

Research

Seasonal correlation of sporadic schizophrenia to *Ixodes* ticks and Lyme borreliosis

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Abstract

Background: Being born in winter and spring is considered one of the most robust epidemiological risk factors for schizophrenia. The aetiology and exact timing of this birth excess, however, has remained elusive so far. Since during phylogeny, *Borrelia* DNA has led to multiple germ-line mutations within the CBI candidate gene for schizophrenia, a meta analysis has been performed of all papers on schizophrenic birth excesses with no less than 3000 cases each. All published numerical data were then plotted against the seasonal distributions of *Ixodes* ticks worldwide.

Results: In the United States, Europe and Japan the birth excesses of those individuals who later in life develop schizophrenia mirror the seasonal distribution of *Ixodes* ticks nine months earlier at the time of conception. South of the Wallace Line, which limits the spread of *Ixodes* ticks and *Borrelia burgdorferi* into Australia, seasonal trends are less significant, and in Singapore, being non-endemic for *Ixodes* ticks and Lyme disease, schizophrenic birth excesses are absent.

Conclusion: At present, it cannot be excluded that prenatal infection by *B. burgdorferi* is harmful to the implanting human blastocyst. The epidemiological clustering of sporadic schizophrenia by season and locality rather emphasises the risk to the unborn of developing a congenital, yet preventable brain disorder later in life.

Background

Microorganisms, including bacteria [1], are capable of transferring part of their genome into mammalian germ lines [2], and such exchange of foreign DNA has been suggested to be of mutual evolutionary advantage [3]. The Lyme disease spirochaete *Borrelia burgdorferi*, in particular, disposes of a unique molecular mechanism of penetrating into germ-line cells of its host, whose genes the intracellular pathogen exploits like a virus owing to its own incomplete genome [4]. Although countercurrent to established views, the neurotropic spirochaete has integrated parts of its genes into our germ line, these serving as putative tem-

plates for further recombination. If prenatal exposure to such phylogenetic traces of foreign DNA reoccurs during ontogeny, a novel type of infectious mutation would occur within the 3' 'hotspot' for pathology of the human cannabinoid receptor gene CB1 [5–7]. The genetic expression of CB1 [8] would subsequently be affected in exactly those areas [9] that mirror the structural [10] and functional [11] brain abnormalities in schizophrenia.

Following the identification of neurosyphilis, caused by the spirochaete *Treponema pallidum*, that led Kraepelin [12] to recognise the distinctive pattern of *dementia prae-*

cox as a disease entity, Bleuler [13] coined the term 'schizophrenia'. Although this 'break' between reality and 'thought' is characterised by a multiplicity of signs and symptoms, the highly prevalent illness is recognised throughout the world, and there is now international agreement on its classification. Apart from known infectious diseases, no other affliction exhibits an equally marked seasonal distribution, thus nurturing the hope that schizophrenia could ultimately be preventable.

Although Hippocrates (460 BC) recognised the importance of "the seasons of the year and the effects they produce ... being common to all countries as well as peculiar to each locality", psychiatrists have been slow to accept this idea. Systematic research into the season of psychiatric birth effects began only with the studies by Tramer [14] and Lang [15] after the turn of the last century. Despite methodological problems, including some cases of neurosyphilis within the ill-defined Swiss cohort, their findings could be widely replicated. Being born during winter and spring is nowadays considered one of the most robust epidemiological risk factors for sporadic schizophrenia. The cause and exact timing of this birth excess, however, has remained elusive so far [16].

Clinically, syphilis, which has long been associated with devastating congenital outcomes, resembles Lyme disease. Like in humans [17], however, overt chronic infection of the unborn by *Borrelia burgdorferi* is rare in mice, as placental transmission of this spirochaete is restricted to an exclusively narrow time window at conception [18]. The present study is therefore focused on the seasonal distribution of schizophrenic birth excesses relative to *Ixodes* tick activity worldwide – with a time lag expected to be nine months apart. Otherwise, the hypothesis of *B. burgdorferi* being a major aetiological factor for congenital sporadic schizophrenia would be falsified.

Methods

For statistical reasons, only publications encompassing more than 3000 cases of schizophrenic birth excesses compared to the normal population have been considered [16]. These include two studies from Denmark and Australia showing both one significant and one non-significant result each, whereas the birth excesses of the remaining studies were all statistically significant. From the comprehensive literature, significant numerical data allowing for seasonal comparison were then used in this meta analysis and plotted against the published data of *B. burgdorferi* transmitting *Ixodes* tick activity (or numbers per area) of the respective macroclimatic regions.

Results

Nine months' interval between tick activity and schizophrenic birth excesses

In the USA, *Ixodes scapularis* ticks exhibit a clearly defined periodicity, increasing their numbers under specific macroclimatic conditions from March to April, in June and October [19]. The seasonal distribution parallels the birth excess for schizophrenia nine months later [20], while the risk of developing schizophrenia is reduced towards a global decline in November. It is to be noted that the deficit of schizophrenic births in late autumn occurs throughout the world and correlates with the lowest number and activity of *Ixodes* ticks in wintertime nine months earlier.

