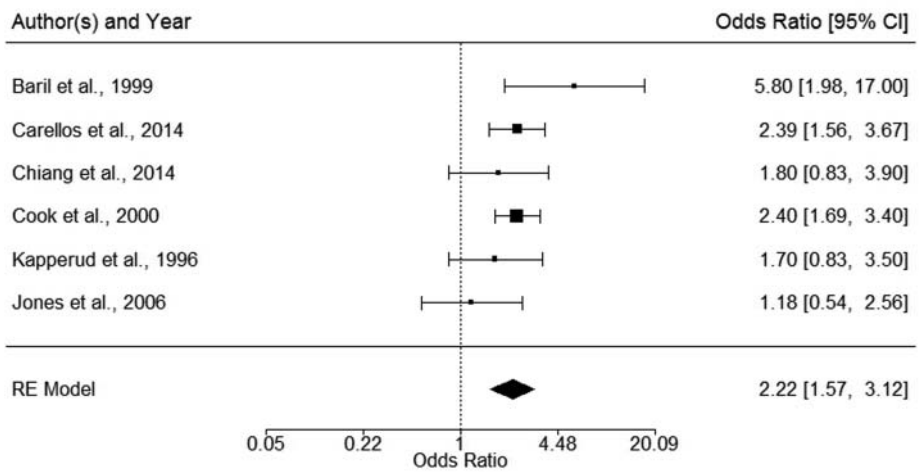

Figure 5. Forest plot of studies investigating the consumption of raw/undercooked beef as a risk factor for *T. gondii* infection in humans.

of *T. gondii* infection. As regards other raw/undercooked meat or fish, data for which were not included in our meta-analysis, there was a high variation in the definitions of risk. Therefore, details from these studies can be found in Table 5.

Interestingly, tasting meat while cooking was found to be a significant risk factor for *T. gondii* infection in 2 studies (Kapperud et al., 1996; Cook et al., 2000), whereas the tasting of condiments in general was not significant (Carellos et al., 2014). Finally, as regards the consumption of vegetables, acquisition of *T. gondii* infection was significantly associated with eating raw vegetables or unpeeled fruit (Kapperud et al., 1996) and with eating raw vegetables away from home (Baril et al., 1999). However, other similar risk factors failed to be significantly associated with *T. gondii* infection in 4 studies (Kapperud et al., 1996; Baril et al., 1999; Carellos et al., 2014; Chiang et al., 2014).

Discussion

Summary of evidence

The consumption of raw/undercooked beef or sheep meat is significantly associated with acute *T. gondii* infection. The recognition of sheep meat as an important risk factor for *T. gondii* infection is not surprising, since sheep meat has been shown to have, on average, the highest prevalence among the commonly eaten livestock species (Belluco et al., 2016). The association of raw/undercooked beef consumption with *T. gondii* infection is more interesting and holds major implications. The role of beef in toxoplasma transmission has not always been acknowledged. Despite epidemiological evidence, now included in our meta-analysis, showing that the consumption of raw/undercooked beef is a risk factor for human *T. gondii* infection (Baril et al., 1996; Cook et al., 2000), and that the seroprevalence in bovines can be as high as 92% (Tenter, Heckeroth, and Weiss, 2000), skepticism exists about the role of this animal species. Experimental studies showed that cattle is a poor host for *T. gondii* (Dubey and Jones, 2008) and in the United States, beef has been judged as an unlikely source of *T. gondii* infection for humans (Dubey et al., 2005). Some authors support the opinion that a conclusive evidence able to correlate *T. gondii* infection with the ingestion of naturally infected beef is lacking (Dubey, 1986; Kijlstra and Jongert, 2008). An outbreak has been reported following consumption of raw beef (Kean, Kimball, and Christenson, 1969), but the evidence was judged to be uncertain (Dubey and Jones, 2008). Our result shows that not only is the overall OR significant, but also that heterogeneity is null and that the effect size of all the 6 individual studies included in the model lie in the same direction. The importance

