



Critique of “Morgellons Disease Etiology and Therapeutic Approach: A Systematic Review” Using Artificial Intelligence to Eliminate Bias

Marianne J Middelveen¹, Melissa C Fesler², Raphael B Stricker^{2*}

Abstract

Background: Morgellons disease (MD) remains a highly contested clinical entity, polarized between a dominant psychiatric etiologic paradigm (pro-psychiatric) and an emerging infectious etiology model (pro-infection). A recent systematic review by Beuerlein et al. (2021) concluded that available literature overwhelmingly supports the psychiatric framework and treatment with low-dose antipsychotic interventions. However, the methodological objectivity of this synthesis warrants critical appraisal.

Objective: Our goal was to evaluate the conceptual framework, evidence hierarchies, search strategy, and appraisal standards applied by Beuerlein et al. (2021) to determine whether equivalent standards of scientific rigor were maintained across the competing etiological models.

Methods: A systematic audit was conducted on the 25 papers included in the 2021 review, alongside an analysis of crucial peer-reviewed, molecular, histopathological, and comparative pathology studies that were omitted from the synthesis. We reassessed the same studies examined in the review using the Joanna Briggs Institute (JBI) framework, and we confirmed our findings using Google Gemini artificial intelligence (AI). The diagnostic parameters and baseline controls of both pro-psychiatric and pro-infectious studies were evaluated for errors using AI.

Results: The audit revealed a pervasive, asymmetrical application of peer-review standards. Beuerlein et al. penalized empirical, host-derived tissue studies for minor reporting brevity while uncritically validating unblinded, retrospective psychiatric chart reviews operating with an absolute baseline of zero experimental controls or healthy-tissue comparisons. Furthermore, the review committed a conceptual category error by filtering literature through an “infestation” lens, ignoring or downplaying reproducible, multi-center data demonstrating intracellular *Borrelia* sequestration within the deep stratum basal, complex dual-species biofilm architectures, and biological filament production and pigmentation. Additionally, the review relied heavily on single-patient case reports (n=1) to advocate for psychiatric interventions while dismissing early pilot pathology studies (n=3 or 4) as statistically underpowered, and fell victim to the therapeutic fallacy by conflating neuroleptic symptom-masking with disease etiology. We found that the pro-infectious etiology model was assessed more favorably than the pro-psychiatric model by AI using the JBI framework.

Conclusion: The pathogenesis of Morgellons disease remains unresolved in the medical literature. By treating negative clinical assumptions as definitive truth while dismissing reproducible, blinded, and controlled tissue architecture as secondary artifacts of scratching, Beuerlein et al. (2021) authored a narrative defense of a preferred paradigm rather than an objective systematic meta-analysis. Future research must abandon the uncritical lumping of psychiatric registries and directly evaluate the condition through standardized case definitions and orthogonal, tissue-based molecular diagnostics. Using AI for future analysis of polemic topics warrants further investigation.

Affiliation:

¹Atkins Veterinary Services, Calgary, AB, Canada

²Union Square Medical Associates, San Francisco, CA, USA

*Corresponding author:

Raphael B Stricker, Union Square Medical Associates, San Francisco, CA, USA.

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Introduction and Central Critique

Systematic reviews are widely considered the most rigorous method for synthesizing research evidence. They play a central role in evidence-based medicine, social and educational policymaking, and the development of practice guidelines, informing critical decisions related to patient treatment, resource distribution, and other areas. As a result, inadequately conducted or poorly reported systematic reviews can have far-reaching consequences for both policy and practice [1]. The importance of methodological rigor is particularly evident in areas of ongoing scientific controversy, where competing interpretations of the available evidence may influence clinical practice and future research directions.

Morgellons disease (MD) represents one such controversy and remains the subject of two competing etiological perspectives: the dominant psychiatric model and a minority infectious disease model. Given the substantial disagreement surrounding the condition, systematic reviews have the potential to play an important role in evaluating the relative strength of the available evidence and clarifying areas of uncertainty.

In their systematic review, Beuerlein, Balogh, and Feldman [2] concluded that the available literature more strongly supports a psychiatric etiology and that low-dose antipsychotic medications currently have the strongest evidence base for treatment [2]. However, despite being presented as an unbiased systematic review, the paper functions largely as a narrative review of the psychiatric-versus-infectious debate rather than a rigorous comparison of evidentiary strength. Studies employing fundamentally different forms of evidence are frequently treated as having equivalent scientific weight despite substantial differences in methodology and evidentiary value. Consequently, the review favors psychiatric interpretations while giving comparatively limited consideration to evidence supporting an infectious etiology.

These methodological concerns are particularly evident in the review's attempt to frame Morgellons disease as a psychiatric disorder. Evidence commonly cited in support of a psychiatric model, including lesion morphology, psychiatric comorbidity, substance use, histopathological findings, fiber analyses, and responses to antipsychotic treatment [2] does not establish that Morgellons disease is primarily psychiatric in origin. Each of these observations is compatible with biological, neurological, or infectious explanations, and none directly demonstrates that psychiatric pathology is the underlying cause of the condition. Consequently, the evidence cited in support of a psychogenic etiology remains open to

alternative interpretations and falls short of conclusively establishing a psychiatric explanation.

A further limitation of the review by Beuerlein et al., [2] is its reliance on a largely binary framework in which Morgellons disease is presumed to be either psychiatric or infectious in origin. This approach leaves little room for potential interaction between biological and psychological processes and may oversimplify the pathophysiology of the condition. The assumption is particularly problematic because spirochetal organisms such as *Borrelia burgdorferi* and treponemes are capable of invading the central nervous system and producing neuropsychiatric symptoms through neuroinflammation, neurotransmitter dysregulation, and direct neurological injury [3]. Within such a model, psychiatric symptoms are not evidence against an infectious etiology but may instead represent manifestations of the underlying disease process [4]. The presence of psychiatric features cannot, by itself, be considered sufficient evidence for a primary psychogenic explanation of Morgellons disease. Therefore, given the influence that systematic reviews can exert on clinical understanding and treatment recommendations, a critical appraisal of the review by Beuerlein et al. [2] is necessary to assess the validity of its methods, interpretations, and conclusions regarding Morgellons disease. Our analysis used Google Gemini AI to help with interpretation of the evidence presented by analysis using Joanna Briggs Institute (JBI) critical appraisal tools [5].

Methodological and Conceptual Problems in Beuerlein et al. [2]

Search strategy, inclusion criteria, and case definition

The review authors searched PubMed for English-language studies published between January 2010 and April 2021 using the terms Morgellons, delusional infestation and fibers, and delusions of parasitosis and fibers. Reference lists were also reviewed. After independent screening by two reviewers, 25 studies met inclusion criteria. Eligible studies involved reported infestations with inanimate material and addressed either disease pathophysiology or treatment.

The review characterizes the pro-psychiatric literature as more substantial than the pro-infection literature; however, the evidence presented does not clearly support this conclusion. Of the 16 studies examining etiology, seven supported a psychiatric explanation and nine supported an infectious explanation. This rebuttal focuses on these 16 etiological studies (Table 3). The remaining nine articles primarily evaluated treatment efficacy rather than disease causation. Notably, despite substantial differences in methodology, study design, and evidentiary content, all studies received the same Oxford Level 4 evidence rating.

A central methodological concern is the use of “infestation” as an inclusion criterion. Researchers

supporting an infectious etiology do not describe Morgellons disease as an infestation with fibers. Rather, they view the fibers as endogenous biological structures, primarily keratin and collagen filaments, produced by the patient's own cells in response to infection, particularly by *Borrelia* species [6]. Within this framework, the fibers are pathological tissue manifestations rather than external contaminants. Applying the term “infestation” to studies advancing an infectious hypothesis imposes a psychiatric construct on a biologically based model and risks introducing bias by defining the infectious hypothesis in terms its proponents explicitly reject.

The debate is further complicated by fundamentally different case definitions. Studies supporting an infectious etiology typically define Morgellons disease by the objective presence of embedded or projecting cutaneous fibers. In contrast, studies supporting psychiatric etiology generally place the condition within the framework of delusional infestation (DI), emphasizing a false belief that fibers or other inanimate materials are infesting regardless of objective clinical findings. Consequently, the two bodies of literature may not be examining the same patient population and may, in some cases, describe different clinical entities.

This distinction has important implications for interpreting the evidence. If one body of literature defines Morgellons disease by observable dermatologic findings and the other by a psychiatric construct, direct comparison becomes problematic. Conclusions regarding etiology are therefore limited by the absence of a consistent case definition, and the review cannot assume that all included studies investigate a single, uniformly defined disorder.

Evidence appraisal

Concerns regarding case definition are compounded by the approach of Beuerlein et al. to evidence appraisal. In their methodology, the authors state that they applied the Oxford Centre for Evidence-Based Medicine Levels of Evidence, assigning all included studies a Level 4 classification [7]. They further note that risk of bias was assessed through consideration of both “author associations” and methodology. However, this description lacks transparency and reproducibility, as no explicit criteria are provided for how methodological quality or author affiliations were evaluated.

