We would like to make several important clarifications with respect to McEvoy's comments about our methodologic approach. The choice of time scale for Kaplan–Meier and other techniques for survival analysis can vary, and it is well established that the "time on study" approach and the "attained age" approach yield similar results when persons who are disease-free are followed after a selected index age.[2] Our approach uses age as the time scale, but we did not average risk-factor levels across the lifespan, as we clearly state in our article: "Participant data were stratified according to risk-factor levels or status as assessed within 5 years of each index age. For example, risk factors measured for participants between 40 and 49 years of age were included in the analyses for the age of 45 years." All reported lifetime-risk estimates for each age group are derived only from the participants with risk factors measured at that reported age. The relatively constant prevalence of low-risk status in men reflects the effects of changes in individual risk factors across the age spectrum. For example, when men with risk factors measured at 45 and 75 years of age are compared, smoking is more prevalent at the younger age (51.0% vs. 20.7%), whereas diabetes is more prevalent at the older age (2.8% vs. 11.7%).

Finally, we appreciate the insightful comments from Burtscher on the importance of physical activity on lifetime risk for cardiovascular disease. Recently, we reported on the association between physical-fitness levels and lifetime risk for cardiovascular disease in the Cooper Center Longitudinal Study using this same analytic approach.[3] We observed that physical fitness represents an important determinant of long-term risk, particularly among persons with established risk factors.

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Since publication of their article, the authors report no further potential conflict of interest.

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IgG4-Related Disease

TO THE EDITOR: In their review, Stone et al. (Feb. 9 issue)[1] describe clinical features of IgG4-related disease. However, it is critical for physicians to be aware of two additional clinical aspects. First, IgG4-related disease affects joints,[2-4] and second, it can affect children[5] as well as adults. We are currently treating a 15-year-old patient who has had IgG4-related disease for 4 years. He first presented with two episodes of bilateral mastoiditis, which required surgery. Both the clinical course and the histologic findings were compatible with chronic nonspecific inflammation. Two years later, the patient had severe headaches, polyuria and polydipsia due to diabetes insipidus, and ankle arthritis. Magnetic resonance imaging of the brain revealed meningeal inflammation and hypophysitis. A brain biopsy showed hypertrophic pachymeningitis with mixed infiltrates of lymphocytes, plasma cells, and eosinophils. The ratio of IgG4-positive to IgG-positive plasma cells was increased (32 per high-power field). The same findings were present on a synovial biopsy of the talocalcaneal joint (Fig. 1). This case suggests that arthritis should be included in the list of organ manifestations in IgG4-related disease in both adults and children.

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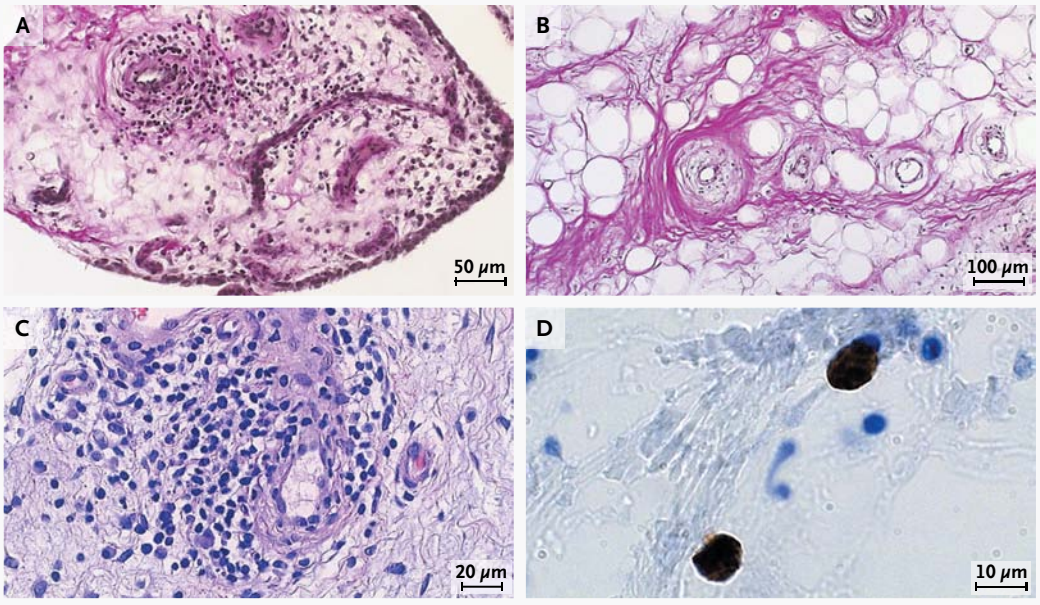

Figure 1. Histopathological Features in a Synovial-Biopsy Specimen.

A tissue specimen from the patient's talocalcaneal joint shows perivascular fibrosis with loose-to-dense storiform and whorled collagen deposits (Panels A and B, elastic van Gieson stain), angiocentric aggregates of lymphocytes and plasma cells and mild eosinophilia (Panel C, hematoxylin and eosin), and IgG4-positive plasma cells (Panel D, immunostain), all consistent with IgG4-related disease.

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TO THE EDITOR: We would like to emphasize that myasthenia gravis with autoantibodies to muscle-specific kinase (MuSK) should also be regarded as an IgG4-mediated disorder. Myasthenia gravis, which is characterized by fatigable muscle weakness, is caused by autoantibodies to the acetylcholine receptor (AChR), MuSK, or low-density lipoprotein receptor–related protein 4, all postsynaptic membrane proteins of the neuromuscular junction.

Clinical, immunologic, pharmacologic, and genetic findings indicate that myasthenia gravis with autoantibodies to MuSK is a distinct disease entity. In this disorder, autoantibodies are mainly IgG4,[1] and antigen-specific IgG4 (but not IgG1) titers correlate with disease severity.[2] Myasthenia gravis with autoantibodies to MuSK is associated with HLA-DR14-DQ5, as is IgG4-related pemphigus vulgaris in a subset of patients with the disorder.[3] This is in contrast to myasthenia gravis with autoantibodies to AChR, a disorder linked to HLA-B8-DR3, in which IgG1 and IgG3 autoantibodies cause complement-mediated damage and IgG4 recombinant antibodies protect against disease.[4] Recently, we found that purified IgG4 (but not IgG1, IgG2, or IgG3) from patients with myasthenia gravis with autoantibodies to MuSK causes muscle weakness in immunodeficient mice.[5] These findings strongly suggest that IgG4 autoantibodies are of patho-