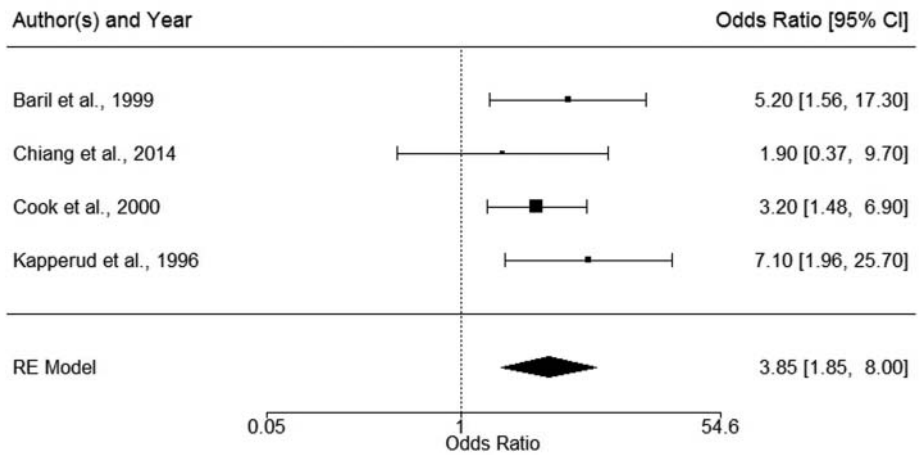

Figure 6. Forest plot of studies investigating the consumption of raw/undercooked sheep meat as a risk factor for *T. gondii* infection in humans.

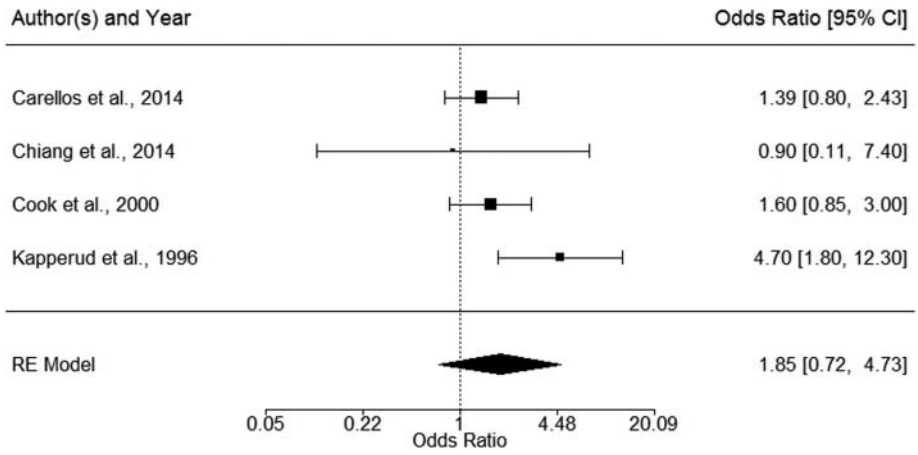

Figure 7. Forest plot of studies investigating the consumption of raw/undercooked pork as a risk factor for *T. gondii* infection in humans.

