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Review Paper

Economic analysis of the costs associated with prematurity from a literature review

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ABSTRACT

Objectives: To analyse published cost-of-illness studies that had assessed the cost of prematurity according to gestational age at birth.
Methods: A review of the literature was carried out in March 2011 using the following databases: Medline, ScienceDirect, The Cochrane Library, Econlit and Business Source Premier, and a French Public-Health database. Key-word sequences related to 'prematurity' and 'costs' were considered. Studies that assessed costs according to the gestational age (GA) at the premature birth (<37 weeks of gestation) in industrialized countries and during the last two decades were included. Variations in the reported costs were analysed using a check-list, which allowed the studies to be described according to several methodological and contextual criteria.
Results: A total of 18 studies published since 1990 were included. According to these studies, costs were assessed for different follow-up periods (short, medium or long-term), and for different degrees of prematurity (extreme, early, moderate and late). Results showed that whatever the follow-up period, costs correlated inversely with GA. They also showed considerable variability in costs within the same GA group. Differences between studies could be explained by the choices made, concerning i/the study populations, ii/contextual information, iii/and various economic criteria. Despite these variations, a global trend of costs was estimated in the short-term period using mean costs from four American studies that presented similar methodologies. Costs stand at over US$ 100,000 for extreme prematurity, between US$ 40,000 and US$ 100,000 for early prematurity, between US$ 10,000 and US$ 30,000 for moderate prematurity and below US$ 4500 for late prematurity.
Conclusion: This review underlined not only the clear inverse relationship between costs and GA at birth, but also the difficulty to transfer the results to the French context. It suggests that studies specific to the French health system need to be carried out.

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Introduction

Because of their consequences in terms of mortality and morbidity, preterm births, defined as childbirths occurring at less than 37 completed weeks or 259 days of gestation, are a public health problem worldwide.[1,2] The rate of prematurity is estimated at 7.5% in developed countries, and is steadily increasing in France (from 6.8% in 1998 to 7.4% in 2010) as in other industrialized countries since the early 1980s.[1,3–6] This evolution can mostly be attributed to the increased use of assisted reproduction and obstetric interventions, such as induced labour and Caesarean section.[6]

Prematurity is known to be associated with a higher risk of adverse consequences for health in the long-term compared with term births, and therefore requires specific health, education and social services.[2,7,8] Children born prematurely are mostly affected in the short term by adverse neonatal outcomes, including chronic lung disease, severe brain injury, retinopathy of prematurity, necrotizing enterocolitis and neonatal sepsis. In the long term, they are at an increased risk of motor and sensory impairment, learning difficulties, behavioural problems and pulmonary dysfunction.[2,9] It has also been estimated that half of the children with severe disabilities were born prematurely.[7]

To be able to justify the size of resource allocations for health strategies, knowledge of the economic burden of prematurity and identification of the main costs associated with its management are of paramount importance. However, the cost of prematurity remains unknown in France. Only two French studies were published on this topic in 1984, but they cannot be extrapolated to the current French health system.[10,11] In addition, questions arise about the transferability of results from other countries to France. Several reviews in the literature analysed the economic consequences of preterm birth. All reported the inverse relationship between costs and degree of prematurity.[8,12–16] However, the main difference between them concerned the choice of criteria to define prematurity. GA is considered the official criterion by the World Health Organization to define prematurity.[1,12] But it was not used exclusively in all studies, and birth weight was also often reported.

Therefore, by carrying out a review of the literature, the objective of this article was to analyse the published cost-of-illness studies that assessed the cost of prematurity according to the GA at birth alone.

Materials and methods

Inclusion of studies for the review of the literature

A large computer search was conducted using medical and economic databanks: Medline, ScienceDirect, The Cochrane Library, Econlit and Business Source Premier, but also the French database in Public Health (named BDSP).[17] Keyword sequences related to 'prematurity' and 'costs' were used (Appendix 1).

The articles for the review of the literature were included following three consecutive steps (Fig. 1). In the first step, all of the studies identified in the databank search were imported using Endnote® software. In the second step, the title and the references of each article were scrutinized to check the inclusion criteria. Finally, included abstracts were carefully checked using the same criteria.

Analysis of the included studies

Cost conversion

All of the costs in non-American studies were converted to US dollars using 'Purchasing Power Parity for actual individual consumption' (PPP-P41), based on Organization for Economic Co-operation and Development (OECD) data.[18] PPP allows international comparisons of prices expressed for the same type of good or service. The conversion implicitly includes exchange rates between countries, and takes into consideration the differences in purchasing power between countries.[19]

Check-list for cost analysis

In order to describe the studies and analyse the costs, a check-list (Appendix 2) was built using criteria mainly based on French,[20] English,[21] and American[22,23] communities of health economists. The check-list included the context, the objectives and research hypotheses, the nature of data collection, the characteristics of the study population (newborn and mothers), the economic evaluation (point of view; time horizon, cost categories, source of economic data, method for cost estimation and discounting) and results (types of analysis, unit costs expression, management of uncertainty associated with data).

Results

General description of included studies

A total of 2760 papers were imported using Endnote® software, leading to a total of 2617 articles after eliminating duplicates. After application of all of the criteria, and the exclusion of studies that assessed childhood costs over only one year,[24,25] 18 articles remained[9,26–42] (Fig. 1). Thirteen were American studies,[26–29,31–33,35,37,39–42] three were English,[9,36,38] and only two were based on mainland European data (one Finnish and one Greek study).[30,34] Three were published before 2000.[29,32,35] Only one study was carried out using prospective data collection,[30] and the other seventeen were retrospective.[9,26–29,31–42] Finally, most of the studies were multicenter.[9,26–31,33,34,37–42]

As shown in Table 1, depending on the study, costs were not estimated for the same GA classes. It was therefore decided to create GA categories to make comparisons between costs possible. Extreme prematurity was defined as births occurring at less than 28 weeks of gestation (wGA), early prematurity as births occurring between 28 and 31 wGA, moderate prematurity as births between 32 and 34 wGA, and late prematurity as births occurring between 35 and 36 wGA.

