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Bacterial Infection and Alzheimer's Disease: A Meta-Analysis

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Abstract. The possibility of an infectious etiology for Alzheimer's disease (AD) has been repeatedly postulated over the past three decades. We provide the first meta-analysis to address the relationship between bacterial infection and AD. Studies examining the association between AD and spirochetal bacteria or *Chlamydophila pneumoniae* (Cpn) were identified through a systematic search of the databases MEDLINE, EMBASE, PubMed, and Google Scholar. Data combined from 25 relevant, primarily case-control studies demonstrated a statistically significant association between AD and detectable evidence of infection of either bacterial group. We found over a ten-fold increased occurrence of AD when there is detectable evidence of spirochetal infection (OR: 10.61; 95% CI: 3.38–33.29) and over a four-fold increased occurrence of AD in a conservative risk estimate (OR: 4.45; 95% CI: 2.33–8.52). We found over a five-fold increased occurrence of AD with Cpn infection (OR: 5.66; 95% CI: 1.83–17.51). This study shows a strongly positive association between bacterial infection and AD. Further detailed investigation of the role of bacterial infection is warranted.

Keywords: Alzheimer's disease, bacteria, *Borrelia, Chlamydophila*, dementia, etiology, infection, inflammation, Spirochaetales, *Treponema*

INTRODUCTION

Alzheimer's disease (AD) was first described over a century ago and is the most common neurodegenerative disease, and yet an understanding of its etiology and pathogenesis remains elusive [1]. The worldwide prevalence of AD was estimated to be 26.6 million people in 2006 and it is predicted to quadruple by 2050, by which time 1 in 85 people worldwide will be living with this debilitating disease [2].

AD is divided into two types, with an early-onset familial type associated with genetic mutations and a much more common late-onset form which is believed to be a multifactorial process that may involve infectious co-factors [3]. The possibility of an infectious etiology for AD has been repeatedly postulated over the past three decades, with the roles of both viruses and bacteria investigated. Evidence for a viral contribution is strongest for herpes simplex virus type 1 (HSV1), with the combination of HSV1 infection and carriage of the type 4 allele of the apolipoprotein E gene (APOE $\varepsilon 4$) found to be a strong risk factor for AD [4]. In terms of bacteria, *Chlamydophila* (formerly *Chlamydia*) *pneumoniae* (Cpn) and spirochetal bacteria have been two of the most frequently implicated bacterial groups in AD pathogenesis.

Cpn is a primary human pathogen which causes respiratory tract infections including bronchitis, pharyngitis, and pneumonia and was officially identified as a separate species within the *Chlamydia* genus only relatively recently in 1989 [5]. The pathogen is transmitted via the respiratory route which is a key reason why its seroprevalence is relatively high at over 50% among adults in the U.S. and various other countries [6].

Spirochetes are helical Gram-negative bacteria that belong to the order Spirochaetales [7]. Syphilis caused by *Treponema pallidum* is one spirochetal disease that can involve cortical atrophy and dementia as late

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manifestations [7]. This has prompted researchers to investigate whether spirochetal infection could contribute to the development of AD in an analogous manner [8].

A number of case-control studies have examined whether there is an association between bacterial infection and AD, however, conflicting results have not yet enabled a consensus to be reached. The main objective of this study was to quantitatively assess all of the published data on the effect of bacterial infection upon the development of AD. To our knowledge, this is the first meta-analysis to address the relationship between bacterial infection and AD. The literature search yielded studies examining the relationship between bacterial infection and AD for various different bacteria. Quantitative data sufficient for meta-analysis however were found only for spirochetes and Cpn, which led to a focus in the present study on these bacteria.

METHODS

Study protocol

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9]. A systematic search of the databases MEDLINE (from 1950), PubMed (from 1946), EMBASE (from 1949), and Google Scholar (from 1993) was conducted through to June 2014, to identify relevant articles. The two terms 'Alzheimer's disease' AND 'infection', were searched as text word and as exploded Medical Subject Headings where possible. The reference lists of relevant articles were also searched for appropriate studies, however, a search for unpublished literature was not performed. No language restrictions were used in either the search or study selection.