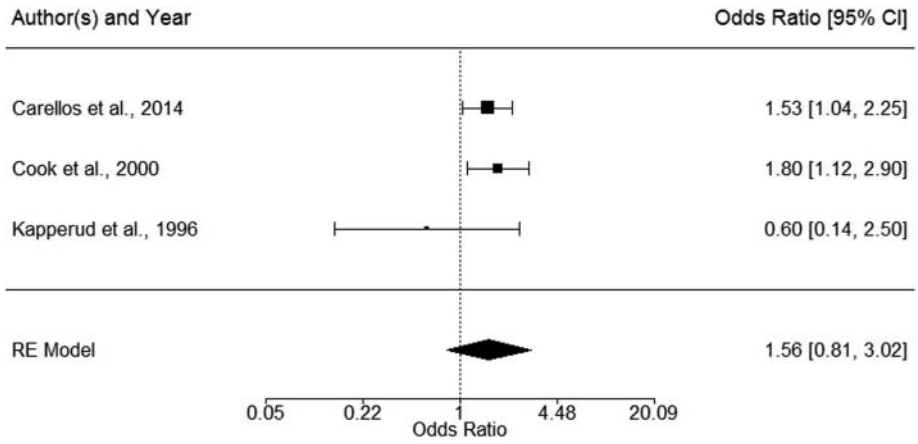

Figure 8. Forest plot of studies investigating the consumption of unpasteurized milk as a risk factor for *T. gondii* infection in humans.

of applying the meta-analytical technique in this case is clear, as using the vote counting technique would have produced inconsistent evidence, whereas looking at individual effect sizes and at their aggregation gives a clear picture. This result is supported by a risk assessment model carried out in the Netherlands where beef, even though it had very low prevalence levels, proved to be the major source of human cases due to consumption habits (Opsteegh et al., 2011).

As regards the general category "raw/undercooked meat," our result is significant but with a high heterogeneity and a prediction interval which also included non-significant values. However, the high heterogeneity is a logical consequence of the

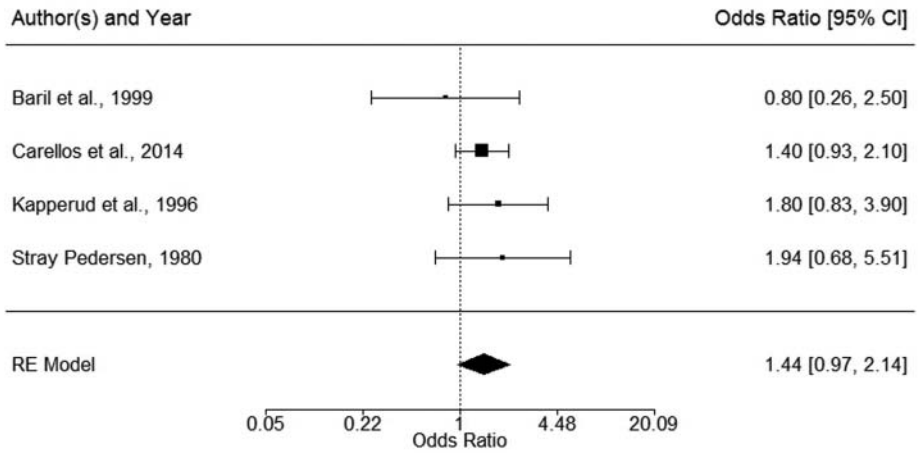

Figure 9. Forest plot of studies investigating the consumption of raw/undercooked eggs as a risk factor for *T. gondii* infection in humans.

Table 3. Results of meta-analyses carried out on different risk factors associated with food-related acquisition of acute *T. gondii* infection.

Food Consumed	*K*	OR (95%CI)	OR Prediction Interval (95%)	*T2* (95%CI)	*I2*	PB
Raw meat	5	3.44 (1.29–9.16)	0.47–25.20	0.39 (0.00–5.20)	73%	Yes, 2.27 (0.98–5.24)
Raw beef	6	2.22 (1.57–3.12)	—	0.00 (0.00–1.50)	0%	Yes, 2.35 (1.89–2.91)
Raw pork	4	1.85 (0.72–4.73)	0.40–8.46	0.14 (0.00–6.36)	45%	Yes, 1.94 (1.13–3.33)
Raw sheep	4	3.85 (1.85–8.00)	—	0.00 (0.00–4.08)	0%	No
Raw milk	3	1.56 (0.81–3.02)	—	0.00 (0.00–13.52)	0%	NC
Raw eggs	4	1.44 (0.97–2.14)	—	0.00 (0.00–1.93)	0%	No

K, number of studies; PB, publication bias; NC, not calculated.

width of this category, with the potential for inclusion of different kinds of meat and meat consumption patterns according to the population studied.

