



Costs of Illness of Spinal Muscular Atrophy: A Systematic Review

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Abstract

Objectives The objective of our study was to conduct a systematic literature review of estimates of costs of illness of spinal muscular atrophy (SMA).

Methods We searched MEDLINE (through PubMed), CINAHL, Embase, Web of Science, National Health Service Economic Evaluation Database, and the National Health Service Health Technology Assessment Database for studies published from inception up until 31 August, 2020, reporting direct medical, direct non-medical, and/or indirect costs of any phenotype of SMA. Two reviewers independently screened records for eligibility, extracted the data, and assessed studies for risk of bias using the Newcastle–Ottawa Scale. Costs were adjusted and converted to 2018 US dollars.

Results The search identified 14 studies from eight countries (Australia, France, Germany, Italy, Spain, Sweden, the UK, and the USA). The mean per-patient annual direct medical cost of illness was estimated at between \$3320 (SMA type III, Italy) and \$324,410 (SMA type I, USA), mean per-patient annual direct non-medical cost between \$25,880 (SMA types I–III, Spain) and \$136,800 (SMA type I, Sweden), and mean per-patient annual indirect cost between \$9440 (SMA type I, Germany) and \$74,910 (SMA type II, Australia). Most studies exhibited a risk of bias.

Conclusions The current body of evidence of costs of illness of SMA is relatively scarce and characterized by considerable variability across geographical settings and disease phenotypes. Our review provides data pertaining to the economic impact of SMA, which is of particular relevance in light of emerging treatments and ongoing research in this field, and underscores the substantial unmet medical need in this patient population.

Key Points for Decision Makers

No study has systematically reviewed the literature for estimates of costs of illness of spinal muscular atrophy.

The body of literature of costs of illness of spinal muscular atrophy is limited to a few geographical settings and characterized by considerable variability across disease phenotypes.

Our review helps inform economic evaluations and future cost research, and highlights the substantial unmet medical need in spinal muscular atrophy.

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1 Introduction

Spinal muscular atrophy (SMA) is a rare inherited neuromuscular disease characterized by progressive muscle degeneration. There are several phenotypes of SMA, from SMA type I (Werdnig–Hoffmann disease) to SMA type IV (adult-onset SMA), with stark differences in onset and severity [1]. The most severe form, SMA type I, accounts for about 60% of all new cases [2, 3] and has been shown to be associated with a median age of death, or need for permanent ventilation support for survival, of less than 12 months [4, 5]. In contrast, patients with SMA types III or IV typically have a normal lifespan, despite significant impairment in functional ability that can include loss of independent ambulation [6]. The prevalence of SMA has been estimated at around 1–2 per 100,000 individuals, with an incidence of approximately 1 in 10,000 live births [3].

Recently, two medications have been approved for 5q-linked SMA, the most common form of the disease caused by mutations in the survival motor neuron gene that is found on chromosome 5: Spinraza[®] (nusinersen; Biogen Idec) and Zolgensma[®] (onasemnogene abeparvovec; Novartis AG/AveXis). Spinraza[®] is an antisense oligonucleotide administered by repeat intrathecal dosing and approved in many countries for the treatment of all disease phenotypes. Zolgensma[®] is a gene replacement therapy administered through a single intravenous dose approved in the USA, Japan, Brazil, and the European Union for children with SMA. Additionally, several treatment strategies for SMA are currently being explored, including splice-modifying therapies [7]. In conjunction with this development, to help inform value-based resource allocation and economic evaluations of forthcoming therapies, as well as describe and raise awareness of the current overall cost burden of disease, there has been an increased interest in understanding the health economic context of SMA. The objective of our study was to conduct a systematic review of estimates of costs of illness of SMA globally. Specifically, this systematic literature review sought to answer the following questions: (1) in which geographical settings have costs of illness of SMA been studied? (2) For which types of SMA have costs of illness been estimated? (3) What types of costs of illness have been estimated in patients with SMA? (4) What are the known costs of illness of SMA? The aims of this study were to review the current body of evidence of direct medical, direct non-medical, and indirect costs of SMA to help inform cost-effectiveness analyses and similar evaluations of forthcoming therapies, map out data gaps to guide future cost research, and describe the current economic burden of illness.

2 Methods

This systematic review was registered at the International Prospective Register of Systematic Reviews (PROSPERO) [identifier: CRD42020160020], and conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [8].

2.1 Search Strategy

We searched MEDLINE (through PubMed), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, Web of Science, National Health Service Economic Evaluation Database, and the National Health Service Health Technology Assessment Database for records of studies published from inception up until 31 August, 2020, reporting estimates of costs of illness of SMA. The search string contained a combination of the following medical subject heading terms, title/abstract, and topic field tags: “Spinal muscular atrophy”, “cost”, “financial”, “burden”, “economic”, “monetary”, “Cost of Illness”, “Costs and Cost Analysis”, “Cost-Benefit Analysis”, “cost-effectiveness”, “cost-utility”, “spending”, and “expenditure” (full search strings are provided in the Electronic Supplementary Material [ESM]).

2.2 Selection Criteria

We included all identified publications reporting estimates of the following cost of illness of SMA in any currency: direct medical costs (i.e., costs of medical resources directly included in the formal management of the disease), direct non-medical costs (i.e., costs of non-medical resources directly included in the formal management of the disease), informal care costs (i.e., costs associated with the informal management of the disease by non-professionals [9]), indirect costs (i.e., production losses from the perspective of society due to absenteeism and presenteeism from work [10]), and the total cost of illness. The provided descriptions represent the working definitions of these costs as employed in this study. We considered publications reporting results from any study type in any language. We excluded studies based on samples comprising fewer than ten patients in total, and also required that results were reported separately for patients with SMA (in case costs of several indications were investigated as part of the same study). We did not consider conference abstracts, as these contain too few details for meaningful synthesis. No further criteria were imposed for study eligibility.

2.3 Screening, Data Extraction, and Assessment of Risk of Bias

Two investigators (EL and AP) independently screened article titles and abstracts for eligibility, and subsequently reviewed full-text versions of selected records. The reasons for article exclusion were recorded and disagreements were resolved by the involvement of a third investigator (TS). For all articles that met the inclusion criteria upon full-text review, the following data were extracted: author, year, geographical setting, design, data sources, type of data, study periods, patient population, estimated cost categories (i.e., direct medical, direct non-medical, informal care, and/or indirect costs, as described above), perspective of analysis (as reported by the included publications, or inferred based on information of the included resources and methods of valuation), and estimated costs. Additionally, we also extracted information of resource categories (e.g., inpatient care, outpatient care, and prescription drugs) included in identified estimates of the per-patient annual direct medical cost of SMA. We did not consider costs of individual resources part of higher level cost categories (e.g., the cost of a general practitioner visit as part of the per-patient annual direct medical cost of illness).

Extracted data from each article were synthesized and reported with respect to the four review questions as stated in the Introduction. Based on the information in the reviewed publications, we structured identified estimates of costs of illness of SMA into the following cost categories: the per-patient annual direct medical cost of illness, the per-patient annual direct non-medical cost of illness (including informal care costs of illness), the per-patient annual indirect cost of illness, and the per-patient annual total cost of illness. Identified costs not estimated per annum (e.g., the per-patient cost per hospitalization) were reported separately. To facilitate comparison, identified costs were adjusted for inflation to 2018 values using country-specific consumer price index data from the World Bank and subsequently converted to US dollars. All reported cost estimates were rounded to the nearest ten.