Study selection

We included studies that met the following inclusion criteria: 1) there was data specific to AD as opposed to other or unspecified dementias; 2) AD was diagnosed by the appropriate clinical or neuropathological protocols; 3) appropriate laboratory methods were used to diagnose infection; 4) the risk point estimate was reported as an odds ratio (OR), or the data was presented such that an OR could be calculated; 5) the 95% confidence interval (CI) was reported, or the data was presented such that the CI could be calculated; and 6) an internal comparison was used when calculating the risk estimate. We excluded studies that did not meet these inclusion criteria. With regards to our second criterion, the majority of included studies involving living patients used the National Institute of Neurological and Communicative Disorder and Stroke-Alzheimer's Disease and Related Disorder Association (NINCDS-ADRDA) criteria for the clinical diagnosis of probable AD, which achieves the maximal certainty obtainable without an autopsy or biopsy [10]. Neuropathological examinations had been conducted to diagnose AD in studies of postmortem brains, typically sourced from brain resource centers, with adherence to the neuropathological criteria developed by the Consortium to Establish a Registry for Alzheimer's disease (CERAD) specifically stated in many studies [11].

Data extraction

Data extraction was performed using a standardized data extraction form, collecting information on the authors, publication year, study design, number of AD cases, number of control cases, total sample size, country, continent, case control matching, the odds ratios or data used to calculate the odds ratios, 95% CIs or data used to calculate CIs, the diagnostic tool used to confirm AD, the type of laboratory investigation used to confirm bacterial infection, and the material tested (cortex, serum, or cerebrospinal fluid (CSF)). The quality of the studies was not assessed. Authors were contacted where clarifications of study data were required. Adjusted odds ratios were extracted in preference to non-adjusted ratios. Where ratios were not provided, unadjusted ORs and CIs were calculated. Zero values in cells were replaced with values of one in order to enable calculations of odds ratios and CIs. Where multiple risk estimates were available in the same study, for example due to the use of different comparator groups, they were included as separate risk estimates.

Statistical analysis

Pooled odds ratios and 95% confidence intervals were calculated for the effect of bacterial infection on the risk of AD using a random effects model [12]. We tested heterogeneity with Cochran's Q statistic, with $p < 0.10$ indicating heterogeneity, and quantified the degree of heterogeneity using the I^2 statistic, which represents the percentage of the total variability across studies which is due to heterogeneity. I^2 values of 25, 50, and 75% corresponded to low, moderate, and high degrees of heterogeneity, respectively [13].

Studies with extreme ORs were excluded in sensitivity analyses where appropriate in order to determine conservative risk estimates with lowered heterogeneity of results.

We quantified publication bias using the Egger's regression model [14], with the effect of bias assessed using the fail-safe number method. The fail-safe number was the number of studies that we would need to have missed for our observed result to be nullified to statistical non-significance at the $p < 0.05$ level. Publication bias is generally regarded as a concern if the fail-safe number is less than 5n+10, with n being the number of studies included in the meta-analysis [15]. All analyses were performed with Comprehensive Meta-analysis (version 2.0, 2005; Biostat, Englewood, New Jersey).

RESULTS

Literature search

Of the 4,039 references screened, we found 23 case-control studies, 3 case series, and 1 randomized controlled trial eligible for inclusion in this meta-analysis, of which 13 studies concerned spirochetes and 14 concerned Cpn. Figure 1 depicts the flowchart of included studies.

Study characteristics

The total numbers of AD and control cases were 723 and 481 cases, respectively. Table 1 provides details of individual studies.

