

# **AN OVERVIEW OF HEALTH ECONOMIC ASPECTS OF LATE PRETERM AND EARLY TERM BIRTH**

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## **Abstract**

Despite an increasing body of knowledge on the adverse clinical sequelae associated with late preterm birth and early term birth, relatively little is known about their economic consequences or the cost-effectiveness of interventions aimed at their prevention or alleviation of their effects. This paper provides an overview of the health economic evidence surrounding late preterm and early term birth. The paper covers evidence surrounding hospital resource use associated with late preterm and early term birth, economic costs associated with late preterm and early term birth, and economic evaluations of prevention and treatment strategies. The paper highlights the limited perspective and time horizon of most studies of economic costs in this area. It also highlights the limited evidence surrounding health economic aspects of early term birth. The paper highlighting gaps in current knowledge and discusses directions for future research in this area, including the need for validated tools for measuring preference-based health-related quality of life outcomes in infants that will aid cost-effectiveness based decision making.

**Keywords:** Cost, cost-effectiveness, late preterm, early term

## Introduction

Preterm births, namely births before 37 completed weeks' gestation, or fewer than 259 days since the first day of the mother's last menstrual period [1], have traditionally been subdivided into a number of subcategories based on gestational age, ranging from extremely preterm birth (<28 weeks' gestation) to late preterm birth ( $34^{+0}$ - $36^{+6}$  weeks' gestation) [2]. More recently, births at term have been subdivided into early term births, which occur between  $37^{+0}$  and  $38^{+6}$  weeks' gestation, and births occurring at full term ( $39^{+0}$ - $41^{+6}$  weeks' gestation) [3]. A recent population-based retrospective analysis of singleton live births conducted in six high income countries revealed that late preterm birth rates during 2006-2014 were 4.8% in Canada, 3.6% in Denmark, 3.3% in Finland, 3.8% in Norway, 3.6% in Sweden, and 6.0% in the United States, whilst early term birth rates were 25.3% in Canada, 18.8% in Denmark, 16.8% in Finland, 17.2% in Norway, 18.7% in Sweden, and 26.9% in the United States [4]. The study provided evidence that late preterm and early term birth rates decreased in the United States over the study period, and an association was observed between early term birth rates and decreasing clinician-initiated obstetric interventions [4]. Of particular concern to clinicians, however, is the increased risk of adverse clinical sequelae during the neonatal period and later childhood associated with late preterm birth and early term birth. Epidemiological evidence suggests that infants born late preterm are at increased risk of acute respiratory disorders immediately after birth [5], delayed feeding development [6], early childhood mortality [7], neurodevelopmental disability at two years of age [8], and cognitive deficits [9], learning difficulties [10] and behaviour problems [9] at school age, when compared to full term infants. Infants born early term are also at increased risk of a host of adverse outcomes, including neonatal admissions [11], prolonged hospitalisations [12], health complications during early childhood [13, 14], and

developmental delay [15], when compared to full term infants. Although the adverse clinical sequelae during childhood associated with late preterm birth and early term birth are likely to affect several areas of the economy, little is known about their economic consequences or the cost-effectiveness of interventions aimed at their prevention or alleviation of their effects. Previous review articles of economic evidence have focussed on preterm birth in its entirety without recourse to the evidence surrounding early term birth, and focussed on economic costs rather than broad health economic aspects [16, 17]. This paper examines the health economic aspects of late preterm birth and early term birth, beginning with an overview of methods, and moving on to discussion of key evidence. It does not systematically review all evidence in the field, but rather highlights key evidence likely to be of interest to the clinical and academic communities.

### **An overview of health economic methods**

Cost-of-illness studies or studies of economic burden estimate the economic costs of a particular disease or condition or health state [18]. Applications can differ in terms of the categories of costs that they cover, which will depend on the study perspective. The perspective of an economic analysis typically falls into one of three categories, namely the healthcare system, public sector or societal. The study perspective should be informed by national methodological guidance; in England, for example, the National Institute for Health and Care Excellence (NICE) recommends including National Health Services (NHS) and personal social services as a minimum [19]. Applications to late preterm birth and early term birth may need to consider economic costs borne by several sectors of the economy, as well as for individuals. The sick infant may require support from social service departments, for example, upon their discharge from hospital. The parents of sick infants may have to forego

other productive activities (paid or unpaid work) in order to spend time with them; their transport costs to and from the neonatal unit may be considerable, and care for other children may have to be arranged. In contexts such as this, there is considerable value in also adopting a broader societal perspective, at least as part of a sensitivity analysis.

The total economic costs for a participant or individual within a cost-of-illness study or study of economic burden can be expressed as a compound formula:

$$C_i = \sum Q_{ij}.UC_j$$

where  $C_i$  represents the total cost for individual  $i$ ,  $Q_{ij}$  represents the quantity of resource item  $j$  by individual  $i$ , and  $UC_j$  represents the unit cost of resource item  $j$ . This requires the estimation of unit costs for each element of resource use consumed by the individual over the time horizon of interest. Quantities of resource can be estimated within the case report forms of randomised controlled trials, through extraction from routine health service information sources, or from primary surveys, reviews of published studies, or from expert opinion (Delphi panels). It is relatively unusual that a complete profile of resource use can be obtained from a single source.

Theoretically, unit costs attached to resource inputs should be based on the economic notion of opportunity cost, which represents the value of the resource in its most highly valued alternative use [19]. In the absence of competitive health markets, however, nationally representative health care tariffs, such as NHS Reference Costs, in England, for clinically similar treatments [20], and the compendia of unit costs covering hospital and community health and social care services [21], in England, are assumed to approximate to opportunity costs. In jurisdictions with systems of billing and fee-for-service payment of providers, market prices are deflated using cost-to-charge ratios to more accurately reflect opportunity costs [22]. There may be circumstances where unit cost estimates for health resources are not readily available and have to be generated from first principles using alternative approaches,

including time and motion studies, diary methods, work sampling, interviews with key caregivers, case note analysis and analyses of patient activity databases. The estimation of total economic costs requires unit cost estimates from previous years to be adjusted using a health care specific price index to reflect a more recent price level. In addition, any costs accruing beyond the first year of follow-up are normally discounted or reduced to present values to take account of differences in potential productivity of resources over time. A final analytic requirement is the need for sensitivity analysis to account for uncertainty surrounding elements of the cost estimation process or calculus.