The duration of follow-up of the premature children in the different studies was not totally comparable either. This led us to classify studies according to this duration: thirteen short-term studies assessed costs during the first year of life;[27–33,35,37,39–42] three medium-term studies assessed costs in the first five years of life;[26,34,38] and two long-term studies assessed costs in the first 18 years of life.[9,36]

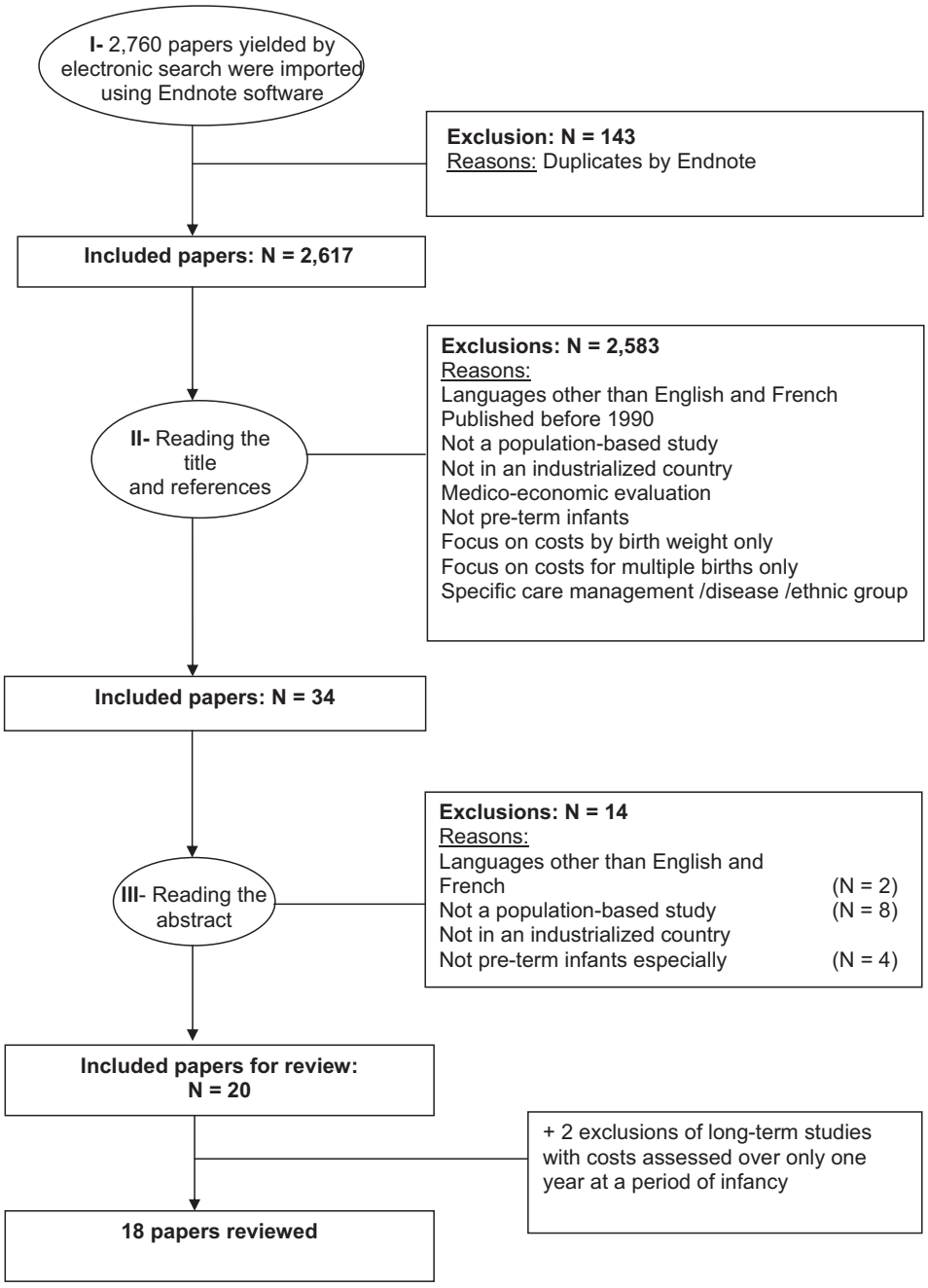

Fig. 1 – Description of the of study inclusion process.
This figure illustrates the study inclusion process according to three steps. Duplicated references were deleted. 1st step: All studies identified by the databank search were imported using Endnote® software. 2nd step: The title and the references of each remaining article were scrutinized in order to check inclusion criteria. Articles that did not meet all the criteria were excluded. 3rd step: Abstracts from the remaining studies were carefully checked using the same criteria, if they had not been identified earlier by assessment of the title. This figure is referred to in the paragraph '!Inclusion of studies for the review of the literature' (Materials and methods).

Cost variations

Detailed mean costs are presented in Appendix 3. Synthesized mean costs are presented in Table 2.

Results showed that GA could be considered the strongest predictor of prematurity costs, as this was highlighted in some of the studies.[9,27,38,41] An inverse relationship between costs and GA was found in all studies. As an illustration, the mean cost varied from $2,362[41] for late prematurity (at 36 wGA) to $297,627[39] for extreme prematurity (at 24 wGA) in the short-term, and from $8176 (at 32–36 wGA)[9] to $446,440 (at 23 wGA)[36] in the long-term. The results for the medium-term were similar though the differences were smaller. Some of studies even confirmed the inverse trend with a statistical test for significance.

Table 1 – Description of the population and study design.

