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Estimating the population attributable fraction for schizophrenia when *Toxoplasma gondii* is assumed absent in human populations

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ABSTRACT

There is increasing evidence that infection with *Toxoplasma gondii*, a common parasite of people, cats and rodents, is associated with an increased risk of a diagnosis of schizophrenia. Although the claim that infection with *T. gondii* is one of the component causes of a diagnosis of schizophrenia remains contentious it is worth asking how important a causal association might be if only to inform our attitude to further work on the subject. The appropriate measure of importance is the population attributable fraction (PAF). The PAF is the proportion of diagnoses of schizophrenia that would not occur in a population if *T. gondii* infections were not present. The assumptions that underlie the derivation of the standard formula for measuring the PAF are violated in the specific instance of *T. gondii* and schizophrenia and so the conventional estimation method cannot be used. Instead, the PAF was estimated using a deterministic model of *Toxoplasma gondii* infection and schizophrenia occurrence in a hypothetical cohort of people at risk of both conditions. The incidence of infection with *T. gondii* in the cohort was assumed to be constant. Under these circumstances, the life-time mean population attributable fraction was estimated to be 21.4%, but it could not be ruled out that it could be as high as 30.6% or as low as 13.7% given the 95% confidence interval pertaining to the point estimate of the OR that was central to the calculation. These estimates (even the lowest) are higher than those obtained using the standard method for the same system and underscore the importance of understanding the limitations of conventional epidemiological formulae.

1. Introduction

Toxoplasma gondii is a protozoan parasite that people acquire by ingesting contaminated food, water or soil – it is also vertically transmitted in people. Completion of the parasite life-cycle depends upon a predator-prey system involving felids (including domestic cats) and their rodent prey. The infection is common in cats and small rodents (De Craeye et al., 2008; Dabritz et al., 2007a, 2008) and spills over into many of the animals that we eat, including pigs, sheep, chickens and hunted wildlife species (Dubey and Jones, 2008; Dubey, 2009; Boughattas et al., 2014). Waterbodies and soil are also frequently contaminated with infective stages (Bowie et al., 1997; Eng et al., 1999; Dabritz et al., 2007b; Dabritz and Conrad, 2010). It is usual in veterinary teaching curricula to deal with this zoonotic infection in terms of the damaging neurological consequences of vertical infection in people (Torgerson and Mastroiacovo, 2013), the deaths attributable to toxoplasmic encephalitis in AIDS patients (Anon, 2006), and the epidemiologically

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interesting (but unusual) epidemics of acute toxoplasmosis (and its *sequelae*) that occur when people ingest oocysts in tap water (Bowie et al., 1997; Eng et al., 1999; de Moura et al., 2006). However, the effect of *T. gondii* infection on human health and well-being may be much more pervasive than this rather narrow focus suggests.

Infection with *T. gondii* alters rodent behavior in ways that can be interpreted as facilitating transmission in a predator-prey cycle: for example, infected rodents are more active at night and less neophobic; and uninfected rodents avoid areas contaminated with cat urine whereas infected rodents prefer them (Webster, 2001; Webster et al., 2013). Similarly, there is evidence that infection with *T. gondii* in people also results in increased activity, decreased reaction times, altered personality profiles and changes in sensory perception (Flegr et al., 1996, 2011; Flegr, 2013; and reviewed in Webster et al., 2013). In addition, Lafferty (2006) argued that the occurrence of specific national cultural traits was associated with the country-wide prevalence of *T. gondii*.