Many health economists argue that cost-of-illness studies or studies of economic burden tell us about the scale, in economic terms, of a particular health problem [18]. However, they tell us little about prioritising finite resources as they do not evaluate interventions to address health or related needs or well-being associated with the disease or condition or health state of interest [18]. In contrast, health economic evaluation compares alternative interventions or programmes in terms of their costs and consequences. A common vehicle for the conduct of health economic evaluation is the randomised controlled trial where individual level costs and consequences are collected for the trial population [23]. However, trial-based economic evaluations have a number of limitations including potentially truncated time horizons, limited comparators, restricted generalisability to different settings or countries, and the failure to incorporate all relevant evidence [23]. As a result, decision analytic modelling, which involves application of mathematical techniques that synthesize data from multiple sources, including randomised controlled trials or studies with other designs, provides an alternative vehicle for the conduct of health economic evaluation [24].

There are four broad approaches to health economic evaluation, namely cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA). These alternative forms broadly adopt the same approach to cost

measurement and valuation, but differ in how consequences are measured and valued. CMA assumes that the competing interventions under consideration are equal with respect to consequences and that the study design allows the equivalence of consequences to be tested [25]. By implication, only costs are important in CMA and the least costly strategy is preferred. A CEA measures the consequences of competing interventions in natural or physical units. The outputs of a CEA are normally summarised in terms of an incremental cost effectiveness ratio (ICER), which represents the difference in costs between two interventions divided by the difference in effects. A CEA can only be used to compare interventions that produce the same kinds of consequences. It cannot be used to compare interventions whose consequences are measured in different units; for example, it cannot compare the treatment of late preterm infants, expressed in terms of acute respiratory disorder avoided, with clinically defined consequences of schizophrenia treatment or cancer treatment. To make these broader comparisons, a common “currency” for measuring consequences is needed. This can be achieved in two different ways, one leading to CUA and the other to CBA. In CUA, a common currency is achieved by valuing consequences using preference-based measures of health, such as quality-adjusted life years (QALYs), which attempt to capture health gains in a single metric combining life-years gained and health-related life-quality enhanced [26]. In CBA, the consequences of health interventions are measured and valued in monetary terms.

In an economic evaluation, a new intervention may turn out to be more effective but also more costly than usual practice, or conceivably may be less effective but also less costly than usual practice. A trade-off then exists between effect and cost. In CBA, this is dealt with by subtracting the incremental cost (relative to the comparator) from the incremental benefit on a linear scale where both are valued in the same monetary metric. Within CEA and CUA, however, the maximum willingness to pay for the unit of effect (the natural or physical unit

in the case of CEA and the QALY in the case of CUA) is required to determine whether the intervention is cost-effective. In England and Wales, for example, a maximum acceptable ICER of £20,000 to £30,000 per QALY gained is recommended for regulatory and reimbursement decisions [19].

The paper now turns to the health economic evidence surrounding late preterm and early term birth.

### **Hospital resource use associated with late preterm and early term birth**

Hospital resource use represents a major driver of additional economic costs associated with late preterm and early term birth. This is initially felt during the neonatal period. A retrospective cohort study of 38,807 singleton live births with no major congenital anomalies, delivered at 34–41 weeks of gestation to Canadian mothers in 2002–11, revealed that infants born late preterm and early term were at increased risk of neonatal intensive care unit admission [late preterm adjusted relative risk (aRR) = 6.14, 95% confidence interval (CI) 5.63, 6.71; early term aRR = 1.54, 95% CI 1.41, 1.68] compared to infants born at term [27]. This pattern varies across health systems and jurisdictions with differing clinical protocols [28].

Several studies have shown that infants born late preterm and early term are also at increased odds of hospital admission beyond the neonatal period and through early childhood [13, 29–32]. For example, a retrospective database analysis covering 599,753 liveborn infants born in New South Wales, Australia, between 2001 and 2007 and linked to hospital discharge records revealed that infants born late preterm and early term were at increased adjusted odds of one hospital readmission (adjusted odds ratio (aOR): 1.52 and 1.20, respectively) and more than one hospital readmission (aOR: 1.87 and 1.36, respectively) during the first year of



life, in comparison with infants born at full term [31]. A separate nation-wide population-based study of 696,698 liveborn infants that used a French medico-administrative database revealed that infants born at 34 weeks gestation and at 37 weeks gestation were at increased relative risk (2.2 (95% CI: 2.1, 2.4) and 1.3 (95% CI: 1.3, 1.3), respectively) of post-neonatal hospital admission during the first year of life, in comparison with infants born at full term [32]. Limited evidence suggests that the re-hospitalization risk remains elevated through later stages of childhood. A retrospective cohort study of all live singleton births in Western Australia dating back to 1980 and without congenital anomalies revealed incidence rate ratios for hospital admission of 1.33 (95%CI: 1.30, 1.36) and 1.13 (95%CI: 1.11, 1.14) between the 5<sup>th</sup> and 12<sup>th</sup> years of life and 1.14 (95%CI: 1.11, 1.18) and 1.08 (95%CI: 1.06, 1.10) between the 12<sup>th</sup> and 18<sup>th</sup> years of life for children born late preterm and early term, respectively, in comparison with children born at full term [33]. Common drivers for hospitalization in children born late preterm and early term included infection, injury, and respiratory related causes between the 5<sup>th</sup> and 12<sup>th</sup> years of life, and injury, oral cavity-related and infection between the 12<sup>th</sup> and 18<sup>th</sup> years of life [34]. Of further note is that some population based cohorts have revealed that infants born late preterm and early term are at also increased risk of hospital emergency department visit through childhood [35], which should be considered as an additional driver of economic costs.