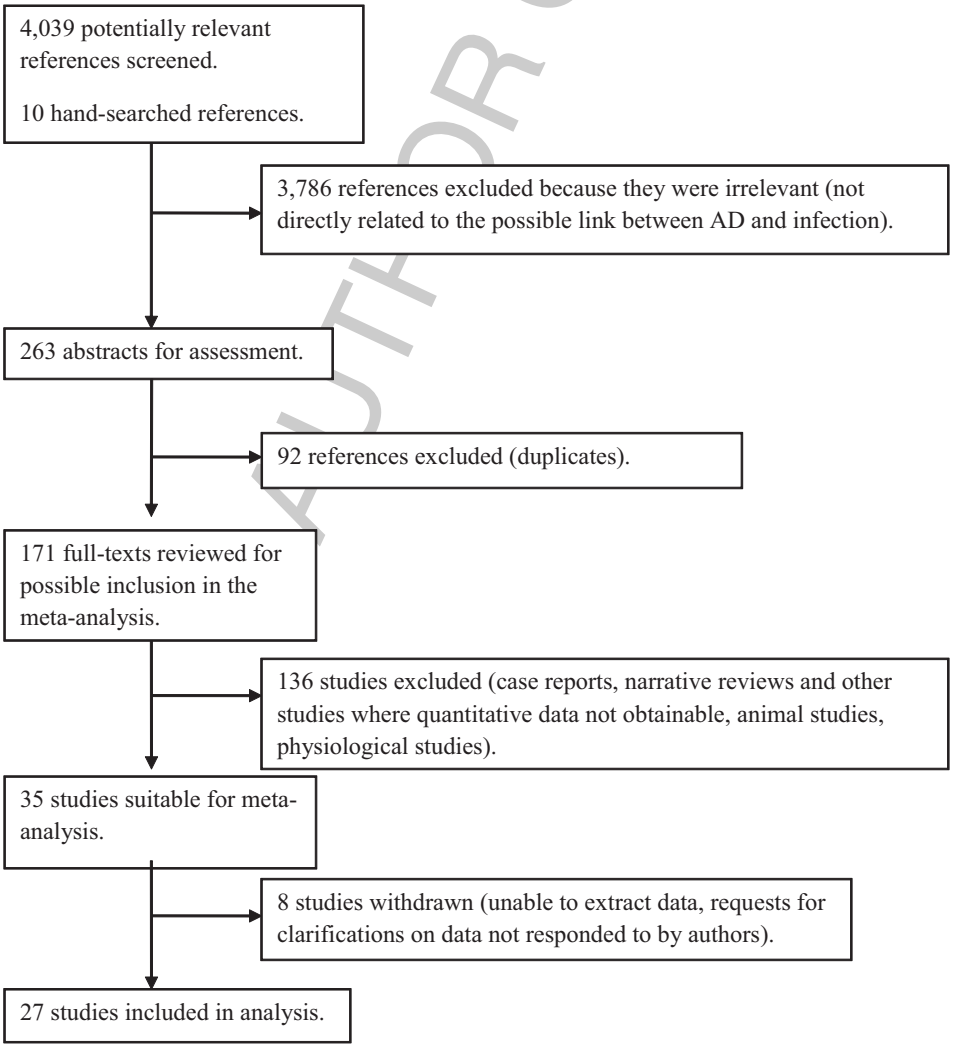

Fig. 1. Flow of included studies.

Table 1
Study characteristics

First author, year	Total sample size	AD cases	Control cases	Detection method for bacteria	Material tested	Country
Spirochetes						
Case-control studies						
Miklossy [17]	27	14	13	DF, culture, EM	Cortex, serum	Switzerland
Miklossy [16]	12	8	4	DF	Cortex	Switzerland
McLaughlin [20]	28	22	6	DF, EM	Serum	Canada
MacDonald [8]	2	1	1	IHC	Cortex	U.S.A.
Pappolla [29]	10	6	4	EM, IHC	Cortex	U.S.A.
MacDonald [49, 50]	11	10	1	PCR, IHC	Cortex	U.S.A.
Riviere [51]	34	16	18	PCR	Cortex	U.S.A.
Marques [30]	30	15	15	PCR	Cortex	U.S.A.
Galbussera [21]	98	50	48	IFA	Serum	Italy
Marquard [52]	200	100	100	ELISA, Wbl	Serum	Germany
Pappolla[a] [29]	47	16	31	ELISA, IFA	CSF	U.S.A.
Miklossy [18]	14	10	4	IHC	Cortex	Switzerland
Miklossy [19]	42	32	10	IHC	Cortex	Switzerland
Case series						
Gutacker [53]	27	27	0	ELISA, Wbl	Serum	Switzerland
Gutacker[a] [53]	10	10	0	PCR, DF	Cortex	Switzerland
Chlamydophila pneumoniae						
Case-control studies						
Balin [35]	38	19	19	PCR	Cortex	U.S.A.
Gérard [25]	52	25	27	PCR	Cortex	U.S.A.
Hammond [54]	10	5	5	IHC	Cortex	U.S.A.
Mahony [26]	31	21	10	PCR	Cortex	Canada
Nochlin [22]	25	12	13	ICC, PCR	Cortex	U.S.A.
Paradowski [44]	104	57	47	PCR	CSF	Poland
Ring [23]	20	15	5	PCR	Cortex	U.S.A.
Taylor [24]	11	9	2	PCR, IHC	Cortex	U.K.
Wozniak [27]	20	4	16	PCR	Cortex	U.K.
Yamamoto [55]	93	61	32	ELISA	Serum	Japan
Ecemis [56]	104	54	50	ELISA	Serum	Turkey
Randomized controlled trials						
Loeb [45]	82	82	0	IFA	Serum	Canada
Case series						
Gieffers [57]	20	20	0	PCR, ICC	Cortex	Germany
Dreses-Werringloer [58]	2	2	0	PCR, culture	Cortex	U.S.A.