Author year. country	Point of view	Size of cohort	Gestational ages	Date of birth	Follow-up period	Source of cohort
Short-term follow-up						
Geitona et al., 2007. Greece[30]	Public insurance system	92 preterm survivors	[24–28]; [28–32]; ≥32	NS[c]	Within a 3-month period	Databases of two institutions
Feldman and Wood, 1997. USA[29]	Private insurers	310 high risk preterm	[25–27]; [28–30] [31–34]; [35–37]	1992–1994	To baby's discharge	State-wide database
McLaurin et al., 2009. USA[37]	Private insurers	4225 preterm	[33–36]	2004	From the birth through the first year of life	National insurance database
Kirkby et al., 2007. USA[33]	Public/private insurers	4932 preterm	32, 33, 34	2001–2004	To 2 weeks after NICU[d] discharge	National care management database
Russel et al., 2007. USA[40]	Public/private insurers; parents	384,000 preterm	<28; [28–36]	NS[c]	Up to 1 year of age	Nationwide inpatient sample
Luke et al., 1996. USA[35]	Public/private insurers; parents	95 twins; 92 GA-sing.[a]; 87 contrl-sing.[b]	[25–27]; [28–30] [31–34]; [35–38]	01/07/1991–30/06/1992	To the day of discharge home for infant	One institution's database
Cuevas et al., 2005. USA[27]	Public/private insurers; parents	41 preterm	<26; [26–28] [29–32]; [33–36]	NS[c]	Through the first year of life	Original chart logs used in a randomized clinical trial
Elliott et al., 2001. USA[28]	'Multiple payer types'	1538 preterm	34, 35, 36	10/1995–02/2000	Prior to hospital discharge	National database
Gilbert et al., 2003. USA[31]	NS[c]	41,137 preterm	25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36	01/01/1996–31/12/1996	Until they were sent home	State-wide database
Phibbs and Schmitt, 2006. USA[39]	NS[c]	100,746 preterm	24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36	1998–2000	To the first discharge home or prior death	State-wide database
Underwood et al., 2007. USA[42]	NS[c]	263,883 preterm	<25, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35	1992–2000		State-wide database
Kilpatrick et al., 1997. USA[32]	NS[c]	138 preterm	24, 25, 26	1990–1994	Birth	One institution's database
St John et al., 2000. USA[41]	NS[c]	621 preterm	24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36	1989–1992	Before the first discharge to home or prior death	2 institutions' database + a random sample of 30 infants
Medium-term follow-up						
Clements et al., 2007. USA[26]	Public/private insurers	14,033 preterm	24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36[e] [24–31][f]; [32–36][f]	01/07/1999–30/06/2000	First three years	State-wide database
Petrou et al., 2003. UK[38]	Hospital	239,694 preterm	<28; [28–31]; [32–36]	01/01/1970–31/12/1993	First five years of life	Regional database
Korvenranta et al., 2010. Finland[34]	NS[c]	588 preterm: 400 with morbidities; 188 without	<32	2001–2002	Fifth year of life	National databases + Questionnaire

Long-term follow-up						
Petrou, 2005. UK[9]	Hospital	5682 preterm	<28; [28–31]; [32–36]	01/01/1979–31/12/1988	The first 10 years of life	Regional database
Mangham et al., 2009. England[36]	Society	669,601 preterm	23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36	NS[c]	First 18 years of life	National databases + Literature

For each category of follow-up period, this table gives a general description of the type of data collection and the cohorts included in each study of the review. It particularly allows analysis of the variability of time horizon and GA considered by each author for the economic evaluation.
This table is referred to in the paragraph '**General description of included studies**' (Results), describing the data collection in all studies. It is also referred to in the paragraph entitled '**Explanatory factors of cost variations**' – sub paragraph entitled '**Characteristics of the study population**' (Results), in order to emphasize the differences in the composition of the cohorts included.

[a] Each twin infant was matched with a singleton for GA, month of birth, maternal payer status, and race.
[b] Each twin infant was matched with two singletons for month of birth, maternal payer status, and race.
[c] Not specified.
[d] Neonatal Intensive Care Unit.
[e] Costs assessed on multiple and singleton infants simultaneously.
[f] Costs assessed on singleton infants only.

The results also showed substantial variations in costs between studies whatever the length of follow-up, for either the same category of prematurity, or the same GA. The greater the degree of prematurity, the greater the variations in costs. In the short-term, for instance, the mean cost of extreme prematurity varied from $12,910[30] to $297,627.[39] For early prematurity, it varied from $11,624[42] to $149,101.[39] For moderate and late prematurity, it varied from $7,200[31] to $46,117,[39] and from $2,362[41] to $7,870,[29] respectively.

Explanatory factors of cost variations

Variations in costs can be explained by the methodological choices concerning the characteristics of the populations, other contextual characteristics, and specific economic criteria.

Characteristics of the study population

As described in Table 1, cohorts of studies differed by size, the years of collection, and data sources. Other clinical and sociodemographic information describing the populations was identified using the check-list. However, this information differed in nature, quantity, and level of detail from one study to another.

Information on clinical characteristics concerned the health states of the newborns and mothers and the type of care provided in the antenatal period, at delivery, in the postpartum period and in infancy. They mainly related to diagnoses, comorbidities, disabilities, type of services provided and their duration, type of visits and the specialty of the professionals, as well as the treatments provided.

Sociodemographic characteristics corresponded to several categories of information. They were demographic (including GA, birth weight, gender, but also survival and mortality rates, maternal age at birth, type of pregnancy, and ethnicity); socioeconomic (e.g. jobs, qualifications and wages of parents, and status with regard to health insurance); geographical (e.g. rural/urban nature of the place of residence). They also concerned living conditions (e.g. owning a car and being a tenant or homeowner); household's characteristics (e.g. marital status and family structure), and behavioural characteristics (e.g. domestic accidents and smoking).

Institutional context and healthcare system

The institutional context and healthcare system were rarely described and were presented in different ways in the different studies. Some of the studies, however, were relatively heterogeneous. This heterogeneity concerned the characteristics of the hospitals included in the studies, and the funding of the medical procedures. Indeed, some hospitals were included because they took part in a specific health program.[26,29,31,33,39,42] Hospitals could be also defined by their legal status,[26,30,31,33–35,40,41] and included teaching hospitals, university hospitals, community hospitals as well as private hospitals, and the type of hospital was associated with the organization of health care.[30,34]The type of ward and the medical procedures performed specifically in these hospitals were given more rarely.[30,32] Finally, information related to the reimbursement tariffs was available in only one study.[29]

Table 2 – Mean costs (in $US) per author and GA category.