### **Economic costs associated with late preterm and early term birth**

Table 1 provides an overview of 17 key studies published since 2000 that have estimated the economic costs associated with late preterm and early term birth [3, 36-51]. The table summarises the methods of each study, including the date of birth of the study population, location, type of study, sample size, comparator groups in terms of gestational ages at birth,

categories of economic costs considered, the currency and price date in which costs were estimated, and study time horizon. The table also summarizes the economic costs estimated by each study for relevant comparator groups. Where individual studies also estimated economic costs for infants born at earlier gestations (<34 weeks), the results for those gestational groups are not presented.

Seven studies reported economic costs associated with late preterm birth during the infant's initial hospitalization with the study perspective limited to the health sector [39, 41, 42, 47, 49-51]. A consistent inverse association was observed between gestational age at birth and initial hospitalization costs regardless of date of publication, country of publication, underpinning study design, costing methodology or the denominators applied within the cost calculus (live births or survivors). Two studies estimated a less than two-fold differential in initial hospitalization costs between infants born late term and a comparator group born at term ( $\geq 37$  weeks) [39, 49], whilst a further two studies estimated an 8-10 fold differential in initial hospitalization costs between infants born at 34 weeks gestation and those born at term [42, 50]. A further study analysed state-level linked vital statistics and hospital discharge records in California covering 84,540 infants born late preterm and 92,241 infants born at term [47]. The authors found that an intervention strategy that is effective at delaying delivery at 34 weeks gestation by one week (two weeks) would result in mean economic savings (in terms of neonatal costs prevented) of \$4,528 (\$7,090) (US\$, 2003 prices).

Ten studies reported health service costs associated with late preterm birth beyond the period of the infant's initial hospitalization [3, 36-38, 40, 43-46, 48]. As with interpretation of studies that focused on the costs associated with the initial hospitalisation, comparability of results across studies is complicated by a number of differences in study design. Notably, the period of follow-up varied between the first year of life [37, 44, 48] and the first eighteen years of life [43]. All studies generated an inverse relationship between gestational age at

birth and long-term health service costs, regardless of period of follow-up. Petrou and colleagues conducted analyses based on data extracted from the Oxford Record Linkage Study (ORLS), a large collection of linked, anonymised birth registrations, death certificates and statistical abstracts of NHS hospital inpatient and day-case admissions within Oxfordshire and West Berkshire in England. An initial analysis revealed a 3.3-fold differential in hospital service costs between infants born at 32-36 weeks gestation (without disaggregation into more granular categories) and those born at term, during the first five years of life [45]. A subsequent analysis that extended the period of follow-up to cover the first ten years of life revealed a 4.5-fold differential in hospital service costs between the same comparator groups, suggesting that the economic effects of impairment associated with moderate and late preterm birth do not dissipate during mid-childhood. Authors from the same research group subsequently developed a decision-analytic model that generated estimates of economic costs associated with late preterm birth, drawing upon evidence from the ORLS, as well as from other cohort studies [43]. The model estimated a mean incremental health and social care cost associated with late preterm birth of £10,498 (£ sterling, 2006 prices) during the childhood years. The model also revealed that mean education costs, parental expenses and the value of lost productivity as a result of the child's health state were all higher following late preterm birth than birth at term.

The studies by Lo *et al.* [42] and Helle *et al.* [3] provide granulated assessments of economic costs within gestational age categories of term-born infants, the former limited to the period of the initial hospitalization whilst the latter covered the first three years of life. The study by Lo *et al.* [42] was based on a retrospective chart analysis of 240,179 singleton deliveries in the United States and provided no indication of a significant difference in initial hospitalization costs for infants born early term compared to those born at full term. In contrast, the prospective cohort study by Helle *et al.* [3], conducted in Finland, showed that

children born early term had greater morbidity and health care costs in each year of the first three years of life compared with infants born at full term, with cost differences primarily driven by airway diseases and ophthalmological and motor problems.

### **Cost-effectiveness of prevention strategies**

The attendant problems and adverse clinical and economic sequelae of late preterm and early term birth have heightened interest in prevention strategies and their cost-effectiveness [52]. Strategies that involve identifying women at high risk of delivering early are constrained by low positive predictive values of existing prediction tests for symptomatic women with threatened preterm birth or for asymptomatic high risk women [52]. Tsoupras and colleagues conducted a decision-analytic modelling based economic evaluation to estimate the potential cost-effectiveness of alternative ‘test-and-treat’ strategies in the prevention of spontaneous preterm birth before 34 and 37 weeks’ gestation [53]. The model drew upon evidence from systematic reviews of clinical effectiveness and predictive accuracy studies. Prophylactic fish oil in asymptomatic women, without prior testing, was highlighted as potentially cost-effective in preventing threatened preterm labor before 34 weeks’ gestation. Furthermore, in symptomatic women with a viable pregnancy, indomethacin without prior testing was identified as a potentially cost-effective strategy to prevent preterm birth occurring before 37 weeks’ gestation.

Einerson and colleagues used a decision-analytic model to estimate the cost-effectiveness of risk-based screening compared to universal cervical length screening or no screening for preterm birth prevention in low-risk women [54]. The authors found that, in comparison to the risk-based strategy, universal screening was associated with an ICER of \$21,144 per QALY gained (US\$, 2014 prices). However, the authors’ analysis was

constrained by a paucity of validated tools for measuring infants' preference-based health-related life-quality outcomes for the purposes of QALY calculation.

Increasing interest in progesterone as a potential preventive intervention for preterm birth led Pizzi and colleagues to conduct an economic evaluation of vaginal progesterone gel [55]. Using a decision-analytic model informed by patient-level data from the PREGNANT trial, and which grouped women into gestational age categories, the authors estimated that vaginal progesterone was associated with cost savings and health benefits, expressed in terms of preterm birth averted. The authors' analysis would benefit from data included in a more recent meta-analysis of vaginal progesterone for preventing preterm birth [56].

Other analysts have examined the cost-effectiveness of prevention strategies implemented after 34 week's gestation in pregnancies complicated by specific disorders, such as gastroschisis [57] or non-severe hypertensive disorders [58]. These analyses inform the most cost-effective timing of delivery under differing clinical scenarios by balancing relative economic costs against the risk of stillbirth, neonatal death or maternal complications.