Risk of bias was established with the Newcastle–Ottawa Scale (NOS) [11] by two investigators (EL and AP). The NOS was developed to assess the quality and risk of bias of non-randomized studies in three dimensions: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. Each category is assigned a score rating (maximum score: $\diamond\diamond\diamond$ for selection, $\diamond\diamond$ for comparability, and $\diamond\diamond$ for outcome). To ascertain selection, we required patients to be diagnosed with SMA (score: \diamond), that the diagnosis was confirmed via standard International Statistical Classification of Diseases

and Related Health Problems (ICD) codes for the disease (i.e., ICD-9: 335.0, 335.1X, and/or 335.21; and ICD-10: G12.0, G12.1, G12.2, G12.8, and/or G12.9 [12]) in an out- or inpatient setting (score: \diamond), and that the sample was not restricted in terms of survival of motor neuron 2 (SMN2) copy number or other markers limiting representativeness (score: \diamond) [assessment of the non-exposed cohort was not applicable, and all studies were thus assigned a score (\diamond) for this criterion]; to ascertain comparability, we required details of the number of patients and distribution of age, sex, and SMA phenotype in the sample population (score for all four details: $\diamond\diamond$; score for at least one detail: \diamond); and to ascertain outcome, we required that resource use and/or costs were extracted from clinical charts or registries/databases containing physician-reported or administrative data [e.g., governmental population-based registries or claims databases] (score: \diamond), a minimal follow-up of 1 month for prospective studies [given the frequency of care reported] (score: \diamond), and that less than 25% of the total sample were lost to follow-up during the study period (score: \diamond). Studies assigned the maximum score in all categories were judged to exhibit a low risk of bias.

3 Results

Our search strategy identified 983 publications (Fig. 1). Of these, 289 were duplicates, 665 were excluded following title and abstract screening, and 29 were selected for full-text review. Finally, 14 articles [13–26] were considered for data extraction and synthesis. The primary reason for article exclusion was lack of relevant cost data. One study [27] was not considered as it referenced cost estimates subsequently published in full by Tan et al. [21]. Summary details of the included publications are presented in Table 1. One of the included articles was written in Italian [22]. Identified estimates of costs of illness of SMA were converted to US dollars using the following rates: Pound sterling £1 = US\$1.29156; Euro €1 = US\$1.10090; and Swedish Krona SEK1 = US\$0.10427 (obtained from Morningstar, Inc. [28] on 29 November, 2019).

3.1 In Which Geographical Settings Have Costs of Illness of SMA Been Studied?

Estimates of costs of illness of SMA were found for samples from a total of eight countries, namely Australia, France, Germany, Italy, Spain, Sweden, the UK, and the USA (Table 1). Five studies (36%) represented research of patients from the USA [14, 16, 18, 19, 21].

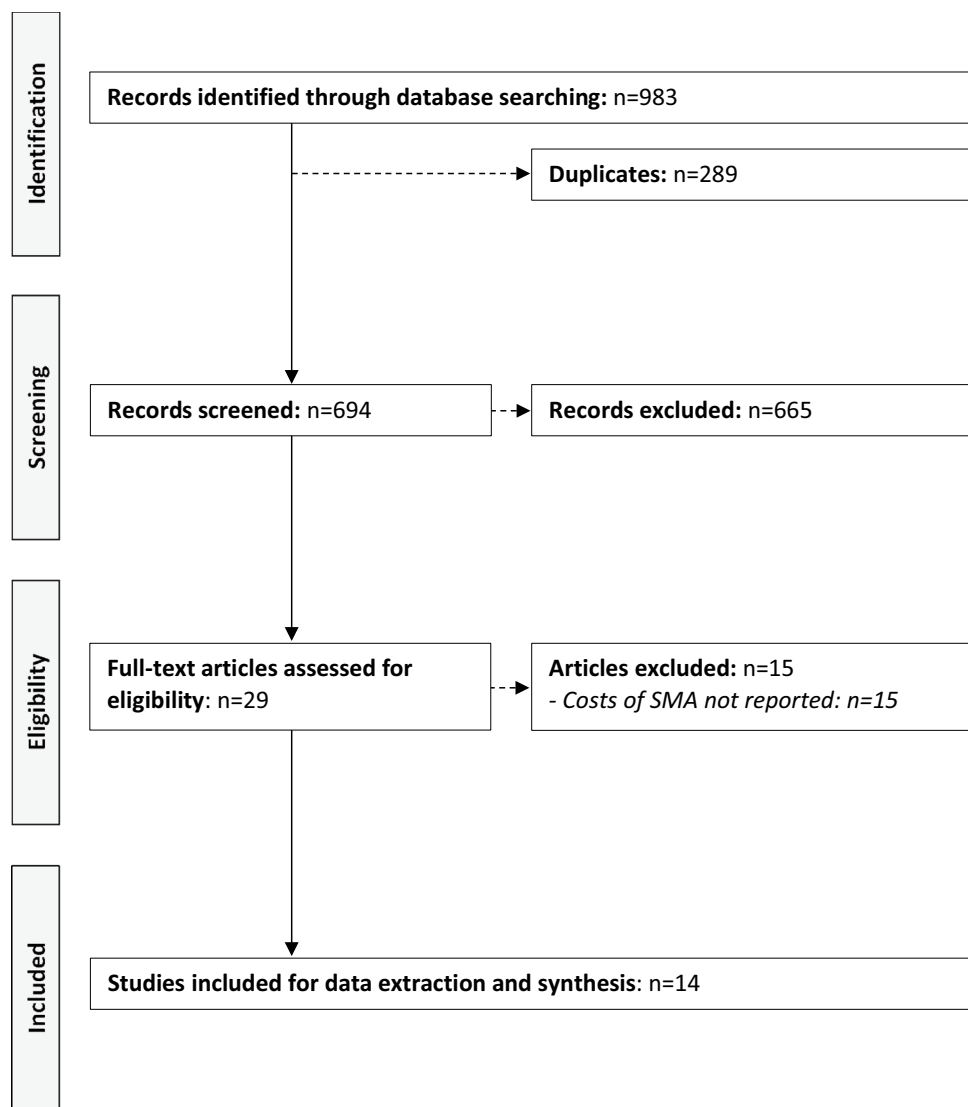


Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of the selection process of the included publications. *SMA* spinal muscular atrophy

3.2 For Which Types of SMA Have Costs of Illness Been Estimated?

Nine (64%) studies reported estimates of costs of SMA type I [15–18, 20–23, 25], four (29%) of costs of SMA type II [13, 20, 22, 25], four (29%) of costs of SMA type III [15, 20, 22, 25], one (7%) of costs of SMA type IV [21], and one (7%) study of costs of progressive SMA, other SMA, and unspecified SMA [15]. Eleven (79%) studies did not explicitly disclose SMA type, or reported pooled results for more than one type of SMA (in some cases in addition to estimates stratified by SMA type, as reported above) [13–15, 18–21, 23–26]. Two studies (14%) estimated costs of “infantile SMA”, “childhood-onset SMA”, and/or “late-onset SMA” [21, 23], for the purpose of this review approximated as SMA type I, SMA type II/III, and SMA type IV, respectively.