CSF, cerebrospinal fluid; DF, dark field microscopy; ELISA, enzyme-linked immunosorbent assay; EM, electron microscopy; ICC, immunocytochemistry; IFA, immunofluorescence assay; IHC, immunohistochemistry; PCR, polymerase chain reaction; Wbl, western blot.

Table 2
Sub-group analyses

OR (& 95% CI) unless otherwise stated	Spirochetes (all studies, primary analysis)	Spirochetes (conservative, secondary analysis)	Cpn
Region: Europe	58.55 (5.63–609.12)	4.35 (1.92–9.85)	2.19 (0.52–9.19)
Region: North America	4.55 (1.53–13.53)	4.55 (1.53–13.53)	19.52 (3.82–99.75)
Detection method: dark field microscopy	41.86 (0.62–2843.94)	0.91 (0.03–25.07)	N/A
Detection method: ELISA	3.94 (1.84–8.41)	3.94 (1.84–8.41)	1.30 (0.71–2.38)
Detection method: IHC	37.40 (1.32–1063.28)	2.20 (0.11–45.89)	15.40 (0.56–425.55)
Detection method: PCR	11.02 (2.13–56.94)	11.02 (2.13–56.94)	9.95 (2.45–40.32)
Percentage of AD cases with infection detected (&95% CI): combined brain, CSF, sera examinations	38% (17–65%)	15% (5–33%)	50% (32–69%)
Percentage of AD brains with infection detected (&95% CI)	55% (18–87%)	23% (4–68%)	41% (14–74%)

We found a significantly increased occurrence of AD when infection with either spirochetes or Cpn was detected.

AD and spirochetes or Cpn

Our analysis demonstrated over a ten-fold increased occurrence of AD when there is detectable evidence of spirochetal infection (see Fig. 2). The pooled odds ratio was 10.61 (95% CI: 3.38–33.29) although a moderate degree of heterogeneity was detected ($I^2 = 51.77$, $p = 0.02$). Four studies found to contribute to this heterogeneity were excluded in a sensitivity analysis to produce a conservative risk estimate (see Fig. 3) with an OR of 4.45 (95% CI: 2.33–8.52) [16–19]. No heterogeneity was detected in this conservative result ($I^2 = 0.00\%$, $p = 0.63$) and Egger's regression suggested no evidence of publication bias ($p = 0.23$).

We found over a five-fold increased occurrence of AD when there is detectable evidence of Cpn infection (see Fig. 4). The pooled odds ratio was 5.66 (95% CI: 1.83–17.51) although notably a high degree of heterogeneity was detected ($I^2 = 73.42\%$, $p < 0.001$). Egger's regression suggested no evidence of publication bias ($p = 0.28$).

Table 2 summarizes the key results of subgroup and other analyses performed, including assessment of the impact upon the risk estimate of region, bacterial detection method, and the material type tested.

DISCUSSION

This is the first meta-analysis to investigate the possible association between AD and bacterial infection. We found over a ten- and five-fold increased occurrence of AD when there is evidence of spirochetal or Cpn infection, respectively. The association between infection and AD is stronger in studies based on testing of brain samples compared to studies analyzing serum samples. Our findings suggest that infection with these bacteria increases the risk of developing AD. Although it remains unclear whether there is a cause and effect relationship or whether infection is a risk factor for AD, given the strength of associations found in the present meta-analysis it is unlikely that infections with Cpn and spirochetes in the context of AD are coincidental findings.

