Economic and Healthcare Burden in Patients with Fragile X Syndrome: A Systematic Literature Review

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Introduction

- Fragile X syndrome (FXS) is a rare genetic disorder that encompasses substantial economic challenges on individuals, families, and healthcare systems. The combination of high per-patient costs, limited treatment options, and fragmented care pathways contribute to a disproportionate financial burden.[1,2] While the clinical impact of FXS is well recognized, the economic and healthcare resource burden remains inadequately quantified.[2]

Objective

– To conduct a systematic literature review (SLR) analyzing the direct costs, indirect costs, and resource utilization associated with patients diagnosed with FXS.

Methods

– The SLR methodology followed the recommendations published in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, the Centre for Reviews and Dissemination, and the Cochrane Collaboration.[3,4]

Eligibility Criteria

– The eligibility criteria for the SLR are outlined below in **Table 1**, according to the PICOS (Patients, Interventions, Comparators, Outcomes, Study Design) statement.

Table 1. Eligibility Criteria of the SLR

PICOS Element	Inclusion Criteria	Exclusion Criteria
Population	Patients with FXS of any age	Non-FXS populations
Intervention/ Comparator	NA	NA
Outcomes	Healthcare costs and resource utilization	Studies not reporting relevant outcomes
Study Design	Observational studies, economic evaluations, survey-based studies	RCTs, case reports, commentaries, letters, reviews, other non-included designs
Other	English only	Non-peer reviewed

Abbreviations: FXS, Fragile X Syndrome; NA, not applicable

Information sources

– Searches for published studies were run in Embase, Medline, EconLit through the OVID platform, combining free-text and Controlled vocabulary terms.

Study Selection

– Abstracts were screened by two independent reviewers, with a third reviewer resolving any disagreements. Relevant abstracts were then advanced to full-text screening using the same process.

Data Extraction and Critical Appraisal

– Data from included studies were extracted into pre-made sheets capturing healthcare costs and resource utilization. Extractions were validated by an independent reviewer.

– Critical appraisal was conducted using the Newcastle-Ottawa Scale[5]

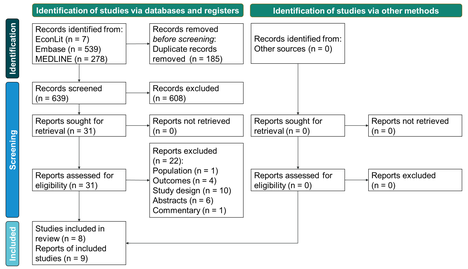
Results

Literature Search Finding

– From 824 initial abstracts identified, 639 were screened after removing 185 duplicates, with 608 excluded during abstract screening.

– After full-text screening of the remaining 31 records, 8 studies (9 records) were included in the final SLR. (**Figure 1**).[1-2,6-12]

Figure 1. PRISMA Flow Diagram



Included Studies

– Five studies used cross-sectional designs, while the remaining three studies used cohort design, with data collected through various methods including surveys, questionnaires, databases, and claims.

– Most studies (n=6) were conducted in the USA, with one was from Australia, and in Europe (n=1), with perspectives primarily being societal (n=4)

Table 2. Included Studies

Study & Country	Study Design	Data	Perspective	Ref. Year (Currency)	Sample Size	NOS Score
Bailey 2012 (USA)[6]	Cross-sec	Survey	Societal	2011 (USD)	350	4
Baker 2021 (AUS)[7]	Cross-sec	Questionnaire	Societal	2019 (AUD)	35	7
BURQOL-RD (EU)[2,8]	Cross-sec	Questionnaire	Societal	2012 (EUR)	241	7
Nazareth 2015 (USA)[9]	Cohort	Claims	Payer	2012 (USD)	697	9
Ouyang 2014 (USA)[10]	Cross-sec	Survey	Patient	- (USD)	189	7
Raspa 2016 (USA)[1]	Cross-sec	Survey	Societal	- (-)	340	7
Sacco 2013 (USA)[11]	Cohort	Claims	Payer/ Healthcare	- (USD)	1505	9
Vekeman 2015 (USA)[12]	Cohort	Database	Payer	2012 (USD)	590	9

Abbreviations: AUD, Australian Dollar; AUS, Australia; FRA, France; EU, Europe; EUR, Euro; NOS, Newcastle-Ottawa Scale, USA, United States of America; USD, US dollar

Patient Characteristics

– Most patients were male (46%[12]-89.5%[8]), with sample sizes ranging from 35[7]-1505[11] and mean ages spanning from approximately 9[7] to 26[12] years.

Healthcare Costs

– The economic burden varies significantly across studies, with direct healthcare costs ranging from €410 (in two patients in the UK)[8] - €2,675 (95 French patients)[8] in European countries to approximately $2,233 in males 12-17 years to $32,606 in females 0-11 years in the United States (US)[12]

– While in Australia, the mean total cost was estimated at AUD$33,219[6].

– Mean medication costs ranged from €4 to €307 in Europe[8] and from $89 in males[6] to $2,358 in the US.[9]

– The hospitalization/inpatient costs in Europe varied from €20[8] in Hungary to €902[8] in France.

– The hospitalization costs in the US were $2,396[9] to a mean of $25,847[11] and $5469 in Australia.

