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# 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, little is known about their economic consequences or the cost-effectiveness of interventions aimed at their prevention or alleviation of their effects. This review assesses the health economic evidence surrounding late preterm and early term birth. Evidence is gathered on 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 article highlights the limited perspective and time horizon of most studies of economic costs in this area; the limited evidence surrounding health economic aspects of early term birth; the gaps in current knowledge; and it 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.

## 1. 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 subcategories based on gestational age, ranging from extremely preterm birth (< 28 weeks gestation) to late preterm birth ($34^{+0}$ to $36^{+6}$ 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 ($39^{+0}$ to $41^{+6}$ 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 USA, whereas 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 USA [4]. The study provided evidence that late preterm and early term birth rates decreased in the USA 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 hospitalizations [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 the prevention or alleviation of their effects. Previous review articles of economic evidence have focused on preterm birth in its entirety without recourse to the evidence surrounding early term birth, and focused on economic costs rather than broad health economic aspects [16,17]. This article 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.

## 2. 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 may 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

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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 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:

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

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 randomized 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 prioritizing 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]. By 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 randomized controlled trial in which 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 generalizability to different settings or countries, and the failure to incorporate all relevant evidence [23]. Thus, decision analytic modelling, which involves application of mathematical techniques that synthesize data from multiple sources, including randomized 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 they 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. CEA measures the consequences of competing interventions in natural or physical units. The outputs of CEA are normally summarized in terms of an incremental cost-effectiveness ratio (ICER), which represents the difference in costs between two interventions divided by the difference in effects. 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 represent an 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].

## 3. 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 are 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 nationwide 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 (1.11–1.14) between the 5th and 12th years of life and 1.14 (1.11–1.18) and 1.08 (1.06–1.10) between the 12th and 18th 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 5th and 12th years of life, and injury, oral cavity-related and infection between the 12th and 18th years of life [34]. Some population-based cohorts have revealed that infants born late preterm and early term are also at increased risk of hospital emergency department visit through childhood [35], which should be considered as an additional driver of economic costs.

## 4. Economic costs associated with late preterm and early term birth

Table 1 lists 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 summarizes 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 economic costs estimated by each study for relevant comparator groups are also summarized. 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 (≥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 $4528 ($7090) (US$, 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 hospitalization, comparability of results across studies is complicated by several differences in study design. Notably, the period of follow-up varied between the first year of life [37,44,48] and the first 18 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, anonymized 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 10 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 (2006 prices) during the childhood years. The model also revealed that mean education costs, parental expenses and the value of lost productivity due to 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 whereas 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 USA and gave 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.

## 5. 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 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

**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 | Cost per live birth (unless otherwise stated) |
|---|---|---|---|---|---|---|---|---|---|
| Berard et al. [36] | 1997–2000 | Canada (Québec) | Retrospective cohort study | 33–36 weeks: 2176<br>≥37 weeks: 33,879 | 33–36<br>≥37 | Hospitalization, physician visits, emergency department visits and prescriptions following initial hospitalization | Can$, 2003 | First three years of life | 33–36 weeks:<br>Re-hospitalizations: 1727<br>Physician visits: 977<br>Emergency department visits: 2<br>Prescriptions: 388<br>≥37 weeks:<br>Re-hospitalizations: 628<br>Physician visits: 766<br>Emergency department visits: 1<br>Prescriptions: 257 |
| Bird et al. [37] | 2001–2005 | USA (Arkansas) | Retrospective analysis of Medicaid claims database | 34–36 weeks: 5188<br>37–42 weeks: 15,303 | 34–36<br>37–42 | Hospital inpatient and outpatient care | US$, price date not specified | First year of life | Inpatient cost per survivor:<br>34–36 weeks: 3027<br>37–42 weeks: 2183<br>Outpatient cost per survivor:<br>34–36 weeks: 1560<br>37–42 weeks: 1316<br>Total health care cost per survivor:<br>34–36 weeks: 4541<br>37–42: 3472 |
| Clements et al. [38] | 1999–2000 | USA (Massachusetts) | Retrospective analysis of claims database | 34–36 weeks: 5682<br>≥37 weeks: 69,274 | 34–36<br>≥37 | Health and social services | US$, 2003 | Initial discharge to three years | Mean cost per survivor:<br>34–36 weeks: 1372<br>≥37 weeks: 725 |
| Gilbert et al. [39] | 1996 | USA (California) | Retrospective analysis of state-level linked vital statistics and discharge records | 34–36 weeks: 32,295<br>≥37 weeks: 106,087 | 34–36<br>≥37 | Hospital | US$, price date not specified | Initial hospitalization | Mean cost per survivor:<br>34–36 weeks: 7232<br>≥37 weeks: 3860 |
| Helle et al. [3] | 2006–2008 | Finland (municipalities of Helsinki, Espoo, Vantaa) | Prospective cohort study | 34–36 weeks: 1164<br>37–38 weeks: 4586<br>39–41 weeks: 21,812<br>> 41 weeks: 2005 | 34–36<br>37–38<br>39–41<br>> 41 | Specialized care, primary care, private health care, medications | €, 2011 | First three years of life | Median cost per survivor:<br>34–36 weeks: 5621<br>37–38 weeks: 2987<br>39–41 weeks: 2700<br>> 41 weeks: 2679 |
| Khan et al. [40] | 2009–2010 | UK (East Midlands) | Prospective cohort study | 34–36 weeks: 984<br>≥37 weeks: 1258 | 34–36<br>≥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:<br>Neonatal care: 2827.01<br>Other hospital care: 1642.21<br>Community care: 1059.32<br>Medications: 7.15<br>Lost earnings: 255.95<br>Special equipment: 4.87<br>Adaptations: 26.97 |