Author year country	Point of view	Extreme prematurity (<28 wGA) mean cost[m]	Early prematurity (28–31 wGA) mean cost[m]	Moderate prematurity (32–34 wGA) mean cost[m]	Late prematurity (35–36 wGA) mean cost[m]
Short-term follow-up					
Geitona et al., 2007. Greece[30]	Public insurance system	12,910	11,923	7516	–
Feldman and Wood, 1997. USA[29]	Private insurers	125,546	75,063	22,443	7870
McLaurin et al., 2009. USA[37]	Private insurers	–	–	38,301	–
Kirkby et al., 2007. USA[33]	Public/private insurers	–	–	22,575–43,667	–
Russel et al., 2007. USA[40]	Public/private insurers; parents	65,600	12,100	–	–
Luke et al., 1996. USA[35]	Public/private insurers; parents	215,777[a] 195,254[b] –	91,098[a] 91,343[b] –	19,158[a] 18,367[b] 15,621[c]	5,163[a] 4,308[b] 3,704[c]
Cuevas et al., 2005. USA[27]	Public/private insurers; parents	239,749	55,792	10,561	–
Elliott et al., 2001. USA[28]	'Multiple payer types'	–	–	10,792	3785–6923
Gilbert et al., 2003. USA[31]	NS[n]	119,600–202,700	29,800–86,200	7200–18,900	2600–4200
Phibbs and Schmitt, 2006. USA[39]	NS[n]	186,894–297,627[d] 178,080–233,538[e]	65,963–149,101[d] 68,446–146,121[e]	22,648–45,710[d] 10,535–46,117[e]	3359–5,751[d] 3444–6,007[e]
Underwood et al., 2007. USA[42]	NS[n]	19,531–21,462[f]	11,624–13,543[f]	8102–9,924[f]	7,090[f]
Kilpatrick et al., 1997. USA[32]	NS[n]	166,215–294,749	–	–	–
St John et al., 2000. USA[41]	NS[n]	80,264–145,892	27,629–63,714	8272–19,548	2362–4733
Medium-term follow-up					
Clements et al., 2007. USA[26]	Public/private insurers	6982–8,690[g] 4819[h]	3245–6,548[g] 1,437[h]	1772–2,994[g] –	1191–1,459[g]
Petrou et al., 2003. UK[38]	Hospital	20,743	21,382	6658	–
Korvenranta et al., 2010. Finland[34]	NS[n]	1,078[i] 3,443[j]	–	–	–
Long-term follow-up					
Petrou, 2005. UK[9]	Hospital	27,101	26,996	8176	–
Mangham et al., 2009. England[36]	Society	199,718–446,440[k] 264,412[l]	150,403–180,527[k] 167,618[l]	99,425–138,567[k] –	80,170–85,534[k] –

For each category of follow-up period, this table gives the mean costs published by each author. When available, the minimum and the maximum of mean costs are reported in this table.
This table is referred to in the paragraph **'Cost variations'** (Results), and describes the inverse relationship between costs and GA whatever the category of follow-up, and the variability of costs between studies in each category of follow-up.

[a] Costs for GA-singletons only.
[b] Costs for all types of pregnancy.
[c] Costs for Control-singletons only.
[d] Costs assessed per survivor.
[e] Costs assessed per infant (survivors + non-survivors).
[f] Mean costs were calculated from results of total costs and number of children for each GA given by the authors.
[g] Costs assessed simultaneously for multiple and singleton infants.
[h] Considering singletons only.
[i] Costs assessed for infants without morbidities.
[j] Costs assessed for infants with morbidities.
[k] Costs assessed per survivor.
[l] Costs assessed per live birth.
[m] Mean costs available in each study for each category of follow-up period. When the calculation concerned several GA in one category, the minimum and the maximum of mean costs are reported.
[n] Not specified.

Table 3 – Economic design of the included studies.

Author year	Point of view	Expenditure items	Sources	Cost estimation	Denominator for mean cost calculation	Discounting	Management of uncertainty
Short-term follow-up							
Geitona et al., 2007. Greece[30]	Public insurance system	Hospital (infrastructures, overheads, personnel, ancillary)	Prices public sector	Bottom up approach	Survivor	No	Yes
Feldman and Wood, 1997. USA[29]	Private insurers	Hospital, providers, ancillary	Claims paid		Survivor	No	No
McLaurin et al., 2009. USA[37]	Private insurers	Hospital (transfer, fees, medication, …)	Claims reimbursed		Survivor	No	No
Kirkby et al., 2007. USA[33]	Public/private insurers	Health care plan for patient in NICU[b]: per diem charges and physicians' fees	Claims data		Infant	No	No
Russel et al., 2007. USA[40]	Public/private insurers; parents	Hospital	Discharge data	C/C ratio[c]	Infant	No	No
Luke et al., 1996. USA[35]	Public/private insurers; parents	Hospital (pharmacy, radiology, inhalation therapy, NICU[b])	Bills		Infant	No	No
Cuevas et al., 2005. USA[27]	Public/private insurers; parents	Hospital charges	Charges data; statistics		Survivor	No	No
Elliott et al., 2001. USA[28]	'Multiple payer types'	Hospital (nursery + NICU[b])	Sample data	Model from cost/day in nursery and NICU[b] and considering regional differences	Survivor	No	No
Gilbert et al., 2003. USA[31]	NS[a]	Hospital	Discharge summary	C/C ratio[c]	Survivor	No	No
Phibbs and Schmitt, 2006. USA[39]	NS[a]	Hospital	Discharge summary	C/C ratio[c]	1. Survivor 2. Infant	No	No
Underwood et al., 2007. USA[42]	NS[a]	Hospital	Discharge summary	C/C ratio[c]	Survivor	No	No
Kilpatrick et al.,1997. USA[32]	NS[a]	Hospital (ancillary services)	Bills	C/C ratio[c]	Survivor	No	No
St John et al., 2000. USA[41]	NS[a]	Hospital charges and fees	Bills	C/C ratio[c]	Survivor	No	No
Medium-term follow-up							
Clements et al., 2007. USA[26]	Public/private insurers	EI[d] program services; travels	Reimbursements + claims data		Survivor	Yes	No

(continued on next page)

Table 3 – (*continued*)

Author year	Point of view	Expenditure items	Sources	Cost estimation	Denominator for mean cost calculation	Discounting	Management of uncertainty
Petrou et al., 2003. UK[38]	Hospital	Hospital specialty (average revenue costs + revenue and capital overheads)	NHS Trust financial returns		Survivor	No	No
Korvenranta et al., 2010. Finland[34]	NS[a]	Hospital; outpatient; municipal and social services	Hospital data + other multiple sources		Survivor	No	No
Long-term follow-up							
Petrou, 2005. UK[9]	Hospital	Hospital (average revenue costs + revenue and capital overheads)	NHS trust financial returns		Survivor	Yes	No
Mangham et al., 2009. England[36]	Society	Hospital; health/social cares; education	Multiple sources	Markov model	Survivor	Yes	Yes

For each category of follow-up period, this table gives the information available in each study concerning main economic criteria that should be considered in the economic evaluation.
This table is referred to in the paragraph '**Explanatory factors of cost variations**' – sub paragraph entitled '**economic criteria**' (Results), and describes the variability of choices made by the authors for these main economic criteria. This emphasizes the possible link with the variability of costs.