Importantly, though, meta-analyses of 38 studies demonstrate that serological evidence of infection with *T. gondii* is associated with an increased risk of a diagnosis of schizophrenia (OR 2.71; 95% CI 1.93–3.80, Torrey et al., 2007, 2012) and subsequent research from around the world continues to support the finding (e.g. Wang et al., 2011). It should be noted that *T. gondii* is not the only infection that has been associated with a diagnosis of schizophrenia. For example, meta-analyses have implicated *Chlamydophila psittici*, *C. pneumoniae*, *Borna Disease Virus*, *Human Herpes Virus 2* and *Human Endogenous Retrovirus W* among others (Yolken and Torrey, 2008; Arias et al., 2012) and it is possible that those with a diagnosis of schizophrenia simply may have an increased risk of various infections as a result of increased hospitalizations or disease associated life style factors. Nevertheless, the association between serological evidence of infection with *T. gondii* and a diagnosis of schizophrenia satisfies many of the criteria for a causal association (Hill, 1965): *strength of association* – the odds ratio exceeds that for genetic or other environmental factor identified to date (Torrey et al., 2007); *temporality* – the association has been demonstrated in populations in which infection with *T. gondii* is known to have occurred before a diagnosis of schizophrenia (Mortensen et al., 2007; Neibuhr et al., 2008; Pedersen et al., 2011); *dose–response curve* – the risk of schizophrenia increases with *T. gondii*-specific IgG level (Hinze-Selch et al., 2007; Pedersen et al., 2011), *coherence* – there are nascent, plausible hypotheses concerning mechanism (Hinze-Selch et al., 2007; Yolken et al., 2009; Henriquez et al., 2009; Hayes et al., 2014); and *consistency* – Mortensen et al. (2007) reported that of "54 studies which examined the issue, 49 reported that individuals with schizophrenia and other psychoses had a higher prevalence of antibodies to *T. gondii* when compared with controls. . .".

The claim that infection with *T. gondii* is one of the component causes (*sensu* Rothman and Greenland, 1998) of a diagnosis of schizophrenia is contentious (see discussions in Brown and Derkits, 2010; Brown, 2011) and one that is trivialized in the popular press (e.g. Anon, 2012). Nevertheless, it is worth asking how important a causal association might be if only to inform our attitude to further work on the subject. The appropriate question is what would be the lifetime reduction in the risk of a diagnosis of schizophrenia if we could prevent human infection with *T. gondii*? In other words, what is the proportion of diagnoses that would not occur in a population if *T. gondii* infections were not present? This parameter is usually called the population attributable fraction (PAF).

The population attributable fraction estimated using the standard epidemiological formula is 13% (Brown and Derkits, 2010). However, it is probably inappropriate to use the conventional methodology in the particular case of schizophrenia and *T. gondii* (see Section 2.1) and so this paper suggests an alternative method of estimating the PAF based upon a deterministic, mathematical model of schizophrenia and *T. gondii* infections in a cohort of people.

2. Methods

2.1. Population attributable fraction (PAF)

The PAF is defined as the proportion of cases that would not occur in a population if a particular risk factor were eliminated. The usual formula for the PAF is derived in Appendix A and discussed below

$$PAF = \frac{p(RR_1 - 1)}{1 + p(RR_1 - 1)} \quad (1)$$

The formula requires that we know the proportion (p) of the at-risk population exposed to the risk factor of interest and also the relative risk (RR_1) of disease in the exposed fraction of the population over the period of interest. There are a number of problems related to the use of this formula (Rockhill et al., 1998) but in the present context the most serious of these are (a) that we need to know the life-time relative risk for a diagnosis of schizophrenia in those infected with *T. gondii* (which we do not), and (b) that the derivation of the formula (see Appendix A) assumes that the proportion of the population infected with *T. gondii* remains constant as the cohort ages – and that the incidence of schizophrenia in the exposed and unexposed groups remains constant as the cohort ages. Neither of these last assumptions is true (Jones et al., 2001; Fromont et al., 2009; Bogren et al., 2010; Kodesh et al., 2012). Given these problems, the next section describes an alternative method of estimating the PAF based upon a determinsistic, mathematical model of schizophrenia and *T. gondii* infections in a cohort of people.

2.2. Model of schizophrenia in a cohort of people

Consider a cohort of people all born on the same day. This cohort lives under conditions typical of those in the USA or Western Europe. The fate of the cohort is followed for 100 years.

The individuals in this cohort can exist in one or more of five states during their lifetimes: X = serologically negative for *T. gondii*/no diagnosis of schizophrenia, Y = serologically positive for *T. gondii*/no diagnosis of schizophrenia, Z_1 = serologically negative for *T. gondii*/diagnosed with schizophrenia, Z_2 = diagnosed with schizophrenia after