Another interesting result occurred for the consumption of raw/undercooked pork; this did not prove to be a significant risk factor in the current study. This result is in contrast with published literature, as swine are recognized as an important source of *T. gondii* (Tenter, Heckeroth, and Weiss, 2000; Dubey and Jones, 2008; Kijlstra and Jongert, 2008). However, the inability of the present meta-analysis to find a significant result could be due to several factors. Firstly, the final estimate of the OR had wide confidence intervals and noticeable heterogeneity (44%). Secondly, the low number of included studies (4) might not be enough to uncover small effects. This consideration is supported by the fact that the effect size of 3 out of 4 studies lie to the right of the plot, showing a positive but not significant

Table 4. Details of the Quality appraisal process for each included study.

	Baril 1999	Bobić 2007	Bobić 2010	Carellos 2014	Chiang 2014	Cook 2000	Jones 2006	Jones 2009	Kapperud 1996	Lopez-Castillo 2005	Stray-Pedersen 1980
SELECTION											
(1) Is the case definition adequate?											
(a) Yes, with independent validation*	1	1	1	1	1	1	1	1	1	1	1
(b) Yes (record linkage or self reports)											
(c) No description											
(2) Representativeness of the cases											
(a) Consecutive/obviously series of cases*	1	1	1	1	1	1	1	1		1	1
(b) Potential for selection biases									1		
(3) Selection of controls											
(a) community controls *	1	1	1			1	1	1	1	1	1
(b) hospital controls				1	1						
(c) no description											
(4) Definition of controls											
(a) No history of disease (endpoint) *	1	1	1		1	1	1	1	1	1	1
(b) No description of source				1							
COMPARABILITY											
(1) Comparability of cases and controls											
(a) Control for age*		1	1		1	1			1	1	1
(b) Control for residency*	1				1	1		1	1	1	
(c) Control for sex			1		1						
(d) Control for gestational age	1								1	1	
(e) Control for period infection-diagnosis			1			1					
EXPOSURE											
(1) Ascertainment of exposure											
(a) Secure record (e.g., surgical records)*											
(b) Interview blind to case/control status*											
(c) Interview not blind (case/control status)	1		1	1		1			1	1	1
(d) Written self report/medical record only					1		1	1			
(e) No description		1									
(2) Same method of ascertainment for cases and controls											
(a) Yes*	1	1	1			1	1	1	1	1	1
(b) No				1	1						
(3) Non-response rate											
(a) Same rate for both groups*							1				
(b) Non-respondents described	1		1			1			1		
(c) Rate different and no designation				1	1						
ADDITIONAL ITEMS FOR QUALITY EVALUATION											
Is the exposure window specified?											
(a) Yes*	1			1		1	1	1	1	1	1
(b) No		1	1		1						
Are selected cases acute?											
(a) Yes*	1		1	1	1	1	1	1	1	1	1
(b) No											
Quality SCORE	8	6	7	4	6	9	8	8	8	9	8

*item that assign a score point according to Newcastle–Ottawa scale.

Table 5. Odds Ratio or eligible risk factors not included in meta-analysis.

