Are the economic studies on the costs of prematurity transferable in France?

Revue of the literature and analyze of methodology.

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ABSTRACT

Context: Prematurity is a public health problem worldwide. The economic burden of prematurity has never been estimated in France, whereas it has been done in other industrialized countries.

Objectives: To analyze published cost-of-illness studies that had assessed the cost of prematurity according to gestational age at birth in other industrialized countries, and to address the question of the possible transferability of cost results to the French health care context. This review of literature is a first step to consider any study in France, analyzing the methodology used in several studies, the expected costs and/or the potential savings related to various health care procedures.

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 selected. Variations in the reported costs were analyzed using a multi-search check-list, which allowed the studies to be described according to several methodological and contextual criteria.

Results: A total of 20 studies published since 1990 were selected. According to these studies, costs were assessed for different time horizon (short, medium or long term), and for different degrees of prematurity (extreme, early, moderate and late). Results showed that, whatever the time horizon, costs correlated inversely with GA. They also showed a great variability in costs within the same GA group. Differences between studies could be explained by the choices made, concerning i/ various economic choices, ii/ the

information available to describe the study populations, and iii/ other less observable contextual information.

Conclusion: This review underlined not only the clear inverse relationship between costs and GA at birth, but also the difficulty to transfer these results to the French context. It suggests that studies specific to the French health system need to be carried out.

Key words: economic burden of prematurity, cost analysis, gestational age, review.

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 7.2% in 2003) as in other industrialized countries since the early 1980s[1, 3-5]. This evolution can mostly be attributed to the increased use of assisted reproduction and obstetric interventions, such as induced labor and Caesarean section[5]. Other multiple characteristics can also be involved, such as demographical characteristics (advancement of the maternal age at birth, higher body mass index, obstetric history), behavioural characteristics (smoking during pregnancy), and the socio-economic level. The contribution of these factors varies according to the gestational age (GA) at birth[6].

Prematurity is also known to be associated with a higher risk of adverse consequences for health in the short-term as in the long-term compared with term births, and therefore requires specific health, education and social services[2, 6-7]. 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, behavioral problems and pulmonary dysfunction[2, 8]. It has also been estimated that half of the children with severe disabilities were born prematurely[6].

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[9-10]. In addition, questions arise about the transferability of results from other countries to France.

Several reviews in the literature analyzed the economic consequences of preterm birth. They reported the main findings, particularly the inverse relationship between costs and the gestational age at birth[7, 11-14]. However, prematurity was not defined in the same way in the different reviews, even though gestational age (GA) is considered the official criterion by the World Health Organization to define prematurity[1, 15].

Therefore, by carrying out a review of the literature, the aim of this article was to analyze the estimated costs of prematurity according to GA at birth from published cost-of-illness studies, and to determine whether or not the findings can be transferred to the French health-care context. In the case of an implementation for France, this work also aims to provide some elements of methodological references.

MATERIALS AND METHODS

1. Identification and 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)[16]. Key words sequences related to "prematurity" and "costs" were used. The list of the key words used in each databank is given in Appendix 1.

The articles for the review of the literature were selected in three steps presented in Figure 1. All of the studies identified in the databank search were imported using Endnote® software. Duplicated references were deleted. In the second step, the title and the references of each article were scrutinized to check the selection criteria. Finally, abstracts issued from this selection were carefully checked using the same criteria.

2. Analysis of the selected studies

2.1. 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[17]. PPP allows international comparisons of prices expressed for a 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[18].

2.2. Check-list for costs' analysis

In order to describe the studies and analyze the costs, a check-list (Appendix 2) was built using criteria mainly based on French[19], English[20], and American[21-22] 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; discounting); results (types of analysis; unit costs expression; management of uncertainty associated to data); and the manner in which the discussion was conducted by the author.

RESULTS

1. Article selection

A total of 2,760 papers were imported using Endnote® software, leading to a total of 2,617 articles after eliminating duplicates. After application of all of the criteria, 20 articles remained[8, 23-41].

2. General description of selected studies

A general description of the study designs is given in Table 1.

2.1. Year of publication and country

Three of the 20 selected studies were published before 2000. Thirteen articles were American studies[23-26, 28-30, 32, 34, 38-41], and five were English studies[8, 33, 35-37]. Only two studies were based on mainland European data (one Finnish and one Greek study)[27, 31].

2.2. Data collection

Most of the studies were multi-center[8, 23-28, 30-31, 33-41]. Only one study was carried out using prospective data collection[27]. The other nineteen studies were retrospective[8, 23-26, 28-41].

2.3. Three main categories of time horizon

The time horizons were not totally comparable between studies. This led us to classify studies according to three categories of time horizons: short-term, medium-term, and long-term horizons. Studies with a short-term horizon were those that assessed costs during the first year of life. Studies with a medium-term horizon were those that assessed costs in the first 5 years of life (and not stopping at the first year of life). Studies with a long-term horizon were those that assessed costs in the first 18 year of life (and not stopping at the first five years of life). Among the twenty studies, thirteen assessed the costs of prematurity according a short-term horizon[24-30, 32, 34, 38-41], three assessed the costs according a medium-term horizon [23, 31, 37], and four assessed the costs according a long-term horizon [8, 33, 35-36].