The quality-assessment approach substitutes established principles of scientific study appraisal with subjective and insufficiently defined criteria. By introducing “author associations” as a marker of potential bias alongside the broad Oxford hierarchy, the review creates an appearance of methodological rigor without providing a transparent framework for assessment. In evidence-based research, the evidentiary value of a study is generally determined by its internal validity, methodological design, completeness of reporting, and reliability of the underlying data. In

contrast, the review appears to place weight on the identity or institutional affiliations of investigators without clearly explaining how such factors were assessed or incorporated into bias evaluations. Placing more value on author credentials or affiliations rather than the content, rigor and findings of each study suggests potential bias that may result in data misinterpretation.

This approach of Beuerlein et al. [2] contributed to an overly homogenized interpretation of heterogeneous literature. By relying on a broad evidentiary hierarchy while applying undefined bias criteria, the review risks obscuring important methodological distinctions between studies. Consequently, highly controlled and independently replicated molecular investigations were evaluated alongside, or even discounted relative to, studies with more substantial methodological limitations, without a clearly articulated rationale.

Given that the evidence base consisted largely of case reports, case series, cross-sectional studies, and retrospective chart reviews, a structured critical appraisal framework such as that developed by the JBI would likely have provided a more appropriate and transparent method for assessing risk of bias [5]. Moreover, the authors did not report explicit criteria for evaluating methodological limitations, conflicts of interest, or other potential sources of bias. As a result, readers are given little insight into how individual studies were comparatively assessed beyond their placement within the Oxford hierarchy, limiting the transparency and reproducibility of the review's conclusions.

The limitations of this approach are reinforced by the nature of the Oxford framework itself. Oxford Levels of Evidence classify studies primarily according to design rather than methodological rigor. Because both the psychiatric and infectious Morgellons literatures consist largely of case reports and case series, most studies were assigned a Level 4 designation. While technically accurate within the framework, this classification obscures substantial differences in evidentiary strength. Studies employing polymerase chain reaction (PCR), DNA hybridization, electron microscopy, immunostaining, histopathology, microbial culture, control groups, and other laboratory methodologies were assigned the same evidentiary level as descriptive case reports and studies based largely on clinical observation.

The Oxford framework does not directly account for laboratory validation, analytical sophistication, reproducibility, blinding, or the use of positive and negative controls. As a result, studies producing direct biological evidence through molecular diagnostics, microbial detection, and tissue analysis were effectively evaluated within the same evidentiary category as studies relying primarily on subjective clinical observation, diagnostic exclusion, or psychiatric interpretation. Although both approaches have limitations, they do not generate the same type of evidence.

Laboratory investigations produce objective, measurable data regarding the presence or absence of biological phenomena. Diagnostic exclusion, by contrast, demonstrates only that alternative explanations have not been identified and does not directly establish the cause of a patient's symptoms. Treating these fundamentally different forms of evidence as methodologically equivalent risks obscuring important distinctions in evidentiary value.

Methodological Selection Bias and Evidence Asymmetry

Despite its stated commitment to transparency and objectivity, the review appears to apply methodological criticism unevenly across competing hypotheses. The same

categories of limitation small sample sizes, single-patient reports, preselected or geographically concentrated cohorts, unreported controls and blinding, and reliance on a narrow group of authors recur throughout the review, but they are treated very differently depending on which paradigm a study supports. Table 1 consolidates this asymmetry identified in this critique, so that the pattern can be assessed as a whole rather than piecemeal. Taken together, these patterns indicate that the same category of limitation is treated as disqualifying when found in a pro-infection study and as a minor or unremarked footnote when found in a pro-psychiatric study. This asymmetry, more than any single methodological choice, is the central weakness of the review's synthesis.

Table 1: The review's asymmetric application of methodological standards

Methodological issue	How it is used to criticize pro-infection studies	How the same issue appears in pro-psychiatric studies	Review's treatment / citations
Small sample size	Laboratory case series of 3–4 patients are repeatedly criticized as too small to support conclusions.	Three of the seven pro-psychiatric studies (Roncati et al., Ohn et al., Yu et al.) are single-patient (n=1) case reports, which have no statistical power at all.	The n=1 reports are incorporated into the evidentiary base for a psychiatric conclusion [8-13].
Reuse / overlap of subjects across studies	Cited as a limitation of several pro-infection case series.	The pro-infection literature progressed from cohorts of 3–4 patients to studies of 25, 29, 30, and eventually 60 and 1,000 patients — evidence of an expanding, not static, research program; transparent subject data was provided; therefore, overlap was disclosed.	Not raised as a comparable concern for the two Mayo Clinic studies in the psychiatric literature. [8-10, 14-16]
Preselected / specialized populations	Pro-infection studies recruited from Lyme-focused practices are criticized for selection bias.	Hylwa et al. and Foster et al. recruited only patients already diagnosed with delusional infestation; Mohandas et al. drew exclusively from a psychodermatology clinic; the CDC study identified cases using predefined psychiatric classifications (“delusional infestation,” “delusions of parasitosis,” “psychogenic parasitosis,” “neurosis”).	Comparable preselection in the psychiatric literature receives no scrutiny. [14,15,17-20]
Self-referred / advocacy-referred cohorts	Raised as a potential source of bias in pro-infection studies. Note: Referral pathway cannot alter an objective laboratory result; many pro-infection analyses performed on coded or blinded specimens, reducing the relevance of this concern	Not applied	Applied more readily to pro-infection recruitment than to psychiatric-clinic referral. [20]
Geographic concentration	Pro-infection studies conducted in limited regions (e.g., California, Texas) are criticized.	The CDC study (Northern California Kaiser Permanente), the Mayo Clinic studies (Minnesota), and Mohandas et al. (London) are equally regionally concentrated.	Except for the CDC study, overlooked for the psychiatric studies. [14,15,17-19]

Unreported controls / blinding	<p>A recurring criticism of pro-infection studies, several of which in fact used coded specimens, independent laboratories, and positive/negative controls.</p> <p>Note: JBI checklist does not require concurrent control groups for case series/reports at all; the pro-infection studies all exceeded JBI expectations.</p>	The CDC study, the two Mayo Clinic retrospective chart reviews (Hylwa et al. and Foster et al.) and the Mohandas, also lack blinded abstraction.	Controls and blinding mentioned for the CDC and Mohandas studies, but not for the 2 Mayo Clinic studies. [8-10,14,15,17,21]
Softened language used to characterize a methodological gap	Equivalent or lesser flaws in pro-infection studies are described in stronger terms (e.g. "improper research techniques," "skewed correlations")	Hylwa et al. "Complete lack of <i>Borrelia</i> testing". Mohandas et al. <i>Borrelia</i> testing in a small unstratified subgroup only; Roncati et al, describes <i>Borrelia</i> testing as "serology without rise", a meaningless result; Ohn et al., has a major contradiction and serious flaw (naming <i>Borrelia</i> PCR testing in the abstract and serology in the text)	Hylwa et al, lack of <i>Borrelia</i> testing softened to "serological and PCR testing for <i>Borrelia burgdorferi</i> was not completed" Roncati et al, softened to "ambiguous terminology", Ohn et al, softened to a "lack of congruency" no mention of flaw's seriousness. Mohandas testing limitations not mentioned [11,12,14, 18]
Author association / "single-source" bias	The pro-infection literature is discounted as originating from a small, recurring group of investigators (Middelveen, Stricker, Sapi, Fesler). Note: Testing performed across five independent, accredited laboratories on different continents (including blinded split-sample verification and participation in international proficiency programs).	No equivalent authorship-network scrutiny is applied to the psychiatric literature The author Ohn appears in two case studies. The authors Hylwa, Foster, Bury, Davis, Pittelkow, and Bostwick appear in both Mayo Clinic studies. Author repetition is present in 4/7 pro-psychiatric studies	Repetition of authors not mentioned in critiques column. [12-15]
Prevalence in population without Lyme disease not determined	Mayne, 2015 [22] discounted for not establishing Morgellons prevalence in the general population, Note: study was not designed as a general population prevalence study. Expecting cross-sectional general population data from a specialized clinical or survey-based design is a methodological mismatch	No equivalent is applied to other studies	[22]

Eligible pro-infection studies omitted from the review

Systematic reviews conducted under PRISMA principles should aim to identify and assess all relevant evidence, not selectively include studies that support a particular conclusion [23]. Including all relevant studies in a systematic review prevents biased conclusions and ensures that the final findings reflect the true state of the total available evidence. The systematic omission of eligible pro-infection literature introduces a profound selection bias that critically undermines the validity of the review's conclusions. The review omitted some mature, methodologically robust pro-infection studies while including early preliminary findings – a form of scholarly gatekeeping. By excluding peer-reviewed studies that present concrete molecular, spectroscopic, and

immunohistochemical (IHC) data, the review manufactures an artificial consensus that shields the pro-psychiatric paradigm from its primary empirical counter arguments. This selective filtering skews the medical narrative in two distinct ways: first, it creates a false impression of an evidentiary deficit within the pro-infection-disease literature; second, it presents a false equivalence between the two positions by replacing a legitimate, data-driven microbiological dispute with a one-sided diagnostic assumption by default. Ultimately, by scrubbing the literature of positive, constructive evidence, the review fails to meet the basic standards of an objective systematic overview, choosing instead to sustain an exclusionary psychiatric narrative over tangible biological proof [2, 23].