Authors	Year	Cases	Controls	Category	Risk Factor	OR	LL	UL
Baril et al.,	1999	80	80	Dairy products	Eating unpasteurized cheese (cow, sheep, goat)	0.6	0.3	1.2
Cook et al.,	2000	252	852	Dry/cured products	Eating dry or cured meat <1/week	1.2	0.8	1.7
Cook et al.,	2000	252	852	Dry/cured products	Eating dry or cured meat >1/week	1.8	1.2	2.8*
Cook et al.,	2000	252	852	Dry/cured products	Eating salami <1/week	1	0.7	1.6
Cook et al.,	2000	252	852	Dry/cured products	Eating salami >1/week	1.6	1.1	2.4*
Stray Pedersen et al.,	1980	27	85	Dry/cured products	Frequently eating cured meat	0.6		
Baril et al.,	1999	80	80	Eating habits	Eating away from home	0.3	0.003	1.3
Carellos et al.,	2014	175	278	Eating habits	Eating away from home during pregnancy	0.68	0.38	1.24
Cook et al.,	2000	252	852	Eating habits	Eating food prepared in a microwave cooker	1.3	0.8	2.2
Kapperud et al.,	1996	63	128	Eating habits	Preferring beef raw or rare	3.5	1.1	10.7*
Kapperud et al.,	1996	63	128	Eating habits	Eating meat at a barbecue	1.1	0.4	2.6
Kapperud et al.,	1996	63	128	Eating habits	Eating meat prepared at a microwave	2	0.6	6.9
Lopez Castillo et al.,	2005	14	34	Eating habits	Eating at restaurant	2.16	0.4	11.6
Baril et al.,	1999	80	80	Frozen meat	Never or rarely freezing meat	2	1	4.2
Carellos et al.,	2014	175	278	Frozen meat	Eating fresh (not frozen) meat	3.59	2.19	5.89*
Cook et al.,	2000	252	852	Frozen meat	Eating frozen meat	0.8	0.5	1.2
Jones et al.,	2006	131	110	Frozen meat	Eating frozen lamb	1.89	1.01	3.52*
Baril et al.,	1999	80	80	Hygienic habits	Not washing hands after food preparation	3.4	0.75	16.7
Baril et al.,	1999	80	80	Hygienic habits	Not washing hands before meals	ND		
Baril et al.,	1999	80	80	Hygienic habits	No washing knives after cutting vegetables	2.5	0.49	12.5
Carellos et al.,	2014	175	278	Hygienic habits	Washing hands after cooking	0.94	0.58	1.54
Carellos et al.,	2014	175	278	Hygienic habits	Washing hands before eating	0.63	0.4	0.99
Kapperud et al.,	1996	63	128	Hygienic habits	Washing hands infrequently	3	0.9	10.4
Kapperud et al.,	1996	63	128	Hygienic habits	Washing knives infrequently	4.6	1.2	17.6*
Kapperud et al.,	1996	63	128	Hygienic habits	Washing cutting boards/chopping blocks infrequently	4	1	15.6
Kapperud et al.,	1996	63	128	Hygienic habits	Washing countertops infrequently	3.7	0.9	14.6
Baril et al.,	1999	80	80	Meat consumption	Eating meat daily	1.3	0.7	2.7
Baril et al.,	1999	80	80	Meat consumption	Eating beef	ND		
Baril et al.,	1999	80	80	Meat consumption	Eating lamb	1.3	0.4	3.6
Baril et al.,	1999	80	80	Meat consumption	Eating pork	0.7	0.2	2.1
Baril et al.,	1999	80	80	Meat consumption	Eating horse meat	2	0.5	9.1
Baril et al.,	1999	80	80	Meat consumption	Eating chicken	ND		
Baril et al.,	1999	80	80	Meat consumption	Eating rabbit meat	0.7	0.3	1.6
Baril et al.,	1999	80	80	Meat consumption	Eating duck	0.6	0.2	1.6
Baril et al.,	1999	80	80	Meat consumption	Eating game	1.8	0.4	8.2