[a] Not specified.
[b] Neonatal Intensive Care Unit.
[c] Cost-to-charge ratio = Total Expenses exclusive of Bad Debt/(Gross Patient Revenue + other Operating Revenue).
[d] Early Intervention program services (developmental and educational services).

Table 4 – Weighted mean costs (US$) in four studies of the short-term follow-up.

Author[a] year Country	Extreme prematurity (<28 wGA)			Early prematurity (28–31 wGA)			Moderate prematurity (32–34 wGA)			Late prematurity (35–36 wGA)		
	GA	Size	Weighted mean cost[b] (±weighted SD)[c]	GA	Size	Weighted mean cost[b] (±weighted SD)[c]	GA	Size	Weighted mean cost[b] (±weighted SD)[c]	GA	Size	Weighted mean cost[b] (±weighted SD)[c]
Gilbert et al., 2003. USA[31]	25	192	170,914 (±27,800.12)	28	402	48,299 (±353.56)	32	1921	10,373 (±41.02)	35	9898	3197 (±773.94)
	26	251		29	585		33	3172		36	16,609	
				30	797		34	5788				
				31	1194							
Phibbs and Schmitt, 2006.USA[39]	25	523	244,608 (±24,976.64)	28	1028	98,599 (±400.81)	32	2754	27,034 (±51.49)	35	25,007	4216 (±1146.81)
	26	663		29	1171		33	4657		36	44,829	
				30	1491		34	14,480				
				31	1943							
Kilpatrick et al., 1997. USA[32]	25	31	172,271 (±7296.46)	–	–	–	–	–	–	–	–	–
	26	45										
St John et al., 2000. USA[41]	25	19	106,635 (±10,285.46)	28	52	41,567 (±774.82)	32	117	16,779 (±332.39)	35	31	3587 (±1184.84)
	26	38		29	64		33	26		36	29	
				30	74		34	27				
				31	98							
Mean[d] (±SD)[e]			173,607 (±56,377.97)			62,822 (±31,166.38)			18,062 (±8404.27)			3667 (±514.15)

This table gives the weighted mean costs calculated from the results of four studies of short-term costs. Indeed, these studies presented similarities in the methodology used for the economic evaluation: time horizon, point of view (not available), use of hospital costs, calculation of mean costs per survivor (as the denominator), the use of a cost-to-charge ratio, no discounting, and no management of uncertainty.

This table was created to attempt to estimate a global trend for mean costs for each category of prematurity.

The inverse relationship between costs and gestational age can be seen.

This table is referred to in the paragraph '**Possible convergence of costs between some studies despite variations**' (Results).

[a] Studies of short-term costs with similar methodologies and from which the authors attempted to estimate a global trend of mean costs for each category of prematurity. Similarities observed: time horizon, the use of hospital costs, calculation of mean costs per survivor (as the denominator), the use of a cost-to-charge ratio, no discounting, no management of uncertainty.

[b] Weighted mean costs were calculated per author and per category of prematurity, only from GAs that were commonly assessed in the 4 studies. For each study, mean cost at each GA was multiplied by the number of patients in the corresponding GA. For each study, results obtained were added and divided by the total number of patients taken into account.

[c] Weighted standard deviations correspond to the root of the average of the squared weighted deviations between each original mean costs and the weighted mean cost obtained in each study.

[d] Averaged weighted mean costs were calculated for each category of prematurity by adding the weighted mean costs obtained for each study and dividing the result by the number of studies.

[e] Standard deviation was calculated with the averaged weighted mean cost results for each category of prematurity.

Economic criteria

As shown in Table 3, choices made concerning the economic criteria such as the point of view, the expenditure items and the cost estimation could differ greatly.

Among the eighteen studies, the point of view could be either clearly indicated, or just implicit. The perspective of the health insurance system was adopted in five studies,[26,29,30,33,37] and included either public health insurance,[30] or private health insurance,[29,37] or both.[26,33] Three other studies also used the perspective of the parents in cases of parents who were uninsured.[27,35,40] Two studies used the hospital point of view,[9,38] while another one adopted the societal perspective,[36] and in one the 'multiple-payer type' perspective,[28] as indicated by the authors, was used. In six others, the point of view was not clarified.[31,32,34,39,41,42] However, despite the use of the same type of point of view, cost differences could be noticed for the same GA category, particularly among short-term studies.[27,35,40] These differences could be explained by the expenditure items, the duration of follow-up, the sources used, as well as method used to calculate costs. However, differences and/or lack of details concerning these items made comparisons between studies difficult. Indeed, although direct hospital medical costs were included in all of the short-term analyses and some of the medium- and long-term studies, differences concerning the choice of items and data sources used for estimations could be noticed. Some studies of the medium- and long-term periods also included other costs such as costs associated with social services, education services, family expenses, and loss of parents' earnings.[26,34,36]

Concerning mean cost calculations, different denominators could be used: mean costs per survivor,[9,26–32,34,36–39,41,42] per non-survivor,[26,29,30,32,36,38,39,41] and per infant (survivor and non-survivor combined).[33,35,39,40] Moreover, two studies estimated costs using modelling techniques,[28,36] one study used a 'bottom-up approach',[30] and six others applied the cost-to-charge ratios method.[31,32,39–42]

Finally, only two studies among the eighteen included tackled the uncertainty of parameters using sensitivity analyses[30,36] and three other used cost discounting.[9,26,36]

Possible convergence of costs between some studies despite variations

Despite the huge variations in the mean costs and differences in study characteristics, it was attempted to gather the results from four short-term studies[31,32,39,41] that seemed to use similar methodological criteria (Table 4). The averaged weighted mean cost was calculated for each category of prematurity. The results confirmed the inverse relationship between costs and GA: the cost of extreme prematurity can be estimated at over $100,000, the cost of early prematurity to vary between $40,000 and $100,000, the cost of moderate prematurity to vary between $10,000 and $30,000, and the cost of late prematurity at under $4500.