3.3 What Types of Costs of Illness Have Been Estimated for Patients with SMA?

In total, nine (64%) studies estimated the per-patient annual direct medical cost of SMA [13, 18–24, 26], five (36%) the per-patient annual direct non-medical cost [13, 20, 22, 23, 26], four (29%) the per-patient annual indirect cost [20, 22, 23, 25], and six (43%) studies the per-patient annual total cost of illness [13, 20, 22, 23, 25, 26] (Table 1). Additionally, three (21%) studies estimated the per-patient cost per hospitalization of SMA [14–16], and one (7%) the per-patient annual hospitalization cost of SMA [17]. Finally, Chambers et al. [25] estimated the per-patient annual direct cost of SMA (comprising both medical and non-medical costs).

Table 1 Characteristics of included studies

Author (year)	Geographical setting(s)	Design	Data source(s)	Type of data	Study period	Patient population
Ali et al. (2019) [17]	UK	Retrospective, observational cohort study	Royal Stoke University Hospital	Paper notes and electronic clinical records	2017–9	11 patients with SMA type I (45% male; median age: 2 years) treated with nusinersen
Armstrong et al. (2016) [19]	USA	Retrospective, observational cohort study	Military Health System Data Repository (MDR)	Defense Health Agency corporate healthcare data	2003–12	239 patients with SMA (45% male; mean age NR) [phenotype NR]
Chambers et al. (2020) [25]	Australia	Cross-sectional, observational study; and retrospective, observational cohort study	Survey administered to caregivers via two neuromuscular clinics and a patient support organization; the Sydney Children's Hospital SMA clinic; and local unit costs	Self-reported data; and health service use and insurance data	2016–17	40 patients with SMA (48% male; mean age: 9 years) [10% with SMA type I, 65% with SMA type II, and 25% with SMA type III]
Cardenas et al. (2019) [16]	USA	Retrospective, observational cohort study	Kids' Inpatient Database (KID) part of the HCUP	Claims data	2012	237 patients with SMA type I (43% male; mean age NR)
Darbà et al. (2019) [15]	Spain	Retrospective, observational cohort study	Spanish claims database Minimum Basic Data Set (Conjunto Mínimo Básico de Datos [CMBD])	Claims data	1997–2015	705 patients with SMA type I, SMA type III, progressive SMA, other SMA, or unspecified SMA (62% male; mean age: 37 years) [distribution of phenotypes NR]
Darbà (2020) [24]	Spain	Retrospective, observational cohort study	Public Data Analysis for Health Research and Innovation Program (PADRIS) database	Electronic clinical records	2014–17	396 patients with SMA (53% male; mean age: 57 years) (6% with SMA type I, 29% with SMA type III, 43% with progressive SMA, 10% with other SMA, and 13% with unspecified SMA)

Table 1 (continued)

Author (year)	Geographical setting(s)	Design	Data source(s)	Type of data	Study period	Patient population
Droege et al. (2019) [18]	USA	Retrospective, observational cohort study	Symphony Health's Integrated Dataverse (IDV)	Claims data	2016–18	349 patients with SMA type I (44% male; mean age: 9 years) receiving conventional therapy; 45 patients with SMA type I (38% male; mean age: 12 years) receiving nusinersen; 5728 patients with SMA types II–IV (52% male; mean age: 31 years) receiving conventional therapy; and 404 patients with SMA types II–IV (49% male; mean age: 15 years) receiving nusinersen
Klug et al. (2016) [20]	Germany	Cross-sectional, observational study	Survey administrated to patients identified via the German SMA patient registry; and local unit costs	Self-reported data	2013	189 patients with SMA (59% male; median age: 19 years) (6% with SMA type I, 39% with SMA type II, and 55% with SMA type III)
Lee et al. (2019) [14]	USA	Retrospective, observational cohort study	HCUP; and the Center for Health Information and Analysis	Claims data	2005–13	229 patients with severe SMA (distribution of sex and mean age NR) [phenotype NR]
López-Bastida et al. (2017) [13]	Spain	Cross-sectional, observational study	Survey administrated to patients via national patient associations; and local unit costs	Self-reported data	2015	81 patients with SMA (42% male; mean age: 7 years) [10% with SMA type I, 74% with SMA type II, and 16% with SMA type III]
Marcellusi et al. (2019) [22]	Italy	Cross-sectional, observational study	Survey administrated to patients via a national patient association; and local unit costs	Self-reported data	2018	118 patients with SMA (41% male; mean age: 18 years) (23% with SMA type I, 48% with SMA type II, and 29% with SMA type III)

Table 1 (continued)

Author (year)	Geographical setting(s)	Design	Data source(s)	Type of data	Study period	Patient population
Peña-Longobardo et al. (2020) [26]	France; Germany; and UK	Cross-sectional, observational study	Survey administered to caregivers via a patient organization/registry; and local unit costs	Self-reported data	2015	27 French patients with SMA (41% male; mean age: 6 years) [19% with SMA type I, 48% with SMA type II, and 33% with SMA type III]; 25 German patients with SMA (28% male; mean age: 10 years) [44% with SMA type I, 48% with SMA type II, and 8% with SMA type III]; and 34 UK patients with SMA (50% male; mean age: 6 years) [21% with SMA type I, 59% with SMA type II, and 21% with SMA type III]
Tan et al. (2019) [21]	USA	Retrospective, observational cohort study	HealthCore Integrated Research Database	Claims data	2006–16	341 patients with SMA (55% male; mean age: 45 years) [7% with SMA type I, 6% with SMA type II/III, and 87% with SMA type IV]
Zuluaga-Sanchez et al. (2019) [23]	Sweden	Modeling study (CEA)	Clinical expert input; and local unit costs	Clinical and economic model input data	2016	Patients with SMA type I (45% male; mean age: 6 months) and SMA types II–IV (47% male, mean age: 4 years) [number of patients NA]

CEA cost-effectiveness analysis, HCUP Healthcare Cost and Utilization Project, NA not applicable, NR not reported, SMA spinal muscular atrophy

Table 2 Costs of illness of spinal muscular atrophy (SMA) reported by included studies