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**Table 1** (*continued*)

| 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 | Cost per live birth (unless otherwise stated) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Total health services: 5535.70<br>Total societal: 5823.49<br>≥37 weeks:<br>Neonatal care: 172.66<br>Other hospital care: 673.76<br>Community care: 1005.24<br>Medications: 7.99<br>Lost earnings: 155.86<br>Special equipment: 3.32<br>Adaptations: 36.70<br>Total health services: 1859.65<br>Total societal: 2055.52 |
| Lim et al. [41] | 2005–2006 | Canada | Retrospective national register study | Singletons:<br>34–36 weeks: 9716<br>≥37 weeks: 189,750<br>Multiples:<br>34–36 weeks: 2370<br>≥37 weeks: 2742 | 34–36<br>≥37 | Hospital | Can$, price date not specified | Initial hospitalization | 34–36 weeks:<br>5047 (singletons)<br>6494 (multiples)<br>≥37 weeks:<br>1050 (singletons)<br>1871 (multiples) |
| Lo et al. [42] | 2000–2008 | USA | Retrospective chart analysis | Singleton deliveries: 240,179 | 24–42 | Hospital | US$, price date not specified | Initial hospitalization | 34 weeks: 9740<br>35 weeks: 5015<br>36 weeks: 2413<br>37 weeks: 1469<br>38 weeks: 1070<br>39 weeks: 994<br>40 weeks: 1017<br>41 weeks: 1058<br>42 weeks: 1072 |
| Mangham et al. [43] | 2006 | England and Wales | Decision-analytic model populated with data from administrative population-based databases | 34–36 weeks: 32,812<br>≥37 weeks: 621,618 | 34–36<br>≥37 | Hospital inpatient, hospital outpatient, community health and social care, education services | £, 2006 | First 18 years of life | 34 weeks: 60,437<br>35 weeks: 52,086<br>36 weeks: 49,029<br>≥37 weeks: 41,813 |
| McLaurin et al. [44] | 2004 | USA | Retrospective analysis of insurance database | 33–36 weeks: 1683<br>≥37 weeks: 33,745 | 33–36<br>≥37 | Inpatient hospitalizations, 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:<br>33–36 weeks: 26,054<br>≥37 weeks: 2087<br>Following initial discharge:<br>33–36 weeks: 12,247<br>≥37 weeks: 4069 |
| Petrou et al. [45] | 1970–1993 | UK (Oxfordshire and West Berkshire) | Retrospective analysis of linked vital statistics and NHS records financial returns | 32–36 weeks: 11,728<br>≥37 weeks: 226,120 | 32–36<br>≥37 | Hospital inpatient services | £, 1998–99 | First five years of life | 32–36 weeks: 4378<br>≥37 weeks: 1333 |
| Petrou et al. [46] | 1978–1988 | UK (Oxfordshire and West Berkshire) | Retrospective analysis of linked vital statistics and NHS records, financial returns | 32–36 weeks: 4485<br>≥37 weeks: 90,236 | 32–36<br>≥37 | Hospital inpatient services | £, 1998–99 | First five years of life | 32–36 weeks: 7394<br>≥37 weeks: 1659 |

