4.6. Reconsidering Etiology

While hEDS is currently classified as a heritable connective tissue disorder, findings from this study raise the hypothesis that connective tissue symptoms may develop in parallel with, or be influenced by, other systemic physiological processes. The observed high prevalence of immune dysregulation, autonomic dysfunction, and gastrointestinal dysmotility supports the possibility that neuroimmune or inflammatory pathways could contribute to the broader clinical phenotype. Although speculative and beyond the causal scope of this cross-sectional survey, these findings suggest that hEDS may, in some cases, reflect overlapping features with autoimmune or autoinflammatory conditions rather than representing a purely connective tissue–based pathophysiology. This hypothesis warrants further investigation through mechanistic and longitudinal studies. As researchers, clinicians and patient communities advocate for updated diagnostic frameworks, expanded research efforts, and improved treatment pathways, it is imperative that patient experiences remain at the forefront of these advancements. Given the significant multimorbidity associated with hEDS and HSD, future research, particularly incorporating biomarker studies and genetic approaches, may help refine classifications and improve our ability to diagnose and treat these conditions.

5. Conclusions

This global survey provides the most comprehensive epidemiological profile to date of individuals with hypermobile Ehlers–Danlos syndrome (hEDS) and hypermobility spectrum disorders (HSDs), revealing a strikingly high burden of multisystemic comorbidities, profound diagnostic delays, and significant unmet clinical needs. Across more than 3900 participants, the study identifies disproportionately high rates of gastrointestinal, autonomic, neurological, immune-mediated, and musculoskeletal complications, often with symptom onset in childhood, disease exacerbation following triggers, and formal diagnosis delayed by over two decades. Compared to both HSD and general population data, individuals with hEDS exhibited elevated risk for manifestations such as postural orthostatic tachycardia syndrome, small-fiber neuropathy, gastrointestinal dysmotility, immune-/mast cell-related conditions, and structural joint and spine abnormalities.

While these findings challenge the traditional view of hEDS and HSDs as isolated connective tissue disorders, we recognize that the study's cross-sectional and self-reported design precludes causal inference. This study was not intended to establish new diagnostic criteria, but rather to generate a large, global dataset that can serve as a foundational resource for hypothesis generation and future studies. These results are meant to inform and complement emerging research in relation to genetic, proteomic, and biomarker signatures, which will be essential for developing validated, data-driven diagnostic frameworks. By illuminating the scope and heterogeneity of hEDS and HSD, this study highlights critical areas for future mechanistic investigation and reinforces the need for multidisciplinary, personalized approaches to care.

This study serves as a critical call-to-action for the medical community. The staggering delays in diagnosis, the overwhelming reliance on self-advocacy, and the systemic lack of treatment options illustrate a glaring gap in healthcare. The lack of standardized care protocols often leads to misdiagnosis, symptom neglect, and, at times, outright denial of these conditions by healthcare providers. Addressing these issues will require collaboration across specialties, heightened awareness among healthcare providers, and a sustained commitment to addressing the full spectrum of challenges faced by this patient population.

Recognizing the full impact of hEDS and HSDs is key to driving meaningful change, breaking down barriers to care, advancing research and ensuring that individuals and families impacted by these conditions receive the medical care and support they deserve.

Supplementary Materials: The following supporting information can be downloaded at: https:// www.mdpi.com/article/10.3390/jcm14165636/s1, Figure S1: Survey questionnaire; Figure S2: List of conditions; Table S1: Patient demographics; Table S2: Sexual orientation; Table S3: US state residency of patient cohort; Table S4: Country of residence of patient cohort; Table S5: Diagnostic process; Table S6: Symptom severity; Table S7: Pain medication use; Table S8: Cardiopulmonary disorders by age.

Denna studie framhäver kritiska områden för framtida mekanistisk undersökning och förstärker behovet av mångdisciplinära, personliga vårdmetoder. Denna studie fungerar som en kritisk uppmaning till den medicinska gemenskapen. De häpnadsväckande fördröjningarna i diagnos, det överväldigande beroendet av egen förvaltning och den systematiska bristen på behandlingsalternativ illustrerar en påtaglig klyfta i vården. Bristen på standardiserade vårdprotokoll leder ofta till felaktiga diagnoser, förbisedd symtom och, ibland, rent av förnekande av dessa tillstånd av vårdgivare. Att ta itu med dessa frågor kommer att kräva samarbete över specialiteter, ökad medvetenhet bland vårdgivare, och ett långsiktigt engagemang för att hantera hela spektrumet av utmaningar som denna patientpopulation står inför. Att erkänna den fulla påverkan av hEDS och HSD är nyckeln till att driva meningsfull förändring, bryta ner hinder för vård, främja forskning och säkerställa att individer och familjer som påverkas av dessa tillstånd får den vård de behöver.