Discussion

The objective of this paper was to analyse the cost of prematurity according to studies published during the two last decades. The studies were identified using a strict search of the literature. In order to compare costs more meaningfully, they were presented according to follow-up periods and GA categories, which is the main originality of this paper. The main results were the inverse relationship between the costs of prematurity and GA, whatever the follow-up period, and the huge variability of costs within the same category of prematurity in the different studies. However, these substantial cost differences led us to look for explanations. Several factors, such as the population characteristics as well as other less easily observable criteria, related to the institutional context and healthcare system, but also economic criteria and particularly the point of view of the analysis could explain this variability. Indeed, the point of view is an important economic criterion that constitutes the thread of all other methodological choices and cost results. However, this criterion was not always explicit. Moreover, expenditure items and the way costs were estimated were not totally comparable. Finally, uncertainty was rarely taken into account. Given these differences, the cost results need to be interpreted with caution.

Despite this variability, it was attempted to calculate an overall trend for the mean short-term costs for each category of prematurity from four studies that used similar methodology and presented similar results. However, they cannot exclude the possibility of other differences between them.

Consequently, the question of transferability of costs to the French context must be addressed. Conducting an economic evaluation is time-consuming and costly.[43,44] The transfer of results can be considered a possible alternative. Several factors concerning the transferability of results have been studied in the literature. However, such data are generally rare. Goerre et al. (2007)[43] suggested seventy-seven potential factors related to the characteristics of the study population, as well as factors concerning pathologies, the characteristics of healthcare providers and health systems, and methodological choices. However, for transfer to be successful it is necessary to consider the relationship between all of these criteria, which is not always possible.[45] The impossibility to transfer results can also be explained by the existence of 'knock-out criteria' related to a lack of data, important differences in the quality of studies or in practices between countries.[46] In any case, it is difficult for decision makers to assess the degree of transferability of study results.[44,45,47,48] Conducting meta-analyses on the cost of prematurity can be an alternative to transferring results. However, meta-analyses are also time consuming and require access to individual data, which are not always readily available.

This literature review presents some limits. Firstly, the evaluations that assessed the cost-effectiveness, cost-utility or cost-benefit ratio of a treatment or prevention strategy were excluded. There were considered too specific and too focused on populations with excessively strict inclusion criteria. Secondly, the use of PPPs could also be criticized. PPPs allow comparisons of prices in the spatial dimension, by equalizing the purchasing power of different currencies and eliminating the difference in prices levels between countries.[49] The 'PPP for actual individual consumption (PPP-P41)' was considered as the most appropriate because it includes 'individual services that general government provides to

specific identifiable households', such as health services.[49] However, for the moment, PPPs do not allow comparisons over time, although they are approaching.[19] Another possibility could have been to translate costs from the included studies into costs for 2012. But this would have required knowing the reference year for each estimated cost, which was not the case.

Other reviews have reported the inverse relationship between costs and GA.[8,12–16] They also underlined the large number of studies performed in the neonatal period[12–16] and the fact that hospital costs were the main expenditure items used, justified by the availability of costs data.[8,15,16] They also reported methodological differences between the included studies. One difference between this work and these reviews concerned the way costs were reported (for example, according to expenditure items).[8] Moreover only two authors used a check-list of criteria validated by the community of health economists as in this work.[8,12] But the main difference concerned the choice of inclusion criteria. Several reviews included studies according to the birth weight and GA simultaneously, therefore making comparisons between costs tricky.[13,14,16] In this review, prematurity was defined as births at less than 37 GA. This choice was justified by the fact that GA is commonly used to define prematurity and its definition is recognized by the World Health Organization (WHO).[1,12] Moreover, GA has been shown to correlate better than birth weight with the morbidity characteristics of prematurity.[50]

In conclusion, this review underlined the clear inverse relationship between costs and GA at birth in all of the studies. The variability of results observed in the international literature and the debate still in progress concerning transferability suggest the importance of conducting a study on the cost of prematurity specific to the French context. The results obtained will allow comparisons with the results gathered in this review.

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Appendix 1. List of key words used in each databank for the inclusion of studies.

Medline: ("Costs and Cost Analysis"[Mesh] OR "Health Care Costs"[Mesh] OR "Direct Service Costs"[Mesh] OR "Hospital Costs"[Mesh] OR "Drug Costs"[Mesh] OR "Cost of Illness"[Mesh] OR "Cost-Benefit Analysis"[Mesh] OR "Economics"[Mesh])
AND ("Infant, Low Birth Weight"[Mesh] OR "Infant, Very Low Birth Weight"[Mesh] OR "Multiple Birth Offspring"[Mesh] OR "Premature Birth"[Mesh] OR "Birth
Weight"[Mesh] OR "Infant, Extremely Low Birth Weight"[Mesh]).

ScienceDirect: ((pub-date > 1989 and premature) OR (pub-date > 1989 and very low birth weight or preterm birth) OR (pub-date > 1989 and multiple birth or gestational age) OR (pub-date > 1989 and prematurity or low birth weight))
AND ((pub-date > 1989 and economics, hospital or economic, medical) OR (pub-date > 1989 and health care costs or direct service costs)).

The Cochrane Library: Costs and Cost Analysis OR Economics, Hospital OR Economics, Medical OR Economics, Medical OR Economics, Pharmaceutical
AND Infant, Low Birth Weight OR Infant,
Premature OR Infant, Premature, Diseases OR Premature Birth OR Multiple Birth Offspring OR Intensive Care Units, Pediatric OR Pediatrics OR Pediatric Nursing OR *prematurity* OR *preterm birth*.

(continued)

Econlit and Business Source Premier: (DE "COST analysis" OR DE "BREAK-even analysis" OR DE "COST effectiveness" OR DE "COST estimates" OR DE "ESTIMATES" OR DE "COST" OR DE "STATISTICS" OR DE "ECONOMICS – Statistical methods" OR DE "DIRECT costing" OR DE "MEDICAL economics" OR DE "PRESCRIPTION pricing")
AND(DE "MEDICAL fees" OR DE "FEE for service (Medical fees)" OR *Health care costs* OR *Hospital costs* OR *Cost of illness* OR *Economics, medical*) **AND**(*prematurity* OR *low birth weight* OR *preterm birth* OR *very low birth weight* OR *pediatrics* OR *neonatology* OR *newborn* OR *multiple birth* OR *gestational age*).