Table 2 summarizes the six studies identified as meeting the review's own stated inclusion criteria (or falling within its described search expansion), yet absent from its synthesis. Full descriptions of each study are provided in Appendix A.

Table 2: Eligible pro-infection studies omitted from the review.

Study	Relationship to stated inclusion criteria	Key finding	Why the omission matters
Middelveen, Rotaru, McMurray et al. (2016) [24]	Not directly indexed in PubMed, but cited within publications the review did include and discoverable via its own reference-search procedure.	<i>Borrelia burgdorferi sensu stricto</i> detected in filament-associated lesions in 9 dogs; healthy controls negative.	Comparative veterinary evidence that filament-associated pathology occurs independent of human belief, expectation, or psychiatric interpretation.
Middelveen and Stricker (2016) [6]	Met all stated criteria: English language, PubMed-indexed, contains "Morgellons," within review period, addresses etiology/pathophysiology.	Spirochetes in dermatological tissue; Congo Red staining suggestive of amyloidosis; independent University of Akron scanning electron microscopy (SEM)/transmission electron microscopy (TEM)/Raman analysis concluding fibers were human-derived, not textile.	Excluded evidence, from investigators outside the core Morgellons research group, supporting a biological (non-contaminant) origin for the filaments.
Middelveen, Fesler, and Stricker (2018) [4]	Met all stated criteria.	Historical critique arguing landmark pro-psychiatric studies were methodologically flawed, including failure to conduct fiber analyses or comprehensive tick-borne serology before classifying patients as "delusional."	Directly addressed the central etiological dispute the review purports to resolve.
Middelveen, Sapi, Burke, Filush et al. (2018) [25]	Not indexed under "Morgellons," but the review states it expanded its search "beyond keyword strings" via hand-searching reference lists — a method that would have surfaced this paper given the small number of contributing investigators.	Positive PCR and culture findings from two Morgellons subjects, including blinded confirmation of a culture specimen by Dr. Alan Barbour's laboratory (UC Irvine).	Directly rebuts the claim that pro-infection molecular findings lack independent verification.
Middelveen, Martinez, Fesler et al. (2020) [26]	Met all stated criteria.	First formal clinical classification/staging system for MD (modeled on syphilis); intracellular <i>Borrelia</i> antigens identified in keratinocytes, macrophages, and MD filaments across 16 patients.	One of the more comprehensive biological investigations available during the review period.
Middelveen, Haggblad, Lewis et al. (2021) [27]	Published slightly after the stated search cutoff, but the review states literature available during manuscript preparation was considered, and this paper was available well before the review's publication.	Erythema migrans lesion with biofilaments and intracellular <i>Borrelia</i> ; confirmed via histochemical, immunostaining, serological, and molecular analyses across multiple North American laboratories.	Directly examined the proposed <i>Borrelia</i> -filament relationship central to the review's conclusions.

Biological evidence minimized in the review's synthesis

The review's final synthesis emphasizes pro-psychiatric interpretations while devoting comparatively little attention to biological findings reported in the pro-infection literature. Although many of the pro-infection studies reported objective laboratory, histological, molecular, and microbiological findings, these observations were often discussed briefly and played only a limited role in the review's final conclusions.

The biological findings reported across the pro-infection literature fall into four recurring categories: (1) evidence that Morgellons filaments are host-derived biological structures rather than textile contaminants, (2) molecular and histological detection of *Borrelia* and other microorganisms in tissue, (3) proposed polymicrobial and biofilm-associated disease mechanisms, and (4) evidence derived from tissue-based detection methods that may not be captured by conventional serological testing.

Collectively, these findings constitute a substantial component of the infectious-disease literature and are directly relevant to the etiological questions addressed by the review. They warrant careful consideration within any balanced assessment of competing hypotheses. By giving limited attention to these findings in its final synthesis, the review's conclusions place greater emphasis on psychiatric interpretations while underrepresenting the cellular, molecular, microbiological, and histopathological evidence reported in support of an infectious etiology.

Overview of the 16 Etiology Studies

Table 3 maps all 16 studies the original review used to address etiology seven supporting a psychiatric interpretation and nine supporting an infectious interpretation consecutively. All 16 were assigned the same Oxford Level 4 rating in the review despite the differences in design and method visible below.

Table 3: The 16 etiologic studies assessed by the review.

Study	Design / N	Etiology supported	Key methods	Review's stated critique (verbatim where quoted)
Pearson et al., 2012 (CDC study) [17]	Cross-sectional; 115 identified, 40 completed evaluation, 12 fiber-analyzed.	Psychiatric	SEM- Energy-Dispersive X-ray Spectroscopy (EDXA) fiber analysis; VIDAS enzyme immunoassay (EIA) + <i>Borrelia</i> testing limited to insensitive two-tiered Western blot serology. No tissue staining, no PCR, no culture was performed for <i>Borrelia</i> spp. although was performed for other organisms.	Positive and negative controls for serology not reported, PCR performed only when pathogen detected by tissue staining. Severe attrition rate not mentioned.
Hylwa et al., 2012 [14]	Retrospective case series (Mayo); N=80 (54 DI patients).	Psychiatric	H&E light microscopy on 20/80 specimens, testing for borreliosis not performed at all.	"Biopsy results not stratified"; "bacterial species in cultures not specified"; "serological and PCR testing not completed".
Foster et al., 2012 [15]	Retrospective case series (Mayo); N=147.	Psychiatric	Clinical/demographic characterization only; no microbiological testing performed at all.	"Serological testing and PCRs for <i>Borrelia burgdorferi</i> were not performed".
Mohandas et al., 2018 [18]	Retrospective case series (psychodermatology clinic, London); N=35.	Psychiatric	Routine skin swabs/scrapings; <i>Borrelia</i> enzyme linked immunosorbent assay (ELISA) in 10/35 patients. Insensitive <i>Borrelia</i> testing performed in a small unstratified subgroup.	"Patients may overrepresent psychiatric comorbidities..."; "inclusion criteria were not reported"; "use of controls and blinding for serology were not reported".
Roncati et al., 2016 [11]	Single-patient case report	Psychiatric	Visual/dermoscopic fiber identification; meaningless serology results for <i>Borrelia</i> described as "without a rise". Methods used cannot differentiate between human and dog hair.	"Method of <i>Borrelia burgdorferi</i> testing not reported"; "results of serology reported with ambiguous terminology". "No blinded electron microscopy, discrimination" to support claim.
Ohn et al., 2017 [12]	Single-patient case report.	Psychiatric	Histology (fiber specimen reported as lost, yet authors concluded it was delusional); silver stain, insensitive for identifying pleomorphic <i>Borrelia</i> . Serious contradiction (PCR in abstract vs. serology in text).	"Lack of congruency between the abstract and text body on the type of test for <i>Borrelia burgdorferi</i> completed (PCR vs. serology)."

Yu et al., 2018 [13]	Single-patient case report	Psychiatric	Dermoscopy used as visual identification of fiber composition, serum PCR. Seum PCR not suitable for detecting a tissue bound organism.	"Fiber composition was not evaluated"; controls/blinding for PCR not reported.
Savely and Stricker, 2010 [21]	Cross-sectional clinical cohort; N=122 fiber-positive.	Infectious	Inclusion for study used objective clinical case definition (~50× magnification); western blot testing and/or clinical diagnoses of Lyme disease in most of the cohort Detection of co-morbidities and co-infecting tickborne diseases.	Criteria for inclusion (fibers) assessed by first author alone. Unspecified method of coinfection testing, use of negative controls and blinding not reported.
Middelveen, Rasmussen, Kahn et al., 2012 [8]	Pilot case series; N=3.	Infectious	Chemical dissolution assays; AE1/AE3 pan-cytokeratin immunohistochemicalstaining (IHC). Controls for chemical studies included comparison with Bovine digital dermatitis fibers and normal human hair. Subjects chosen on the basis of meeting clinical criteria of having unusual cutaneous filaments. Immunostaining was performed at a licensed commercial pathology laboratory using standardized and tested protocols.	Small sample size. Subject selection process not provided, preselection bias suggested, several fiber samples not attached to epithelia tissue, no blinded microscopic differentiation, no report of controls and blinding for chemical and immunostains.
Middelveen, Mayne, Kahn et al., 2013 (2013a) [9]	Case series; N=4	Infectious	Histopathology; Gömöri trichrome/Fontana-Masson; transmission and scanning electron microscopy (TEM/SEM); Dieterle silver stain; PCR. Reuse of subjects provided longitudinal follow up, subject details transparently reported, histological staining provided by commercial pathology laboratory using standardized methodology, JBI does not require blinding controls for small case series. Normal hair and Morgellons fibers visibly different impossible to blind.	Small sample; reused subjects, reused 2 cases from previous study, no negative control of tissue specimens and blinding for microscopy. No blinding between modified hair and normal hairs. No blinding and controls for immunostaining reported
Middelveen, Burugu, Poruri et al., 2013 (2013b) [10]	Pilot case series (longitudinal follow-up); N=4.	Infectious	Histopathology, PCR, culture, IHC, serology. Reuse of subject provided longitudinal follow-up and transparently reported, positive serology reported and showed important association, prior testing for <i>Borrelia</i> was not required, PCR performed at licensed commercial lab using positive and negative controls, immunofluorescent assay (IFA) microscopy of cultured long slender spirochete provided convergent evidence.	Small sample; reused subjects. Reporting positive serology for <i>Borrelia</i> (implying preselection bias), no negative control tissue specimens for microscopy, conflicting descriptions of negative control Immunofluorescent microscopy, Blinding not reported.
Mayne, 2015 [22]	Large cross-sectional/prevalence study; N=500.	Infectious	Serology; PCR performed by licensed commercial laboratories. Cross-sectional cohort study of a specific clinical population to find the rate of MD occurrence among Lyme-positive patients, not to ratios against the general public. Baseline prevalence represented as rare in established literature. A 6% prevalence of MD within the seropositive is comparatively very high.	Prevalence in the population without Lyme disease not determined.
Middelveen, Bandoski, Burke et al., 2015 [16]	Case series; N=25.	Infectious	5-laboratory multi-method study: histology, IHC, TEM/SEM, PCR, culture, Sanger sequencing. Positive testing prior to study not required. Reusing subjects: longitudinal follow-up, consistency across experimental phases, in niche populations recruiting new cohorts logistically impractical. Patient details were transparently provided, new and different subjects were continually recruited.	Five subjects reused from previous study; four with positive testing, no explanation for failure to perform testing on all samples.

