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Controversies About Lyme Disease-Reply

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Ultimately, these findings demonstrate the need to further study and characterize low-grade disease in black men. This study was limited by short follow-up and possible unadjusted confounding variables. Future studies with longer follow-up will be needed to further characterize low-grade disease in black men and to determine the clinical significance of the small absolute differences and whether they continue to increase over time.

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Concept and design: Mahal, Huang.

Acquisition, analysis, or interpretation of data: All authors.

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COMMENT & RESPONSE

Controversies About Lyme Disease

To the Editor There are a number of inaccuracies in the Viewpoint by Drs Shapiro and Wormser on Lyme disease.¹

First, they stated that “...there has not been a statistically significant increase in the number of reported cases of Lyme disease in the United States during the most recent 4 years (2013-2016) for which data are available.” Quest Diagnostics has reported a significant increase of positive Lyme disease test results, with Lyme disease being detected in each of the 50 states and the District of Columbia.²

Second, the authors wrote “The vast majority of patients with Lyme disease (≥90%) develop the characteristic skin lesion, erythema migrans.” The department of health in Maine reported that between 2009 and 2012 only 48.25% of patients with Lyme disease had a typical rash.^{3,4}

Third, I disagree with the statement that “For extracutaneous manifestations of Lyme disease, the sensitivity of antibody tests is excellent (87%-100%).” A PubMed search for seronegativity in Lyme borreliosis⁵ identified a large number of cases. It is well known that untreated streptococcal pharyngitis can progress to rheumatic fever, causing irreversible heart damage. Untreated syphilis leads to progressive disability and dementia, and untreated human immunodeficiency virus infection progresses to AIDS with significant disability and death. What happens to a patient with Lyme disease who goes months, years, or decades before diagnosis because of a false-negative serological test result? Shapiro and Wormser do not discuss the consequences of untreated Lyme disease in their Viewpoint.

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Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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To the Editor The Viewpoint on Lyme disease¹ contained statements that are not entirely supported by current data. For example, the authors stated that “The vast majority of patients with Lyme disease (≥90%) develop the characteristic skin

lesion, erythema migrans.” According to the Centers for Disease Control and Prevention (CDC), only 70% to 80% of patients with Lyme disease reported to its surveillance system have an erythema migrans rash.² Schutzer et al³ state that erythema migrans may not occur or be recognized in 30% of cases, and studies note uncharacteristic variants of erythema migrans. The general public and even some clinicians find it challenging to decide whether a rash is erythema migrans. Aucott et al⁴ reported that of 3104 people participating in a rash identification survey, 72.7% correctly identified the classic erythema migrans rash associated with Lyme disease, whereas 24.2% incorrectly identified a tick-bite reaction as erythema migrans. Although 20.5% of participants correctly identified the 4 nonclassic rashes included in the survey, a large percentage of people would be misidentified and potentially not seek prompt medical attention.⁴ These individuals are at increased risk of developing more severe Lyme disease sequelae, such as posttreatment Lyme disease syndrome, which was not discussed in the article.

Drs Shapiro and Wormser also wrote that “There is a common misconception that poor sensitivity of antibody tests for Lyme disease is a major limitation.” Two-tier testing of early Lyme disease patients at baseline is only 40% sensitive, and sensitivity increases to only 67.5% after treatment.⁵ Poor diagnostic performance during early Lyme disease is problematic because more positive clinical outcomes are associated with earliest possible diagnosis and initiation of treatment.

The authors went on to say, “However, this is a problem only if clinicians erroneously depend on serologic tests to make a diagnosis of Lyme disease in patients with erythema migrans, which typically precedes the development of detectable antibodies.” Most patients do not recall a tick bite, 20% to 30% patients do not present with erythema migrans,² and not all rashes that appear to be erythema migrans are.³ Thus, clinicians often must rely on an individual’s case history combined with serological testing to make a timely and accurate differential diagnosis.

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Mr Santarella reported being the chief executive officer and Dr Sellati reported being the chief scientific officer of the Global Lyme Alliance.

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In Reply Mr Tuttle and Mr Santarella and Dr Sellati cite data from passive surveillance systems as evidence that our statement that erythema migrans develops in 90% or more of patients with Lyme disease was inaccurate.¹ However, multiple large clinical studies^{2,3} have estimated the proportions of pediatric and adult patients with Lyme disease with erythema migrans. These estimates, which are much more reliable because patients were carefully assessed for the presence of erythema migrans, have consistently equaled or exceeded 90%. Lower proportions (eg, 70%) among cases reported to the CDC likely reflect reporting bias toward clinical manifestations associated with seropositivity.⁴ The CDC also estimates that 90% of cases of Lyme disease go unreported. Among cases reported to the CDC, 30% had Lyme arthritis, in contrast to the 6% or lower frequency of this manifestation in prospective clinical studies.^{2,3}

The numbers of cases of Lyme disease reported to the CDC, despite limitations in estimates, are a good way to monitor trends in incidence. They confirm our statement that there has not been a statistically significant increase in reported cases during the last 4 years.⁴ There also is no significant difference in incidence of reported cases in the most recent 5-year period compared with the preceding 5-year period.⁴ There has been a substantial increase in incidence over the past 20 to 30 years, but this has been a gradual, modest increase, with substantial year-to-year variation, rather than a sudden explosion of cases.

