

Early Cutaneous and Gastrointestinal Manifestations in Lysosomal Storage Disorders: Diagnostic Clues and Prognostic Implications from a Global Real-World Dataset

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Introduction

- Lysosomal storage diseases (LSDs) are a heterogeneous group of 70+ inherited metabolic disorders caused by deficiency of lysosomal enzymes.
- Incidence is 1 in 7,700 live births, affecting an estimated 1.5 million individuals globally.
- Often involve multiple organ systems including skin, GI, CNS, renal, and cardiovascular.
- Dermatologic signs may be visible before visceral symptoms, yet their association with GI complications has not been explored.
- Study Aims:
 - Assess relationship between cutaneous manifestations and GI complications in LSD.
 - Understand prognostic relationship for those with early symptomatology.

Methods

- Retrospective TriNetX cohort study, using 143 healthcare systems in 18 countries and 163 million patient records.
- Propensity score matching to pair cohorts for age, sex, and race.
- Aim 1: Comparing GI outcomes:

Cohort A:	Cohort B:
LSD with cutaneous manifestations	LSD without cutaneous manifestations

- Aim 2: Systemic involvement and treatment regimens with GI/Skin:

Cohort C:	Cohort D:
LSD with GI +cutaneous manifestations	LSD without GI+cutaneous manifestations