### **Cost-effectiveness of treatment strategies**

A number of pharmacological and surgical interventions, forms of developmental care, organisational approaches and other intervention strategies targeted at infants born late preterm or early term have been evaluated using randomised controlled trials and quasi-experimental designs. This accumulation of evidence on clinical effectiveness has been accompanied by a limited number of economic evaluations of treatment options. Petrou and colleagues conducted a trial-based economic evaluation of neonatal extracorporeal membrane oxygenation (ECMO), compared to conventional management, in mature (gestational age at birth  $\geq 35$  weeks, birth weight  $\geq 2000$  g) newborn infants with severe respiratory failure (oxygenation index  $\geq 40$ ) [59]. Data were collected about all major health service

resource inputs through trial case report forms, routine data sources and parental interviews. Deaths were captured by the trial monitoring procedures, whilst standardized neurodevelopmental assessments were performed in the homes of surviving infants by a single paediatrician. Over four years of follow-up, the incremental cost of neonatal ECMO was £16,707 (95% CI: £9828 to £37,924) per life year gained and £24,775 (95% CI: £13,106 to £69,690) per disability-free life year gained (£ sterling, 2001 prices). Notably, the authors highlight the lack of validated tools for QALY measurement in this age group, thereby limiting the potential for cost-effectiveness comparisons with interventions in other areas of health care. A subsequent economic evaluation conducted by the authors that was based on seven year follow-up data within the same trial estimated the incremental cost per disability-free life year gained associated with neonatal ECMO at £23,566 (£ sterling, 2002-3 prices). Xie and colleagues using a decision-analytic model to estimate the incremental cost-effectiveness of a system-based approach for the management of neonatal jaundice and the prevention of kernicterus in late-preterm and term ( $\geq 35$  weeks) infants, compared with the traditional practice based on visual inspection and selected bilirubin testing [60]. The incremental cost-effectiveness of the system-based approach was estimated at \$26,279 per life year gained and \$65,698 per QALY gained (Can\$, 2008 prices), but the QALY-based analysis was again constrained by a lack of validated tools for measuring infants' preference-based health-related life-quality outcomes.

A number of economic evaluations have estimated the cost-effectiveness of palivizumab as a prophylaxis against respiratory syncytial virus infection in moderate and late preterm infants with [61, 62] and without [63, 64] additional risk factors. All the evaluations concluded that palivizumab is a cost-effective prophylactic despite variations in the jurisdictions in which the evaluations were conducted and concomitant variations in health care practices.

## Discussion

Infants born late preterm are at increased risk of acute respiratory disorders immediately after birth [5], delayed feeding development [6], early childhood mortality [7], neurodevelopmental disability at two years of age [8], and cognitive deficits [9], learning difficulties [10] and behaviour problems [9] at school age, when compared to full term infants. Infants born early term are also at increased risk of a host of adverse outcomes, including neonatal admissions [11], prolonged hospitalisations [12], health complications during early childhood [13, 14], and developmental delay [15], when compared to full term infants. Given the adverse clinical sequelae associated with late preterm and early term birth, it is imperative to understand their potential economic consequences. This paper provides an overview of the health economic evidence on late preterm birth and early term birth.

Although the published data are sparse, they consistently show that the inverse association between gestational age at birth and economic costs observed at earlier gestations [16, 65] extends to later gestational ages at birth, regardless of study date, jurisdiction, underpinning study design, costing methodology, the denominators applied within the cost calculus or period of follow-up. It is noteworthy that existing economic research in this area is hampered by a paucity of epidemiological studies that accurately quantifies neonatal morbidity and longer term adverse outcomes, in particular for infants born early term, or that identify risk factors contributing to these outcomes. There is therefore a clear need for prospective, comprehensive data collection for infants born between 34 and 38 weeks' gestation to allow quantification of economic outcomes for this group. This is essential, first, to highlight areas in which changes in perinatal care may improve outcomes and, second, to inform efficient allocation of finite health care resources for children born at these gestational ages and their families.

Only three studies, to the knowledge of the authors, have attempted to quantify the non-health service costs associated with late preterm birth [38, 40, 43], whilst no attempt has been made to quantify the non-health service costs associated with early term birth. Where disaggregated cost values are presented, they suggest that non-health service costs borne by infants born late preterm exceed those borne by term-born infants. The potential to inform budgetary and service planning extends therefore to non-health service providers, such as social and education service providers. Moreover, there are several other categories of economic costs that could usefully be considered in future economic analyses. These include costs borne by local authorities and voluntary organisations, such as adaptations that have to be made to the child's home as a result of their impaired state of health, and additional costs borne by families and informal carers as a result of adjustments to their lifestyles and working patterns. Methods for estimating these broader economic costs include incorporating economic questionnaires and diaries into prospective cohort studies, although the value of these data should be balanced against the potential burden imposed on families.

Turning to economic evaluation, there are several prevention and treatment strategies surrounding late preterm and early term birth for which cost-effectiveness evidence is lacking, for example, cooling for newborns with hypoxic ischaemic encephalopathy [66], surfactant for meconium aspiration syndrome [67], and pulse oximetry screening for critical congenital heart defects [68]. Future randomised controlled trials of intervention strategies targeting late preterm and early infants, with and without additional risk factors, should ideally incorporate prospective economic evaluations, and measure and value both costs and health consequences over extended periods of follow-up. Such evidence is required to inform the efficient allocation of scarce resources. However, there will clearly be circumstances where randomised controlled trials will not be feasible and assessments of cost-effectiveness will have to be based on evidence from decision-analytic models. A particular



methodological challenge faced by these economic evaluations is the lack of validated tools for measuring preference-based health-related quality of life outcomes in infants.

Development of such tool will be needed to aid cost-effectiveness based decision-making using the incremental cost per QALY gained metric.

In conclusion, this paper provides an overview of health economic aspects of late preterm birth and early term birth. Future research should focus particularly on the economic costs associated with early term birth and the cost-effectiveness of strategies aimed at its prevention or amelioration of its effects.