Author (year)	Estimated cost categories	Perspective of analysis	Currency; year of valuation	Estimated costs [in 2018 US dollars ^a]	Risk of bias ^b
Ali et al. (2019) [17]	Per-patient annual hospitalization cost (excluding the cost of nusinersen and its administration)	Healthcare/payer	Pound sterling (£); year NR ^c	Mean per-patient annual hospitalization cost <ul style="list-style-type: none"> SMA type I (<i>n</i> = 11): £99,960 [\$129,100] 	Selection: ◇◇◇◇◇ Comparability: ◇◇ Outcome: ◇◇◇◇
Armstrong et al. (2016) [19]	Per-patient annual direct medical cost	Healthcare/payer	US dollar (\$); year NR ^d	Mean per-patient annual direct medical cost <ul style="list-style-type: none"> Pooled sample, SMA type NR (<i>n</i> = 239): \$47,860 [\$52,350] Diagnosis ≤ 1 year of age (<i>n</i> = 45): \$112,640 [\$123,200] Diagnosis > 1 year of age (<i>n</i> = 194): \$30,540 [\$33,400] 	Selection: ◇◇◇◇◇ Comparability: ◇ (age and phenotype NR) Outcome: ◇◇◇◇
Chambers et al. (2020) [25]	Per-patient annual direct cost (medical and non-medical); per-patient annual indirect cost (i.e., production losses for caregivers estimated using the HCA, as well as informal care costs); and per-patient annual total cost of illness	Societal; caregiver; and patient	US dollar (\$); 2017	Mean per-patient annual direct cost <ul style="list-style-type: none"> SMA types I–III (<i>n</i> = 40): \$80,560 [\$82,250] SMA type I (<i>n</i> = 4): \$185,250 [\$189,760] SMA type II (<i>n</i> = 26): \$77,780 [\$79,670] SMA type III (<i>n</i> = 10): \$52,220 [\$53,490] Mean per-patient annual indirect cost <ul style="list-style-type: none"> SMA types I–III (<i>n</i> = 40): \$63,150 [\$64,680] SMA type I (<i>n</i> = 4): \$44,100 [\$45,170] SMA type II (<i>n</i> = 26): \$73,130 [\$74,910] SMA type III (<i>n</i> = 10): \$42,770 [\$43,810] Mean per-patient annual total cost of illness <ul style="list-style-type: none"> SMA types I–III (<i>n</i> = 40): \$143,710 [\$147,200] SMA type I (<i>n</i> = 4): \$229,350 [\$234,930] SMA type II (<i>n</i> = 26): \$150,910 [\$154,580] SMA type III (<i>n</i> = 10): \$94,980 [\$97,300] 	Selection: ◇◇◇◇ (uncertain diagnosis) Comparability: ◇◇ Outcome: ◇◇ (self-reported data)
Cardenas et al. (2019) [16]	Per-patient cost per hospitalization (i.e., total hospital costs derived from total charges)	Healthcare/payer	US dollar (\$); 2012	Mean per-patient cost per hospitalization <ul style="list-style-type: none"> SMA type I (<i>n</i> = 237): €50,190 [\$54,890] 	Selection: ◇◇◇◇◇ Comparability: ◇ (age NR) Outcome: ◇◇◇◇

Table 2 (continued)

Author (year)	Estimated cost categories	Perspective of analysis	Currency; year of valuation	Estimated costs [in 2018 US dollars ^a]	Risk of bias ^b
Darbà et al. (2019) [15]	Per-patient cost per hospitalization (i.e., total hospital costs)	Healthcare/payer	Euro (€); 2015	<p>Mean per-patient cost per hospitalization</p> <ul style="list-style-type: none"> • Pooled sample (<i>n</i> = 705): €6270 [\$7150] • SMA type I (<i>n</i> = NR): €9420 [\$10,740] • SMA type III (<i>n</i> = NR): €5770 [\$6580] • Progressive SMA (<i>n</i> = NR): €5750 [\$6560] • Other SMA (<i>n</i> = NR): €5380 [\$6130] • Unspecified SMA (<i>n</i> = NR): €5290 [\$6,030] 	<p>Selection: ◊◊◊◊◊</p> <p>Comparability: ◊ (uncertain classification of phenotypes; distribution of phenotypes NR)</p> <p>Outcome: ◊◊◊</p>
Darbà (2020) [24]	Per-patient annual direct medical cost	Healthcare/payer	Euro (€); 2013	<p>Mean per-patient annual direct medical cost</p> <ul style="list-style-type: none"> • SMA type I, SMA type III, progressive SMA, other SMA, and unspecified SMA (<i>n</i> = 396): €58,610 [\$66,410] 	<p>Selection: ◊◊◊◊◊</p> <p>Comparability: ◊ (uncertain classification of phenotypes)</p> <p>Outcome: ◊◊◊</p>
Droege et al. (2019) [18]	Per-patient annual direct medical cost	Healthcare/payer	US dollar (\$); 2018	<p>Mean per-patient annual direct medical cost</p> <ul style="list-style-type: none"> • SMA type I, conventional therapy (<i>n</i> = 349): \$137,630 • SMA type I, nusinersen (<i>n</i> = 45): \$1,000,280 (\$92,620 excluding treatment cost) • SMA types II–IV, conventional therapy (<i>n</i> = 5728): \$49,180 • SMA types II–IV, nusinersen (<i>n</i> = 404): \$1,109,060 (\$76,370 excluding treatment cost) 	<p>Selection: ◊◊◊◊◊</p> <p>Comparability: ◊ (uncertain phenotype definition)</p> <p>Outcome: ◊◊◊</p>

Table 2 (continued)

Author (year)	Estimated cost categories	Perspective of analysis	Currency; year of valuation	Estimated costs [in 2018 US dollars ^a]	Risk of bias ^b
Klug et al. (2016) [20]	Per-patient annual direct medical cost; per-patient annual direct non-medical cost (including informal care costs); per-patient annual indirect cost (i.e., production losses for the patient and one caregiver estimated using the HCA); and per-patient annual total cost of illness	Societal	Euro (€); 2013	<p>Mean per-patient annual direct medical cost</p> <ul style="list-style-type: none"> • SMA types I–III (<i>n</i> = 189): €14,340 [\$16,620] • SMA type I (<i>n</i> = 12): €53,710 [\$62,230] • SMA type II (<i>n</i> = 73): €15,310 [\$17,730] • SMA type III (<i>n</i> = 104): €9130 [\$10,570] <p>Mean per-patient annual direct non-medical cost</p> <ul style="list-style-type: none"> • SMA types I–III (<i>n</i> = 189): €40,380 [\$46,790] • SMA type I (<i>n</i> = 12): €45,960 [\$53,520] • SMA type II (<i>n</i> = 73): €58,610 [\$67,910] • SMA type III (<i>n</i> = 104): €26,940 [\$31,220] <p>Mean per-patient annual indirect cost</p> <ul style="list-style-type: none"> • SMA types I–III (<i>n</i> = 189): €15,850 [\$18,360] • SMA type I (<i>n</i> = 12): €8140 [\$9440] • SMA type II (<i>n</i> = 73): €16,360 [\$18,950] • SMA type III (<i>n</i> = 104): €16,380 [\$18,980] <p>Mean per-patient annual total cost of illness</p> <ul style="list-style-type: none"> • SMA types I–III (<i>n</i> = 189): €70,570 [\$81,770] • SMA type I (<i>n</i> = 12): €107,810 [\$124,920] • SMA type II (<i>n</i> = 73): €90,270 [\$104,600] • SMA type III (<i>n</i> = 104): €52,440 [\$60,770] 	<p>Selection: ◇◇◇◇◇</p> <p>Comparability: ◇◇</p> <p>Outcome: ◇◇ (self-reported data)</p>

Table 2 (continued)