One possible contribution to the development of the heterogeneity present in the spirochetal results of the primary analysis and the Cpn results is the methodological differences between the studies meta-analyzed. For example, the material examined ranged from samples of brains, to sera and CSF. Further, there were differing detection methods utilized to diagnose infection, including PCR, immunohistochemistry, and ELISA. For both spirochetes and Cpn, studies assessing infection status based on examination of brain samples such as by PCR yielded considerably stronger associations with AD than serology-based studies. This is particularly significant because PCR analyses for bacterial DNA definitively establish the bacteria's presence in the brain, whereas serology-based findings of the presence or otherwise of antibodies cannot confirm or exclude bacterial presence in the brain. Further, serological testing is not performed for all types of spirochetes, and in fact such tests are lacking for the majority of oral spirochetes. This suggests that standardized detection methods would assist in developing more precise and accurate risk estimates.

The positive associations found in the present meta-analysis need to be considered in the context of a number of studies having failed to find significant differences in Cpn and spirochete infection rates between AD and control cases [20–24]. The cause for the conflicting conclusions between these studies and others that have found very strong associations between infection and AD is likely to be multifactorial. Methodological differences between studies and the lack of standardized techniques are likely key factors. It has been postulated that one of the reasons why some groups have not had success in finding evidence of infection in AD brains is a low sensitivity of PCR analyses when sufficient replicate testing is not performed [25, 26]. Further, obtaining DNA of a sufficiently high quality for PCR from paraffin-embedded or other fixed tissue is notoriously more difficult than from frozen brain samples and this may also help to account for the diverse results given that some studies involved fixed tissue samples [25, 27].

Additionally, spirochetal and Cpn bacteria may be present only in small, focal regions of brains such that testing may yield negative results despite repeated and methodical testing of the same specimens [27]. Differences in DNA preparation such as whether proteases were used and differing cut-off values of immunoglobulin titers could also help explain the contradictory results [28]. In both the early and late phases of infection with the Lyme disease-causing spirochete *Borrelia burgdorferi*, the antibody levels may be within normal limits thus suggesting that direct measurement of antigens within the brain may be needed to confirm serology results [21]. Thus, a standardized set of protocols and procedures for assessing infection status seems key to the development of more definitive

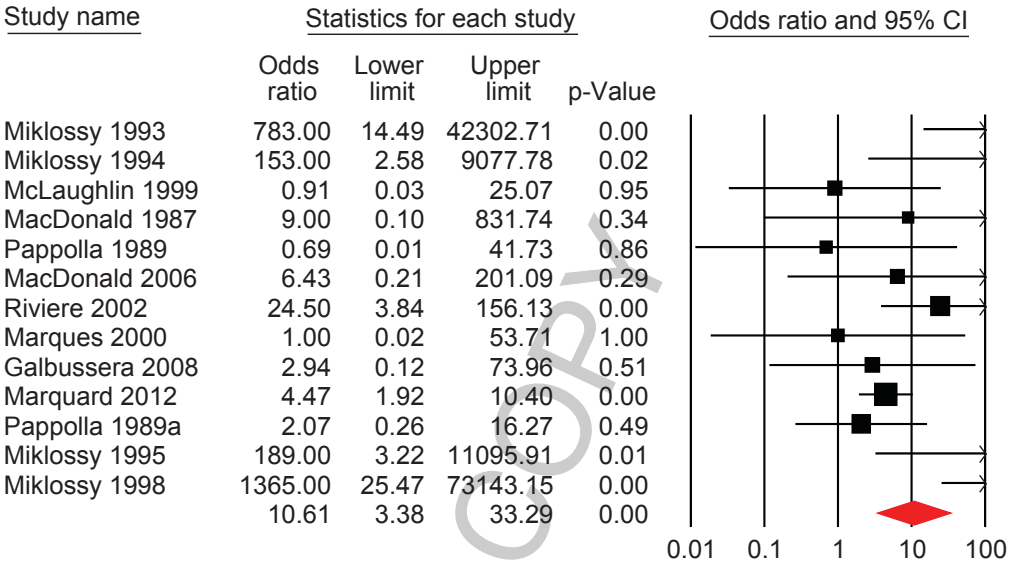

Fig. 2. Spirochetes and AD, a risk estimate with inclusion of all studies. The pooled odds ratio of 10.61 demonstrates a statistically significant association of spirochetes with AD ($p < 0.05$, $I^2 = 51.77$).