As in Europe, the spring peak of tick activity in the USA with a first climax in March [19] correlates with the rising numbers of schizophrenic births between December and January. In the Far East, the unimodal peak of *Ixodes persulcatus* from April to July [21] reflects the unimodal winter-spring birth excess in Japan followed by a relative decline of schizophrenia in May [22].

Macroclimatic parameters

The distribution of schizophrenic births across Europe [14,15,23,24], by contrast, mirrors the more complex seasonal concentration of tick populations, separated by a midsummer decrease in humidity [19]. In Ireland, where the maritime climatic conditions remain relatively mild throughout the year, nymphal activity continues into midsummer followed by a smaller peak in early autumn. Although this bimodal pattern remains evident, it resembles the moderating environmental effects on the life cycle of the tick *Dermatocentor variabilis* [19]. When the adult ticks emerge from nymphs fed in the same year, they tend to surge towards a midsummer peak from early May to August, overlapping with the older cohort of adult ticks in autumn [19]. In Ireland, this fusion into a more uniform pattern of midsummer *Ixodes ricinus* activity [19] might therefore account for the somewhat delayed, but pronounced schizophrenic birth excess in spring [23].

While in central Europe a few autumn-feeding *I. ricinus* ticks are active up to October [19], the temperature falls below zero in Finland. Like in the Alps, the minimal mean temperature of seven degrees required for tick activity [19] allows only one summer peak in northern Europe, including the Karelian border between Russia and Finland [21]. The seasonal periodicity of *I. ricinus*, in turn, reflects the typical unimodal schizophrenic birth excess in Finland [24] and Denmark [25]. The harsh weather conditions in the north might furthermore reflect the stochastic fluctuations [26] of ticks in Scandinavia [27] and possibly schizophrenic births in Finland [28].