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**Table 1** (*continued*)

| 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 | Cost per live birth (unless otherwise stated) |
|---|---|---|---|---|---|---|---|---|---|
| Phibbs and Schmitt [47] | 1998–2000 | USA (California) | Retrospective analysis of state-level, linked vital statistics and discharge records | 34–36 weeks: 84,540<br>≥37 weeks: 92,421 | 34–36<br>≥37 | Hospital | US$, 2003 | Initial hospitalization | 34–36 weeks: 5424<br>≥37 weeks: 2027 |
| Ringborg et al. [48] | 1998–2001 | Sweden | Retrospective analysis of hospital discharge records | 34–36 weeks: 4727<br>≥37 weeks: 16,852 | 34–36<br>≥37 | Hospital | €, 2001 | First year of life | Inpatient cost per survivor:<br>34–36 weeks: 14,177<br>≥37 weeks: 6801 |
| St John et al. [49] | 1989–1992 | USA (Alabama) | Retrospective analysis of hospital charts and billing database | 34–36 weeks: 103<br>≥37 weeks: 197 | 34–36<br>≥37 | Hospital | US$, price date not specified | Initial hospitalization | 34–36 weeks: 10,961<br>≥37 weeks: 6953 |
| van Baaren et al. [50] | 2006–2012 | Netherlands | Retrospective analysis of one prospective cohort study and three randomized controlled trials | 4552<br>1090 singletons<br>3462 multiples | 24–28<br>28–32<br>32–36<br>≥37 | Hospital | €, 2011 | Initial hospitalization | 34 weeks:<br>Singletons: 11,222<br>Multiples: 21,457<br>35 weeks:<br>Singletons: 6492<br>Multiples: 14,306<br>36 weeks:<br>Singletons: 2924<br>Multiples: 8618<br>≥37 weeks:<br>Singletons: 1434<br>Multiples: 5201 |
| Xu et al. [51] | 2003 | USA (Michigan) | Retrospective analysis of regional birth cohort | < 37 weeks: 9780<br>≥37 weeks: 101,484 | ≥20 | Hospital | US$, 2007 | Initial hospitalization | 34 weeks: 18,617<br>35 weeks: 15,864<br>36 weeks: 12,305<br>≥37 weeks: 6368 |

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 weeks 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.

## 6. Cost-effectiveness of treatment strategies

Several pharmacological and surgical interventions, forms of developmental care, organizational approaches, and other intervention strategies targeted at infants born late preterm or early term have been evaluated using randomized 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$40) [59]. Data were collected on all major health service resource inputs through trial case-report forms, routine data sources, and parental interviews. Deaths were captured by the trial monitoring procedures, while standardized neurodevelopmental assessments were performed in the homes of surviving infants by a single pediatrician. Over four years of follow-up, the incremental cost of neonatal ECMO was £16,707 (95% CI: £9828 to £37,924) per life-year gained and £24,775 (£13,106 to £69,690) per disability-free life-year gained (2001 prices). Notably, the authors highlight the lack of validated tools for QALY measurement in this age group, thereby limiting the potential for cost-effectiveness comparisons with interventions in other areas of health care. A subsequent economic evaluation conducted by the authors that was based on seven-year follow-up data within the same trial estimated the incremental cost per disability-free life-year gained associated with neonatal ECMO at £23,566 (2002–3 prices). Xie and colleagues, using a decision-analytic model, estimated the incremental cost-effectiveness of a system-based approach for the management of neonatal jaundice and the prevention of kernicterus in late-preterm and term ($\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 (Canadian $, 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.

## 7. 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 deficit [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 hospitalizations [12], health complications during early childhood [13,14], and developmental delay [15], when compared to full-term infants. In view of the adverse clinical sequelae associated with late preterm and early term birth, it is imperative to understand their potential economic consequences. 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 author's knowledge, have attempted to quantify the non-health service costs associated with late preterm birth [38,40,43], while 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 born 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 organizations, such as adaptations that have to be made to the child's home due to their impaired state of health, and additional costs borne by families and informal carers arising from 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 randomized 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 randomized 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 tools will be needed to aid cost-effectiveness-based decision-making using the incremental cost per QALY gained metric.

## Conflict of interest statement

None declared.

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