– The mean annual indirect costs in France was €31,240 (SD €9,991)[2]

Table 3. Healthcare Costs

Study	Total Costs - Mean (SD)	Total Direct Costs - Mean (SD)	Medication cost (Mean [SD])	Hosp./ Inpatient cost (Mean [SD])
Bailey 2012[6]	-	-	• Males $89 (range $2–$1000) • Females $95 (range $1–$888)	-
Baker 2021[7]	-	-	• $300 (95% CI 100–500)	• $5469 (95% CI 3504–7434)
BURQOL-RD[2,8]	• France: €35,737 • Hungary: €4951 • Italy: €21,586 • Spain: €31,008 • Sweden: €58,862 • UK: €430	• France: €2,675 (€5,519) • Hungary: €110 (€127) • Italy: €2,485 (€3,099) • Spain: €948 (€1,213) • Sweden: €953 (€998) • UK: €410 (€579)	• France: €55 (€157) • Hungary: €4 (€14) • Italy: €98 (€222) • Spain: €307 (€459) • Sweden: €86 (246) • UK: €62 (€87)	• France: €902 (€4717) • Hungary: €20 (€46) • Italy: €264 (€731) • Spain: €29 (€149) • Sweden: €42 (€171) • UK: €0 (0)
Nazareth 2015[9]	-	-	$2,358 ($5,155)	$2,396 ($15,281)
Sacco 2013[11]	-	Medicare • 0-11 yrs: $2955 • 12-17 yrs: $2222 • ≥18 yrs: $2384 Medicaid • 0-11 yrs: $4548 • 12-17 yrs: $4581 • ≥18 yrs: $5154	-	Medicare • $21,677 Medicaid • $25,847
Vekeman 2015[13]	-	$14,677 ($46,752)	$2,331 ($6,171)	$4,509 ($17,989)

Healthcare Costs – Age Variation

– Total direct costs varied by age and insurance type. Medicare costs were highest in children aged 0–11 years ($2,955) vs Medicaid costs that were consistently higher across all age groups ($4,548 to $5,154).[11]

Healthcare Costs – Sex Variation

– The average medication costs for males and females are similar ($89 vs. $95) but show a high variability in ranges ($1-2 to $1,000).[6]

Loss of Productivity

– Six studies reported loss of productivity, from 35%[6] of families with at least one caregiver quitting working to 40%[10] of US respondents who reported quit their job. One US study reported a mean absenteeism due to medical visits of $4,477.[12]

– One Australian study reported mean employment loss costs of $3,735.[7] In Europe, labor productivity losses ranged from €0 to €2,880 (SD €89,73).[8]

Resource Use

– FXS patients showed consistently higher healthcare utilization than those without FXS, with over 90% requiring outpatient care, 7-35% needing emergency services, and 2-13% requiring hospitalization.

Table 4. Resource Use

Study	Inpatient visits – n (%)	Emergency Visits - n (%)	Outpatient visits – n (%)
Bailey 2012[6]	• Males: 4 (2%) • Females: 1 (2%)	• Males: 19 (7%) • Females: 0 (0%)	Males • ≥1 PCP visit: 274 (94%) • ≥1 specialist visit: 283 (97%) Females • ≥1 PCP visit: 52 (89%) • ≥1 specialist visit: 283 (97%)
Nazareth 2015[9]	• With FXS: 93 (13%) • Without FXS: 199 (6%)	• With FXS: 243 (35%) • Without FXS: 925 (27%)	• With FXS: 644 (92%) • Without FXS: 2,231 (64%)
Raspa 2016[1]	-	-	• ≥5 specialist visits in past year: 147 (44%)
Sacco 2013[11]	• Medicare 74 (9%) • Medicaid 90 (13%)	-	• Medicare 747 (95%) • Medicaid 702 (97%)

Abbreviations: PCP, primary care provider

Length of Hospitalization

– FXS patients require significantly longer hospital stays than non-FXS individuals, with Nazareth 2015 showing FXS patients average 3.5 days vs only 1.2 days for those without the condition.

– Vekeman 2015 found FXS patients had higher hospitalization rates (all-cause IRR: 1.23, FXS-related IRR:1.12) compared to a non-FXS controls.

Table 5. Length of Hospitalization

Study	Patients	n/N (%)	Mean Length of Stay
Bailey 2012[6]	FXS Males	4/292 (2%)	1-2 nights
	FXS Female	1/58 (2%)	2 nights
Nazareth 2015[9]	FXS	NR	3.53 days
	Without FXS	NR	1.17 days
Vekeman 2015[12]	Overall FXS	NR	IRR all-cause: 1.23 IRR FXS-related: 1.12
	Non-FXS	NR	Reference

Abbreviations: FXS, Fragile X Syndrome; IRR, Incidence Rate Ratio

Limitations

– The overall evidence is limited by a small number of eligible studies and restricted geographic diversity.

– Three US-based analyses rely on the same 2011 caregiver survey which could derive in patient overlap and affect generalizability of the results.

– Most data comes from high-income countries, with little to no representation from low- and middle-income settings. As a result, the economic burden of FXS in diverse healthcare systems and socioeconomic contexts remains largely unknown.

– Because of the considerable methodological differences across studies in data sources, study designs, cost reporting and outcome measures the comparison in findings across studies was difficult.

– Several studies had small sample sizes and relied on self-reported data which could lead to recall bias and limit precision of estimates.

Conclusions

– FXS places a heavy financial burden on healthcare systems and families, specially through non-medical costs like lost productivity.

– Direct medical costs were often outweighed by societal costs; this highlights the needs of FXS patients across their lifespan.

– Most of the available evidence comes from a small number of high-income countries and overlapping patient populations, offering only a limited view of the real-world impact. This means that this data is providing only a partial view of the global economic burden of FXS.

– There's a clear need for more inclusive, globally representative and standardized research to fully understand the global economic impact of FXS.

– A more comprehensive understanding of FXS burden could guide resource allocation and inform the development of strategies that better support families living with FXS around the world.

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