**Conflicts of interest**

None

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## References

- [1] WHO: recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Modifications recommended by FIGO as amended October 14, 1976. *Acta Obstet Gynecol Scand* 1977;56:247-53.
- [2] Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet* 2012;379:2162-72. 10.1016/S0140-6736(12)60820-4
- [3] Helle E, Andersson S, Hakkinen U, Jarvelin J, Eskelinen J, Kajantie E. Morbidity and Health Care Costs After Early Term Birth. *Paediatr Perinat Epidemiol* 2016;30:533-40. 10.1111/ppe.12321
- [4] Richards JL, Kramer MS, Deb-Rinker P, Rouleau J, Mortensen L, Gissler M, et al. Temporal Trends in Late Preterm and Early Term Birth Rates in 6 High-Income Countries in North America and Europe and Association With Clinician-Initiated Obstetric Interventions. *JAMA* 2016;316:410-9. 10.1001/jama.2016.9635
- [5] Consortium on Safe Labor, Hibbard JU, Wilkins I, Sun L, Gregory K, Haberman S, et al. Respiratory morbidity in late preterm births. *JAMA* 2010;304:419-25. 10.1001/jama.2010.1015
- [6] Dodrill P, McMahon S, Ward E, Weir K, Donovan T, Riddle B. Long-term oral sensitivity and feeding skills of low-risk pre-term infants. *Early Hum Dev* 2004;76:23-37.
- [7] Crump C, Sundquist K, Sundquist J, Winkleby MA. Gestational age at birth and mortality in young adulthood. *JAMA* 2011;306:1233-40. 10.1001/jama.2011.1331
- [8] Johnson S, Evans TA, Draper ES, Field DJ, Manktelow BN, Marlow N, et al. Neurodevelopmental outcomes following late and moderate prematurity: a population-based cohort study. *Arch Dis Child Fetal Neonatal Ed* 2015;100:F301-8. 10.1136/archdischild-2014-307684

- [9] Talge NM, Holzman C, Wang J, Lucia V, Gardiner J, Breslau N. Late-preterm birth and its association with cognitive and socioemotional outcomes at 6 years of age. *Pediatrics* 2010;126:1124-31. 10.1542/peds.2010-1536
- [10] Lipkind HS, Slopen ME, Pfeiffer MR, McVeigh KH. School-age outcomes of late preterm infants in New York City. *Am J Obstet Gynecol* 2012;206:222 e1-6. 10.1016/j.ajog.2012.01.007
- [11] Sengupta S, Carrion V, Shelton J, Wynn RJ, Ryan RM, Singhal K, et al. Adverse neonatal outcomes associated with early-term birth. *JAMA Pediatr* 2013;167:1053-9. 10.1001/jamapediatrics.2013.2581
- [12] Engle WA, Kominiarek MA. Late preterm infants, early term infants, and timing of elective deliveries. *Clin Perinatol* 2008;35:325-41, vi. 10.1016/j.clp.2008.03.003
- [13] Boyle EM, Poulsen G, Field DJ, Kurinczuk JJ, Wolke D, Alfirevic Z, et al. Effects of gestational age at birth on health outcomes at 3 and 5 years of age: population based cohort study. *BMJ* 2012;344:e896. 10.1136/bmj.e896
- [14] Edwards MO, Kotecha SJ, Lowe J, Richards L, Watkins WJ, Kotecha S. Early-term birth is a risk factor for wheezing in childhood: A cross-sectional population study. *J Allergy Clin Immunol* 2015;136:581-7 e2. 10.1016/j.jaci.2015.05.005
- [15] Schonhaut L, Armijo I, Perez M. Gestational age and developmental risk in moderately and late preterm and early term infants. *Pediatrics* 2015;135:e835-41. 10.1542/peds.2014-1957
- [16] Petrou S, Eddama O, Mangham L. A structured review of the recent literature on the economic consequences of preterm birth. *Arch Dis Child Fetal Neonatal Ed* 2011;96:F225-32. 10.1136/adc.2009.161117
- [17] Petrou S, Khan K. Economic costs associated with moderate and late preterm birth: primary and secondary evidence. *Semin Fetal Neonatal Med* 2012;17:170-8. 10.1016/j.siny.2012.02.001
- [18] Byford S, Torgerson DJ, Raftery J. Economic note: cost of illness studies. *BMJ* 2000;320:1335.
- [19] National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. London, UK: NICE; 2013.
- [20] Department of Health. NHS reference costs 2012-2013. Appendix 1, National schedule of reference costs 2014.

- [21] Curtis L. Unit costs of health and social care 2013: Personal Social Services Research Unit; 2013.
- [22] Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in Health and Medicine. . New York, USA: Oxford University Press; 1996.
- [23] Petrou S, Gray A. Economic evaluation alongside randomised controlled trials: design, conduct, analysis, and reporting. *BMJ* 2011;342:d1548. 10.1136/bmj.d1548
- [24] Petrou S, Gray A. Economic evaluation using decision analytical modelling: design, conduct, analysis, and reporting. *BMJ* 2011;342:d1766. 10.1136/bmj.d1766
- [25] Briggs AH, O'Brien BJ. The death of cost-minimization analysis? *Health Econ* 2001;10:179-84. 10.1002/hec.584
- [26] Torrance GW, Feeny D. Utilities and quality-adjusted life years. *Int J Technol Assess Health Care* 1989;5:559-75.
- [27] Brown HK, Speechley KN, Macnab J, Natale R, Campbell MK. Neonatal morbidity associated with late preterm and early term birth: the roles of gestational age and biological determinants of preterm birth. *Int J Epidemiol* 2014;43:802-14. 10.1093/ije/dyt251
- [28] Loftin RW, Habli M, Snyder CC, Cormier CM, Lewis DF, Defranco EA. Late preterm birth. *Rev Obstet Gynecol* 2010;3:10-9.
- [29] Ray KN, Lorch SA. Hospitalization of early preterm, late preterm, and term infants during the first year of life by gestational age. *Hosp Pediatr* 2013;3:194-203.
- [30] Dietz PM, Rizzo JH, England LJ, Callaghan WM, Vesco KK, Bruce FC, et al. Early term delivery and health care utilization in the first year of life. *J Pediatr* 2012;161:234-9 e1. 10.1016/j.jpeds.2012.02.005
- [31] Lain SJ, Nassar N, Bowen JR, Roberts CL. Risk factors and costs of hospital admissions in first year of life: a population-based study. *J Pediatr* 2013;163:1014-9. 10.1016/j.jpeds.2013.04.051
- [32] Iacobelli S, Combi E, Roussot A, Cottenet J, Gouyon JB, Quantin C. Gestational age and 1-year hospital admission or mortality: a nation-wide population-based study. *BMC Pediatr* 2017;17:28. 10.1186/s12887-017-0787-y