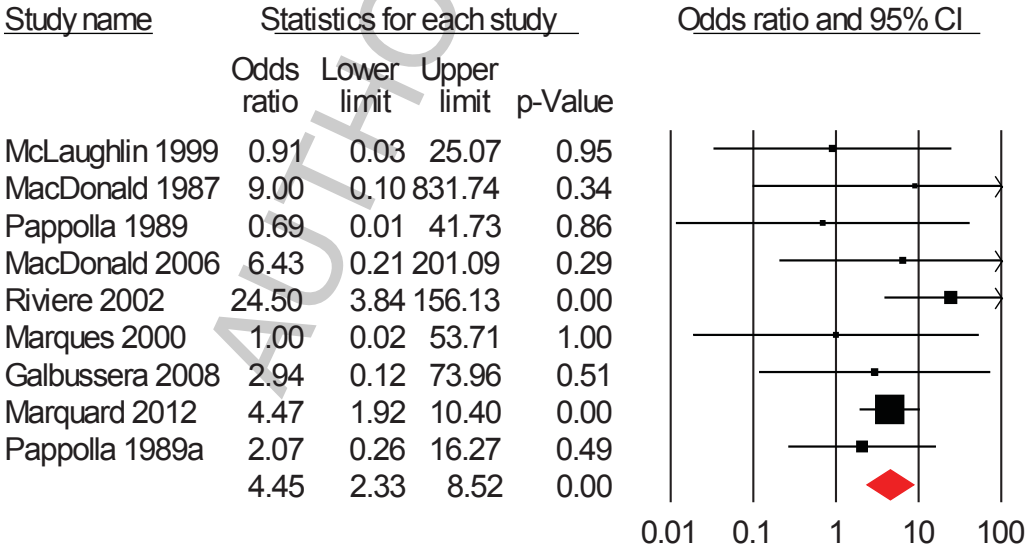

Fig. 3. Spirochetes and AD, a conservative risk estimate: the pooled odds ratio of 4.45 still demonstrates a statistically significant association of spirochetes with AD ($p < 0.05$, $I^2 = 0.00$).

conclusions regarding the contributions of bacterial infections to AD pathogenesis. Another possible contributor to the diverse results in existing spirochetal studies is that a number of studies found AD and control cases to be negative specifically for the spirochete *Borrelia burgdorferi* whereas other spirochetes were not tested for [21, 29, 30]. Importantly, their results leave open the possibility of spirochetes other than *Borrelia burgdorferi* having been present differently in AD and control cases. Their methodologies contrast to the methodologies used in two of the studies whose exclusion in a secondary analysis reduced the heterogeneity to undetectable levels, with all types of spirochetes being tested for in the latter two studies [16, 17]. This may help to explain the moderate degree of heterogeneity within the spirochetal data in the primary analysis.

The amyloid cascade hypothesis of AD pathogenesis has been the most dominant hypothesis for AD and

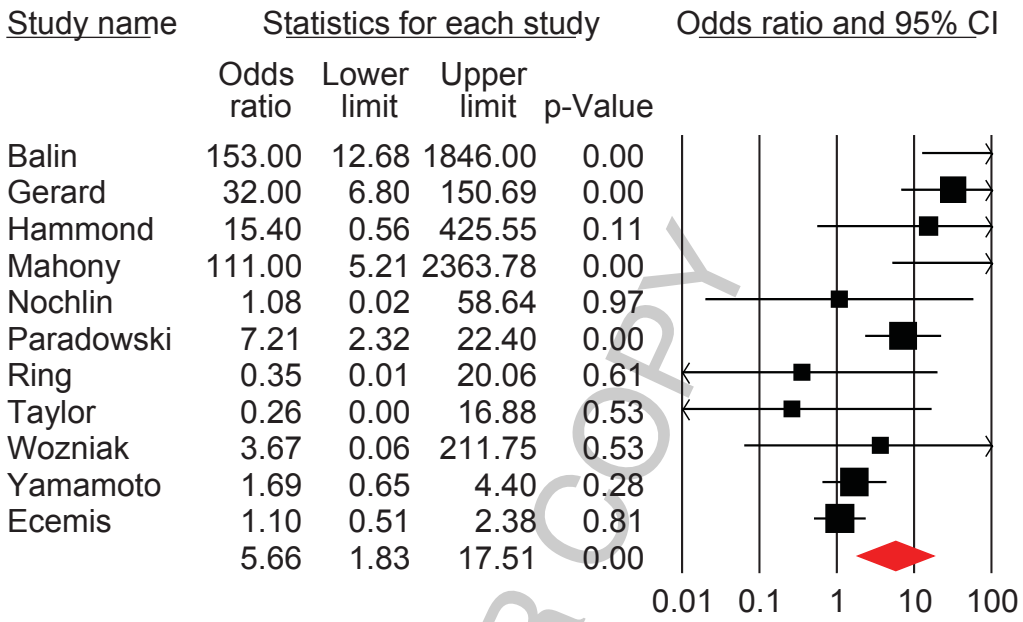

Fig. 4. Cpn and AD: the pooled odds ratio of 5.66 demonstrates a statistically significant association of Cpn with AD ($p < 0.05$).