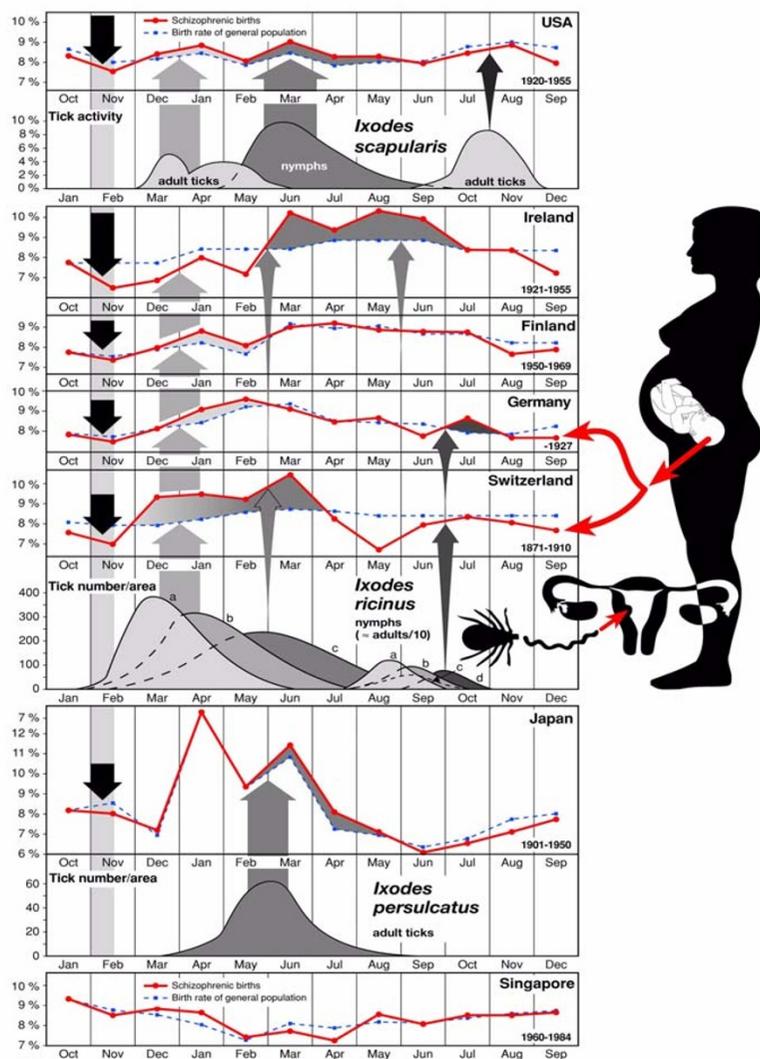


Figure 1

Seasonal correlation of sporadic schizophrenia to *Ixodes* ticks The seasonal periodicity of the adult and juvenile stages of *Ixodes scapularis* in the State of New York [19] exactly mirrors the dynamics of schizophrenic births in the north-eastern United States [20]. The spring and autumn populations of *Ixodes ricinus* in central Europe are affected by microclimatic conditions and a drop in humidity in midsummer (a = exposed meadow, b = dense hill vegetation or secondary deciduous woodland, c = highly sheltered habitat, d = spring-derived but autumn-feeding cohort). In northern Europe, however, there exists no late autumn cohort (d) as tick activity comes to a halt due to falling ambient temperature. Data adapted from [14,15,19,23,24]. The seasonal distribution of *Ixodes persulcatus* ticks in the Far East [21] appears to have given rise to schizophrenic births between February and March along with the typical decline in summer and late autumn [22]. In the case of a prenatal infection at the time of conception, nine months later these variables run parallel to the birth excess number of individuals with schizophrenia. In Singapore, by contrast, the non-significant birth excess in schizophrenia [41] is in line with the apparent absence of *Ixodes* ticks and *B. burgdorferi* from that part of the world [40].

Due to the central European midsummer decrease in air humidity and thus reduced tick activity [19], the relative decline towards a schizophrenic birth deficit in April appears earlier and more pronounced the further south we move. See Switzerland [14] and Germany [15] in figure 1.

Epidemiological gradients

That exposure precedes infection is self-evident. Like other environmental causes, however, this relation is also expected to show a correlated biological gradient [29]. In maritime Ireland and the sheltered microclimatic environment at the foot of the Swiss Alps, for example, tick abundance and the transmission of three pathogenic species of *B. burgdorferi sensu lato* [19,30,31] coincide with the highest rates of schizophrenic births worldwide (see figure 1). Lower tick concentrations and infection rates by *B. burgdorferi sensu stricto* [32] appear to score relatively lower rates of schizophrenic birth excesses in the United States [16]. Within the USA (see figure 2), however, the Pacific Coast, New England and Great Lakes states score an approximately three times higher rate of schizophrenia compared to other states [33]. Schizophrenic birth excesses, in particular, are more pronounced in New England and the Midwest than in the South [20]. This trend, which has been remarkably consistent over a long period, correlates with the highest risk of Lyme disease and the largest populations of *Ixodes* ticks in the USA [34–37] (see figure 2).

Contrary to current belief [38], neither the incidence nor the winter-spring birth excess of schizophrenia occurs at a constant, global rate. The risk of schizophrenia [16] actually reflects the uneven distribution of *B. burgdorferi* endemicity worldwide [19]. South of the Wallace Line, which limits the spread of *Ixodes* ticks by mammals into New Guinea and Australia [19], seasonal schizophrenic trends are less significant compared to the northern hemisphere [39]. In Singapore, which is still a non-endemic area for *Ixodes* ticks and *B. burgdorferi* [40], there is no significant schizophrenic birth excess [41].

Discussion

One of the greatest triumphs of epidemiology stems from the control of cholera before the responsible organism, let alone its mechanism of action, had been identified. Major progress in prevention is thus possible by focusing on those variables that are known and can be influenced. Although the concept of cause is the source of much controversy, as it is in other sciences, a correct temporal relation between exposure and effect is essential in epidemiology [29].

Migratory birds

Like in other parts of the southern hemisphere [42], polar birds travelling from the northern hemisphere sporadically via the Antarctic introduce *Ixodes uriae* ticks harbouring

Borrelia garinii into Australia. These, in turn, may infect people in New South Wales [43] and adjacent coastal areas. However, *B. burgdorferi* could neither be detected in [44], nor experimentally be transmitted by [45] the endemic species *Ixodes holocyclus*. Such maladaptation to local tick vectors might account for the low incidence of borreliosis and thus the reportedly lower rate of schizophrenia in New South Wales [46] and other parts of Australia [47].

In the remote interior of New Guinea, on an island which is reportedly non-endemic for Lyme disease [48], schizophrenia appears to be almost non-existent [47]. In a neuropsychiatric survey comprising more than 10,000 Papuans from the Indonesian part of New Guinea [49], we found only one overtly psychotic case that had recently arrived from his home town Merauke on the western coast. In the interior of Papua New Guinea, schizophrenic prevalence is also much lower than expected [50]. Yet in the western coastal districts, where migratory birds are known to introduce ticks from New South Wales and Queensland [see [34]], and where Rusa deer (*Cervus timorensis*) originally imported by the Dutch abound, the prevalence of schizophrenia is significantly higher [50].

Migratory sea birds are also known to introduce *I. persulcatus* and *B. garinii* from their origin on the Eurasian mainland into pockets of northern Japan [51,52]. As in Australia, however, the risk of acquiring Lyme disease is relatively low, since the spirochaetes have not yet fully adapted to the local *Ixodes ovatus* ticks. In contrast to *I. persulcatus*, this endemic tick species found all over Japan is only capable of acquiring but not transmitting *B. garinii* to its human hosts [53]. From that perspective, the relatively recent introduction of *B. garinii* might possibly explain the recent rise of schizophrenic birth excesses in Tokyo after the turn of the last century [22].