Author (year)	Estimated cost categories	Perspective of analysis	Currency; year of valuation	Estimated costs [in 2018 US dollars ^a]	Risk of bias ^b
Lee et al. (2019) [14]	Per-patient cost per hospitalization (i.e., total hospital costs derived from total charges)	Healthcare/payer	US dollar (\$); 2017	<p>Mean per-patient cost per hospitalization</p> <ul style="list-style-type: none"> • Pooled sample, SMA type NR (<i>n</i> = 229): \$104,200 [\$106,740] • Tracheostomy, SMA type NR (<i>n</i> = 99): \$115,250 [\$118,070] • No tracheostomy, SMA type NR (<i>n</i> = 130): \$89,120 [\$91,290] 	<p>Selection: ◇◇◇◇</p> <p>Comparability: ◇ (age, sex, and phenotype NR)</p> <p>Outcome: ◇◇◇</p>
López-Bastida et al. (2017) [13]	Per-patient annual direct medical cost; per-patient annual direct non-medical cost (including informal care costs); and per-patient annual total cost of illness	Societal	Euro (€); 2014	<p>Mean per-patient annual direct medical cost</p> <ul style="list-style-type: none"> • SMA types I–III (<i>n</i> = 81): €10,880 [\$12,330] • SMA type II (<i>n</i> = 60): €11,580 [\$13,120] <p>Mean per-patient annual direct non-medical cost</p> <ul style="list-style-type: none"> • SMA types I–III (<i>n</i> = 81): €22,840 [\$25,880] • SMA type II (<i>n</i> = 60): €26,090 [\$29,560] <p>Mean per-patient annual total cost of illness</p> <ul style="list-style-type: none"> • SMA types I–III (<i>n</i> = 81): €33,720 [\$38,210] • SMA type II (<i>n</i> = 60): €37,670 [\$42,690] 	<p>Selection: ◇◇◇ (uncertain diagnosis)</p> <p>Comparability: ◇◇</p> <p>Outcome: ◇◇ (self-reported data)</p>

Table 2 (continued)

Author (year)	Estimated cost categories	Perspective of analysis	Currency; year of valuation	Estimated costs [in 2018 US dollars ^a]	Risk of bias ^b
Marcellusi et al. (2019) [22]	Per-patient annual direct medical cost; per-patient annual direct non-medical cost; per-patient annual indirect cost (i.e., production losses for the patient and one caregiver estimated using the HCA, as well as costs associated with paid informal care); and per-patient annual total cost of illness	Societal	Euro (€); 2017	<p>Mean per-patient annual direct medical cost</p> <ul style="list-style-type: none"> • SMA type I ($n = 27$): €4630 [\$5130] • SMA type II ($n = 57$): €5240 [\$5810] • SMA type III ($n = 34$): €3000 [\$3320] <p>Mean per-patient annual direct non-medical cost</p> <ul style="list-style-type: none"> • SMA type I ($n = 27$): €18,200 [\$20,150] • SMA type II ($n = 57$): €14,910 [\$16,510] • SMA type III ($n = 34$): €4990 [\$5530] <p>Mean per-patient annual indirect cost</p> <ul style="list-style-type: none"> • SMA type I ($n = 27$): €13,050 [\$14,460] • SMA type II ($n = 57$): €10,730 [\$11,880] • SMA type III ($n = 34$): €9520 [\$10,550] <p>Mean per-patient annual total cost of illness</p> <ul style="list-style-type: none"> • SMA type I ($n = 27$): €35,680 [\$39,520] • SMA type II ($n = 57$): €30,410 [\$33,680] • SMA type III ($n = 34$): €16,070 [\$17,790] 	<p>Selection: ◇◇◇ (uncertain diagnosis)</p> <p>Comparability: ◇◇</p> <p>Outcome: ◇◇ (self-reported data)</p>

Table 2 (continued)

Author (year)	Estimated cost categories	Perspective of analysis	Currency; year of valuation	Estimated costs [in 2018 US dollars ^a]	Risk of bias ^b
Peña-Longobardo et al. (2020) [26]	Per-patient annual direct medical cost; per-patient annual direct non-medical cost (including informal care costs); and per-patient annual total cost of illness	Societal	Euro (€); 2014	<p>Mean per-patient annual direct medical cost</p> <ul style="list-style-type: none"> France, SMA types I–III (<i>n</i> = 27): €4670 [\$5290] Germany, SMA types I–III (<i>n</i> = 25): €7310 [\$8,290] UK, SMA types I–III (<i>n</i> = 34): €11,080 [\$12,560] <p>Mean per-patient annual direct non-medical cost</p> <ul style="list-style-type: none"> France, SMA types I–III (<i>n</i> = 27): €27,370 [\$31,020] Germany, SMA types I–III (<i>n</i> = 25): €44,670 [\$50,620] UK, SMA types I–III (<i>n</i> = 34): €43,210 [\$48,970] <p>Mean per-patient annual total cost of illness</p> <ul style="list-style-type: none"> France, SMA type I–III (<i>n</i> = 27): €32,040 [\$36,310] Germany, SMA types I–III (<i>n</i> = 25): €51,980 [\$58,910] UK, SMA types I–III (<i>n</i> = 34): €54,300 [\$61,530] 	<p>Selection: ◇◇◇◇</p> <p>Comparability: ◇◇</p> <p>Outcome: ◇◇ (self-reported data)</p>
Tan et al. (2019) [21]	Per-patient annual direct medical cost	Healthcare/payer	US dollar (\$); 2015	<p>Mean per-patient annual direct medical cost</p> <ul style="list-style-type: none"> SMA type I (<i>n</i> = 23): \$306,200 [\$324,410] SMA types II–III (<i>n</i> = 23): \$76,280 [\$80,820] SMA type IV (<i>n</i> = 296): \$29,990 [\$31,770] 	<p>Selection: ◇◇◇◇</p> <p>Comparability: ◇◇</p> <p>Outcome: ◇◇◇◇</p>

Table 2 (continued)

Author (year)	Estimated cost categories	Perspective of analysis	Currency; year of valuation	Estimated costs [in 2018 US dollars ^a]	Risk of bias ^b
Zuluaga-Sanchez et al. (2019) [23]	Per-patient annual direct medical cost; per-patient annual direct non-medical cost; per-patient annual indirect cost (i.e., production losses for one caregiver estimated using the HCA); and per-patient annual total cost of illness	Societal	Swedish krona (SEK); 2016	<p>Mean per-patient annual direct medical cost</p> <ul style="list-style-type: none"> • SMA type I (year 1): SEK 339,980 [\$36,790] • SMA type I (year 2): SEK 224,340 [\$24,280] • SMA types II–IV (year 1): SEK 299,970 [\$32,460] • SMA types II–IV (year 2): SEK 368,460 [\$39,870] <p>Mean per-patient annual direct non-medical cost</p> <ul style="list-style-type: none"> • SMA type I (year 1): SEK 1,264,190 [\$136,800] • SMA type I (year 2): SEK 1,263,940 [\$136,770] • SMA types II–IV (year 1): SEK 1,011,360 [\$109,440] • SMA types II–IV (year 2): SEK 1,011,480 [\$109,450] <p>Mean per-patient annual indirect cost</p> <ul style="list-style-type: none"> • SMA type I (year 1 and 2): SEK 523,850 [\$56,690] • SMA types II–IV (year 1): SEK 261,920 [\$28,340] • SMA types II–IV (year 2): SEK 130,960 [\$14,170] <p>Mean per-patient annual total cost of illness</p> <ul style="list-style-type: none"> • SMA type I (year 1): SEK 2,128,020 [\$230,270] • SMA type I (year 2): SEK 2,012,130 [\$217,730] • SMA types II–IV (year 1): SEK 1,573,250 [\$170,240] • SMA types II–IV (year 2): SEK 1,510,900 [\$163,490] 	<p>Selection: $\diamond\diamond\diamond\diamond$</p> <p>Comparability: $\diamond\diamond$</p> <p>Outcome: $\diamond\diamond$ (clinical expert input)</p>