it describes the accumulation of the amyloid-β peptide (Aβ) leading to neuronal death and dysfunction and consequently dementia [31]. Whilst familial AD is known to be caused by genetic mutations resulting in increased amyloid accumulation, the late-onset form of AD (LOAD) has been shown not to directly arise from an identical or other genetic defect, thus making it likely that the pathogenesis of LOAD is a multifactorial process [31]. The type 4 allele of the apolipoprotein E gene (APOE ε4) is a strongly confirmed genetic risk factor for LOAD [32]. This genetic predisposition represents one factor which may determine the outcome of infection with Cpn and spirochetes. Thus a synergistic action of bacterial infection with factors such as the carriage of APOE ε4 may cause the development of AD. Parallels may then be drawn between AD and other disease entities such as tuberculosis where microbes infect some people only asymptomatically and cause disease in other individuals due to other factors causing increased susceptibility to disease.

Apart from respiratory infections, Cpn has also been associated with chronic inflammatory diseases and atherosclerosis, although its exact role has been difficult to establish in most chronic disease contexts and thus its role has not drawn widespread support within the clinical and research communities [33]. A key basis for the chlamydial infection hypothesis for AD is that the organism can switch from an acute replicative phase to a state of chronic, latent infection, provoking neuroinflammation that precedes or coincides with the deposition of Aβ [3]. While Cpn infection can cause cell death by necrosis, it can also inhibit apoptosis and thereby sustain a prolonged neuronal infection and contribute to chronic inflammation in the brain [34]. Chronic infection in the AD brain may promote amyloidogenesis.

Many cell types in the AD brain have been found to be infected with Cpn of confirmed viability and metabolic activity, including monocytes, neurons and glial cells [25, 35]. The latter may be evidence of infection-initiated inflammation contributing to AD pathology given that the stress response of glial cells involves the production of reactive oxygen species and pro-inflammatory cytokines [31]. Cpn-infected cells were found to co-localize closely with both neuritic senile plaques (NSPs) and neurofibrillary tangles (NFTs) in one of the studies incorporated into the meta-analysis [25]. Cpn has also been identified by immunohistochemistry in the olfactory neuroepithelia, bulbs, and endothelia of mice and the brains of the mice inoculated with Cpn were shown to undergo Aβ deposition [36]. This suggests that the olfactory pathway may be a mode of Cpn entry into the central nervous system and that Cpn may be capable of accelerating or inducing AD-like pathology [36]. A higher Cpn load being found in the brains of ε4-carrying AD patients

compared to non-ε4 carrying patients is significant given that carriage of the APOE ε4 is a well-established risk factor for AD [37]. This suggests there is a link between Cpn infection, the product of the APOE ε4 allele and AD.

Analogously to Cpn, spirochetes have been implicated in a number of chronic inflammatory conditions in body tissues other than in the brain, including periodontitis and ulcerative gingivitis [38]. It is widely accepted that chronic infections caused by spirochetes such as *Treponema pallidum* can cause chronic neuropsychiatric disorders including dementia. First investigated in 1913, it is now well-established that in a late-stage form of syphilis known as general paresis, *Treponema pallidum* causes dementia by inducing cortical atrophy, microgliosis, and amyloid deposition [39]. Dementia has also been reported to occur in Lyme disease, caused by the spirochete *Borrelia burgdorferi* [40]. Spirochetes have been found intracellularly within neurons and glial cells and capable of establishing chronic infection and causing cellular dysfunction and apoptosis [41]. A rigorous experimental exposure of primary mammalian neuronal and glial organotypic cell cultures to *Borrelia burgdorferi* spirochetes was found to induce the pathological hallmarks of AD including Aβ deposition, increased levels of amyloid-β protein precursor (AβPP) and hyperphosphorylated tau in the form of NSP- and NFT-like structures [42].