Deer and hedgehogs

Residential development favours small tree-enclosed meadows interspersed with strips of woodland, much prized by deer, hedgehogs, mice and cats. The widely reported correlation of schizophrenic birth excesses to more densely populated urban and suburban areas [16] might thus reflect the activity of ticks, now attacking people in metropolitan areas [32]. At first sight this phenomenon might appear counterintuitive. Yet, while deer play a crucial role in the development and recent geographical dispersal of adult ticks [32,35,54], their spirochaetocidal antibodies exert a protective effect by clearing the borrelia from the questing ticks' endolymph. Thereby the ticks lose their infectious potential for human beings living in the countryside [55]. This so-called zooprophyllactic effect particularly applies to the southern United States, where ticks feed abundantly on lizards and skinks which poorly

maintain *B. burgdorferi* infection [37]. Compared to southern states such as Mississippi, where lizards are endemic, by contrast Michigan poses a relatively higher risk for Lyme disease despite the relative scarcity of ticks in that state.

Due to the continuous peridomestic parcellation of nature, hedgehogs (*Erinaceus europaeus*) also abound as excellent hosts for *Ixodes* nymphs as well as the particularly dangerous adult *Ixodes* ticks (personal observation). What is worse, their apparent lack of zooprophyllaxis contributes to the periurban transmission of borreliosis [56] in our gardens.

Mice and cats

In peridomestic sites, various mice, *Peromyscus leucopus* in eastern North America and *Apodemus agrarius* in Europe, are the most important reservoirs of *B. burgdorferi* infection [30,32]. As cats go for these mice, they reportedly spread *Ixodes* nymphs near or in households (see [34]). Not surprisingly, therefore, there is significantly more often a cat in the household at the time of birth of an individual who later develops schizophrenia [57].

Biological plausibility of cause and effect

The nine months' interval between tick activity and schizophrenic birth excesses implies an infection at conception or shortly afterwards. It is tempting to speculate that a mutagenic interaction between the implanting blastocyst and pathogen depends on the simultaneous epigenetic exposure of both embryonic and microbial DNA reading frames [58] – weeks before neurons differentiate and embryonic brain development sets in. As ontogeny reflects phylogeny, the fast-switching ionotropic neuroreceptors dominate in the adult mammalian brain, whereas earlier in life and evolution the slow metabotropic neuroreceptors appear during implantation as critical elements in intercellular signalling before neurons differentiate [59]. There exists only one metabotropic neuroreceptor gene implicated in both schizophrenia [8,60,61] and embryonic implantation [62]: the CB1 cannabinoid receptor gene. Likewise, within human CB1, the phylogenetic trace of a microbial virulence factor, the flagellar basal rod protein originating from *B. burgdorferi*[5], cannot be entirely coincidental, since this foreign DNA codes for spirochaetal intrusion into foreign tissue as well.

For successful implantation into foreign tissue, and in order to suppress HLA mediated antigen presentation to maternal tissue [63], the implanting embryo secretes interferon gamma [64]. Worse still, interferon gamma also up-regulates the molecular machinery of genetic recombination and variation by *B. burgdorferi*[65]. Through this cytokine mediated mutagenesis, the co-expression and genetic exposure of both embryonic and spirochaetal

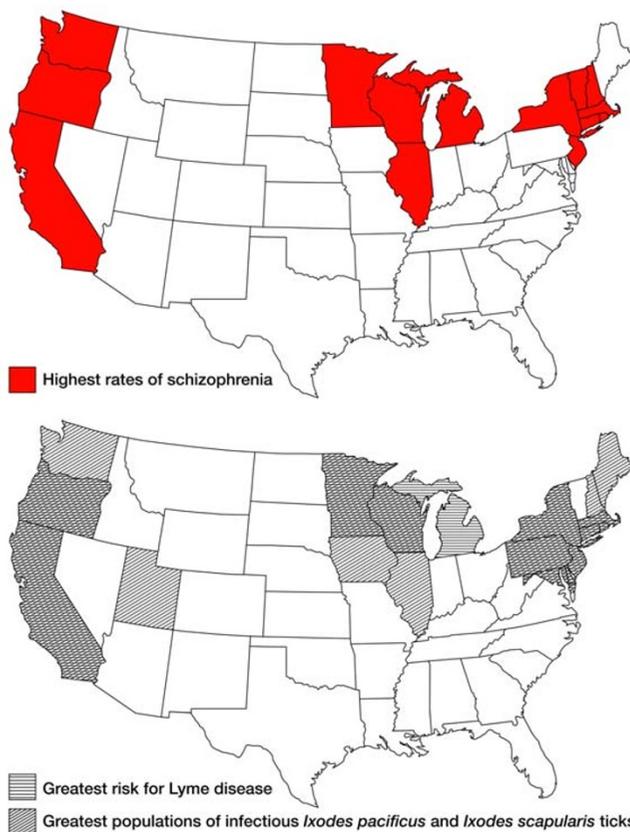


Figure 2
Geographical correlation of schizophrenia to Ixodes ticks and Lyme disease in the USA The epidemiological correlation between *Ixodes* ticks and schizophrenia originally published by Brown [34] has been adjusted according to the more recent epidemiological data on the risk of Lyme disease including zooprophyllaxis [35–37,55].

