Concerns about the external validity of the study ‘prevalence of persistent symptoms after treatment for Lyme borreliosis: A prospective observational cohort study’-authors’ reply

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We thank Dessau et al. for their critical appraisal and compliments regarding our study.1−3 We are somewhat surprised about their statement that persistent symptoms after erythema migrans (EM) cannot be associated with Lyme borreliosis (LB), as there would have been no improvement after treatment. This is a misunderstanding: fatigue severity of EM patients during follow-up had a decreasing trend that was significant compared to both reference groups (Table S8). This was a substantial improvement of 6−8% on the fatigue severity scale range. In disseminated LB patients, improvement in symptoms after treatment was more explicit, due to more severe acute symptoms compared to EM. Despite the improvement, at 12 months follow-up fatigue severity in EM patients was still significantly higher than in both reference groups. Persistent symptoms are of course long-lasting by definition, and for LB have indeed previously been described to last up to 12 months or even longer.

Furthermore, Dessau et al. have questioned the external validity of our LB patient group. We aimed to recruit patients representative of LB patients seen in daily clinical practice. Although patients often self-registered (see Supplementary methods), we also extensively recruited through GPs and other physicians. This led to recruitment through physicians of 27% of the patients included in the primary analysis. If we restrict the primary analysis solely to these patients, we would still have detected a 6% higher prevalence of persistent fatigue in EM patients as compared to the reference groups, which is significant for the population cohort (p=0.01), and the tick bite cohort (p=0.05). For cognitive impairment and pain, no consistent differences were found in this additional analysis, which is in line with the primary analysis results (Figure 2).

Therefore, our inclusion of voluntarily self-registered EM patients does not seem to have led to different results and conclusions than by solely clinical recruitment. Of note, recruitment through physicians was voluntary as well. That is also the case for the reference groups, i.e. participants reporting a tick bite at the online study platform, and individuals invited from the general population, whereas from the latter a low response rate was to be expected, like in most population studies. Regarding the question about recruitment through clinical Lyme centers: all consecutive patients with confirmed LB who had started antibiotic treatment within the last 7 days were invited by the research physicians. We applied statistical methods that corrected for differences in age, sex, co-morbidity and education between the LB and reference cohorts. This, together with the frequency matching of the population cohort, is expected to have corrected for selection bias. As acknowledged by Dessau et al., we confirmed the robustness of our results in sensitivity analyses, including a restriction to subjects reporting no pre-existing...
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The background prevalence is well in line with results of symptoms. Furthermore, the 4-6% higher prevalence of virus infection, Q-fever and COVID-19 −LB and other infectious diseases sonal pattern. Because tick bites and LB follow the same sea-
tick bite cohort was automatically frequency matched by recruiting the population cohort (Methods section). The inclusion periods between cohorts led to selection bias, because individuals were included in the analysis population instead of “were included in the primary analysis”.

It would have been favorable if the reference cohorts had similar follow-up rates as the LB cohort, but both independently recruited reference cohorts did not significantly differ in prevalence of persistent symptoms (23.3% versus 21.2%, p=0.10), and prevalence of severe fatigue at baseline in both reference cohorts was consistent with a Dutch population study (N=78,363). This strongly suggests that our reference cohorts were representative.

We corrected for missing data in the analyses to further reduce the risk of selection bias. In contrast to the assumption by Dessau et al., we did not apply multiple imputation. Instead, we performed the primary analysis with linear interpolation of missing data combined with carrying forward and backward of first and final observations, and then tested its robustness in sensitivity analyses with pre-defined alternative substitution procedures (Table S4A/B). All analyses pointed towards the same conclusion: LB patients, including EM, have a somewhat higher level of persistent symptoms than the background prevalence.

Baseline was included in our definition of persistent symptoms with an onset within 6 months from the LB manifestation and that lasted for at least 6 months in the year after treatment. We do not think that different inclusion periods between cohorts led to selection bias, because we took seasonal variation into account when recruiting the population cohort (Methods section). The tick bite cohort was automatically frequency matched by season, because tick bites and LB follow the same seasonal pattern.

Our results are in line with reported associations of LB and other infectious diseases – e.g. Epstein-Barr virus infection, Q-fever and COVID-19 – with chronic symptoms. Furthermore, the 4-6% higher prevalence of persistent symptoms in our LB cohort compared to background prevalence is well in line with results of another Dutch study where GPs reported persistent symptoms attributed to LB in 4–10% of LB patients. Some studies may have found no significant difference between EM cases and controls, but these had less power, did not include persistence and severity of symptoms in their case definition, and some may have suffered from selection bias, since controls had significantly higher levels of symptoms than cases. In addition, two of these studies report possible post-treatment Lyme disease syndrome in a subset of patients.

Taken together, we believe that our results are robust and generalizable. Nevertheless, in daily clinical practice it will remain challenging to distinguish between persistent symptoms after LB, and symptoms due to many other possible causes, i.e. background prevalence.

Contributors

CW drafted the response; HV, JU, CW performed literature search; all authors reviewed and contributed to drafts of the response.

Declaration of interests

All authors have no conflicts of interests to disclose.

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