A study used in the generation of the meta-analysis that found evidence of spirochetal infection in all 14 of its AD brains and in none of its 13 control brain tissue samples also found that the spirochetes in the AD cases demonstrated positive immunoreaction with a monoclonal antibody targeted against AβPP [17]. This indicates that spirochetes may contain AβPP and thus the pathogens may be the source of excess Aβ in the AD brain [17]. A parallel can be drawn with HSV1, as AβPP has been an identifiable component of HSV1 intracellular viral particles although it is unclear whether AβPP joins HSV1 particles *in vivo* or during procedures to isolate the virus [43]. A study supporting the role of spirochetes in AD found that bacterial peptidoglycan (an inflammatory and amyloidogenic cell wall component of bacteria including spirochetes) co-localizes with the Aβ in NSPs and NFTs [19]. Morphologically, the senile plaques were observed to be similar to spirochetal colonies in the cortex in established spirochetal disease [19]. These observations collectively implicate Cpn and spirochetal infection in the development of the hallmark neuropathology of AD, although the exact mechanisms by which the bacteria may contribute to neuronal cell injury and death and Aβ accumulation continue to be investigated.

It has been suggested that an impaired blood-brain barrier in the AD brain may facilitate entry of bacteria thereby causing the differences in the positive results of AD patients and control cases rather than the bacteria contributing to the pathogenesis of AD [44]. An important direction of future research would be to conduct prospective, longitudinal studies which would enable an observation of the temporal order of infection and AD development and to enable more definitive conclusions to be drawn on whether a causal relationship exists between AD and spirochetal or Cpn infection.

The present study has several strengths. First, our systematic search of multiple, major databases combined with a hand-searching of references meant that our literature search was exhaustive in an attempt to gather together all the available evidence on the possible association between bacterial infection and AD. Second, authors of individual studies were contacted to clarify information from original articles in order to maximize the validity of our results. Third, data was sought on all bacteria with relevant literature as opposed to a focus on one bacterial group. For this reason, we believe the data collection considered a wide range of cases.

Our study also has limitations. The relatively small sample sizes in the studies meta-analyzed meant that the statistical power to detect an association between bacterial infection and AD was somewhat attenuated during the meta-analysis. Therefore the study findings should be interpreted with caution in view of the increased likelihood of a Type 1 error. Also, crude odds ratios were used in our analysis where adjusted odds ratios were not provided in studies, thus leaving the analysis potentially vulnerable to confounding variables not taken into account in the original studies. Another limitation of this meta-analysis is that studies wherein bacterial presence was assessed by examination of brains were grouped with studies based on serological analysis during the creation of one set of pooled data for each bacterial group. Nevertheless, our study results have some important implications for clinical practice and the development of therapeutic strategies. A randomized controlled trial showed that combination treatment for 3 months with antibiotics active against Cpn was found to reduce cognitive deterioration at 6 months of follow-up in patients with mild to moderate AD [45]. At the present time, further confirmation of the association between bacterial infection and AD is required before treatment with such antibiotics and/or anti-inflammatories of at-risk

populations or following early diagnosis can be fully justified.

The importance of a standardization of the techniques and protocols used to assess infection with Cpn, spirochetes, and other bacteria in future studies is further highlighted given the inconsistencies within the existing literature. The seropositivity for *Borrelia burgdorferi* is plausibly very low in the general population meaning that a very large sample size ideally needs to be recruited in order to develop sufficient statistical power to confirm the results of the present meta-analysis for that spirochete [21]. We also recommend future studies investigating this hypothesis have larger sample sizes in order to reduce sampling error. Strong positive associations have been reported between AD and infections with *Helicobacter pylori*, periodontal pathogens, and *Toxoplasma gondii* [46–48]. We advocate for further studies to be done to confirm these associations given the paucity of existing data for these bacteria. Demographic differences between patients groups including geographic location may be a factor in the inconsistent data on the association of bacterial infection with AD. The majority of the studies meta-analyzed were from North America or Europe, so future studies conducted in other regions may provide further insight on the association between bacterial infection and AD.

The aging of the global population means that the social and economic burdens associated with AD will grow alongside the dramatic increase in the number of people with AD, making invaluable any advances in better understanding this disease to aid efforts to develop disease-modifying treatments. The results of our meta-analysis clearly justify the value of further, thorough testing of the bacterial hypothesis for AD.

DISCLOSURE STATEMENT

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=2439).

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