Cook et al.,	2000	252	852	Meat consumption	Eating cooked meat <1/week	0.8	0.3	2.1
Cook et al.,	2000	252	852	Meat consumption	Eating cooked meat >1/week	0.8	0.3	1.9
Kapperud et al.,	1996	63	128	Meat consumption	Frequency of meat consumption	1.5	0.7	3
Baril et al.,	1999	80	80	Raw/undercooked meat	Eating undercooked meat outside home	8.3	2.5	43.1*
Carellos et al.,	2014	175	278	Raw/undercooked meat	Eating raw or undercooked meat (<1 a week)	1.31	0.58	2.97
Carellos et al.,	2014	175	278	Raw/undercooked meat	Eating raw or undercooked chicken	ND		
Cook et al.,	2000	252	852	Raw/undercooked meat	Eating raw sausage <1/week	1.2	0.7	2
Cook et al.,	2000	252	852	Raw/undercooked meat	Eating raw sausage >1/week	3.2	1.2	9*
Cook et al.,	2000	252	852	Raw/undercooked meat	Eating other raw/undercooked meat	3.9	1.6	9.5*
Kapperud et al.,	1996	63	128	Raw/undercooked meat	Eating raw or undercooked minced meat	3.2	1.5	6.6*
Kapperud et al.,	1996	63	128	Raw/undercooked meat	Eating raw or undercooked poultry	8.9	1.9	41.5*
Kapperud et al.,	1996	63	128	Raw/undercooked meat	Eating tartare meat	4.6	1.4	15.1*
Kapperud et al.,	1996	63	128	Raw/undercooked meat	Eating roast beef	0.7	0.4	1.2
Kapperud et al.,	1996	63	128	Raw/undercooked meat	Eating gravet meat	8	0.9	71.6
Jones et al.,	2006	89	79	Raw/undercooked meat	Eat raw ground beef	0.787		
Jones et al.,	2006	88	78	Raw/undercooked meat	Eat raw ground chicken	ND		
Lopez Castillo et al.,	2005	14	34	Raw/undercooked meat	Eating raw/undercooked meat	ND		
Carellos et al.,	2014	175	278	Raw/undercooked fish	Eating raw or undercooked fish	ND		
Chiang et al.,	2014	30	224	Raw/undercooked fish	Eating raw fish	1.4	0.6	3.5
Chiang et al.,	2014	30	224	Raw/undercooked fish	Eating raw oysters	1.5	0.6	3.4
Chiang et al.,	2014	30	224	Raw/undercooked fish	Eating raw clams	3.6	1.4	9.3*
Carellos et al.,	2014	175	278	Tasting while cooking	Tasting condiments while cooking	1.05	0.67	1.65
Cook et al.,	2000	252	852	Tasting while cooking	Tasting meat when cooking <1/week	2.5	1.5	3.4*
Cook et al.,	2000	252	852	Tasting while cooking	Tasting meat when cooking >1/week	4.7	2.1	10.9*
Kapperud et al.,	1996	63	128	Tasting while cooking	Tasting raw meat while preparing food	5.6	2.4	13.1*
Baril et al.,	1999	80	80	Vegetables	Raw vegetables prepared at home	ND		
Baril et al.,	1999	80	80	Vegetables	Frequently eating raw vegetables outside the home	2.8	1.4	5.9*
Baril et al.,	1999	80	80	Vegetables	Eating garden produce	2	0.5	9.1
Carellos et al.,	2014	175	278	Vegetables	Eating raw vegetables outside the home	1.1	0.74	1.64
Chiang et al.,	2014	30	224	Vegetables	Eating uncooked vegetables	1.5	0.5	3.9
Kapperud et al.,	1996	63	128	Vegetables	Eating unwashed raw vegetables	5.7	2	15.7*
Kapperud et al.,	1996	63	128	Vegetables	Eating unwashed unpeeled fruit	2.4	1.2	4.8*
Kapperud et al.,	1996	63	128	Vegetables	Eating unwashed raw vegetables/unpeeled fruit	2.3	1.2	4.5*
Kapperud et al.,	1996	63	128	Vegetables	Eating unwashed berries	1.6	0.7	3.4