DNA coding for foreign intrusion has arguably led to the germ-line mutations of our ancestral CB1. In the course of evolution, exposure of complementary DNA templates has furthermore led to genetic recombination with other loci whose distribution is not entirely random. Rather, the chromosomal scatter of the respective spirochaetal nucleotides presents surprising explanatory power for some schizophrenic linkage and genetic coincidence studies that have remained so far unaccounted for [6].

Lyme disease is easily missed in psychiatry [66–69]. The case report of a 19 year-old patient suffering from neuroborreliosis is perhaps the most illuminating. He presented at the Department of Psychiatry in Munich (Germany) with acute catatonic and paranoid symptoms including negativism, stereotyped movements, delusional ideas of persecution as well as acoustic hallucinations. Upon isolation of *B. burgdorferi* from the CSF and the demonstration of intrathecal IgG antibodies, the patient

completely recovered after antibiotic therapy [68]. However, this type of adult-onset, schizophrenia-like encephalitis – which closely resembles the cataleptic symptoms of CB1 knockout mice [70] – is rather the exception to the rule. In the United States, from where the highly neurotropic *B. garinii* is absent, a search for antibodies in schizophrenic patients has, compared to normal controls, yielded negative results (Torrey, 2001; unpublished data). In the Czech Republic, however, a subtle, yet significant correlation between elevated antibody titers against *B. burgdorferi* and schizophrenia has recently been demonstrated [71].

Prenatal infection restricted to parts of the fetal brain always results in a brain disorder, whose severity depends on the proportion of neurons involved. Like neuroborreliosis, sporadic schizophrenia therefore appears to be characterised by an excess of focal neurological damage [72]. If the mutation also affects germ-line cells, initiating familial schizophrenia in the offspring of the next generation (born at any season throughout the year), all neurons will be affected. The phenotype of disordered integrative functions is then expected to be more severe. In familial schizophrenia, this is in fact the case [72]. Conversely, attempts to correlate the schizophrenic birth excess with its symptomatology have yielded a negative family history and, more specifically, a lesser severity of illness [16].

The contribution of genetic factors to the risk of developing schizophrenia has been demonstrated in family, twin and adoption studies. The majority of patients, however, do not marry or have children, and the magnitude is such that any genetic predisposition would be eliminated from the genetic pool within a few generations. But it is not, nor do the majority of patients have a family history of the disease, and the 50% concordance rate in monozygotic twins falls short of the 100% that would be expected from genetically identical individuals. The answer possibly lies "in having above all a strong enough hypothesis that can be tested with linkage data" [73], and in considering "that epigenetic modification of the gene(s), rather than a crucial variation in DNA sequence, leads to illness." [74,75]

Conclusion

At present, it cannot be excluded that sporadic prenatal infection by *B. burgdorferi* poses a psychiatric hazard to the unborn. On the contrary; the epidemiological clustering by season and locality, being characteristic of an acute contagious disease [29], rather points to a causal relation between global *Ixodes* tick endemicity and sporadic schizophrenia.