Results

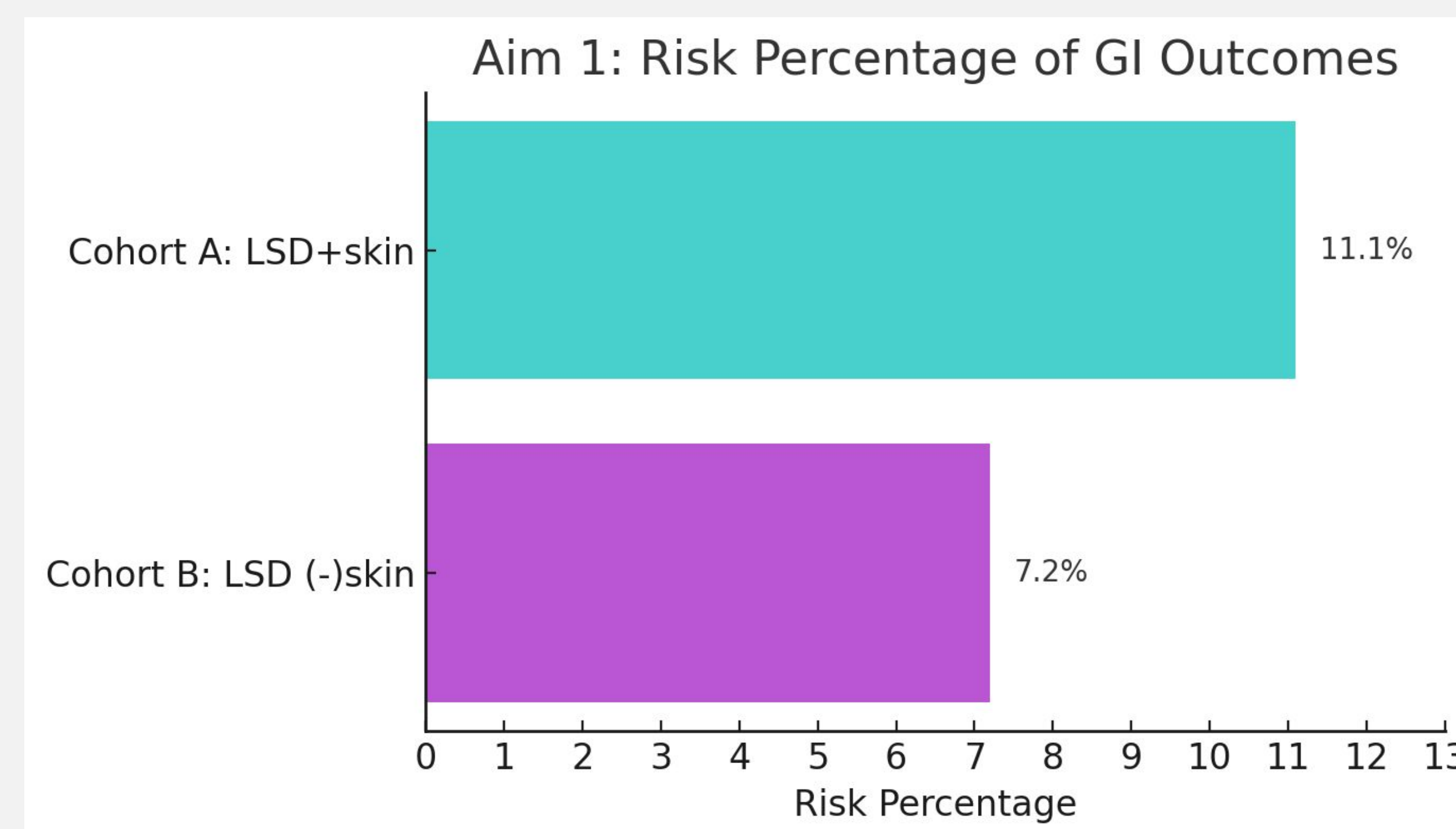


Figure 1. Risk percentage of gastrointestinal (GI) outcomes in Cohort A (LSD with cutaneous manifestations) and Cohort B (LSD without cutaneous manifestations).

Risk Ratio	95% CI
1.54	(1.37, 1.73)

Table 1. Risk ratio (RR) of gastrointestinal outcomes in patients with lysosomal storage disorders (LSD) versus without cutaneous manifestations.