Reactive serological test results from Quest Diagnostics are not a validated measure of the number of cases of Lyme disease that occur in the United States. There are numerous commercial laboratories. An increase in the number of positive results reported by a given laboratory may simply reflect a change in the number of tests performed rather than a true increase in incidence of disease. In addition, it is not clear whether 1 patient could be represented multiple times, and the results do not distinguish between a new-onset (incident) event and a positive result that could have been present for many years.

We did not suggest that persons with Lyme disease should not be treated. However, if the decision to treat a patient who has a skin lesion that might be erythema migrans is based solely on a positive serological test result, most patients with Lyme disease will not be treated or treatment will be delayed because the skin lesion typically develops before antibodies are detectable (ie, sensitivity is poor in early disease, but it is rarely required because the rash is very characteristic).⁵ Conversely, to confirm Lyme disease as the cause of extracutaneous manifestations, a positive serological test result usually is needed. Almost all such patients will have positive serology (ie, sensitivity is excellent); however, a small proportion of patients with early neurological Lyme disease (<15%) will not have seropositivity until repeat testing is performed 1 to 2 weeks after initial presentation. In contrast, patients with late Lyme disease (eg, Lyme arthritis) will usually have seropositivity for IgG antibodies at the time of presentation.^{5,6} Seronegative late Lyme disease is not an established entity.⁶

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Shapiro reported receiving an honorarium from Valneva; providing expert testimony in malpractice suits related to Lyme disease for various law firms; receiving grants from the National Institute of Allergy and Infectious Diseases and National Center for Advancing Translational Sciences; receiving payments for Grand Rounds talks; and receiving royalties from UpToDate. Dr Wormser reported serving on the board of the American Lyme Disease Foundation; providing expert testimony in Lyme disease cases; receiving grants to his institution from the National Institutes of Health, Centers for Disease Control and Prevention, Immunetics, Quidel Corporation, Rarecyte, and Institute for Systems Biology; receiving payment for lectures at medical centers and professional organizations; having patent applications for diagnostic tests for Lyme disease and southern tick-associated rash illness; and owning stock in Abbott/AbbVie.

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Cardiovascular Health and Cognitive Decline

To the Editor In their population-based cohort study, Dr Samieri and colleagues¹ found that positive measures of cardiovascular health were associated with a lower risk of dementia and lower rates of cognitive decline. An important limitation of the data analysis, however, is that the investigators did not address the potential influence of depression or antidepressant treatment on their cognitive outcomes of interest.

Depression is an independent risk factor for all-cause and cardiac morbidity and mortality in patients with acute coronary syndromes, may be an independent risk factor for incident coronary heart disease, and is associated with a significantly increased risk of stroke morbidity and mortality.^{2,3} Depression also is an accepted risk factor for dementia. Approximately 10% of Alzheimer disease cases can be attributed to depression, comparable with the attribution rate for smoking and higher than the rates attributable to diabetes, midlife hypertension, or midlife obesity.⁴ The largest proportion of Alzheimer disease cases can be attributed to physical inactivity and low educational attainment.⁴

Depression, midlife hypertension, midlife obesity, diabetes, smoking, physical inactivity, and low educational attainment are all risk factors for dementia, but they are not independent of each other. At baseline, approximately 20% of patients in the Three-City Study had a history of treated depression, but depression occurrence and antidepressant treatment during follow-up were not reported.

Antidepressant drugs activate and regulate intracellular neurotrophic and neuroprotective processes.⁵ These intracellular processes promote neurogenesis and are protective in models of neurodegenerative diseases (including dementia) and ischemia. Increased activity or overexpression of glycogen synthase kinase 3 (GSK3) is associated with an increase in tau hyperphosphorylation and alterations in amyloid- β processing, which are related to the formation of neurofibrillary tangles and plaques in dementia. Antidepressant drugs inhibit GSK3 activity and increase brain-derived neurotrophic factor, which is involved in learning and memory and may be protective against the development of dementia.⁵

Because depression and antidepressant drug treatment have a strong potential for modifying the neurobiological risk of developing dementia, they should be considered in conjunction with other cardiovascular risk factors.

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In Reply We agree with Dr Howland that depression is a comorbidity of primary importance in both cardiovascular diseases and dementia. Depressive symptoms are prevalent in older persons (eg, 12.6% of our study participants had high depressive symptomatology based on validated cutoffs on the Center for Epidemiologic Studies–Depression Scale, and 6.4% consumed antidepressant medications at baseline¹), and depression may represent both a risk factor and a prodrome of dementia.²

Moreover, higher depressive symptoms have been related to lower cardiovascular health levels in epidemiological studies,^{3,4} suggesting that depression could represent a barrier to reach optimal cardiovascular health. Our analyses in the Three-City Study cohort confirmed the strong relationships between depressive symptomatology and both decreased levels of cardiovascular health and increased dementia risk, as previously reported. The proportions of individuals with high depressive symptoms or antidepressant use at baseline for