Fesler, Middelveen, and Stricker, 2018 [19]	Cross-sectional prevalence study; N=1,000 screened / 60 MD subgroup.	Infectious	Morgellons found in 6% of the Lyme disease population, correlating with Mayne, 2015. Serology; tick-borne co-infection panel. Co-infections common among Morgellons group. Same rebuttal as Mayne 2015 concerning selection bias. Testing performed by a licensed commercial lab using standardized testing protocols.	Referral-based, tertiary-clinic selection bias. Subjects selected from a Lyme disease population. Use of controls for serological testing not provided.
Middelveen, Cruz, Fesler et al., 2018 [20]	Cross-sectional case series; N=30.	Infectious	Immunoblot serology; PCR including Lyme and relapsing-fever <i>Borrelia</i> , detected in 90% of the subjects. <i>Bartonella henselae</i> detected in a subgroup. No evidence that patients were selected with advertising for tickborne detection. Subjects, methods indicate selection based on presence of cutaneous filaments.	Patients self-volunteered for study advertising tickborne disease detection causing overrepresentation in cohort. Use of controls not reported potential for false positive results. .
Middelveen, Filush, Bandoski et al., 2019 [28]	Case series / N=14 / laboratory study; small tissue-specimen cohort.	Infectious	Convergent, multimethod, detection of <i>Borrelia burgdorferi</i> and <i>Helicobacter pylori</i> in biofilm aggregates. Confocal microscopy; IHC (p-tau, β -amyloid, alginate, thioflavin); fluorescent <i>in situ</i> hybridization (FISH). PCR not performed for spectrum of <i>Borrelia</i> , so less robust association is expected. False positive PCR highly unlikely; Sanger sequencing confirmation and 0% of negative control tested positive: including healthy human foot calluses, normal human skin, and human foreskin, convergent data, provided corroborative evidence.	Patient selection not reported, positive PCR for multiple organisms may reflect false-positive non-specific results. Association with <i>Borrelia burgdorferi</i> less robust than for <i>Helicobacter pylori</i> . Cannot exclude secondary infection of lesion because non-lesion skin was negative.

Evidence Supporting a Psychiatric Etiology

Seven studies were identified in the review as supporting a psychiatric etiology: the Centers for Disease Control and Prevention (CDC) cross-sectional study by Pearson et al.; three retrospective chart reviews - two Mayo Clinic-based and one from a London psychodermatology clinic; and three patient case reports [11-15,17,18]. Notably, three of the seven studies were single case reports. While useful for hypothesis generation, case reports represent a low level of clinical evidence and cannot support conclusions about disease prevalence, pathophysiology, or etiology in a broader population. Drawing population-level inferences from an individual case constitutes overgeneralization and lacks statistical validity. Unlike a case series, which can identify patterns across multiple patients and reduce the influence of individual outliers, a single case report (n=1) has no statistical power and cannot distinguish disease characteristics from patient-specific factors. Consequently, such studies provide only limited evidence and should be interpreted with caution.

As for the retrospective studies, relying on a retrospective case series to declare a condition “delusional” is a profound methodological misstep. Because these studies are restricted entirely to historical, non-standardized clinical notes, they are fundamentally vulnerable to information bias and

chronological confusion: the investigators cannot determine whether the original physicians omitted appropriate microbiological testing, nor establish whether psychiatric comorbidities preceded or followed the onset of tissue damage. Transforming inconsistent, backward-looking clinical files into a definitive epidemiological verdict represents a significant inflation of low-tier medical evidence.

The review's structural treatment of the CDC study

The review's structural imbalance is evident in its disproportionate emphasis on the CDC's single-region, retrospectively selected, database-driven cross-sectional survey [17], including the allocation of a dedicated standalone analysis table. By centering much of its results and conclusions on a single, older study, the review places substantial weight on findings that predate more than a decade of subsequent molecular and histopathological research.

The review also fails to adequately address several important limitations of the CDC study, including its high attrition rate, reliance on conventional biopsy and laboratory methods, lack of sensitive *Borrelia*-specific molecular testing, and concerns regarding cohort representativeness [24-28]. As noted by Dr. Randy Wymore, a member of the external review panel, many Kaiser Permanente Morgellons patients with documented cutaneous fibers reportedly distrusted

the study and were reluctant to participate because of prior experiences in which their symptoms had been dismissed as delusional [29]. Furthermore, because verified cutaneous filaments were not required for inclusion, it remains unclear how many participants met the defining clinical criterion [29]. Notably, the CDC investigators themselves stopped short of concluding that participants suffered from a delusional disorder, stating only that they were unable to determine whether the unexplained dermatopathy represented a new condition or the recognition of an existing one a distinction the review does not clearly preserve [17].

This preferential treatment extends to the structure of the review's summary tables: while a dedicated "Critiques" column is applied to every pro-psychiatric study and to all pro-infection studies, no equivalent appraisal accompanies Table 2, the CDC study's rows, despite well-documented limitations the lack of an appropriate clinical comparison group, reliance on relatively insensitive commercial serological testing, substantial participant attrition, and the absence of patients with deeply embedded cutaneous fibers. This selective exemption creates an artificial hierarchy in which the CDC study appears uniquely authoritative while other investigations are systematically qualified by their limitations.

The CDC study experienced significant attrition, raising concerns about the representativeness of the findings. Of the 115 case patients identified, only 41 completed the clinical evaluation, 36 completed neuropsychological testing, 31 provided biopsy or other biological samples, 28 submitted routine culture swabs, and only 12 contributed dermatological specimens for fiber analysis. Furthermore, its case definition did not require embedded cutaneous fibers indeed, no deeply embedded fibers were observed clinically. The material subjected to its SEM-EDXA analysis therefore consisted primarily of superficial wound crusts and loose surface debris; pointing a sophisticated X-ray microprobe at environmental contaminants that settle into open, chronic skin lesions predictably returns an "inorganic" or "textile" readout regardless of the underlying condition [17].

Serologically, the study relied on standard two-tier Lyme testing (VIDAS EIA plus Marblot Western blot) [17], an assay whose clinical sensitivity for early, localized, or tissue-bound infection has been reported as low as 30–40% [30], and whose overall sensitivity for detecting *Borrelia* has been likened to a coin toss [31]. Although the review describes the finding as "one borderline positive for *Borrelia burgdorferi*," the original CDC data report EIA reactivity in two separate patients (one positive and one borderline), a distinction the review's compressed wording obscures. Among the 41 patients who completed full evaluation, this result represents a 5% first-tier seropositivity rate, which is roughly tenfold the 0.47% first-tier seroprevalence reported in a California

blood-donor population [32] and a comparison neither the CDC study nor the review draws.

Other pro-psychiatric studies with laboratory components

Full study-by-study narratives for this subsection are provided in Appendix B; the summaries below focus on how the review characterized each study's limitations.

Mohandas et al. [18]

This retrospective chart review examined 35 patients referred to a specialist psycho-dermatology clinic over 13 years. Nearly one-third of patients (28.5%) were self-diagnosed after internet or newspaper research, and the cohort included patients with peripheral neuropathy, intracranial hemorrhage, scabies, lice, severe eczema, substance misuse, and paranoid schizophrenia — a heterogeneous population unlikely to represent a single underlying condition. *Borrelia* serology (ELISA) was performed in only 10 of 35 patients and was negative, but ELISA's known sensitivity limitations combined with testing under 30% of the cohort mean the study's claim of "no proven association with any infection" is considerably more definitive than the data support [31].