Classification of studies according to three main categories of time horizon is not without clinical and economic meanings. These three categories were validated by expert advice and are adequate in relation to the literature focused on epidemiology of preterm births[6, 42]. The short-term horizon category is justified by the fact that premature newborns are subject to greater risks of severe complications occuring at birth and requiring specific management of care in the first year of life. As an example, preterm newborns are mostly subject to higher risks of periods of respiratory distress that implies heavy treatments in the neonatal period. Moreover, the occurrence of these

complications in the short-term period and their severity are particularly known to influence the long-term complications.

In the period from one year of age to 5 years of age, children are in a pre-school period and are subject to early screenings of disabilities in their development and their evolution. More or less easily depending on the age, infants' examinations concern mainly language (communication), vision, hearing, emotional, socialization, but also cerebral, intellectual and motor development.

Finally, after 5 years of age, children have access to education and are subject to screening of more difficulties (especially for learning) and handicaps, and to evaluation of their evolution. These problems suggest multiple services in the long-term, mainly services of special education and social services.

The medium-term horizon and the long term horizon categories were then justified.

2.4. Four main categories of prematurity

As shown in Table 1, depending on the study, costs were not estimated for the same GA, or for the same GA classes. This led us to present costs results according to four categories of prematurity, which were also validated by experts' advices. 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 combination of GA in categories according to the degree of prematurity is commonly used and scientifically accepted in so far as they meet some relevance in terms of medical care consumption. These categories are particularly relevant as far as

they concern the hospitalizations, the readmissions, the outpatient visits, the specialists' visits, the physiotherapy visits. They are also relevant as far as they concern the medical reasons of these healthcare consumptions[43] .

3. Cost variations

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

3.1. An inverse trend between costs and GA

An inverse relationship between costs and GA was found in all studies. As an illustration, the mean cost varied from $2,362[40] for late prematurity (at 36 wGA) to $297,627[38] for extreme prematurity (at 24 wGA) in the short-term, and from $8,176 (at 32-36 wGA)[8] to $446,440 (at 23 wGA)[33] 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. The strong inverse trend between costs and GA is associated with a statistically justified assertion that GA is the first predicator of the costs of prematurity[8, 24, 35-37, 40]. In any case, this inverse trend is comprehensively associated with the reality of an inverse and continuous trend between GA and the medical care consumption, especially with regard to specialist visits[43].

3.2. High variations in costs within the same category of prematurity

The results also showed substantial variations in costs between studies whatever the time horizon, for either the same category of prematurity, or the same GA. The greater the degree of prematurity, the greater the variations in costs. Indeed, in the short-term period for instance, the mean cost of extreme prematurity varied from $12,910[27] to $297,627[38]. For early prematurity, they varied from $11,624[41] to $149,101[38]. For moderate and late prematurity, they varied from $7,200[28] to $46,117[38], and from $2,362[40] to $7,870[26], respectively.

Substantial cost differences observed within the same category of prematurity and within the same time horizon led us to look for explanations. Firstly, they can lead us to address the question of the role of the classifications of GAs adopted. However, this last point is not obvious to be clarified. Second, they led us to analyze the methodological choices and the health care context in which the studies were conducted, which are necessarily involved in the cost estimated.

4. Explanatory factors of cost variations

Variations in costs can be explained by the methodological choices concerning not only economic criteria, but also the populations concerned and other external characteristics. Major criteria were analyzed.

4.1. Economic criteria

As shown in Table 3, choices made concerning the following economic criteria could differ greatly.

4.1.1. Point of view:

The first main economic criterion that we are able to find in a cost study is the point of view. Indeed, this criterion directly depends on the objectives of the study and constitutes the thread of the all other methodological choices and costs results[22, 44-45].

Among the twenty studies, this point of view could be either clearly expressed, or just implied. The perspective of the health insurance system was adopted in five studies[23, 26-27, 30, 34], and included either public health insurance[27], or private health insurance [26, 34], or both[23, 30]. Three other studies also used the perspective of the parents in cases of parents who were uninsured[24, 32, 39]. Two studies used the hospital point of view[8, 37], while three others adopted the societal perspective[33, 35-36], and in one the "multiple-payer type" perspective[25], as indicated by the authors, was used.

In six others, the point of view was not clarified[28-29, 31, 38, 40-41]. Therefore, this lack of clarity regarding a major criterion does not allow an easy understanding of the choices of methodology used and may be prohibitive for the assessment of the entire study.

4.1.2. Expenditure items:

Directly related to the objectives and the point of view, but also on the individual time horizons, we observed also inevitably some differences in the use of expenditure items for the costs estimations.