Note: Costs were rounded to nearest ten. Details of resources included in estimates of per-patient annual direct medical costs are presented in Table 3

HCA human capital approach, NR not reported

^aAdjusted for inflation to 2018 values using country-specific consumer price index data from the World Bank and subsequently converted to US dollars

^bAssessed with the Newcastle–Ottawa Scale. Maximum score: $\diamond\diamond\diamond\diamond$ for selection, $\diamond\diamond$ for comparability, and $\diamond\diamond$ for outcome (see the Methods section for details)

^cIn the absence of data, year of valuation was assumed to be 2018

^dIn the absence of data, year of valuation was assumed to be 2012

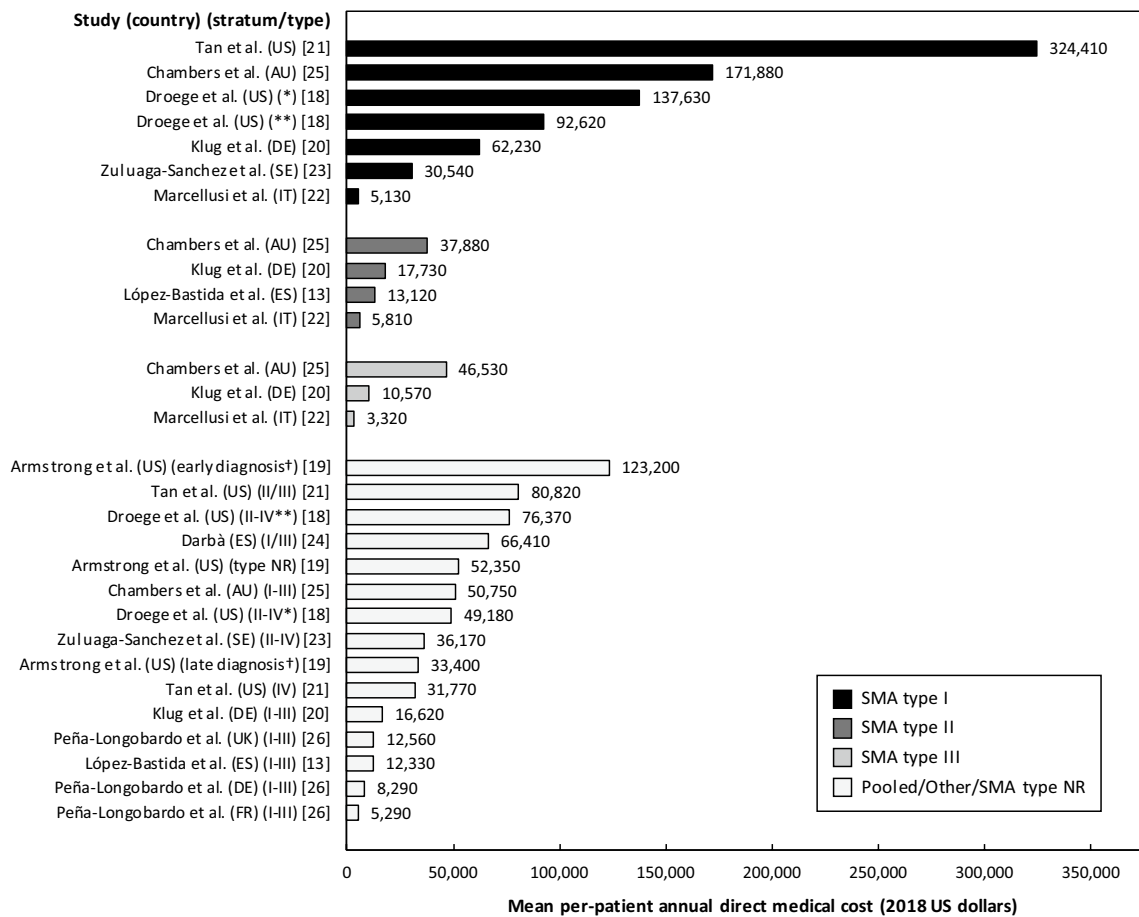


Fig. 2 Mean per-patient annual direct medical cost of spinal muscular atrophy (SMA). AU Australia, DE Germany, ES Spain, FR France, IT Italy, NR not reported, US USA. Subgroups from Droege et al. [18]: (*) Conventional therapy, (**) nusinersen (excluding the mean treatment cost of nusinersen of \$907,660 and \$1,032,690 per patient and year for SMA type I and types II–IV, respectively). Subgroups from Armstrong et al. [19]: (†) Early diagnosis (≤ 1 year of age) and late diagnosis (> 1 year of age); SMA type not reported. Estimates from

Zuluaga-Sanchez et al. [23] are presented as averages of costs for year 1 and year 2. The sample from Darbà [24] includes progressive SMA, other SMA, and unspecified SMA. Costs from Chambers et al. [25] were derived by deducting items typically considered non-medical resources from the reported estimate of the per-patient annual direct cost of illness. Costs were adjusted for inflation to 2018 values using country-specific consumer price index data from the World Bank and subsequently converted to US dollars

Table 3 Resources included in identified estimates of the per-patient annual direct medical cost of spinal muscular atrophy

Author (year)	Inpatient care	Outpatient care	Emergency care	Prescription drugs	OTC drugs	Medical devices and aids	Co-payments
Armstrong et al. (2016) [19]	×	×	NR	×			
Chambers et al. (2020) [25]	×	×	×	×	×	×	×
Darbà (2020) [24]	×	×	×				
Droege et al. (2019) [18]	×	×	NR	×			
Klug et al. (2016) [20]	×	×	NR	×		×	
López-Bastida et al. (2017) [13]	×	×	×	×		×	
Marcellusi et al. (2019) [22]	×	×				×	×
Peña-Longobardo et al. (2020) [26]	×	×	×	×	NR	×	
Tan et al. (2019) [21]	×	×	×	×			
Zuluaga-Sanchez et al. (2019) [23]	×	×	×	×		×	

NR not reported (i.e., that the information was not provided, but that the specific resource category could have been included in the estimation, for example as part of higher level cost categories), OTC over-the-counter

3.4 What Are the Known Costs of Illness of SMA?

Costs of illness of SMA reported by the included studies are summarized in Table 2. Estimates of the mean per-patient annual direct medical cost of illness (excluding nusinersen-related costs), also illustrated in Fig. 2, were between \$3320 for SMA type III in Italy [22] and \$324,410 for SMA type I in the USA [21]. When accounting for the cost of nusinersen, the per-patient annual direct medical cost was estimated at \$1,000,280 (SMA type I) and \$1,109,060 (SMA types II–IV) in the USA [18]. As shown in Table 3, there was variability across studies concerning resource categories included in identified estimates of the direct medical cost of illness. Deducting items typically considered non-medical resources (i.e., non-medical travel costs, respite care, and costs associated with vehicle and home modifications) from the estimate of the per-patient annual direct cost of illness reported by Chambers et al. [25] yields an inferred estimate of the per-patient annual direct medical cost of illness in Australia of \$171,880 for SMA type I, \$37,880 for SMA type II, and \$46,530 for SMA type III.