The review's own "Critiques" column for this study flags the absence of reported controls and blinding for serology — a standard inapplicable to a routine, centrally processed hospital ELISA rather than an experimental assay. Focusing on this administrative technicality diverts attention from the study's more substantive flaws: a heterogeneous cohort, insensitive testing of an unstratified subgroup, an untested 71% of the cohort, multimodal confounded treatment, and a genuinely heterogeneous case mix.

Roncati et al. [11]

This single-patient case report concluded that recovered fibers consisted of dog hair and synthetic textile. The methods used could not reliably distinguish human from canine hair even with blinding, and the fibers were collected superficially rather than from embedded tissue. In a later publication, the same authors acknowledged the keratin-based fibers could have been human hair rather than dog hair [33] — consistent with independent bio-profiling data describing microscopic human hair among Morgellons fibers [6]. The review's critique is limited to the absence of blinded electron-microscopy discrimination between human, canine, and synthetic fibers, without noting the retraction or the sampling depth issue. The study's serology is also described only as "without a rise" — an ambiguous, non-diagnostic result that establishes neither infection nor its absence — characterized by the review merely as "method ... not reported" and "results ... reported with ambiguous terminology."

Ohn et al. [12]

This single-patient case report described a fiber protruding from the dermis that was lost during specimen processing

and never analyzed; the authors nonetheless speculated it was synthetic. The report also contains an internal contradiction — the abstract states PCR for *Borrelia burgdorferi* was negative, while the main text states serology was negative — two different tests with different performance characteristics. The review's critique describes this only as a “lack of congruency between the abstract and text body,” a characterization that understates a fundamental failure to document the study's own primary methodology.

Yu et al. [13]

Fibers were classified as inorganic by dermoscopic inspection alone, without spectroscopy, electron microscopy, or histochemical staining — a category error the review reduces to “fiber composition was not evaluated.” A reported negative serum PCR for *B. burgdorferi* is of limited value because *Borrelia* is a predominantly tissue-resident organism typically present at low concentration in blood, and no assay methodology, target sequence, or validation data were reported. The review addresses this only as an absence of reported controls/blinding.

Studies justifying psychiatric etiology through psychiatric characterization alone

Two retrospective Mayo Clinic case series, Hylwa et al. and Foster et al., were cited by the review in support of a psychiatric interpretation, though neither was designed to investigate etiology directly [14,15]. Both focused on psychiatric histories, demographics, and patient-reported symptoms rather than microbiological investigation, systematic fiber characterization, or advanced dermatopathology. Both also grouped fiber-reporting patients together with those reporting insects, parasites, and other perceived infestations, reporting results at the aggregate delusional-infestation level rather than stratified by belief subtype — a limitation the review does acknowledge — so it is unclear whether any reported findings apply specifically to patients meeting a Morgellons case definition.

The review's treatment of pathogen testing in these two studies is notably uneven. For Hylwa et al., where no serological, PCR, or any other testing for borreliosis was performed at all, the critique column lists “biopsy results not stratified,” “bacterial species in cultures not specified,”

and “serological and PCR testing not completed” wording that frames a complete absence of investigation as a series of minor omissions. For Foster et al., the review states plainly that “serological testing and PCRs for *Borrelia burgdorferi* were not performed,” which, while accurate, similarly understates that no serology, PCR, immunohistochemistry, or FISH testing of any kind was attempted. The CDC study likewise performed no direct tissue-based *Borrelia* testing, yet this omission receives comparatively little emphasis despite its obvious relevance to a conclusion about infectious etiology.

Psychiatric etiology as a diagnosis of exclusion

Delusional mental illness is a diagnosis of exclusion that requires plausible physical causes to be systematically investigated and ruled out [4]. None of the studies cited in support of a psychiatric interpretation performed comprehensive infectious testing, detailed fiber analyses, or other investigations capable of evaluating competing biological hypotheses. Under such circumstances, negative findings may reflect limitations of testing rather than definitive evidence against an infectious process.

Similarly, the presence of psychiatric comorbidities does not establish psychiatric causation. Conditions such as depression and anxiety may arise secondary to chronic illness, disability, or prolonged diagnostic uncertainty [4]. The reviewed studies may provide some useful information regarding psychiatric associations, but they do not resolve the central question of whether those associations are causal, consequential, or coincidental. Taken together, the studies supporting a psychogenic interpretation are methodologically heterogeneous and vary considerably in their ability to address disease etiology. Rather than constituting a single, uniform body of evidence demonstrating a psychiatric disorder, they represent a mixture of case reports, retrospective analyses, epidemiological studies, and clinical observations whose interpretation remains disputed.

The Review's Core Arguments for Psychiatric Etiology, and Their Rebuttals

The review advances a psychiatric interpretation based on several recurring arguments, summarized with their rebuttals in Table 4.

Table 4: Evidence cited for psychiatric etiology and its rebuttal.

Cited Evidence	Review's argument	Rebuttal	Key citations
Absence of a consistent infectious pattern	No consistent infectious pattern has been identified across studies	Pro-infection studies report endogenous filament production, inflammatory abnormalities, neurological manifestations, detection of <i>Borrelia</i> and other microorganisms, co-infections, and biofilm formation — together constituting a reproducible biological syndrome rather than an isolated psychiatric phenomenon	[8-10,16,19-21,28]

Lesion distribution / excoriation	Lesions concentrated in reachable areas suggest self-inflicted scratching	Photographic evidence shows lesions in areas inaccessible to the patient. Lesion localization alone does not establish causation — syphilis (<i>Treponema pallidum</i>) and scabies (<i>Sarcoptes scabiei</i>) are textbook infectious dermatopathies with strong anatomical localization and/or secondary excoriation that masks the primary lesion	[8,16,34,35]
Histopathology consistent with chronic irritation	Biopsy findings are consistent with chronic irritation rather than infection	Routine histopathology may not reliably detect stealth organisms such as <i>Borrelia</i> ; failure to visualize an organism on standard staining is not evidence of its absence. Pro-infection studies documented spirochetes using immunohistochemistry, silver staining, FISH, and PCR	[36]
Sensory symptoms (crawling, tingling, stinging)	Interpreted as evidence that scratching precedes lesion formation	Formication is a sub-type of paresthesia with numerous non-psychiatric causes (multiple sclerosis, Parkinson disease, diabetes, neurosyphilis, Lyme disease, vitamin deficiencies); a sensation preceding a lesion may be a genuine organic prodrome	[37]
Substance use	Elevated substance use rates support a psychiatric interpretation	Substance use may arise secondarily from chronic pain, pruritus, insomnia, or distress; many Morgellons patients report no substance-use history, and elevated rates were concentrated in a small, distinct, younger sub-demographic	[14,17,21,38]
Response to antipsychotics	Improvement with antipsychotic treatment supports psychogenic causation	This risks the therapeutic <i>ex juvantibus</i> fallacy — treatment response is not proof of diagnosis. Antipsychotics have sedating, antihistaminic, and neuromodulatory effects that can reduce itching and sensory symptoms independent of any delusion; the pro-psychiatric literature cited in the review also reports poor responses to antipsychotic monotherapy and improvement with antimicrobial monotherapy	[39,40]
Psychiatric comorbidities (depression, anxiety)	Cited as evidence of a psychiatric etiology	Depression, anxiety, and social isolation are recognized sequelae of chronic, painful, disfiguring illness, not necessarily evidence of a primary psychiatric disorder; chronic <i>Borrelia</i> infection has itself been linked to neuroinflammation and mood disturbance. Treating a secondary symptom as the primary cause risks circular reasoning	[14,15,17, 41, 42]

Evidence Supporting an Infectious Etiology

Objective evidence supporting the pro-infection framework

Of the 16 studies presented in the review that examined etiology, nine supported an infectious explanation. Two of these provided detailed structural, biochemical, and histological analysis of Morgellons fibers, challenging the hypothesis that they are environmental contaminants; eight investigated the association between Morgellons disease and pathogens, including *Borrelia*, other tick-borne organisms, and opportunistic pathogens.

The review's core methodological limitation is its flat, unweighted application of the Oxford Level 4 taxonomy across studies of very different evidentiary character. A transparent, detailed “Materials and Methods” section is not an administrative formality; it is a baseline requirement for scientific validity. Measured against frameworks such

as the JBI assessment tool, the Cochrane Risk of Bias tool or the Newcastle-Ottawa Scale, the three pro-psychiatric case reports and the retrospective studies by Hylwa et al., Foster et al., and Mohandas et al. provide no reproducible laboratory protocol, no objective intake criteria beyond clinical impression, and cohorts confounded by neurological, psychiatric, and substance-use comorbidity that was never stratified out of the analysis [14,15,18].