BDSP: ((coûts OR dépenses OR économique) **AND** (prématurité OR nouveau-né OR naissance multiple OR néonatologie)) **AND** *(TypDoc=(ARTICLE OR FASCICULE))*.

This list gives the keywords (Mesh terms or *free text*) used and combined for each query in medical and economic bibliographic databanks. Limits of dates of publication, countries, language of publication, type of paper, and age structure of the population could be also taken into account. This appendix was referred to in the paragraph entitled **'Inclusion of studies for the review of the literature'** (Materials and methods).

Appendix 2. Check list for assessing economic evaluations of prematurity cost.

I - Article identity

Authors	
Country	
Title	
Publication	Journal: Year: Volume: Pages:
Date of reading	DD/MM/YYYY: …./…./….

II - Objectives

Context, justifications for the study	□ Yes □ No
Clearly defined objective	□ Yes □ No Main objective: Secondary objective:
Research Hypotheses	□ Yes □ No □ NS[a]

III - Data collection

Nature of collection	Prospective □ Yes □ No □ NS Retrospective □ Yes□ No □ NS Mixed □ Yes □ No □ NS
Multicenter study	□ Yes □ No □ NS Number of centers :
Modeling study	□ Yes □ No □ NS

[a]NS: not specified

IV - Study population

4.1. Population of newborns

Sample size	N = infants
Inclusion criteria	
Exclusion criteria	
Included	N = infants N = premature □ Gestational age categories: □ Yes □ No Details: □ Birth weight categories: □ Yes □ No Details:
Dates of inclusion	Start of the inclusion : End of the inclusion :
Duration of follow-up	Follow-up duration: □ NS
Characteristics of children	Comorbidities: - at birth: □ Yes □ No - during hospitalization : □ Yes □ No Care management: - at birth: □ Yes □ No - during all hospitalizations: □ Yes □ No
Other characteristics	

4.2. Population of mothers

Sample size	N = women
Morphologic and clinic characteristics (ante natal and at birth).	Morphologic characteristics (age, weight, …): Comorbidities:
Care management	Healthcare sector: Care management: - antenatal - at birth - postpartum
Environmental and contextual characteristics	Socioeconomic status: Behavior (tobacco, alcohol…): Geographical information:
Other characteristics	

4.3 Sources

Source of the study population (specify the source)	□ Literature review: □ Survey: □ Registry □ Meta-analysis: □ Others: □ NS
Representativeness	□ Yes □ No □ NS If yes, reason(s): If no, reason(s):

V – Economic evaluation

5.1. Economic data

Point of view	□ Patient: □ Family / friends: □ Funders: □ Society: □ Company: □ Other:
Time horizon	
Cost categories (specify the expenditure items)	□ Direct medical costs: □ Direct non-medical costs: □ Indirect costs: □ Intangible costs: □ NS
Source of costs	□ Literature review: □ Survey: □ Database: □ Micro-costing: □ Billing: □ Others: □ NS
Year of currency value for cost estimation	
Consistency of cost data with the objectives	□ Yes □ No If no, reason(s):
Consistency of cost data with the point of view	□ Yes □ No If no, reason(s):

5.2. Cost evaluation

Method used for cost estimation	□ Top down: □ Bottom up: □ Econometric: □ Others
Outcome measurements	Main: Secondary:
Adjustment of costs (cost-to-charge ratio)	□ Yes □ No □ NS
Monetary valuation	Reference money: □ NS Reference year: □ NS
Monetary conversion	□ Yes □ No □ NS If yes, - Reference money - Reference year - Type of conversion - Exchange rate - Purchasing Power Parity (PPP)
Cost discounting	□ Yes □ No □ NS If yes, rate: If no, justification

VI – Results analysis

Modeling of the analysis	□ Yes □ No □ NS *If yes*: 1) Statistical model (regression) Type of regression: 2) Modeling Type:
Subgroup analysis	□ Yes □ No *If yes,* type of subgroup?
Independent variables	About the newborn/child: About the mother:

	About the management of care (antenatal and postanatal): About environmental data and behavior: Other independent variables:
Unit of costs	□ Mean cost □ Median cost □ Marginal cost □ Incremental cost □ Total cost
Uncertainty	□ Analysis of stochastic data □ Yes □ No If yes: - Monte Carlo □ - Bootstrap □ - Other □ □ Sensitivity analysis □ Yes □ No If yes: - univariate □ - multivariate □ - scenario □ - threshold □ Specify the variables tested:

Detailed Results

VII – Conclusion, discussion, perspectives

The results help answer the question	□ Yes □ No If no, reason(s):
Interpretation of results by the authors	□ Yes □ No
Comparisons of methodology / results with other publications	□ Yes □ No □ NS
Extrapolation of results	□ Yes □ No □ NS
Bias and possible difficulties discussed by authors	□ Yes □ No □ NS *If yes,* □ missing data □ Outliers □ Data lost (> 10%) □ Small sample □ Single-center study □ Short period of time □ Others
Perspectives	□ Yes □ No □ NS If yes, what?

Legend Appendix 2

This check-list was built in order to describe the studies and analyze the costs using criteria mainly based on French, English and American communities of health economists.

It includes description of the study design, the population included and their characteristics, the sources of data, methodology used for the economic evaluation, the results and the potential limits or discussions provided by the authors.

This check-list is referred to in the paragraph entitled **'Analysis of the included studies'** – sub paragraph **'Check-list for cost' analysis'** (Materials and methods).

Appendix 3. Mean costs (in US$) of prematurity, per author and GA category.