OR, Odds Ratio; LL, lower limit; UL, upper limit; ND, undetermined.

association. Thirdly, the potential for missing studies, as disclosed by Trim and Fill, suggests that the real OR could be significant. Finally, the categorization of pork meat in the primary studies is a concern, as it was not always clear if cured meat was included or excluded, nor how the meat was categorized. In our opinion, the consumption of undercooked pork could often be an accidental event due to improper cooking, but consumers may not be aware of the cooking status of pork they cook and/or eat.

As regards milk and eggs, no statistically significant evidence of association with *T. gondii* infection was found. The literature contains only sporadic evidence of *T. gondii* isolation from eggs (Pande, Shukla, and Sekariah, 1961).

Milk could be theoretically a source for *T. gondii* tachyzoites, the infective *T. gondii* stage responsible for mother-to-fetus transmission. However, their low resistance to environmental stresses makes tachyzoites unlikely to survive the acidic conditions of the stomach during digestion. The available evidence about the potential for *T. gondii* transmission, highlighting the potential for goat milk to act as a transmission vehicle, has been discussed elsewhere (Tenter, Heckeroth, and Weiss, 2000; Dubey and Jones, 2008). Significant prevalence rates were found in a study conducted in Iran (Dehkordi et al., 2013) but results have been debated (Dubey and Jones, 2014; Boughattas, 2015a), and a demand for analysis repetition has been invoked to produce more conclusive evidence. A more detailed discussion about milk and *T. gondii* transmission can be found elsewhere (Boughattas, 2015b).

The results from the studies we were unable to include in our meta-analysis (Lopez-Castillo, Diaz-Ramirez, and Gomez-Marin, 2005; Jones et al., 2009) agree with what we observed and these data, if included, would have strengthened our outcomes. The only difference between the results of our meta-analysis and other studies regards the risk of acquiring infection after milk consumption. However, in Jones et al. (2009), only goat milk was considered, whereas in our current systematic review, milk was included as a general category, and was not species-specific. Finally, we were unable to include some interesting risk factors in the meta-analysis due to the absence of a sufficient number of studies dealing with them. Those were the habit of tasting raw meat while cooking and the consumption of vegetables, as these factors were found to be significant risks for *T. gondii* infection in some studies.

Limitations

Our systematic review has some limitations that have been taken into account during the analysis and discussion stages. Firstly, a limitation could be linked to the search strategy, as it lacked complex search strings. Although we made every attempt to find additional evidence for case-control studies not included in the initial search strategy, all such attempts failed. This was despite our recourse to forward and backward reference searches of both the included studies and of relevant reviews. A second limitation is due to our not searching in the gray literature, and this could account for publication bias due to the file drawer effect. However, the studies we finally included were never based on the evaluation of a single exposure and thus, it is unlikely that a non-significant result for a relevant risk factor could have influenced the publication success of any of the 11 primary studies, despite the potential for publication bias which we observed in 3 meta-analyses. The included studies were of varied quality, and the main risk of bias at individual study level was linked to exposure assessment for 2 main reasons: the absence of blinding and the recall bias. As regards our meta-analysis, it is noteworthy that the number of studies for each risk factor was limited. In spite of that, the major results, concerning the link of *T. gondii* infection with consumption of raw/undercooked beef or sheep meat, were in agreement among individual studies, as discussed before. On the other hand, the low number of studies could have impaired the ability to disclose other significant relationships and further studies are warranted in this direction. Another strategy to increase the number of studies could be to include cross-sectional designs. In this case, the amount of evidence would greatly increase, as the results of our mapping exercise showed. This is an interesting solution that should, however, take into account the different effect sizes and also the limitation of cross-sectional studies in disclosing causality.

Conclusions

Consumption of raw or undercooked beef or sheep meat is an important source of *T. gondii* transmission to humans as shown by epidemiological studies. It is important to take this risk into account, particularly when counselling at-risk individuals, due to the severe effects of toxoplasmosis in particular circumstances. In general, proper cooking is needed for meat of all species. Moreover, even for healthy individuals, caution must be suggested for the consumption of undercooked meat due to the unknown effect of chronically encysted *T. gondii* bradyzoites. Furthermore the role of improper cooking, tasting while cooking, and/or consumption of cured and/or dried products deserves to be elucidated in future studies on the epidemiology of *T. gondii* in humans.

Conflict of interest

The authors have no conflict of interest associated with the work reported in this paper.

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