Three studies [14–16] examined the per-patient cost per hospitalization of SMA (Table 2). Cardenas et al. [16] estimated the mean per-patient cost per hospitalization (derived from total hospital charges) at \$54,890 for 237 US patients (43% male, distribution of age not reported) with SMA type I. The second study, Darbà and Marsa, estimated the mean per-patient cost per hospitalization (including costs associated with medical staff, equipment, and resources per tariffs from the Spanish Ministry of Health) at \$7150 for a sample of 705 Spanish patients (62% male, mean age: 37 years) with different types of SMA (as reported in Table 1), and at \$10,740, \$6580, \$6560, \$6130, and \$6030 for SMA type I, SMA type III, progressive SMA, other SMA, and unspecified SMA, respectively (number of patients not reported by SMA type) [15]. Finally, Lee Jr et al. [14] estimated the mean per-patient cost per hospitalization (derived from total hospital charges) at \$106,740 for 229 US patients with “severe” SMA (defined as diagnosis during the first year of life, and/or diagnosis for SMA and tracheostomy during the first 3 years of life). For patients with and without tracheostomy, the cost was \$118,070 and \$91,290, respectively [14]. Different from the per-patient cost per hospitalization of SMA, Ali et al. [17] estimated the mean per-patient annual hospitalization cost of illness for 11 UK patients with SMA type I treated with nusinersen at \$129,100 (excluding the cost of nusinersen and its administration).

The mean per-patient direct non-medical cost of SMA was estimated at between \$25,880 and \$136,800 (Table 2). The lowest estimate was derived from a sample of 81 Spanish patients (SMA types I–III) and included informal care costs (based on the number of hours devoted to informal care recorded using the recall method, estimated at 4 hours

per day on average, valued using the proxy good method, i.e., at a shadow price of a market substitute), as well as disease-related costs for personal assistants, travel expenses, legal advice, modifications/investments to the house or car, and other expenses [13]. The highest estimate was based on clinical expert input of the expected duration of personal assistance per day (estimated at 12 hours, on average) and transportation costs for patients with SMA type I in a Swedish setting [23]. Additionally, Marcellusi et al. [22] estimated the mean per-patient total cost of car and home modifications and paid informal care in Italy at \$20,150 for SMA type I, \$16,510 for SMA type II, and \$5530 for SMA type III. Summating costs of items typically considered direct non-medical resources from Chambers et al. [25] (i.e., non-medical travel, respite care, vehicle and home modifications, and informal care) yields an inferred estimate of the per-patient annual direct non-medical cost of illness in Australia at \$46,830 for SMA type I, \$76,500 for SMA type II, and \$20,050 for SMA type III.

Four studies [20, 22, 23, 25] reported indirect costs of SMA. Klug et al. [20] estimated the mean per-patient annual indirect cost of SMA, quantified as disease-related production losses due to patient and caregiver absenteeism and presenteeism from work, at between \$9440 (SMA type I) and \$18,980 (SMA type III) in Germany. Corresponding costs for Italy and Australia (excluding costs associated with informal care to facilitate comparison) were estimated at between \$8940 (SMA type III) and \$14,230 (SMA type I) [22], and \$16,210 (SMA type I) and \$40,200 (SMA type II) [25], respectively. Finally, Zuluaga-Sanchez et al. [23] estimated the mean per-patient annual indirect cost of SMA (quantified as production losses for one caregiver) in a Swedish setting at between \$14,170 (SMA types II–IV) and \$56,690 (SMA type I) based on clinical expert input (assuming that one caregiver is fully absent from work for SMA type I, and partially absent for SMA types II–IV).

The mean per-patient annual total cost of illness of SMA, including direct medical, direct non-medical, and indirect costs, was estimated at between \$97,300 (SMA type III) and \$234,930 (SMA type I) in Australia [25], \$60,770 (SMA type III) and \$124,920 (SMA type I) in Germany [20], \$17,790 (SMA type III) and \$39,520 (SMA type I) in Italy [22], \$38,210 (SMA types I–III) and \$42,690 (SMA type II) in Spain [13], and \$163,490 (SMA types II–IV) and \$230,270 (SMA type I) in Sweden [23]. Peña-Longobardo et al. [26] estimated the mean per-patient annual total cost of illness of SMA, comprising direct medical and non-medical costs (including informal care, but not indirect costs) for SMA types I–III at \$36,310 in France, \$58,910 in Germany, and \$61,530 in the UK. Additional details of identified costs are presented in Table 2.

3.5 Risk of Bias

Two (14%) studies [17, 21] were judged to exhibit a low risk of bias as assessed using the NOS (Table 2). Reasons for a risk of bias included uncertain representativeness owing to the lack of details concerning confirmation of diagnosis of SMA [13, 22, 25], limited comparability owing to inadequate description of the distribution of age, sex, and/or SMA phenotype in the studied samples, or uncertain classification of SMA phenotypes [14–16, 18, 19, 24], and self- or clinical expert reported data [13, 20, 22, 23, 25, 26].

4 Discussion

The objective of this study was to conduct a systematic review of costs of illness of SMA globally. We found the current body of evidence of the per-patient annual direct medical cost of SMA to be subject to considerable heterogeneity between individual studies (Tables 2 and 3). Reasons for this variability concern differences regarding (1) the scope of included medical resources (as used or consumed because of SMA), (2) measured quantities of included resources, and/or (3) prices/unit costs of included resources used in the calculation. For example, in their assessment of the direct medical cost of SMA, Chambers et al. [25] included inpatient care, outpatient care, and emergency care, prescription and over-the-counter drugs, as well as costs associated with medical devices and aids and co-payments, whereas Darbà only considered the first three of these categories [24]. Moreover, there may be non-trivial differences between studies also within defined resource categories (e.g., including all outpatient visits vs visits to a selected set of practitioners). For these reasons, cost estimates are typically not directly comparable between studies, in particular if conducted in different geographical settings. That being said, the range in direct medical costs identified as part of this review was still somewhat surprising.

Because of differences in costing methodologies and healthcare systems, and considering the broad range in estimates identified as part of this review, it is not straightforward to directly compare costs of SMA with those of other diseases. Interestingly, Armstrong et al. [19] also studied a cohort of individuals without SMA in the USA. The authors found that the mean per-patient annual direct medical cost of SMA was about 2600% greater than estimates for those without the disease. In addition, Cardenas et al. [16] estimated the mean per-patient cost per hospitalization for SMA type I to be around 850% higher than for patients without any complex chronic conditions in the USA. Although not directly applicable to other settings, these data should help readers interpret and contextualize the magnitude of these cost components of the total burden of illness of SMA. Moreover, the

high variability in costs between studies also characterized estimates within samples. Indeed, in some cases, such as Armstrong et al. [19], a small proportion of patients (about 2%) had costs equal to or exceeding \$1,000,000 (and about 13% equal to or exceeding \$500,000) per year. These findings highlight the importance of deriving estimates from adequately powered studies for a meaningful inference in diseases with a heterogeneous presentation, such as SMA.