Indeed, although direct hospital medical costs were included in all of the short-term studies and some of the medium- and long-term studies, there were differences concerning the choice of items and data sources used for the estimations. 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[23, 31, 33, 35-36]. Therefore, in any case, these findings seem to compromise any comparisons between studies.

4.1.3. Cost estimations:

Regarding the manner the mean costs were estimated, we observe also some variability.

The mean costs were mostly estimated using the following denominator: Mean costs per survivor[8, 23-29, 31, 33-38], per non-survivor[23, 26-27, 33, 37-38, 40], and per infant (survivor and non-survivor combined)[30, 32, 38-39].

However, only one study specified the type of approach used: a "bottom-up approach"[27]. The "bottom-up approach is a micro-economic approach, requiring the input to be gathered at a certain level of detail and multiplying the quantity of health input used with their unit costs estimated[46].

Moreover, two other studies estimated costs using modeling techniques[25, 33]. The first one used a model considering regional differences in the estimated costs per day in nursery and in neonatal intensive care unit (NICU)[25]. The second one used a decision analytic model (named a Markov model) in order to "estimate the costs to the public sector over the first 18 years after birth". "The model estimates the costs associated with a hypothetical cohort"[33].

Finally, six others applied the cost-to-charge ratios method[28-29, 38-41]. A cost-to-charge ratio is "defined as the relationship between the hospital's cost of providing services and the charges assessed by the hospital for a service" that are billed to the patient.

4.1.4. Management of uncertainty:

Only two studies among the twenty selected tackled the uncertainty of parameters using sensitivity analyses[33, 36]. However, any estimations of cost contain a certain degree of uncertainty. Taking into account uncertainty consists in supposing hypothetical or estimated variations in some criteria and testing the sensitivity of results induced by these modifications[44] . This practice is paramount to be performed in a cost study.

Presumably, all of these methodological differences and a certain lack of precision lead to some results variations. They also confirm the assessment of studies and the comparison between studies difficult.

Beyond methodological choices, the clinical and socio-demographic characteristics, but also the health system contexts were analyzed.

4.2. Characteristics of the study population

As described in Table 1, cohorts of studies differed by the years of collection, size and data sources. Other clinical, socio-demographic and contextual information describing the populations was identified using the check-list. While this information has a role in influencing costs, it differed in nature, quantity and level of detail from one study to another.

4.2.1. Clinical characteristics:

Whatever the category of time horizon is, information on clinical characteristics in the twenty studies concerned the health states of the newborns and the type of care

provided, in the postnatal period and/or 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.

According to the studies, information could also be available on the health states of the mothers and the type of care provided in the antenatal period and/or at delivery. However, neither detailed descriptions of clinical characteristics and services provided, nor the assessment of their impact on costs outcomes were currently available in all studies.

Particularly, GA is recognized as the main driver of costs of prematurity, and a necessary and sufficient criterion to define prematurity[47]. Its impact on costs would be related to differences in clinical and needs of cares according to the GA, and must be included in the interpretation of cost differences. Although the main impact of GA on the costs results was underlined in some of the studies [8, 24, 35-37, 40], as a close association between GA and other clinical criteria, the variability of information available does not make comparisons possible between studies. This led us addressing caution in the analysis and interpretation of costs results.

4.2.2. Sociodemographic characteristics:

Socio-demographic characteristics would be also important to consider in the analyze of costs differences. Indeed, their association with prematurity and multiple perinatal disabilities are recognized. However, it is not easy to assess because of difficulties in their availability and of potential bias[6]. As an illustration, precarity is known to explain prematurity, associated with a lack of medical follow-up, nutritional deficits, or growth retardation in utero[6]. Other social and environmental factors are also

known to be implied in occurrence of prematurity and disabilities, such as unemployment, low education level of the mothers, or marital status[6, 48]

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

The limited availability of information and the limited assessment of their impact on costs outcomes also led us addressing caution in the analysis and interpretation of costs results.

4.3. Health care systems

Finally, the whole health care system has a direct impact on the organization of care, its accessibility, and the health status of populations[49] . Therefore, these characteristics would be interesting to be considered in the analysis of the costs variations.

However, contextual information on the health care system was rarely described and was presented in different ways according to the studies. They concerned mostly 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[23, 26, 28, 30, 38, 41]. Hospitals could be also defined by their legal status[23, 27-28, 30-32, 39-40], 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 [27, 31]. The type of ward or the medical procedures performed specifically in these hospitals were given more rarely[27, 29]. Finally, information related to the reimbursement tariffs was available in only one study[26].

No other information was available concerning the other characteristics of the health systems.

DISCUSSION

The aim of this paper was to analyze the cost of prematurity according to studies published during the two last decades in industrialized countries.

