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VERY PRETERM INFANTS IN FINLAND – USE OF HEALTH CARE SERVICES AND ECONOMIC CONSEQUENCES DURING THE FIRST FIVE YEARS OF LIFE

by

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ABSTRACT

Emmi Korvenranta. Very preterm infants in Finland - Use of health care services and economic consequences during the first five years of life. Department of Pediatrics, University of Turku.

The aim of this thesis was to study the health, the hospitalisations, and the use of communal health care services in very preterm children during the first five years of life. In addition, the effect of very preterm birth and prematurity-related morbidities on the costs of hospitalisations, other health care services and the cost per quality adjusted life years (QALY) were studied. This population-based study included all very preterm children (gestational age (GA) <32 weeks or birth weight<1501g, N=2 064) and full-term controls (GA 37+0−41+6, N=200 609) born in Finland during 2000-2003. The data sources included national register data, costing data from the participating hospitals and parental questionnaires.

This study showed that most very preterm infants born in Finland survived without prematurity-related morbidities diagnosed during the first years of life. They required relatively little hospital care after the initial discharge, which accounted for the vast majority of the total four-year hospitalisation costs. However, a minority of children born very preterm later developing morbidities had a long initial length of stay and more re-admissions and outpatient visits during the five-year follow-up period. In particular, the number and costs of non-emergency outpatient visits were considerable in individuals with prematurity-related morbidities. The need and costs of hospitalisations decreased clearly with each follow-up year, even in individuals with morbidities. The health-care related costs during the fifth year of life in children born very preterm without prematurity-related morbidities were close to the costs in infants born healthy at term.

The cost per QALY of 19,245 € was at an acceptable level already by four years of age in the very preterm population as a whole. Prematurity-related later morbidities and decreasing GA increased the costs per QALY. As the initial hospital stay accounted for a great majority of the total four-year costs, and the costs of hospitalisation decreased with each follow-up year, the cost per QALY is likely to decrease with age.

In conclusion, the majority of costs arising after the initial hospitalisation were associated with morbidities related to prematurity. Therefore offering high-quality neonatal care to prevent later morbidities in very preterm survivors has a long-term impact on the cost per QALY. In addition, this study indicates that when estimating the costs of prematurity after the first year of life, one should calculate not only the hospitalisation costs, but also other costs for social welfare services, primary care, and therapies, as these exceed the hospitalisation costs in very preterm infants during the fifth year of life.

Key Words: Cost-effectiveness; Health-care resource use; Hospitalisations; Quality adjusted life years; Very preterm infant.

TIIVISTELMÄ

Emmi Korvenranta. Pikkukeskoset Suomessa - terveydenhuollon palvelujen käyttö ja taloudelliset seuraamukset viiden ensimmäisen elinvuoden aikana. Lastenklinikka, Turun yliopisto.

Vastasyntyneiden tehohoidon kehittyminen viime vuosikymmenien aikana on johtanut yhä pienempien keskosten selviämiseen. Pikkukeskosten alkuhoito on kuitenkin kallista. Pitkän ensimmäisen hoitojakson lisäksi he tarvitsevat enemmän sairaalahoitoja ensimmäisten elinvuosien aikana kuin muut vastasyntyneet.

Tämän tutkimuksen tavoitteena oli selvittää keskosuuden ja siihen liittyvien sairauksien vaikutusta sairaalahoidon ja muiden terveydenhuollon palvelujen käyttöön viiden ensimmäisen elinvuoden aikana. Lisäksi selvitettiin hoidon kustannusvaikuttavuutta kustannusten ja laatupainotteisien elinvuosien valossa (QALY). Tutkimuksessa oli mukana kaikki Suomessa 2000-2003 syntyneet pikkukeskoset (N=2 064) ja kaikki täysaikaiset lapset (N=200 609). Tutkimus perustui kansallisten rekisterien ja sairaaloiden taloushallinnon järjestelmien tallentamiin tietoihin sekä lasten vanhemmille tehdyn kyselylomaketutkimuksen vastauksiin.

Tutkimus osoitti, että kaksi kolmesta pikkukeskosesta selvisi ilman keskosuuteen liittyviä, ensimmäisten elinvuosien aikana todettavia pitkäaikaissairauksia. Ensimmäinen hoitojakso oli pitkä ja kustannuksiltaan huomattava. Sen jälkeen pikkukeskosten sairaalahoitojen tarve oli kuitenkin suhteellisen vähäistä. Niillä keskosilla, joilla oli keskosuuteen liittyviä pitkäaikaissairauksia, oli sekä pidempi ensimmäinen hoitojakso että suurempi riski joutua myöhemmin uudelleen sairaalaan. Heillä myös avohoidon käyntien määrä oli suurempi viiden vuoden seurantajakson aikana. Sairaalahoidon tarve ja kustannukset laskivat kuitenkin kaikilla keskosilla vuosien mittaan. Terveydenhoitopalvelujen kustannukset viidennen elinvuoden aikana olivat lähellä täysaikaisina syntyneiden kustannuksia niillä pikkukeskosilla, joilla ei ollut todettu pitkäaikaissairauksia.