List of abbreviations

DNA: Desoxyribonucleic acid

CB1: Central cannabinoid receptor gene

HLA: Major histocompatibility complex

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References

1. Waters VL: **Conjugation between bacterial and mammalian cells.** *Nat Genet* 2001, **29**:375-376
2. Gosden CM, Liloglou T, Nunn J, Gardener D, Nickson P, Crampton JM, Field JK: **The Knights of the Round Table hypothesis of tumour suppressor gene function – noble sacrifice or sexual dalliance: Genes, including p53, BRCA1/2 and RB have evolved by horizontal and vertical transmission of mating factor genes and are involved in gametogenesis, implantation, development and tumourigenesis.** *Int J Oncol* 1998, **12**:5-35
3. Howell MJ: **Gene exchange between hosts and parasites.** *Int J Parasitol* 1985, **15**:597-600
4. Fraser CM, Casjens S, Huang WM, Sutton GG, Clayton R, Lathigra R, White O, Ketchum KA, Dodson R, Hickey EK, Gwinn M, Dougherty B, Tomb JF, Fleischmann RD, Richardson D, Peterson J, Kerlavage AR, Quackenbush J, Salzberg S, Hanson M, van Vugt R, Palmer N, Adams MD, Gocayne J, Venter JC, et al: **Genomic sequence of a Lyme disease spirochaete, *Borrelia burgdorferi*.** *Nature* 1997, **390**:580-586
5. Fritzsche M: **Are cannabinoid receptor knockout mice animal models for schizophrenia?** *Med Hypotheses* 2001, **56**:638-643
6. Fritzsche M: **Lateral gene transfer – the missing link between cannabis psychosis and schizophrenia.** *Am J Med Gen* 2002, **114**:512-515
7. Conne B, Stutz A, Vassalli JD: **The 3' untranslated region of messenger RNA: A molecular 'hotspot' for pathology?** *Nat Med* 2000, **6**:637-641
8. Dean B, Sundram S, Bradbury R, Scarr E, Copolov D: **Studies on [³H]CP-55940 binding in the human central nervous system: regional specific changes in density of cannabinoid-1 receptors associated with schizophrenia and cannabis use.** *Neuroscience* 2000, **103**:1009-1015
9. Glass M, Dragunow M, Faull RL: **Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain.** *Neuroscience* 1997, **77**:299-318
10. Schultz SK, Andreasen NC: **Schizophrenia.** *Lancet* 1999, **353**:1425-1430
11. Silbersweig DA, Stern E, Frith C, Cahill C, Holmes A, Grootenok S, Seaward J, McKenna P, Chua SE, Schnorr L, et al: **A functional neuroanatomy of hallucinations in schizophrenia.** *Nature* 1995, **378**:176-179
12. Kraepelin E: **Psychiatrie, Ein Lehrbuch für Studierende und Aerzte. Dementia praecox.** Leipzig, Barth 1899 (Edited by: Barclay RM) Scotland, Livingston 1919
13. Bleuler E: **Handbuch der Psychiatrie. Dementia praecox oder Gruppe der Schizophrenien.** Leipzig, Deuticke 1911 (Edited by: Zukin J) New York, International Universities Press 1950
14. Tramer M: **Ueber die biologische Bedeutung des Geburtsmonates, insbesondere für die Psychoseerkrankung.** *Schweiz Arch Neurol Psychiatrie* 1929, **24**:17-24
15. Lang T: **Zur Frage: Geisteskrankheit und Geburtsmonat.** *Arch Rassen-Gesellschaftsbiologie* 1931, **25**:42-57
16. Torrey EF, Miller J, Rawlings R, Yolken RH: **Seasonality of births in schizophrenia and bipolar disorder: a review of the literature.** *Schizophhr Res* 1997, **28**:1-38
17. Schlesinger PA, Duray PH, Burke BA, Steere AC, Stillman MT: **Maternal-fetal transmission of the Lyme disease spirochete, *Borrelia burgdorferi*.** *Ann Intern Me* 1985, **103**:67-68
18. Silver RM, Yang L, Daynes RA, Branch DW, Salafia CM, Weis JJ: **Fetal outcome in murine Lyme disease.** *Infect Immun* 1995, **63**:66-72
19. Sonenshine DE: **Biology of Ticks.** New York, Oxford University Press 1989