The main result was the inverse relationship between the costs of prematurity and GA, regardless of the time horizon, the used methodology, and the other clinical, socio-demographic and contextual characteristics. This result was identifiable in any study of costs of prematurity, since GA has been also recognized to be the main drivers of clinical complications and costs consequences of prematurity. Second, we may also be confronted to the huge variability of costs within a same category of prematurity in the different studies, whatever the time horizon category. This leads us to addressing the question of the actual transferability of costs to France. Several factors, such as economic criteria and population characteristics as well as other less easily observable criteria related to the institutional context and health care system could explain the costs variability. However, the analyze of main criteria did neither allow concluding to a possible comparison between studies, nor to a possible transferability.

Several factors concerning the transferability of results to a target jurisdiction have been studied in the literature. Goerre, et al. (2007)[50] suggested seventy-seven potential factors related to the characteristics of the study population (demographic, clinical and socioeconomic characteristics, attitudes concerning consumption and perceived usefulness in terms of health care, status of health insurance…), the characteristics of pathologies (incidence, evolution, severity…), the characteristics of providers (remuneration, clinical practices…), the characteristics of health systems (characteristics, unit prices, type of resources…), and the methodology used (choice of perspective, time horizon, opportunity costs, discounting rates, presentation of results…). However, such data are generally rare. Moreover, for transfer to be successful, it is necessary to consider the relationship between all of these criteria, which is not always possible[51].

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[52]. In any case, it is difficult for decision makers to assess the degree of transferability of study results[51, 53-55].

Conducting a meta-analyse on the cost of prematurity can be an alternative to transferring results. However, a meta-analysis requires access to detailed methodological and contextual information, which was not always readily available.

Finally, other methods to evaluate transferability based either on modeling approaches that consist in substituting prices, or in adapting data (quantity of resources, level of prices) to the target country[50-51] require multidisciplinary expertise[51].

In another part, the only possibility of comparisons between studies was also compromised. Indeed, this would also require a detailed description on the methodology used and the assurance with compliance of rules, concerning the point of view or the cost discounting for example[56]. Moreover, a lack of precision in the type of approach used and in the definition of certain terms (ex. “charges” vs “costs”) makes the assessment of the cost study difficult.

Comparisons between studies are also compromised in the case of lack of information related to the health care context, as far as concerned the management of cares for example (that really depends on other multiple characteristics, such as organizational, medical, but also social, ethical and cultural choices)[6].

The possibility of an overall trend of mean costs for each category of prematurity, based on results we still attempted to gather, did not succeed, given the widest diversity of studies. Therefore, it was not possible to estimate an overall difference between each category of prematurity or between GAs from our literature.

We could only observe that less the degree of prematurity, the lower the differences of cost between GA.

A number of other costs estimated were not addressed in our review. The incremental costs for example between two GAs or two categories of prematurity were estimated in only few studies[28, 33, 38]. These can give important information in terms of avoided costs in case of delay of a preterm birth. Moreover the estimation of indirect costs in some medium-term or long-term studies was subjected to a certain confusion

with respect to the definition of indirect costs. Finally, the estimation of intangible costs concerning perinatality remains difficult to be assessed.

Our literature review presents some limits.

Firstly, we excluded completed evaluations that assessed the cost-effectiveness, cost-utility or cost-benefit ratio of a treatment or prevention strategy. We considered them 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[57]. We considered the "PPP for actual individual consumption (PPP-P41)" as the most appropriate because it includes "individual services that general government provides to specific identifiable households", such as health services[57]. However, for the moment, PPPS do not allow comparisons over time, although they are approaching[18].

Second, we can still assume that rankings of GAs and the definition of time horizon categories made the comparisons of costs criticism.

Other reviews on the topic of the costs of prematurity [7, 11-15] reported the inverse relationship between costs and GA. They also underlined the large number of studies performed in the neonatal period[11-15] and hospital costs were also identified as the main expenditure items used, justified by the availability of data on costs[7, 13-14]. However, these reviews differ from our work in the choice of inclusion criteria. Indeed, several reviews selected studies according to the birth weight and GA simultaneously, therefore making comparisons between cost stricky[11-12, 14]. In our review, prematurity

was defined as births at less than 37 GA, and not on the birth weight exclusively. This choice was justified by the fact that the GA is commonly used to defined prematurity and its definition is recognized by the World Health Organization (WHO)[1, 15]. Moreover, the parallel between GA and the birth weight does not seem relevant. Indeed, the two distributions of GA and birth weight were recognized to be globally comparable, but not when regarding in terms of subgroups of GAs [58].

Finally, they could also differ from our work in the inclusion of older studies.

In conclusion, this review underlined the clear inverse relationship between costs and GA at birth in all of the studies and a great variability of costs results between studies. This review of the literature showed that transferability and meta-analysis are impossible. Therefore, it demonstrates the need for a specific study in France, since no French study exists.

The estimation of the costs of prematurity in France and its multiple costs components would reveal multiple interests. It would constitute a first step of decision making, by justifying allocation of resources or any budget and by providing process in planning of cares[56] **"**at different levels of the health care organizations"[46]. Moreover, estimating the resources induced by a health status or a specific disease would allow estimating the costs that could be avoided by strategies of screening or reduction of prematurity. It could be the costs avoided for the society, for the government or other funders of health[6].