Outcomes of our review revealed that costs were also markedly different across SMA phenotypes. In particular, the per-patient annual direct medical cost of SMA type I was notably higher than that of the other types of the disease. This is not unexpected given the complete dependency on 24-h care and ventilation in these children if they survive the first year of life, at least prior to the institution of disease-modifying treatments.

We identified two studies investigating costs in relation to nusinersen (excluding the cost of nusinersen and its administration). Ali et al. [17] estimated the per-patient annual hospitalization cost at \$129,100 in a sample of 11 patients treated with nusinersen in the UK. Droege et al. [18] found nusinersen compared with conventional therapy to be associated with lower per-patient annual direct medical costs for SMA type I (\$92,620 vs \$137,630), but not SMA type II–III (\$76,370 vs \$49,180), and estimated the mean per-patient annual cost of nusinersen at \$907,660 for SMA type I and \$1,032,690 for SMA types II–IV in the USA. These findings show that although nusinersen may be associated with lower resource utilization for some patients, at the group or population level, overall resource use and associated costs remain high, even after excluding the cost of the treatment.

In articles reporting estimates of the per-patient annual total direct cost of illness of SMA (comprising direct medical and non-medical costs), direct non-medical costs (including informal care costs, if available) were found to make up a considerable proportion of total direct costs. In fact, across included studies, this cost category accounted for an average of 68% of the per-patient annual total direct cost, between 21% (SMA type I, Australia) and 86% (SMA types I–III, Germany) [13, 20, 22, 23, 25, 26]. These findings may be compared with corresponding estimates for other serious neuromuscular diseases, such as Duchenne muscular dystrophy, where direct non-medical costs comprised between 47% and 73% of total direct costs in Germany, Italy, the UK, and the USA [29]. Time devoted to informal caregiving in SMA also varied between studies, settings, and phenotypes, from 9 hours per day on average in France [26], to 4 hours per day on average in Spain [13], 4–15 hours in Germany [20, 26], 10–12 h in Sweden [23], and 13 hours in the UK [26] (data not reported by Chambers et al. [25]). However, because of different methods, direct comparison of these estimates should be made with caution. Nonetheless, these findings underscore the substantial burden of informal caregiving in SMA.

Identified estimates of production losses and associated costs of SMA varied substantially across studies and settings. Considering the relative magnitude of this cost category noted in this review, and the range in estimates, future study of indirect costs in SMA appears warranted to increase the understanding of the total economic burden of the disease from the perspective of society.

The outcomes of this review have several implications for health policy and future research. First, up-to-date cost estimates are lacking for most settings. This implies that further cost research will be necessary to map out the health economic context of SMA in most countries. Second, given the very high variability in identified costs, it is not readily apparent how the current evidence base should best inform economic evaluations. This also concerns the lack of longitudinal cost data in this indication to enable assessment of long-term outcomes. Third, our review shows that in most settings, little is known of costs associated with specific treatments, including nusinersen. This constitutes an important topic for future research, especially considering the growing battery of novel high-cost therapies in this indication. Last, several studies included in this review were judged to be subject to a risk of bias, mainly relating to incomplete reporting, documentation, and/or stratification, which serve as a reminder of the importance of providing sufficient details for meaningful interpretation and contextualization of outcomes from cost studies in SMA. Indeed, averaging costs across SMA types (in particular SMA type I with other types of the disease) would be expected to render pooled estimates of ambiguous magnitude and unclear external validity (as illustrated in Fig. 2).

There are two main limitations to this literature review. First, we did not systematically search for relevant gray literature, which means that some estimates of costs of illness of SMA might not have been identified. However, given the absence of thorough peer review and critical appraisal of most literature published outside the traditional scientific/academic distribution channels, such as journals, the importance of this limitation for the overall interpretation of the review results is expected to be minor. Second, the NOS assesses aspects of quality and bias of non-randomized studies, not specifically cost research. Therefore, some studies that were assigned a perfect score rating based on the NOS might still be subject to non-trivial limitations and bias (relating to e.g., the relevance of included medical and non-medical resources, and valuation methods). In this regard, it is also worth noting that for some cost types (e.g., informal care costs), primary data collection (via e.g., surveys) is likely necessary (despite being associated with potential bias), as this type of information would not be expected to be available from administrative or disease-specific registries, or clinical charts. Additionally, as expected given the generic nature of the instrument, aspects of some criteria of

the NOS (e.g., disease-specific requirements and thresholds) are defined by the researcher, which means that there is a degree of subjectivity in the application of the scale and assessment of the risk of bias. Finally, it is important to keep in mind that there is no universal classification of costs of illness. Informal care costs, for example, can be considered a direct non-medical or an indirect cost of illness. In this study, we extracted and reported all identified costs of illness of SMA separately (in Table 2), but also synthesized them into a set of pre-defined cost categories, in which we considered the informal care cost of illness a direct non-medical cost under the assumption that the assistance/aid otherwise would have to be provided by paid professionals.

5 Conclusions

We show that the current body of evidence of costs of SMA is generally scarce and characterized by considerable heterogeneity across geographical settings and disease phenotypes. Our review provides data pertaining to the economic impact of SMA, which is of particular relevance in light of emerging treatments and ongoing research in this field, and underscores the substantial unmet medical need in this patient population.

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Declarations

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Conflict of interest Erik Landfeldt is an employee of ICON plc (Stockholm, Sweden), outside the submitted work. Astrid Pechmann reports receiving compensation for presentations and training activities from Biogen, and research funding from Biogen and AveXis, outside the submitted work. Thomas Sejersen reports receiving honoraria for lectures and participation in advisory board meetings from Biogen, AveXis, and Roche, outside the submitted work. Hugh J. McMillan has participated in an advisory board for AveXis, and reports research funding from Roche, outside the submitted work. Hanns Lochmüller has no conflicts of interest that are directly relevant to the content of this article

Availability of Data and Material All data analyzed as part of this study are included in this published article (and its supplementary information files).

Authors' Contributions Erik Landfeldt conceptualized and designed the study, conducted the literature review and the analysis, led the interpretation of findings, drafted the manuscript, critically reviewed the manuscript for important intellectual content, and approved the final manuscript version as submitted. Astrid Pechmann conducted the literature review, interpreted the findings, critically reviewed the manuscript for important intellectual content, and approved the final

manuscript version as submitted. Hugh J. McMillan interpreted the findings, critically reviewed the manuscript for important intellectual content, and approved the final manuscript version as submitted. Hanns Lochmüller interpreted the findings, critically reviewed the manuscript for important intellectual content, and approved the final manuscript version as submitted. Thomas Sejersen conceptualized and designed the study, interpreted the findings, critically reviewed the manuscript for important intellectual content, and approved the final manuscript version as submitted.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Code Availability Not applicable.

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