20. Torrey EF, Torrey BB, Peterson MR: **Seasonality of schizophrenic births in the United States.** *Arch Gen Psychiatry* 1977, **34**:1065-1070
21. Korenberg El: **Seasonal population dynamics of ixodes ticks and tick-borne encephalitis virus.** *Exp Appl Acarol* 2000, **24**:665-681
22. Shimura M, Nakamura I, Miura T: **Season of birth of schizophrenics in Tokyo, Japan.** *Acta Psychiatr Scand* 1977, **55**:225-232
23. O'Hare A, Walsh D, Torrey F: **Seasonality of schizophrenic births in Ireland.** *Br J Psychiatry* 1980, **137**:74-77
24. Suvisaari JM, Haukka JK, Lonnqvist JK: **Season of birth among patients with schizophrenia and their siblings: evidence for the procreational habits hypothesis.** *Am J Psychiatry* 2001, **158**:754-757
25. Videbech T, Weeke A, Dupont A: **Endogenous psychoses and season of birth.** *Acta Psychiatr Scand* 1974, **50**:202-218
26. Bjornstad ON, Grenfell BT: **Noisy clockwork: time series analysis of population fluctuations in animals.** *Science* 2001, **293**:638-643
27. Talleklint L, Jaenson TG: **Seasonal variations in density of questing Ixodes ricinus (Acari: Ixodidae) nymphs and prevalence of infection with B. burgdorferi s.l. in south central Sweden.** *J Med Entomol* 1996, **33**:592-597
28. Fritzsche M, Schmidli J: **Seasonal fluctuation in schizophrenia.** *Am J Psychiatry* 2002, **159**:499-500
29. Beaglehole R, Bonita R, Kiehlstrom T: **Basic Epidemiology.** Geneva, World Health Organization Press 1993
30. Steere AC: **Borrelia burgdorferi (Lyme Disease, Lyme Borreliosis).** In: *Principles and Practice of Infectious Diseases* (Edited by: GL Mandell, JE Bennett, R Dolin) Churchill Livingstone, Philadelphia 2000, 2504-2518
31. Parola P, Raoult D: **Ticks and tickborne bacterial diseases in humans: an emerging infectious threat.** *Clin Infect Dis* 2001, **32**:897-928
32. Spielman A: **The emergence of Lyme disease and human babesiosis in a changing environment.** *Ann N Y Acad Sci* 1994, **740**:146-156
33. Torrey EF, Bowler A: **Geographical distribution of insanity in America: evidence for an urban factor.** *Schizophr Bull* 1990, **16**:591-604
34. Brown JS Jr: **Geographic correlation of schizophrenia to ticks and tick-borne encephalitis.** *Schizophr Bull* 1994, **20**:755-775
35. Barbour AG, Fish D: **The biological and social phenomenon of Lyme disease.** *Science* 1993, **260**:1610-1616
36. Dennis DT, Nekomoto TS, Victor JC, Paul WS, Piesman J: **Reported distribution of Ixodes scapularis and Ixodes pacificus (Acari: Ixodidae) in the United States.** *J Med Entomol* 1998, **35**:629-638
37. Piesman J, Clark KL, Dolan MC, Happ CM, Burkot TR: **Geographic survey of vector ticks (Ixodes scapularis and Ixodes pacificus) for infection with the Lyme disease spirochete, Borrelia burgdorferi.** *J Vector Ecol* 1999, **24**:91-98
38. Sartorius N, Jablensky A, Korten A, Ernberg G, Anker M, Cooper JE, Day R: **Early manifestations and first-contact incidence of schizophrenia in different cultures. A preliminary report on the initial evaluation phase of the WHO Collaborative Study on determinants of outcome of severe mental disorders.** *Psychol Med* 1986, **16**:909-928
39. McGrath JJ, Welham JL: **Season of birth and schizophrenia: a systematic review and meta-analysis of data from the Southern Hemisphere.** *Schizophr Res* 1999, **35**:237-242
40. Goh CL, Kamarudin A, Khatija M: **Lyme disease is not prevalent in patients presenting with annular erythema in Singapore.** *Singapore Med J* 1996, **37**:250-251
41. Parker G, Mahendran R, Koh ES, Machin D: **Season of birth in schizophrenia: no latitude at the equator.** *Br J Psychiatry* 2000, **176**:68-71
42. Olsen B, Duffy DC, Jaenson TG, Gylfe A, Bonnedahl J, Bergstrom S: **Transhemispheric exchange of Lyme disease spirochetes by seabirds.** *J Clin Microbiol* 1995, **33**:3270-3274
43. Hudson BJ, Stewart M, Lennox VA, Fukunaga M, Yabuki M, Macorison H, Kitchener-Smith J: **Culture-positive Lyme borreliosis.** *Med J Aust* 1998, **168**:500-502
44. Russell RC, Doggett SL, Munro R, Ellis J, Avery D, Hunt C, Dickeson D: **Lyme disease: a search for a causative agent in ticks in south-eastern Australia.** *Epidemiol Infect* 1994, **112**:375-384
45. Piesman J, Stone BF: **Vector competence of the Australian paralysis tick, Ixodes holocyclus, for the Lyme disease spirochete Borrelia burgdorferi.** *Int J Parasit* 1991, **21**:109-111
46. Goldstein G, Hall W, Andrews G: **The incidence of schizophrenia in New South Wales, Australia. A psychiatric register study.** *Acta Psychiatr Scand* 1984, **70**:220-227
47. Dohan FC, Harper EH, Clark MH, Rodrigue R, Zigas V: **Where is schizophrenia rare?** *Lancet* 1983, **2**:101
48. Burkot TR, Schriefer ME, Larsen SA: **Cross-reactivity to Borrelia burgdorferi proteins in serum samples from residents of a tropical country nonendemic for Lyme disease.** *J Infect Dis* 1997, **175**:466-469
49. Fritzsche M, Gottstein B, Wigglesworth MC, Eckert J: **Serological survey of human cysticercosis in Irianese refugee camps in Papua New Guinea.** *Acta Trop* 1990, **47**:69-77
50. Torrey EF, Torrey BB, Burton-Bradley BG: **The epidemiology of schizophrenia in Papua New Guinea.** *Am J Psychiatry* 1974, **131**:567-573
51. Ishiguro F, Takada N, Masuzawa T, Fukui T: **Prevalence of Lyme disease Borrelia spp. in ticks from migratory birds on the Japanese mainland.** *Appl Environ Microbiol* 2000, **66**:982-986
52. Wang J, Masuzawa T, Yanagihara Y: **Characterization of Borrelia garinii isolated from Lyme disease patients in Hokkaido, Japan, by sequence analysis of OspA and OspB genes.** *FEMS Microbiol Lett* 1997, **154**:371-375
53. Nakao M, Miyamoto K: **Susceptibility of Ixodes persulcatus and I. ovatus (Acari: Ixodidae) to Lyme disease spirochetes isolated from humans in Japan.** *J Med Entomol* 1994, **31**:467-473
54. Isogai E, Isogai H, Masuzawa T, Postic D, Baranton G, Kamewaka Y, Kimura K, Nishikawa T, Fuji N, Ishii N, Ohno S, Yamaguti N: **Borrelia burgdorferi sensu lato in an endemic environment: wild sika deer (Cervus nippon yesoensis) with infected ticks and antibodies.** *Microbiol Immunol* 1996, **40**:13-19
55. Matuschka FR, Heiler M, Eiffert H, Fischer P, Lotter H, Spielman A: **Diversification role of hoofed game in the transmission of Lyme disease spirochetes.** *Am J Trop Med Hyg* 1993, **48**:693-699
56. Gern L, Rouvinez E, Toutoungi LN, Godfroid E: **Transmission cycles of Borrelia burgdorferi sensu lato involving Ixodes ricinus and/or I. hexagonus ticks and the European hedgehog, Erinaceus europaeus, in suburban and urban areas in Switzerland.** *Folia Parasitol* 1997, **44**:309-314
57. Torrey FE, Yolken RH: **Familial and genetic mechanisms in schizophrenia.** *Brain Res Brain Res Rev* 2000, **31**:113-117
58. Turner B: **Chromatin and Gene Regulation. Mechanisms in Epigenetics.** Oxford, Blackwell 2001
59. Herlenius E, Lagercrantz H: **Neurotransmitters and neuromodulators during early human development.** *Early Hum Dev* 2001, **65**:21-37
60. Leroy S, Griffon N, Bourdel MC, Ollie JP, Poirier MF, Krebs MO: **Schizophrenia and the cannabinoid receptor type 1 (CB1): Association study using a single-base polymorphism in coding exon 1.** *Am J Med Genet* 2001, **105**:749-752
61. Ujike H, Takaki M, Nakata K, Tanaka Y, Takeda T, Kodama M, Fujiwara Y, Sakai A, Kuroda S: **CNRI, central cannabinoid receptor gene, associated with susceptibility to hebephrenic schizophrenia.** *Mol Psychiatry* 2002, **7**:515-518
62. Paria BC, Song H, Wvang X, Schmid PC, Krebsbach RJ, Schmid HH, Bonner TI, Zimmer A, Dey SK: **Dysregulated cannabinoid signaling disrupts uterine receptivity for embryo implantation.** *J Biol Chem* 2001, **276**:20523-20528
63. van den Elsen PJ, Gobin SJ, van der Stoep N, Datema G, Vietor HE: **Transcriptional control of MHC genes in fetal trophoblast cells.** *J Reprod Immunol* 2001, **52**:129-145
64. Ashkar AA, Croy BA: **Interferon-gamma contributes to the normalcy of murine pregnancy.** *Biol Reprod* 1999, **61**:493-502
65. Anguita J, Thomas V, Samanta S, Persinski R, Hernanz C, Barthold SW, Fikrig E: **Borrelia burgdorferi-induced inflammation facilitates spirochete adaptation and variable major protein-like sequence locus recombination.** *J Immunol* 2001, **167**:3383-3390
66. Fallon BA, Nields JA: **Lyme disease: a neuropsychiatric illness.** *Am J Psychiatry* 1994, **151**:1571-1583
67. Roelcke U, Barnett W, Wilder-Smith W, Sigmund D, Hacke W: **Untreated neuroborreliosis: Bannwarth's syndrome evolving into acute schizophrenia-like psychosis. A case report.** *J Neurol* 1992, **239**:129-131