Author year Country	Cost denominator	US$ year[a]	Point of view	Extreme prematurity (<28 wGA)		Early prematurity (28–31 wGA)		Moderate prematurity (32–34 wGA)		Late prematurity (35–36 wGA)	
				GA[b]	Mean costs	GA[b]	Mean costs	GA[b]	Mean costs	GA[b]	Mean costs
Short-term follow-up											
Geitona et al., 2007. Greece[30]	Survivors[c,h]	2004	Public insurance system	[24–28]	$ 12,910	[28–32]	$ 11,923	≥32	$ 7516		
Feldman and Wood, 1997. USA[29]	Survivors[c,g]	NS[p]	Private insurers	[25–27]	$ 125,546	[28–30]	$ 75,063	[31–34]	$ 22,443	[35–37]	$ 7870
McLaurin et al., 2009. USA[37]	Survivors[j]	NS[p]	Private insurers					[33–36]	$ 38,301		
Kirkby et al., 2007. USA[33]	Infant[c,h]	NS[p]	Public/Private insurers					32 33 34	$ 43,667 $ 31,535 $ 22,575		
Russel et al., 2007. USA[40]	Infant[c]	NS[p]	Public/Private insurers; Parents	<28	$ 65,600	[28–36]	$ 12,100				
Luke et al., 1996. USA[35]	Infant[c]	NS[p]	Public/Private insurers; Parents	[25–27] [25–27]	$ 215,777[d] $ 195,254[e]	[28–30] [28–30]	$ 91,343[d] $ 91,098[e]	[31–34] [31–34] [31–34]	$ 18,367[d] $ 19,158[e] $ 15,621[f]	[35–38] [35–38] [35–38]	$ 4,308[d] $ 5,163[e] $ 3,704[f]
Cuevas et al., 2005. USA[27]	Survivors[g,j]	NS[p]	Public/Private insurers; Parents	<26 [26–28]	>$ 200,000 $ 239,749	[29–32]	$ 55,792	[33–36]	$ 10,561		
Elliott et al., 2001. USA[28]	Survivors[i,j]	NS[p]	'Multiple payer types'					34	$ 10,792	35 36	$ 6923 $ 3785
Gilbert et al., 2003. USA[31]	Survivors[j]	NS[p]	NS[p]	25 26 27	$ 202,700 $ 146,600 $ 119,600	28 29 30 31	$ 86,200 $ 62,600 $ 46,400 $ 29,800	32 33 34	$ 18,900 $ 11,000 $ 7200	35 36	$ 4200 $ 2600
Phibbs and Schmitt, 2006. USA[39]	Survivors[c]	2003	NS[p]	24 25 26 27	$ 297,627 $ 272,730 $ 222,425 $ 186,894	28 29 30 31	$ 149,101 $ 115,975 $ 92,662 $ 65,963	32 33 34	$ 45,710 $ 29,627 $ 22,648	35 36	$ 5751 $ 3359
	Infants[c] (survivors and not)			24 25 26 27	$ 222,563 $ 233,538 $ 207,637 $ 178,080	28 29 30 31	$ 146,121 $ 115,801 $ 92,882 $ 68,446	32 33 34	$ 46,117 $ 30,145 $ 10,535	35 36	$ 6007 $ 3444
Underwood et al., 2007. USA[42]	Survivors[j]	NS[p]	NS[p]	<25 25 26 27	$ 21,462 $ 17,541 $ 14,447 $ 19,351	28 29 30 31	$ 13,543 $ 11,624 $ 11,856 $ 12,039	32 33 34	$ 9924 $ 9525 $ 8102	35	$ 7090
Kilpatrick et al.,1997. USA[32]	Survivors[c,h]	1994	NS[p]	24 25 26	$ 294,749 $ 181,062 $ 166,215						

(continued on next page)

Appendix 3. (*continued*)

Author year Country	Cost denominator	US$ year[a]	Point of view	Extreme prematurity (<28 wGA)		Early prematurity (28–31 wGA)		Moderate prematurity (32–34 wGA)		Late prematurity (35–36 wGA)	
				GA[b]	Mean costs	GA[b]	Mean costs	GA[b]	Mean costs	GA[b]	Mean costs
St John et al., 2000. USA[41]	Survivors[c]	NS[p]	NS[p]	24	$145,892	28	$ 63,714	32	$ 19,548	35	$ 4733
				25	$121,181	29	$ 49,540	33	$ 13,153	36	$ 2362
				26	$ 99,362	30	$ 37,569	34	$ 8272		
				27	$ 80,264	31	$ 27,629				
Medium-term follow-up											
Clements et al., 2007. USA[26]	Survivors[c,k]	2003	Public/Private insurers	24	$ 7,214[l]	28	$ 6,548[l]	32	$ 2,994[l]	35	$ 1,459[l]
				25	$ 8,690[l]	29	$ 5,217[l]	33	$ 2,601[l]	36	$ 1,191[l]
				26	$ 6,982[l]	30	$ 4,865[l]	34	$ 1,772[l]		
				27	$ 7,211[l]	31	$ 3,245[l]				
				[24–31]	$ 4,819[m]	[32–36]	$ 1,437[m]				
Petrou et al., 2003. UK[38]	Survivors[c]	1999	Hospital	<28	$ 20,743	[28–31]	$ 21,382	[32–36]	$ 6658		
Korvenranta et al., 2010. Finland[34]	Survivors[j]	2008	NS[p]			<32	$ 1,078[n]				
						<32	$ 3,443[o]				
Long-term follow-up											
Petrou, 2005.UK[9]	NS[p]	1999	Hospital	<28	$ 27,101	[28–31]	$ 26,996	[32–36]	$ 8176		
Mangham et al., 2009. England[36]	Survivors[c]	2006	Society	23	$ 446,440	28	$ 180,527	32	$ 138,567	35	$ 85,534
				24	$ 342,203	29	$ 165,773	33	$ 114,641	36	$ 80,170
				25	$ 217,122	30	$ 167,935	34	$ 99,425		
				26	$ 203,185	31	$ 150,403				
				27	$ 199,718						
	Live birth[c]			<28	$ 264,412	<33	$ 167,618				

This table gives all mean costs published in the studies of the review, detailed by category of follow-up period and category of prematurity, by author and by GA class. This table is a complement to Table 1.
It provides readers with additional information to that in Table 1.
This Appendix is referred to in the paragraph entitled '**Explanatory factors of cost variations**' – sub paragraph entitled '**Characteristics of the study population**' (Results).

[a] Corresponds to the year of currency value (when clearly available in the article).
[b] Gestational age.
[c] Initial population of survivors and non-survivors.
[d] Costs for GA-singletons only.
[e] Costs for all twins + GA-singletons + Control-singletons.
[f] Costs for Control-singletons only.
[g] Population of high-risk pregnancies.
[h] Population of infants admitted to Intensive Care.
[i] Population of Non-Indicated singleton deliveries.
[j] Initial population of survivors.
[k] Initial population of singletons and multiple births.
[l] Costs assessed for multiples and singletons simultaneously.
[m] Costs assessed for singletons only.
[n] Costs per survivor without morbidities.
[o] Costs per survivor with morbidities.
[p] Not specified.