In other cases, knowledge on the economic burden of prematurity (or associated comorbidities or interventions) could also be useful for professionals decision

concerning their own practices or prescriptions[59], partly by planning the provision of health care services and "forecasting the future consumption of health care services"[46] . Finally, the only French costs studies in the field of prematurity concern specific health strategies, however no really engaged medico-economic studies can be found[6].

This review of the literature allowed analyzing the methodology used in the international literature and the difficulties related. It constitutes a useful tool to be clear with the methodological need, and is an essential step to conducting a reliable study of the costs of prematurity in France.

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Ethical approval

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Figure 1: Description of the of study selection process

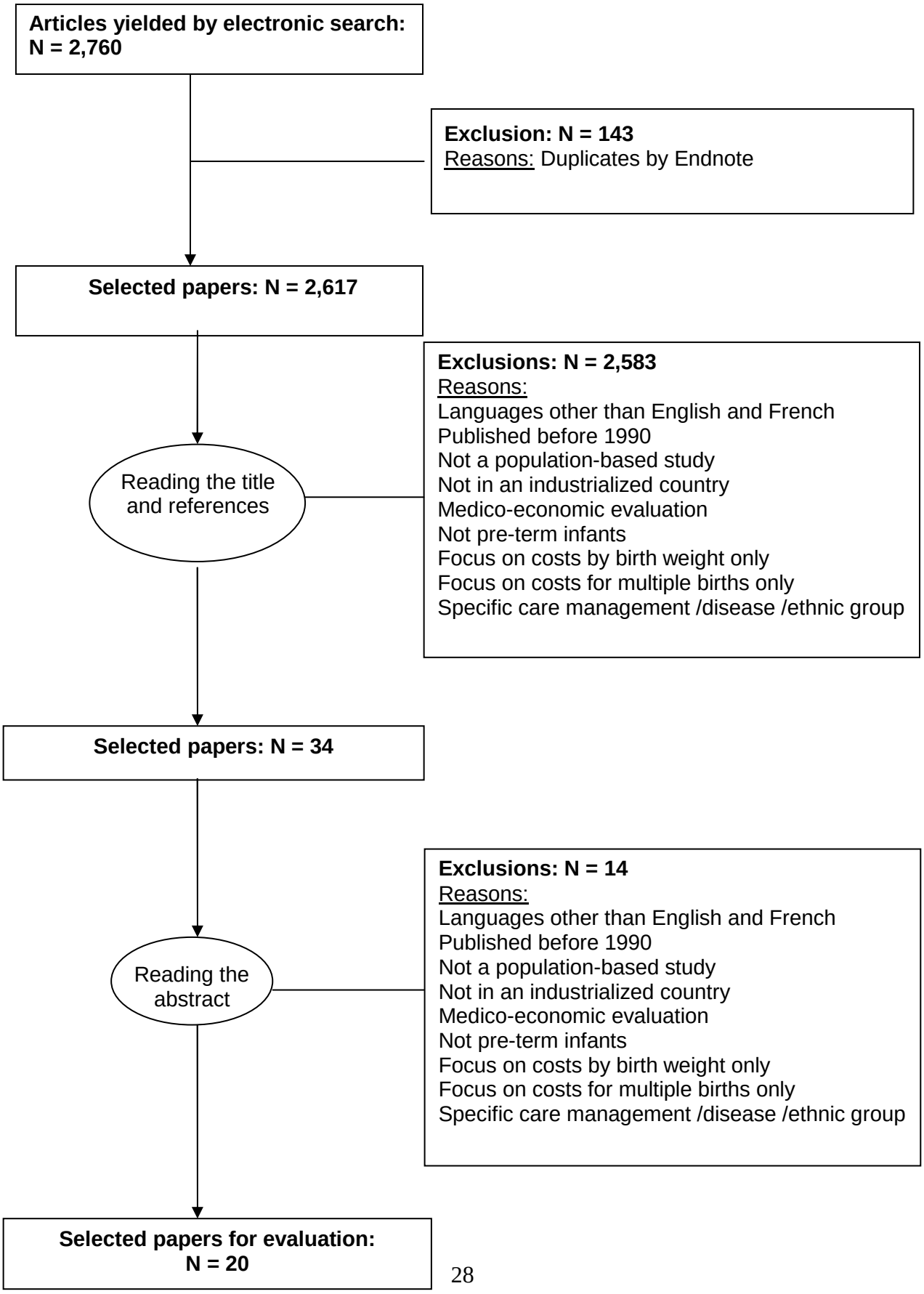

Table 1. Description of the population and study design

Author Year. country	Size of cohort	Date of birth	Follow-up period	Gestational ages	Source of cohort	Data collection	Number of centers
SHORT TERM PERIOD							
Luke *et al.*, 1996. USA[32]	95 twins ; 92 GA-sing.[a] ; 87 contrl-sing.[b]	01/07/ 1991 - 30/06/1992	To the day of discharge home for infant	[25-27]; [28-30] [31-34]; [35-38]	One institution's database	Retrospective	1 center
Feldman and Wood, 1997. USA[26]	310 high risk preterm	1992 - 1994	To Baby's discharge	[25-27]; [28-30] [31-34]; [35-37]	State-wide database	Retrospective	Multicenter
Kilpatrick *et al.*1997. USA[29]	138 preterm	1990 - 1994	Birth	24, 25, 26	One institution's database	Retrospective	1 center
St John *et al.*, 2000. USA[40]	621 preterm	1989 - 1992	Before the first discharge to home or prior death	24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36	2 institutions' database +A random sample of 30 infants	Retrospective	Multicenter
Elliott *et al.*, 2001. USA[25]	1,538 preterm	10/1995 - 02/2000	Prior to hospital discharge	34, 35, 36	National database	Retrospective	Multicenter
Gilbert *et al.*, 2003. USA[28]	41,137 preterm	01/01/1996 - 31/12/1996	Until they were sent home	25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36	State-wide database	Retrospective	Multicenter
Cuevas *et al.*, 2005. USA[24]	41 preterm	NS[c]	Through the first year of life	<26; [26-28] [29-32]; [33-36]	Original chart logs used in a randomized clinical trial	Retrospective	Multicenter
Phibbs and Schmitt, 2006. USA[38]	100,746 preterm	1998 - 2000	To the first discharge home or prior death	24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36	State-wide database	Retrospective	Multicenter
Geitona *et al.*, 2007. Greece[27]	92 preterm survivors	NS[c]	Within a 3-month period	[24-28]; [28-32] ≥ 32	Databases of two institutions	Prospective	Multicenter
Kirkby *et al.*, 2007. USA[30]	4,932 preterm	2001 - 2004	To 2 weeks after NICU[d] discharge	32, 33, 34	National care management database	Retrospective	Multicenter