The mature pro-infection literature, by contrast, achieves what the psychiatric literature does not: reproducibility across independent, geographically separated laboratories using validated analytical techniques and detailed methodological reporting. These studies repeatedly identify the cellular proteins composing the cutaneous filaments — demonstrating a tissue-based origin rather than a consequence of superficial excoriation — and detect pathogens through complementary visual, molecular, direct, indirect, systemic, and lesion-specific approaches, in several cases including microbial

culture with subsequent antigenic and genetic confirmation of isolate identity, widely regarded as the gold standard for pathogen detection. It should also be noted that bovine and canine animal models support the infectious etiology of Morgellons disease [4,6,8,24].

Studies supporting the pro-infection framework

Full study-by-study narratives are provided in Appendix B; the summaries below give the core finding of each.

Savely and Stricker [21]

Examined 122 patients with Morgellons-associated filaments against Lyme patients without fibers, identifying a distinct symptom constellation (crawling sensations, slow-healing lesions, pruritus, hyperpigmented scarring, firmly anchored multicolored fibers) significantly associated with Lyme disease and hypothyroidism, predominantly in middle-aged Caucasian women. Depression was present in 29% of patients, but no pre-existing delusional disorders were identified. The study established a formal case definition requiring visual confirmation of embedded fibers under ~50× magnification.

Middelveen, Rasmussen, Kahn et al. [8]

An exploratory 3-patient proof-of-concept study. Filaments showed chemical dissolution behavior in sodium hypochlorite/hydroxide and potassium hydroxide closely paralleling normal human hair, and stained positive for keratin using AE1/AE3 pan-cytokeratin antibodies. In one case, filaments were directly observed arising from the inner root sheath of hair follicles, establishing a tissue-based point of origin.

Middelveen, Mayne, Kahn et al. [9]

A 4-subject case series (2 followed longitudinally from the 2012 study) using histopathology, TEM/SEM, and immunohistochemistry. Filaments showed hair-like medulla/cortex structure, stained for keratin or collagen, and were photographically documented as continuous with adjacent epidermal cells, with nuclei visible extending into the fibers at points of attachment. A companion pilot analysis using Warthin-Starry and Dieterle silver staining identified helical, spirochetes within sectioned tissue in all four subjects — in contrast to the CDC study, which reported finding nothing using the same staining category — offering a proposed mechanism (intracellular infection driving keratinocyte/fibroblast overproduction) linking infection to filament formation.

Middelveen, Burugu, Poruri et al. (10)

A longitudinal follow-up of 4 subjects combining histopathology, PCR, culture, immunohistochemistry, and serology. *Borrelia* DNA, positive serology, cultured spirochetes, and antigen-specific immunohistochemical staining converged on the same organism, providing visual,

antigenic, and immunological — not merely epidemiological — evidence of infection within lesion tissue. The successful culture of viable organisms distinguishes this study's evidentiary weight from the pro-psychiatric case reports evaluated at the same Oxford level.

Middelveen, Cruz, Fesler et al. [10]

A 30-patient study combining serology, immunoassay, and PCR; 90% tested positive for *Borrelia* species, with markers of relapsing-fever *Borrelia* detected more frequently than *B. burgdorferi sensu lato*, plus evidence of *Bartonella henselae* co-infection. The authors argue standard two-tier Lyme assays, which do not target relapsing-fever genospecies, may systematically under-detect infection in this population.

Mayne [22]

A 500-patient cross-sectional study of complex vector-borne illness, in which Morgellons disease was identified in ~6% of cases, alongside substantial rates of *Borrelia* and tick-borne co-infection. This is the largest epidemiological investigation in the literature and required visual confirmation of embedded/erupting filaments as a diagnostic criterion, in contrast to the CDC study (no tissue-embedded filaments observed in any patient) and Mohandas et al. (no hallmark lesion confirmation reported).

Middelveen, Bandoski, Burke et al. [16]

A 25-patient study using histology, electron microscopy, microbial culture, PCR, in situ DNA hybridization, and sequencing across five independent laboratories. *Borrelia* DNA was detected in 24 of 25 participants; histopathology showed spirochetal infection within epithelial tissue in all patients; viable *Borrelia burgdorferi* was cultured from blood (7 patients) and vaginal secretions (3 patients). Genetic sequencing was independently verified by two laboratories. The authors proposed a four-stage clinical classification system modeled on syphilis staging.

Fesler, Middelveen, and Stricker [19]

Examined 60 North American MD patients; 100% were seropositive for *B. burgdorferi*, and 77% carried at least one additional tick-borne co-infection (*Babesia* 62%, *Bartonella* 25%, *Rickettsia* 25%, *Ehrlichia* 15%, *Anaplasma* 10%). Most patients (78%) presented with late disseminated disease. This is among the largest structured clinical datasets in the literature, shifting the discussion from anecdotal association toward a reproducible clinical pattern.

Middelveen, Filush, Bandoski et al. [28]

Reported mixed *Borrelia burgdorferi*–*Helicobacter pylori* biofilms within an amyloid-rich extracellular matrix in Morgellons lesions, with healthy control tissue testing negative; both microbial antigens and host-cell markers were identified within the filaments themselves. This

polymicrobial, biofilm-based framework offers a plausible mechanism for antimicrobial treatment resistance and for inconsistent molecular detection rates (via PCR inhibition from residual bacterial enzymes).

Methodological Convergence, Controls, and Independent Verification

A key feature of the pro-infection literature is methodological convergence: histology, electron microscopy, immunostaining, FISH, PCR, DNA sequencing, serology, microbial culture, and epidemiological analysis were applied across multiple studies and repeatedly converged on similar pathological features or evidence of microbial involvement. Because these techniques are subject to different sources of error, convergence across them strengthens confidence in the underlying observation. Visual verification methods (silver staining, immunostaining, FISH) provide the morphological and locational “ground truth” that validates PCR results; PCR alone is highly sensitive but cannot distinguish live organisms from dead fragments or contamination, so pairing the two methods plus culture produces a more solid diagnostic framework, particularly for a technically difficult pathogen such as a spirochete. The review raises legitimate concerns regarding small sample sizes, overlapping cohorts, selection bias, and limited independent replication. These are worth considering, but methodological limitations do not negate the repeated observation of similar findings across multiple studies, laboratories, and investigative techniques.

Rather than a mere clash of evidentiary priorities, the debate reveals a fundamental disparity in proof. Proponents of an infectious etiology offer multi-method biological evidence visual confirmation of the organism alongside genetic identification while the psychiatric paradigm relies heavily on a diagnosis of exclusion, inferring delusion from negative test results rather than presenting independent causative biological data. Viewed collectively, the pro-infection literature does not provide definitive proof of causation, but by consistently detecting a specific pathogen (including via culture), localizing it within characteristic lesions via IHC and FISH, and linking its presence to the aberrant keratin/collagen filaments that define the disease, it moves beyond simple statistical association toward a coherent, biologically plausible mechanism.

Additional Points in the Review's Critique of Pro-Infection Studies

Most of the review's specific criticisms of individual pro-infection studies (small cohorts, subject reuse, preselected or self-referred populations, unreported controls/blinding, and author-association bias) restate the asymmetry already catalogued in Table 1, and are not repeated here. Three further, more technical points raised in the review's critique columns are addressed below, since the underlying facts there go beyond what Table 1 can summarize in a single row.

Fiber attachment and histological interpretation

The review questions early histological studies in which some examined filaments appeared detached from surrounding tissues. However, interpretation of two-dimensional histological sections is inherently constrained by tissue orientation and sectioning plane: a filament may appear detached in one section while connected elsewhere in the specimen, and other images from the same studies reportedly showed filaments embedded within or continuous with adjacent tissue. The existence of individual detached-appearing sections does not invalidate the broader observation of integration.

Secondary colonization versus primary pathology

The review suggests that microorganisms identified in lesions may reflect secondary colonization of wounds caused by scratching rather than primary disease. Characterizing *Borrelia* species as superficial surface contaminants drawn to excoriation wounds fundamentally misrepresents their established biological nature. As deeply invasive, systemic pathogens rather than opportunistic skin dwellers, their intracellular localization and organized biofilm architecture cannot be reconciled with simple surface contamination resulting from scratching. Dismissing these findings as an unresolved epiphenomenon ignores known microbial physiology and tissue tropism, as the physical evidence within the tissue architecture fails to support mechanical migration via excoriation. Intracellular localization and organized biofilm architecture are difficult to reconcile with simple surface contamination.

Epidemiological association

The review criticizes studies reporting ~6% Morgellons prevalence within Lyme-associated cohorts for lacking population-based comparison groups. This limitation restricts causal inference but does not eliminate the value of the finding as a signal warranting further investigation. Several psychiatric studies share the same limitation of relying on highly selected clinical populations rather than representative baselines, so the absence of population-wide controls is not unique to the infectious-disease literature.

Author Association and Independent Laboratory Verification

The review advances what is essentially a “single-source” critique of the pro-infection literature, arguing that it lacks broad medical consensus because most positive findings involve a recurring group of investigators particularly Marianne Middelveen, Raphael Stricker, Eva Sapi, and Melissa Fesler raising the possibility of institutional confirmation bias and a lack of independent external replication.