- [33] Slimings C, Einarsdottir K, Srinivasjois R, Leonard H. Hospital admissions and gestational age at birth: 18 years of follow up in Western Australia. *Paediatr Perinat Epidemiol* 2014;28:536-44. 10.1111/ppe.12155
- [34] Srinivasjois R, Slimings C, Einarsdottir K, Burgner D, Leonard H. Association of Gestational Age at Birth with Reasons for Subsequent Hospitalisation: 18 Years of Follow-Up in a Western Australian Population Study. *PLoS One* 2015;10:e0130535. 10.1371/journal.pone.0130535
- [35] Corchia C, Lapucci E, Franco F, Farchi S, Petrou S, Di Lallo D. Gestational age and hospital utilization: three-years follow-up of an area-based birth cohort. *Ann Ist Super Sanita* 2016;52:543-9. 10.4415/ANN\_16\_04\_14
- [36] Berard A, Le Tiec M, De Vera MA. Study of the costs and morbidities of late-preterm birth. *Arch Dis Child Fetal Neonatal Ed* 2012;97:F329-34. 10.1136/fetalneonatal-2011-300969
- [37] Bird TM, Bronstein JM, Hall RW, Lowery CL, Nugent R, Mays GP. Late preterm infants: birth outcomes and health care utilization in the first year. *Pediatrics* 2010;126:e311-9. 10.1542/peds.2009-2869
- [38] Clements KM, Barfield WD, Ayadi MF, Wilber N. Preterm birth-associated cost of early intervention services: an analysis by gestational age. *Pediatrics* 2007;119:e866-74. 10.1542/peds.2006-1729
- [39] Gilbert WM, Nesbitt TS, Danielsen B. The cost of prematurity: quantification by gestational age and birth weight. *Obstet Gynecol* 2003;102:488-92.
- [40] Khan KA, Petrou S, Dritsaki M, Johnson SJ, Manktelow B, Draper ES, et al. Economic costs associated with moderate and late preterm birth: a prospective population-based study. *BJOG* 2015;122:1495-505. 10.1111/1471-0528.13515
- [41] Lim G, Tracey J, Boom N, Karmakar S, Wang J, Berthelot JM, et al. CIHI survey: Hospital costs for preterm and small-for-gestational age babies in Canada. *Healthc Q* 2009;12:20-4.
- [42] Lo J MK, Henry E, Weng HY, Hopkins P, Esplin MS. The cost of prematurity: The association between gestational age at delivery and overall neonatal cost. *Reprod Sci* 2011;18:377A.
- [43] Mangham LJ, Petrou S, Doyle LW, Draper ES, Marlow N. The cost of preterm birth throughout childhood in England and Wales. *Pediatrics* 2009;123:e312-27. 10.1542/peds.2008-1827

- [44] McLaurin KK, Hall CB, Jackson EA, Owens OV, Mahadevia PJ. Persistence of morbidity and cost differences between late-preterm and term infants during the first year of life. *Pediatrics* 2009;123:653-9. 10.1542/peds.2008-1439
- [45] Petrou S, Mehta Z, Hockley C, Cook-Mozaffari P, Henderson J, Goldacre M. The impact of preterm birth on hospital inpatient admissions and costs during the first 5 years of life. *Pediatrics* 2003;112:1290-7.
- [46] Petrou S. The economic consequences of preterm birth during the first 10 years of life. *BJOG* 2005;112 Suppl 1:10-5. 10.1111/j.1471-0528.2005.00577.x
- [47] Phibbs CS, Schmitt SK. Estimates of the cost and length of stay changes that can be attributed to one-week increases in gestational age for premature infants. *Early Hum Dev* 2006;82:85-95. 10.1016/j.earlhumdev.2006.01.001
- [48] Ringborg A, Berg J, Norman M, Westgren M, Jonsson B. Preterm birth in Sweden: what are the average lengths of hospital stay and the associated inpatient costs? *Acta Paediatr* 2006;95:1550-5. 10.1080/08035250600778636
- [49] St John EB, Nelson KG, Cliver SP, Bishnoi RR, Goldenberg RL. Cost of neonatal care according to gestational age at birth and survival status. *Am J Obstet Gynecol* 2000;182:170-5.
- [50] van Baaren GJ, Peelen MJ, Schuit E, van der Post JA, Mol BW, Kok M, et al. Preterm birth in singleton and multiple pregnancies: evaluation of costs and perinatal outcomes. *Eur J Obstet Gynecol Reprod Biol* 2015;186:34-41. 10.1016/j.ejogrb.2014.12.024
- [51] Xu X, Grigorescu V, Siefert KA, Lori JR, Ransom SB. Cost of racial disparity in preterm birth: evidence from Michigan. *J Health Care Poor Underserved* 2009;20:729-47. 10.1353/hpu.0.0180
- [52] Shennan AH. Prediction and prevention of preterm birth: a quagmire of evidence. *Ultrasound Obstet Gynecol* 2018;51:569-70. 10.1002/uog.19063
- [53] Tsourapas A, Roberts TE, Barton PM, Honest H, Forbes C, Hyde CJ, et al. An economic evaluation of alternative test-intervention strategies to prevent spontaneous pre-term birth in singleton pregnancies. *Acta Obstet Gynecol Scand* 2009;88:1319-30. 10.3109/00016340903410873