Underwood *et al.*, 2007. USA[41]	263,883 preterm	1992 - 2000	First year of life	<25, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35	State-wide database	Retrospective	Multicenter
Russel *et al.*, 2007. USA[39]	384,000 preterm	NS[c]	Up to 1 year of age	<28 ; [28-36]	Nationwide Inpatient Sample	Retrospective	Multicenter
McLaurin *et al.*, 2009. USA[34]	4,225 preterm	2004	From the birth through the first year of life	[33-36]	National insurance database	Retrospective	Multicenter
MEDIUM TERM PERIOD							
Petrou *et al.*, 2003. USA[37]	239,694 preterm	01/01/1970 - 31/12/1993	First five years of life	<28; [28-31]; [32-36]	Regional database	Retrospective	Multicenter
Clements *et al.*, 2007. USA[23]	14,033 preterm	01/07/1999 - 30/06/2000	First three years	24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36[e] [24-31][f]; [32-36][f]	State-wide database	Retrospective	Multicenter
Korvenranta *et al.*, 2010. Finland[31]	588 preterm: 400 with morbidities ; 188 without	2001 - 2002	Fifth year of life	< 32	National databases + Questionnaire	Retrospective	Multicenter
LONG TERM PERIOD							
Petrou,2005.UK[8]	5,682 preterm	01/01/1979 - 31/12/1988	The first 10 years of life	< 28; [28-31]; [32-36]	Regional database	Retrospective	Multicenter
Petrou *et al.*, 2006. UK[36]	308 preterm	03/1995 – 12/1995	The 6th year after birth	≤ 23, 24, 25	National database + Questionnaire	Retrospective	Multicenter
Mangham *et al.*, 2009. England[33]	669,601 preterm	NS[c]	First 18 years of life	23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36	National databases + Literature	Retrospective	NS[c]
Petrou *et al.*, 2009. UK[35]	190 preterm	03/1995 – 12/1995	At 11 year of age	≤ 23, 24, 25	National database + Questionnaire	Retrospective	Multicenter

[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.

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

Author year country	Extreme prematurity (< 28 wGA)	Early prematurity (28-31 wGA)	Moderate prematurity (32-34 wGA)	Late prematurity (35-36 wGA)
	Mean cost[m]	Mean cost[m]	Mean cost[m]	Mean cost[m]
SHORT TERM PERIOD				
Luke *et al.*, 1996. USA[(32)]	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]
Feldman and Wood, 1997. USA[(26)]	125,546	75,063	22,443	7,870
Kilpatrick *et al.*, 1997. USA[(29)]	166,215 – 294,749	-	-	-
St John *et al.*, 2000. USA[(40)]	80,264 – 145,892	27,629 – 63,714	8,272 – 19,548	2,362 – 4,733
Elliott *et al.*, 2001. USA[(25)]	-	-	10,792	3,785 – 6;923
Gilbert *et al.*, 2003. USA[(28)]	119,600 - 202,700	29,800 – 86,200	7,200 – 18,900	2,600 – 4,200
Cuevas *et al.*, 2005. USA[(24)]	239,749	55,792	10,561	-
Phibbs and Schmitt, 2006. USA[(38)]	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]	3,359 – 5,751[d] 3,444 – 6,007[e]
Geitona *et al.*, 2007. Greece[(27)]	12,910	11,923	7,516	-
Kirkby *et al.*, 2007. USA[(30)]	-	-	22,575 – 43,667	-
Underwood *et al.*, 2007. USA[(41)]	19,531 – 21,462[f]	11,624 – 13,543[f]	8,102 – 9,924[f]	7,090[f]
Russel *et al.*, 2007. USA[(39)]	65,600	12,100	-	-
McLaurin *et al.*, 2009. USA[(34)]	-	-	38,301	-