Cohort A	Cohort B	p-value
86.0%	92.1%	<0.001

Table 2. Kaplan-Meier analysis

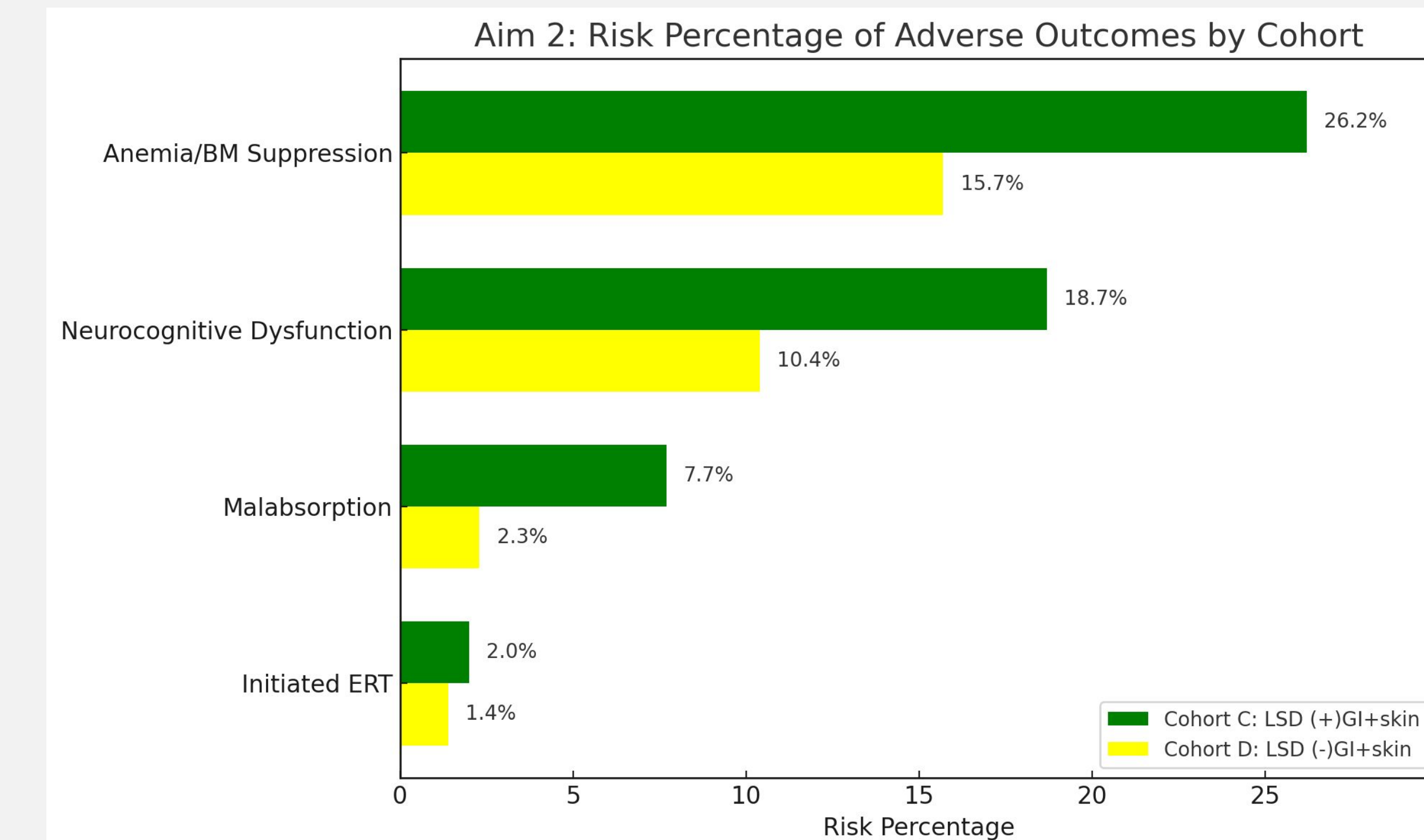


Figure 2. Risk percentage of adverse outcomes in Cohort C (LSD with GI and cutaneous manifestations) compared to Cohort D (LSD with cutaneous manifestations only). BM=Bone Marrow. ERT=Enzyme Replacement Therapy.

	Risk Ratio	p-value
Anemia/BM suppression	1.67	p<0.0001
Neurocognitive Dysfunction	1.80	p<0.0001
Malabsorption	3.32	p<0.0001
ERT Therapy Initiation	1.42	p<0.0001

*Hepatosplenomegaly was not different between cohorts (RR: 1.069, p=0.63).

Table 3. Risk ratios for adverse clinical outcomes in Cohort C (LSD with GI and cutaneous manifestations) compared to Cohort D (LSD with cutaneous manifestations only).

Discussion

- Early cutaneous and GI symptoms in LSDs were consistently associated with increased systemic complications and worse outcomes.
- Patients with skin manifestations faced a 54% higher risk of GI complications within one year of diagnosis.
- Those with early skin/GI symptoms experienced significantly greater rates of anemia, neurocognitive dysfunction, malabsorption, and need for enzyme replacement therapy.
- Dermatologic and GI signs - often preceding overt diagnosis - are not only common but also prognostically significant.
- Recognizing these early clues may enable timely diagnosis and proactive intervention in multisystem LSDs, potentially mitigating irreversible disease progression.

Limitations

- Such data are dependent on diagnostic coding accuracy, symptom severity and duration were not captured and causal inferences are limited due to observational design.
- Use of ICD-10 codes in de-identified EHR data may underreport certain diagnoses or misclassify symptom timing.

Future Research

- Future studies could develop and validate clinical screening algorithms that incorporate specific cutaneous findings to predict underlying LSDs, enabling earlier referral for confirmatory genetic or enzymatic testing
- Longitudinal cohort studies should assess whether earlier diagnosis and treatment correlate with improved quality of life, reduced organ damage, and lower healthcare utilization in patients with LSDs.

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