- [54] Einerson BD, Grobman WA, Miller ES. Cost-effectiveness of risk-based screening for cervical length to prevent preterm birth. *Am J Obstet Gynecol* 2016;215:100 e1-7. 10.1016/j.ajog.2016.01.192
- [55] Pizzi LT, Seligman NS, Baxter JK, Jutkowitz E, Berghella V. Cost and cost effectiveness of vaginal progesterone gel in reducing preterm birth: an economic analysis of the PREGNANT trial. *Pharmacoeconomics* 2014;32:467-78. 10.1007/s40273-014-0133-2
- [56] Romero R, Conde-Agudelo A, Da Fonseca E, O'Brien JM, Cetingoz E, Creasy GW, et al. Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data. *Am J Obstet Gynecol* 2018;218:161-80. 10.1016/j.ajog.2017.11.576
- [57] Harper LM, Goetzinger KR, Biggio JR, Macones GA. Timing of elective delivery in gastroschisis: a decision and cost-effectiveness analysis. *Ultrasound Obstet Gynecol* 2015;46:227-32. 10.1002/uog.14721
- [58] van Baaren GJ, Broekhuijsen K, van Pampus MG, Ganzevoort W, Sikkema JM, Woiski MD, et al. An economic analysis of immediate delivery and expectant monitoring in women with hypertensive disorders of pregnancy, between 34 and 37 weeks of gestation (HYPITAT-II). *BJOG* 2017;124:453-61. 10.1111/1471-0528.13957
- [59] Petrou S, Edwards L, Trial UKCE. Cost effectiveness analysis of neonatal extracorporeal membrane oxygenation based on four year results from the UK Collaborative ECMO Trial. *Arch Dis Child Fetal Neonatal Ed* 2004;89:F263-8.
- [60] Xie B, da Silva O, Zaric G. Cost-effectiveness analysis of a system-based approach for managing neonatal jaundice and preventing kernicterus in Ontario. *Paediatr Child Health* 2012;17:11-6.
- [61] Lazaro y de Mercado P, Figueras Aloy J, Domenech Martinez E, Echaniz Urcelay I, Closa Monasterolo R, Wood Wood MA, et al. [The efficiency (cost-effectiveness) of palivizumab as prophylaxis against respiratory syncytial virus infection in premature infants with a gestational age of 32-35 weeks in Spain]. *An Pediatr (Barc)* 2006;65:316-24.



- [62] Nuijten MJ, Wittenberg W, Lebmeier M. Cost effectiveness of palivizumab for respiratory syncytial virus prophylaxis in high-risk children: a UK analysis. *Pharmacoeconomics* 2007;25:55-71.
- [63] Lanctot KL, Masoud ST, Paes BA, Tarride JE, Chiu A, Hui C, et al. The cost-effectiveness of palivizumab for respiratory syncytial virus prophylaxis in premature infants with a gestational age of 32-35 weeks: a Canadian-based analysis. *Curr Med Res Opin* 2008;24:3223-37. 10.1185/03007990802484234
- [64] Bentley A, Filipovic I, Gooch K, Busch K. A cost-effectiveness analysis of respiratory syncytial virus (RSV) prophylaxis in infants in the United Kingdom. *Health Econ Rev* 2013;3:18. 10.1186/2191-1991-3-18
- [65] Petrou S, Sach T, Davidson L. The long-term costs of preterm birth and low birth weight: results of a systematic review. *Child Care Health Dev* 2001;27:97-115.
- [66] Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev* 2013:CD003311. 10.1002/14651858.CD003311.pub3
- [67] El Shahed AI, Dargaville PA, Ohlsson A, Soll R. Surfactant for meconium aspiration syndrome in term and late preterm infants. *Cochrane Database Syst Rev* 2014:CD002054. 10.1002/14651858.CD002054.pub3
- [68] Plana MN, Zamora J, Suresh G, Fernandez-Pineda L, Thangaratinam S, Ewer AK. Pulse oximetry screening for critical congenital heart defects. *Cochrane Database Syst Rev* 2018;3:CD011912. 10.1002/14651858.CD011912.pub2

**Table 1: Studies published since 2000 reporting economic costs associated with late preterm birth and early term birth**

Study	Date of birth of study population	Location	Type of study	Sample size	Gestational age(s) (weeks)	Type of economic costs	Currency, price date	Time horizon	Results <sup>±</sup>
Berard <i>et al</i> [36]	1997-2000	Canada (Quebec)	Retrospective cohort study	33-36 weeks: 2176 ≥37 weeks: 33,879	33-36 ≥37	Hospitalisation, physician visits, emergency department visits and prescriptions following initial hospitalisation	Can\$, 2003	First three years of life	33-36 weeks: Re-hospitalisations: 1727 Physician visits: 977 Emergency department visits: 2 Prescriptions: 388 ≥37 weeks: Re-hospitalisations: 628 Physician visits: 766 Emergency department visits: 1 Prescriptions: 257
Bird <i>et al</i> [37]	2001-2005	USA (Arkansas)	Retrospective analysis of Medicaid claims database	34-36 weeks: 5188 37-42 weeks: 15,303	34-36 37-42	Hospital inpatient and outpatient care	US\$, price date not specified	First year of life	Inpatient cost per survivor: 34-36: 3027 37-42: 2183 Outpatient cost per survivor: 34-36: 1560 37-42: 1316 Total health care cost per survivor: 34-36: 4541 37-42: 3472
Clements <i>et al</i> [38]	1999-2000	USA (Massachusetts)	Retrospective analysis of claims database	34-36 weeks: 5682 ≥37 weeks: 69,274	34-36 ≥37	Health and social services	US\$, 2003	Initial discharge to three years	Mean cost per survivor: 34-36: 1372 ≥37: 725
Gilbert <i>et al</i> [39]	1996	USA (California)	Retrospective analysis of state-level linked vital statistics and discharge records	34-36 weeks: 32,295 ≥37 weeks: 106,087	34-36 ≥37	Hospital	US\$, price date not specified	Initial hospitalization	Mean cost per survivor: 34-36 weeks: 7,232 ≥37 weeks: 3,860