MEDIUM TERM PERIOD				
Petrou*et al.*, 2003. USA[(37)]	20,743	21,382	6,658	-
Clements *et al.*, 2007. USA[(23)]	6,982 - 8,690[g] 4,819 [h]	3,245- 6,548[g] 1,437[h]	1,772- 2,994[g] -	1,191- 1,459[g]-
Korvenranta *et al.*, 2010. Finland[(31)]	1,078[i] 3,443[j]	-	-	-
LONG TERM PERIOD				
Petrou,2005.UK[(8)]	27,101	26,996	8,176	-
Petrou *et al.*, 2006. UK[(36)]	6,273 - 19,359	-	-	-
Mangham *et al.*, 2009. England[(33)]	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] -
Petrou *et al.*, 2009. UK[(35)]	9,629 – 11,800	-	-	-

[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.

Table 3. Economic design of the selected studies

Author year Country	Point of view	Expenditure items	Sources	Cost estimation	Denominator for mean cost calculation	Discounting	Management of Uncertainty
SHORT TERM PERIOD							
Luke *et al.*, 1996. USA[32]	Public/private insurers; parents	Hospital (pharmacy, radiology, inhalation therapy, NICU[b])	Bills		Infant	No	No
Feldman and Wood, 1997. USA[26]	Private insurers	Hospital, providers, ancillary	Claims paid		Survivor	No	No
Kilpatrick *et al.*1997. USA[29]	NS[a]	Hospital (ancillary services)	Bills	C/C ratio [c]	Survivor	No	No
St John *et al.*, 2000. USA[40]	NS[a]	Hospital charges and fees	Bills	C/C ratio [c]	Survivor	No	No
Elliott *et al.*, 2001. USA[25]	'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[28]	NS[a]	Hospital	Discharge summary	C/C ratio [c]	Survivor	No	No
Cuevas *et al.*, 2005. USA[24]	Public/private insurers; parents	Hospital charges	Charges data; statistics		Survivor	No	No
Phibbs and Schmitt, 2006. USA[38]	NS[a]	Hospital	Discharge summary	C/C ratio [c]	1.Survivor 2.Infant	No	No
Geitona *et al.*, 2007. Greece[27]	Public insurance system	Hospital (infrastructures, overheads, personnel, ancillary)	Prices public sector	Bottom up approach	Survivor	No	Yes
Kirkby *et al.*, 2007. USA[30]	Public/Private insurers	Health care plan for patient in NICU[b]: per diem charges and physicians' fees	Claims data		Infant	No	No
Underwood *et al.*,	NS[a]	Hospital	Discharge	C/C ratio[c]	Survivor	No	No

2007. USA[41]			summary				
Russel *et al.*, 2007. USA[39]	Public/private insurers; parents	Hospital	Discharge data	C/C ratio [c]	Infant	No	No
McLaurin *et al.*, 2009. USA[34]	Private insurers	Hospital (transfer, fees, medication, ...)	Claims reimbursed		Survivor	No	No
MEDIUM TERM PERIOD							
Petrou *et al.*, 2003. USA[37]	Hospital	Hospital specialty (Average revenue costs + revenue and capital overheads)	NHS Trust Financial Returns		Survivor	No	No
Clements *et al.*, 2007. USA[23]	Public/Private insurers	EI[d] program services; travels	Reimbursements + claims data		Survivor	Yes	No
Korvenranta *et al.*, 2010. Finland[31]	NS[a]	Hospital; outpatient; municipal and social services	Hospital data + other multiple sources		Survivor	No	No
LONG TERM PERIOD							
Petrou, 2005.UK[8]	Hospital	Hospital (Average revenue costs + revenue and capital overheads)	NHS Trust Financial Returns		Survivor	Yes	No
Petrou *et al.*, 2006. UK[36]	Society	Hospital ; health/social cares; drugs; education; family expenses; loss of earnings	NHS Trust Financial Returns + other multiple sources		Survivor	No	Yes
Mangham *et al.*, 2009. England[33]	Society	Hospital ; health/social cares; education	Multiple sources	Markov Model	Survivor	Yes	Yes
Petrou *et al.*, 2009. UK[35]	Society	Hospital; health/social; drugs; education	Multiple sources		Survivor	No	No

[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).