This criticism overlooks the distinction between manuscript authorship and laboratory execution. While a core group of investigators coordinated the studies and appears repeatedly as authors, the testing itself was distributed across at least five independent institutions, including the University of New Haven, Clemson University, Australian Biologics (Sydney), IGeneX Reference Laboratories, McClain Laboratories, and Interscope Laboratories. The repeated appearance of certain author names does not mean the laboratory analyses were conducted within a single organization.

A significant omission in the review's assessment is its failure to acknowledge the use of blinded and controlled laboratory procedures. Independent laboratories reportedly processed de-identified and blinded split samples alongside negative-control specimens; when separate facilities operating independently on different continents identified the same *Borrelia* DNA sequences from blinded samples, this constitutes a form of methodological replication regardless of manuscript authorship overlap. Australian Biologics, for instance, maintained quality assurance through international proficiency-testing programs including those administered by Quality Control for Molecular Diagnostics (QCMD) in Scotland, and McClain Laboratories (directed by a board-certified dermatopathologist) and Interscope Laboratories/Pathology Medical Group provided accredited clinical pathology services — regulated diagnostic entities rather than informal research labs. In addition, the University of New Haven used positive and negative controls and tested in triplicate.

The review's emphasis on recurring authorship is also applied unevenly: numerous reports supporting psychiatric

interpretations originate from individual clinicians or small groups, often without objective microbiological testing, yet receive no comparable scrutiny of their own professional associations. More broadly, the argument that findings should be discounted because they originate from a relatively small group of investigators risks conflating scientific validity with popularity — the central question in evidence-based medicine is whether methods are rigorous, controls are adequate, and results are reproducible, not how many researchers support a hypothesis. Historically, novel technologies and methodologies have often first been championed by small groups before broader validation.

This discussion also raises a broader concern about paradigm bias operating in the other direction: existing clinical guidelines, reimbursement structures, and diagnostic algorithms create incentives to maintain current interpretations of a contested condition, so institutional resistance to a novel interpretation may reflect sociological and institutional dynamics as much as scientific disagreement. Ultimately, even accepting that a limited number of investigators has driven much of the pro-infection research, that fact alone does not invalidate the findings; studies are properly refuted by demonstrating methodological flaws, inadequate controls, or failed reproducibility not by the size of the group that produced them. Given the involvement of multiple independent universities, accredited pathology facilities, federally licensed diagnostic laboratories, international sequencing centers, blinded testing procedures, and external quality-assurance programs, characterizing this body of research as the product of a single insular group overlooks substantial evidence of laboratory-level independence and cross-institutional validation.

Table 5: JBI critical appraisal verdicts.

Study	JBI checklist applied	Verdict	Principal reasons
Pearson et al., 2012 (CDC) [17]	Analytical Cross-Sectional	EXCLUDE	Attrition from 115→40→12 participants; population-level conclusions drawn from a 10.4% fiber-analysis subsample; single-site (Kaiser N. California) retrospective, keyword-based case ascertainment.
Hylwa et al., 2012 [14]	Retrospective Case Series	EXCLUDE	Only 25% of specimens received formal pathological analysis; referral cohort of treatment-resistant, pre-labeled patients; no molecular or advanced diagnostic testing performed.
Foster et al., 2012 [15]	Retrospective Case Series	EXCLUDE	No standardized diagnostic protocol; no molecular testing; 87% of participants were second/third-opinion seekers (referral bias); no consecutive inclusion.
Mohandas et al., 2018 [18]	Retrospective Case Series	EXCLUDE	Tertiary psychodermatology referral bias; heterogeneous cohort with no phenotypic stratification; <i>Borrelia</i> serology performed in only 10 of 35 patients; fails JBI items 4, 5, 6, and 9.
Roncati et al., 2016 [11]	Case Report	EXCLUDE	"Serology without rise" treated as sufficient to exclude infection; no direct tissue-based testing performed; diagnostic methods and results not clearly described.

Ohn et al., 2017 [12]	Case Report	EXCLUDE	Abstract (PCR) contradicts main text (serology) on the test performed; diagnostic method not clearly described; conclusion not adequately evidence-based.
Yu et al., 2018 [13]	Case Report	EXCLUDE	Negative serum PCR with no assay methodology reported; biologically mismatched specimen (serum) for a tissue-tropic organism; exclusion of infection scientifically unsupported.
Savely and Stricker, 2010 [21]	Analytical Cross-Sectional	INCLUDE	Clear, objective inclusion criteria (visual fiber confirmation); detailed, standardized cohort characterization; limited screening of psychiatric confounders and referral-based sampling noted as limitations.
Middelveen, Rasmussen, Kahn et al., 2012 [8]	Case Series	INCLUDE	Rigorous chemical- and immunohistochemistry-based measurement with human-hair and bovine comparator controls; small, non-consecutive sample (n=3) limits external validity only.
Middelveen, Mayne, Kahn et al., 2013a [9]	Case Series	INCLUDE	Multi-method laboratory protocol (histochemistry, SEM/TEM, silver stain, PCR) exceeding comparator studies' H&E-only approach; small, non-consecutive sample (n=4).
Middelveen, Burugu, Poruri et al., 2013b [10]	Case Series	INCLUDE	Four independent, convergent diagnostic modalities identifying <i>Borrelia burgdorferi</i> antigenically and genetically; small sample (n=4) limits generalizability.
Mayne, 2015 [22]	Prevalence Study / Large Descriptive Case Series	INCLUDE	Large sample (n=500), standardized 55-parameter intake protocol, blinded dual-laboratory verification, strong statistical association ($r^2=0.999485$); convenience/referred sample limits external validity.
Middelveen, Bandoski, Burke et al., 2015 [16]	Case Series	INCLUDE	Five-laboratory methodological convergence; objective inclusion criterion; viable spirochete culture in multiple patients; non-consecutive convenience sample.
Fesler, Middelveen, and Stricker, 2018 [19]	Analytical Cross-Sectional / Prevalence Study	INCLUDE	Large denominator (1,000 seropositive Lyme patients); standardized, objective MD case definition; transparent outcome reporting; tertiary-referral selection bias noted.
Middelveen, Cruz, Fesler et al., 2018b [20]	Analytical Cross-Sectional / Laboratory Case Series	INCLUDE	Standardized multi-method testing via federally accredited laboratories; objective inclusion criterion; 90% <i>Borrelia</i> positivity; convenience/referral sample.
Middelveen, Filush, Bandoski et al., 2019 [28]	Case Series / Advanced Laboratory Study	INCLUDE	Sophisticated confocal-microscopy and immunohistochemical measurement with negative healthy-tissue controls; small, exploratory scale.

JBICritical Appraisal of the 16 Etiology Studies

Because the evidence base consists largely of case reports, case series, and cross-sectional studies, the Joanna Briggs Institute (JBI) Critical Appraisal Checklists provide a more discriminating lens than the review's flat Oxford Level 4 classification. Table 5 summarizes the JBI-based verdict reached for each of the 16 etiology studies. All 16 studies were run through AI: Google Gemini was prompted through a series of questions to verify the determined verdict of whether each study should be included or excluded based on the JBI criteria. A full study-by-study appraisal, including the specific JBI checklist items that each study passed or failed, are reproduced in Appendix C.

Viewed as a whole, the JBI appraisal exposes a structural divide in the literature. The pro-psychiatric studies consistently fail core JBI domains for internal validity and detection bias: the Hylwa et al., and Foster et al., Mayo Clinic studies and the Mohandas et al, London clinic review operate as retrospective chart reviews built on cohorts already administratively labeled “delusional,” without uniform or sensitive molecular testing; the three case reports contain internal reporting contradictions [12], unvalidated single-modality testing [11], or a biologically mismatched specimen type [13]; and even the CDC study fails basic sample-sufficiency checks given its attrition to a 10.4% fiber-analysis subgroup.

The pro-infection laboratory studies, by contrast,

consistently satisfy JBI standards for inclusion and measurement validity: enrollment is anchored to an objective, provider-verified physical case definition, and findings are cross-validated through blinded testing across independent, accredited laboratories using electron microscopy, nested PCR, and confocal imaging producing reproducible results such as a *Borrelia* core surrounded by a *Helicobacter pylori* containing matrix, and human phosphorylated tau and β -amyloid proteins detected directly within the fibers. Under a JBI framework, the pro-psychiatric literature's difficulty lies in its inability to look for a pathogen with adequate methods, whereas the pro-infection literature's difficulty lies in the small scale of an otherwise methodologically convergent body of work.

Conclusion

The central weakness of the review by Beuerlein et al. [2] is not that it critiques infectious-disease research, but that equivalent methodological standards do not always appear to be applied across competing explanatory models. Evidence supporting infectious hypotheses is subjected to extensive scrutiny regarding cohort size, controls, recruitment, and laboratory methodology, while comparable limitations in psychiatric studies often receive less attention. As a result, the review may create the impression that the psychiatric hypothesis is supported by stronger evidence than is demonstrated by the underlying literature. Many of the studies cited in support of psychogenic explanations rely on retrospective analyses, diagnostic exclusion, psychiatric classification, and correlations rather than direct investigation of Morgellons-associated filaments or proposed infectious mechanisms. Consequently, Beuerlein et al. [2] should be viewed as one interpretation of a contested literature rather than a definitive resolution of the Morgellons debate.