Helle <i>et al</i> [3]	2006-2008	Finland (Municipalities of Helsinki, Espoo, Vantaa)	Prospective cohort study	34-36 weeks: 1164 37-38 weeks: 4586 39-41 weeks: 21,812 >41 weeks: 2005	34-36 37-38 39-41 >41	Specialized care, primary care, private health care, medications	€, 2011	First three years of life	Median cost per survivor: 34-36 weeks: 5621 37-38 weeks: 2987 39-41 weeks: 2700 >41 weeks: 2679
Khan <i>et al</i> [40]	2009-10	UK (East Midlands)	Prospective cohort study	34-36 weeks: 984 ≥37 weeks: 1258	34-36 ≥37	Postnatal, neonatal, transfers, post-mortems, surgery, investigations, community care, special equipment, adaptations, lost earnings	£, 2010-11	First two years of life	34-36 weeks: Neonatal care: 2827.01; Other hospital care: 1642.21; Community care: 1059.32; Medications: 7.15; Lost earnings: 255.95; Special equipment: 4.87; Adaptations: 26.97; Total health services: 5535.70; Total societal: 5823.49 ≥37 weeks: Neonatal care: 172.66; Other hospital care: 673.76, Community care: 1005.24; Medications: 7.99; Lost earnings: 155.86 Special equipment: 3.32; Adaptations: 36.70; Total health services: 1859.65; Total societal: 2055.52
Lim <i>et al</i> [41]	2005-2006	Canada	Retrospective national register study	Singletons: 34-36 weeks: 9716 ≥37 weeks: 189,750 Multiples: 34-36 weeks: 2370 ≥37 weeks: 2742	34-36 ≥37	Hospital	Can\$, price date not specified	Initial hospital-ization	34-36 weeks: 5047 (singletons) 6494 (multiples) ≥37 weeks: 1050 (singletons) 1871 (multiples)
Lo <i>et al</i> [42]	2000-2008	USA	Retrospective chart analysis	Singleton deliveries: 240,179	24-42	Hospital	US\$, price date not specified	Initial hospital-ization	34 weeks: 9740 35 weeks: 5015 36 weeks: 2413

									37 weeks: 1469 38 weeks: 1070 39 weeks: 994 40 weeks: 1017 41 weeks: 1058 42 weeks: 1072
Mangham <i>et al</i> [43]	2006	England and Wales	Decision-analytic model populated with data from administrative population-based databases	34-36 weeks: 32,812 ≥37 weeks: 621,618	34-36 ≥37	Hospital inpatient, hospital outpatient, community health and social care, education services	£, 2006	First 18 years of life	34 weeks: 60,437 35 weeks: 52,086 36 weeks: 49,029 ≥37 weeks: 41,813
McLaurin <i>et al</i> [44]	2004	USA	Retrospective analysis of insurance database	33-36 weeks: 1683 ≥37 weeks: 33,745	33-36 ≥37	Inpatient hospitalisations, well-infant physician office visits, outpatient hospital services, home health/private nurse, acute care physician office visits, prescription drugs, other professional	US\$, price date not specified	First year of life	Initial hospitalization: 33-36 weeks: 26,054 ≥37 weeks: 2087 Following initial discharge: 33-36 weeks: 12,247 ≥37 weeks: 4069
Petrou <i>et al</i> [45]	1970-1993	UK (Oxfordshire and West Berkshire)	Retrospective analysis of linked vital statistics and NHS records financial returns	32-36 weeks: 11,728 ≥37 weeks: 226,120	32-36 ≥37	Hospital inpatient services	£, 1998-99	First five years of life	32-36 weeks: 4378 ≥37 weeks: 1333
Petrou <i>et al</i> [46]	1978-1988	UK (Oxfordshire and West Berkshire)	Retrospective analysis of linked vital statistics and NHS records financial returns	32-36 weeks: 4485 ≥37 weeks: 90,236	32-36 ≥37	Hospital inpatient services	£, 1998-99	First five years of life	32-36 weeks: 7394 ≥37 weeks: 1659

Phibbs and Schmitt [47]	1998-2000	USA (California)	Retrospective analysis of state-level linked vital statistics and discharge records	34-36 weeks: 84,540 ≥37 weeks: 92,421	34-36 ≥37	Hospital	US\$, 2003	Initial hospital-ization	34-36 weeks: 5,424 ≥37 weeks: 2,027
Ringborg <i>et al</i> [48]	1998-2001	Sweden	Retrospective analysis of hospital discharge records	34-36 weeks: 4727 ≥37 weeks: 16,852	34-36 ≥37	Hospital	€, 2001	First year of life	Inpatient cost per survivor: 34-36 weeks: 14,177 ≥37 weeks: 6,801
St John <i>et al</i> [49]	1989-1992	USA (Alabama)	Retrospective analysis of hospital charts and billing database	34-36 weeks: 103 ≥37 weeks: 197	34-36 ≥37	Hospital	US\$, price date not specified	Initial hospital-ization	34-36 weeks: 10,961 ≥37 weeks: 6,953
van Baaren <i>et al</i> [50]	2006-2012	Netherlands	Retrospective analysis of one prospective cohort study and three randomised controlled trials	4,552 1090 singletons 3462 multiples	24-28 28-32 32-36 ≥37	Hospital	€, 2011	Initial hospital-ization	34 weeks: Singletons: 11,222; multiples: 21,457 35 weeks: Singletons: 6492; multiples: 14,306 36 weeks: Singletons: 2924; multiples: 8618 ≥37 weeks: Singletons: 1434; multiples: 5201
Xu <i>et al</i> [51]	2003	USA (Michigan)	Retrospective analysis of regional birth cohort	<37 weeks: 9780 ≥37 weeks: 101,484	≥20	Hospital	US\$, 2007	Initial hospital-ization	34 weeks: 18,617 35 weeks: 15,864 36 weeks: 12,305 ≥37 weeks: 6368

± Cost per live birth unless otherwise stated.