Appendix 1.List of key words used in each databank for the selection 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*.

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)).*

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. Populationof 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
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 measures	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) <u>Statistical model (regression)</u> Type of regression: 2) <u>Modeling</u> 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?

Appendix 3. Costs

Author year Country	Cost denominator	Money (year)	PPP[a]	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 PERIOD											
Luke *et al.*, 1996. USA[(32)]	Infant [c]	$US	No	[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]
Feldman and Wood, 1997. USA[(26)]	Survivors [c,g]	$US	No	[25-27]	$ 125,546	[28-30]	$ 75,063	[31-34]	$ 22,443	[35-37]	$ 7,870
Kilpatrick *et al.*1997. USA[(29)]	Survivors [c,h]	$US (1994)	No	24 25 26	$ 294,749 $ 181,062 $ 166,215						
St John *et al.*, 2000. USA[(40)]	Survivors [c]	$US	No	24 25 26 27	$145,892 $121,181 $ 99,362 $ 80,264	28 29 30 31	$ 63,714 $ 49,540 $ 37,569 $ 27,629	32 33 34	$ 19,548 $ 13,153 $ 8,272	35 36	$ 4,733 $ 2,362
Elliott *et al.*, 2001. USA[(25)]	Survivors [i, j]	$US	No					34	$ 10,792	35 36	$ 6,923 $ 3,785
Gilbert *et al.*, 2003. USA[(28)]	Survivors [j]	$US	No	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 $ 7,200	35 36	$ 4,200 $ 2,600
Cuevas *et al.*, 2005. USA[(24)]	Survivors [g, j]	$US	No	< 26 [26-28]	> $ 200,000 $ 239,749	[29-32]	$ 55,792	[33-36]	$ 10,561		

Phibbs and Schmitt, 2006. USA[38]	Survivors [c]	$ US (2003)	No	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	$ 5,751 $ 3,359
	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	$ 6,007 $ 3,444
Geitona *et al.*, 2007. Greece[27]	Survivors [c, h]	$US (2004)	Yes	[24-28[	$ 12,910	[28-32[	$ 11,923	≥ 32	$ 7,516		
Kirkby *et al.*, 2007. USA[30]	Infant [c, h]	$US	No					32 33 34	$ 43,667 $ 31,535 $ 22,575		
Underwood *et al.*, 2007. USA[41]	Survivors [j]	$US	No	<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	$ 9,924 $ 9,525 $ 8,102	35	$ 7,090
Russel *et al.*, 2007. USA[39]	Infant [c]	$US	No	< 28	$ 65,600	[28-36]	$ 12,100				
McLaurin *et al.*, 2009. USA[34]	Survivors [j]	$US	No					[33-36]	$ 38,301		
MEDIUM TERM PERIOD											
Petrou *et al.*, 2003. USA[37]	Survivors [c]	$ US (1999)	Yes	<28	$ 20,743	[28-31]	$ 21,382	[32-36]	$ 6,658		
Clements *et al.*, 2007. USA[23]	Survivors [c, k]	$US (2003)	No	24 25 26 27 [24-31]	$ 7,214[l] $ 8,690[l] $ 6,982[l] $ 7,211[l] $ 4,819[m]	28 29 30 31 [32-36]	$ 6,548[l] $ 5,217[l] $ 4,865[l] $ 3,245[l] $ 1,437[m]	32 33 34	$ 2,994[l] $ 2,601[l] $ 1,772[l]	35 36	$ 1,459[l] $ 1,191[l]

Korvenranta *et al.*, 2010. Finland[31]	Survivors [j]	$US (2008)	Yes			< 32 < 32	$ 1,078[n] $ 3,443[o]				
LONG TERM PERIOD											
Petrou, 2005.UK[8]	NS[p]	$US (1999)	Yes	<28	$ 27,101	[28-31]	$ 26,996	[32-36]	$ 8,176		
Petrou *et al.*, 2006. UK[36]	NS[p]	$ US (2003)	Yes	≤ 23 24 25	$ 19,359 $ 13,312 $ 6,273						
Mangham *et al.*, 2009. England[33]	Survivors [c]	$US (2006)	Yes	23 24 25 26 27	$ 446,440 $ 342,203 $ 217,122 $ 203,185 $ 199,718	28 29 30 31	$ 180,567 $ 165,773 $ 167,935 $ 150,403	32 33 34	$ 138,567 $ 114,641 $ 99,425	35 36	$ 85,534 $ 80,170
	Live birth [c]			< 28	$ 264,412	< 33	$ 167,618				
Petrou *et al.*, 2009. UK[35]	Survivors [j]	$US (2007)	Yes	≤ 23 24 25	$ 11,800 $ 10,711 $ 9,629						

[a] Purchasing Power Parity. [b] Gestational Age. [c] Initial population of survivors and non-survivors. [d] Costs for Ga-singletons only. [e] Costs for all twins + Ga-singletons + Ctrl 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.