The question of Morgellons disease pathogenesis remains unresolved in mainstream literature. A more balanced assessment would focus less on the numerical predominance of psychiatric publications and more on directly comparing the relative strengths and weaknesses of the molecular, histopathological, microbiological, epidemiological, clinical, and psychiatric evidence supporting competing hypotheses. Ultimately, the current literature does not conclusively establish either a psychiatric or infectious etiology. Instead, it reflects an ongoing scientific disagreement regarding the interpretation of available evidence. Future progress will likely require larger prospective studies, standardized case definitions, independent replication of laboratory findings, comprehensive pathogen testing, and direct comparison of biological and psychiatric models within the same patient populations. Despite AI favoring the infectious etiology model, future studies should determine the impact and accuracy of using AI for scientific analysis.

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Author Contributions

Marianne J Middelveen, Raphael B Stricker and Melissa C Fesler meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). All authors made substantial contributions to the conception, design and revisions of the current article and were involved in the analysis and interpretation of data. All authors have approved the final version.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

References

1. Uttley L, Quintana DS, Montgomery P, et al. The problems with systematic reviews: a living systematic review. *J Clin Epidemiol* 156 (2023): 30-41.
2. Beuerlein KG, Balogh EA, Feldman SR. Morgellons disease etiology and therapeutic approach: a systematic review. *Dermatol Online J* 27 (2021): 8.
3. Hamill MM, Ghanem KG, Tuddenham S. State-of-the-art Review: Neurosyphilis. *Clin. Infect. Dis.* 78(2024):e57 -e 68.
4. Middelveen MJ, Fesler MC, Stricker RB. History of Morgellons disease: from delusion to definition. *Clin Cosmet Investig Dermatol*. 2018 Feb 9;11:71-90.
5. Joanna Briggs Institute. JBI critical appraisal tools. Joanna Briggs Institute, Adelaide, AU (2006). <https://jbi.global/critical-appraisal-tools>
6. Middelveen MJ, Stricker RB. Morgellons disease: a

- filamentous borreliac dermatitis. *Int J Gen Med* 9 (2016): 349-354.
7. Howick J, Chalmers I, Glasziou P, et al. Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence. Oxford Centre for Evidence-Based Medicine (2011). <https://www.cebm.ox.ac.uk/resources/levels-of-evidence/explanation-of-the-2011-ocbm-levels-of-evidence/>
8. Middelveen MJ, Rasmussen EH, Kahn DG, et al. Morgellons disease: a chemical and light microscopic study. *J Clin Exp Dermatol Res* 3 (2012): 140.
9. Middelveen MJ, Mayne PJ, Kahn DG, et al. Characterization and evolution of dermal filaments from patients with Morgellons disease. *Clin Cosmet Invest Dermatol* 6 (2013): 1-21.
10. Middelveen MJ, Burugu D, Poruri A, et al. Association of spirochetal infection with Morgellons disease. *F1000Res* 2 (2013): 25.
11. Roncati L, Gatti AM, Pusiol T, et al. The first investigative science-based evidence of Morgellons psychogenesis. *Ultrastruct Pathol* 40 (2016): 249-253.
12. Ohn J, Park SY, Moon J, et al. Morgellons disease. *Ann Dermatol* 29 (2017): 223-225.
13. Yu DA, Ohn J, Kim KH. Morgellons disease: a manifestation of psychiatric disorder. *Ann Dermatol* 30 (2018): 362-363.
14. Hylwa SA, Foster AA, Bury JE, et al. Delusional infestation is typically comorbid with other psychiatric diagnoses: review of 54 patients receiving psychiatric evaluation at Mayo Clinic. *Psychosomatics* 53 (2012): 258-265.
15. Foster AA, Hylwa SA, Bury JE, et al. Delusional infestation: clinical presentation in 147 patients seen at Mayo Clinic. *J Am Acad Dermatol* 67 (2012): 673.e1-10.
16. Middelveen MJ, Bandoski C, Burke J, et al. Exploring the association between Morgellons disease and Lyme disease: identification of *Borrelia burgdorferi* in Morgellons disease patients. *BMC Dermatol* 15 (2015): 1.
17. Pearson ML, Selby JV, Katz KA, et al. Clinical, epidemiologic, histopathologic and molecular features of an unexplained dermatopathy. *PLoS One* 7 (2012): e29908.
18. Mohandas P, Bewley A, Taylor R. Morgellons disease: experiences of an integrated multidisciplinary dermatology team to achieve positive outcomes. *J Dermatol Treat* 29 (2018): 208-213.
19. Fesler MC, Middelveen MJ, Stricker RB. Clinical evaluation of Morgellons disease in a cohort of North American patients. *Dermatol Reports* 10 (2018): 7660.
20. Middelveen MJ, Cruz ID, Fesler MC, et al. Detection of tick-borne infection in Morgellons disease patients by serological and molecular techniques. *Clin Cosmet Invest Dermatol* 11 (2018): 561-569.
21. Savely VR, Stricker RB. Morgellons disease: analysis of a population with clinically confirmed microscopic subcutaneous fibers of unknown etiology. *Clin Cosmet Invest Dermatol* 3 (2010): 67-78.
22. Mayne PJ. Clinical determinants of Lyme borreliosis, babesiosis, bartonellosis, anaplasmosis, and ehrlichiosis in an Australian cohort. *Int J Gen Med* 8 (2014): 15-26.
23. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372 (2021): n71.
24. Middelveen MJ, Rotaru GM, McMurray JL, et al. Canine filamentous dermatitis associated with *Borrelia* infection. *J Vet Sci Med Diagn* 5 (2016): 212.
25. Middelveen MJ, Sapi E, Burke J, et al. Persistent *Borrelia* infection in patients with ongoing symptoms of Lyme disease. *Healthcare (Basel)* 6 (2018): 33.
26. Middelveen MJ, Martinez RM, Fesler MC, et al. Classification and staging of Morgellons disease: Lessons from syphilis. *Clin Cosmet Invest Dermatol* 13 (2020): 145-164.
27. Middelveen MJ, Haggblad JS, Lewis J, et al. Dermatological and genital manifestations of Lyme disease including Morgellons disease. *Clin Cosmet Invest Dermatol* 14 (2021): 425-436.
28. Middelveen MJ, Filush KR, Bandoski C, et al. Mixed *Borrelia burgdorferi* and *Helicobacter pylori* biofilms in Morgellons disease dermatological specimens. *Healthcare (Basel)* 7 (2019): 70.
29. Wymore RS. The CDC, unexplained dermatopathy and the future of Morgellons diagnosis, research and treatment. Charles E Holman Foundation 6th Annual Medical Scientific Conference on Morgellons Disease (2013).
30. Molins CR, Delorey MJ, Replogle A, et al. Evaluation of bioMérieux's dissociated Vidas Lyme IgM II and IgG II as a first-tier diagnostic assay for Lyme disease. *J Clin Microbiol* 55 (2017): 1698-1706.
31. Cook MJ, Puri BK. Commercial test kits for detection of Lyme borreliosis: a meta-analysis of test accuracy. *Int J Gen Med* 9 (2016): 427-440.
32. Brummitt SI, Kjemtrup AM, Harvey DJ, et al. *Borrelia*

- burgdorferi and Borrelia miyamotoi seroprevalence in California blood donors. PLoS One 15 (2020): e0243950.
33. Roncati L, Pisciolli F. Morgellons disease: Truth & belief. Ann Dermatol 30 (2018): 361-362.
 34. Muna B, Shanmugam S. Syphilis resurrected: Case series of palmoplantar secondary syphilis. Cureus 15 (2023): e46926.
 35. Roh YS, Choi J, Sutaria N, et al. Itch: Epidemiology, clinical presentation, and diagnostic workup. J Am Acad Dermatol 86 (2022): 1-14.
 36. Barnhill RL, Magro CM, Crowson AN, eds. Barnhill's Dermatopathology. 4th ed. McGraw Hill Professional (2019).
 37. Mauermann ML, Staff NP. Peripheral neuropathy: a review. JAMA 335 (2025): 243-256.
 38. Boucher LM, Shoemaker ES, Liddy CE, et al. "The drug use unfortunately isn't all bad": Chronic disease self-management complexity and strategy among marginalized people who use drugs. Qual Health Res 32 (2022): 871-886.
 39. Laragh JH, Lamport B, Sealey J, et al. Diagnosis ex juvantibus. Individual response patterns to drugs reveal hypertension mechanisms and simplify treatment. Hypertension 12 (1988): 223-226.
 40. Robles DT, Olson JM, Combs H, et al. Morgellons disease and delusions of parasitosis. Am J Clin Dermatol 12 (2011): 1-6.
 41. Mora T. Burden of comorbidities in people with multiple sclerosis: a population-based study in Catalonia. Front Neurol 16 (2025): 1699641.
 42. Brackett M, Potts J, Mehofer A, et al. Neuropsychiatric manifestations and cognitive decline in patients with long-standing Lyme disease: a scoping review. Cureus 16 (2024): e58308.



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