68. Pfister HW, Preac-Mursic V, Wilske B, Rieder G, Forderreuther S, Schmidt S, Kapfhammer HP: **Catatonic syndrome in acute severe encephalitis due to Borrelia burgdorferi infection.** *Neurology* 1993, **43**:433-435
69. Hess A, Buchmann J, Zetl UK, Henschel S, Schlaefke D, Grau G, Benicke R: **Borrelia burgdorferi central nervous system infection presenting as an organic schizophrenialike disorder.** *Biol Psychiatry* 1999, **45**:795
70. Zimmer A, Zimmer AM, Hohmann AG, Herkenham M, Bonner TI: **Increased mortality, hypoactivity, and hypoalgesia in cannabinoid CBI receptor knockout mice.** *Proc Natl Acad Sci U S A* 1999, **96**:5780-5785
71. Hajek T, Paskova B, Janovska D, Bahbouh R, Hajek P, Libiger J, Hoschl C: **Higher prevalence of antibodies to Borrelia burgdorferi in psychiatric patients than in healthy subjects.** *Am J Psychiatry* 2002, **159**:297-301
72. Griffiths TD, Sigmundsson T, Takei N, Rowe D, Murray RM: **Neurological abnormalities in familial and sporadic schizophrenia.** *Brain* 1998, **121**:191-203
73. DeLisi LE: **Critical overview of current approaches to genetic mechanisms in schizophrenia research.** *Brain Res Brain Res Rev* 2000, **31**:187-92
74. DeLisi LE, Mesen A, Rodriguez C, Bertheu A, LaPrade B, Llach M, Riondet S, Razi K, Relja M, Byerley W, Sherrington R: **Genome-wide scan for linkage to schizophrenia in a Spanish-origin cohort from Costa Rica.** *Am J Med Genet* 2002, **114**:497-508
75. Petronis A, Gottesman II, Crow TJ, DeLisi LE, Klar AJ, Macciardi F, McInnis MG, McMahon FJ, Paterson AD, Skuse D, Sutherland GR: **Psychiatric epigenetics: a new focus for the new century.** *Mol Psychiatry* 2000, **5**:342-346

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