Pikkukeskosen laatupainotteisen elinvuoden kustannus oli keskimäärin 19 245 € neljän ensimmäisen elinvuoden aikana. Keskosuuteen liittyvät pitkäaikaissairaudet ja syntymä erittäin ennenaikaisesti kasvattivat laatupainotteisen elinvuoden hintaa. Koska ensimmäinen sairaalahoitojakso muodosti suurimman osan neljän ensimmäisen elinvuoden sairaalakustannuksista, voidaan olettaa, että laatupainotteisen elinvuoden kustannus pienenee iän myötä.

Johtopäätöksenä voidaan todeta, että suurin osa ensimmäisen hoitojakson jälkeisistä kustannuksista aiheutuu keskosuuteen liittyvien pitkäaikaissairauksien seurannasta ja hoidosta. Korkeatasoinen vastasyntyneiden tehohoito vähentää tällaisia pitkäaikaissairauksia ja parantaa keskoshoidon kustannusvaikuttavuutta. Tutkimus osoitti myös, että keskosuuteen liittyviä ensimmäisen elinvuoden jälkeisiä kustannuksia arvioitaessa on tärkeää huomioida sairaalahoitojen lisäksi muut terveydenhuoltoon liittyvät kustannukset, koska viidennen elinvuoden aikana ne ylittivät sairaalahoidon kustannukset.

Avainsanat: Kustannusvaikuttavuus; Laatupainotteinen elinvuosi; Pikkukeskonen; Terveydenhuollon palvelujen käyttö; Sairaalahoidon tarve.

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ABBREVIATIONS

AGA	Average for gestational age
BPD	Bronchopulmonary dysplasia
CI	Confidence interval
CLD	Chronic lung disease
CP	Cerebral palsy
DRG	Diagnosis-related group
ELBW	Extremely low birth weight
GA	Gestational age
GLM	Generalized linear model
GP	General practitioner
HRQoL	Health –related quality of life
ICD-10	International classification of diseases
IH	Inguinal hernia
IQR	Interquartile range
IVH	Intraventricular hemorrhage
LGA	Large for gestational age
LOS	Length of stay
NEC	Necrotising enterocolitis
NICHD	National Institute of Child Health and Human Development
NICU	Neonatal intensive care unit
OR	Odds ratio
OT	Occupational therapist
PLV	Periventricular leukomalacia
PT	Physiotherapist
QALY	Quality adjusted life year
RDS	Respiratory distress syndrome
ROP	Retinopathy of prematurity
SD	Standard deviation
SGA	Small for gestational age
THL	National Institute For Health and Welfare
VLBW	Very low birth weight
VON	Vermont-Oxford Network

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original publications, which are referred to in the text by Roman numerals (I-IV):

I Korvenranta Emmi, Linna Miika, Häkkinen Unto, Peltola Mikko, Andersson Sture, Gissler Mika, Hallman Mikko, Korvenranta Heikki, Leipälä Jaana, Rautava Liisi, Tammela Outi, and Lehtonen Liisa. Differences in the length of initial hospital stay in very preterm infants. Acta Paediatrica 2007; 96(10):1416-1420

II Korvenranta Emmi, Lehtonen Liisa, Häkkinen Unto, Peltola Mikko, Andersson Sture, Gissler Mika, Hallman Mikko, Leipälä Jaana, Rautava Liisi, Tammela Outi, and Linna Miika. Prematurity related morbidities and use of hospital resources during the first three years of life. Pediatrics 2009; 124(1):128-134.

III Korvenranta Emmi, Linna Miika, Rautava Liisi, Andersson Sture, Gissler Mika, Hallman Mikko, Häkkinen Unto, Leipälä Jaana, Peltola Mikko, Tammela Outi, and Lehtonen Liisa. Hospital costs and quality of life of preterm infants during the four years following very preterm birth. Archives of Pediatrics and Adolescent Medicine 2010; In press.

IV Korvenranta Emmi, Lehtonen Liisa, Rautava Liisi, Häkkinen Unto, Andersson Sture, Gissler Mika, Hallman Mikko, Leipälä Jaana, Peltola Mikko, Tammela Outi, and Linna Miika. Impact of very preterm birth on health care costs at five years of age. Pediatrics 2010: 125(5): e1109-e1114 E-pub ahead of print.

1 INTRODUCTION

About 60 000 infants are born in Finland each year, and 1% of these are born very preterm, with a birth weight under 1501g or at a gestational age (GA) of under 32 weeks (National Birth register, 2007). The survival of these infants has improved markedly during the last decades (Fanaroff et al. 2007, Doyle et al. 2004). However, preterm birth is still associated with increased mortality, chronic morbidity, and disability. Some studies have reported a poorer health status of adolescents or young adults born extremely or very preterm compared to their full-term peers, while others have reported the self-perceived health to be similar in these groups (Gäddlin et al. 2009, Saigal et al. 2006, Dinesen et al. 2001, Bjerager et al. 1995).

The care of very preterm infants is resource-demanding. Children born very preterm require substantial health care services during the first year of life and still require more care later in childhood than full-term infants. Previous studies have demonstrated that the costs of the initial hospitalisation in very preterm infants are high, and that the costs increase with decreasing GA or birth weight (Phibbs et al. 2006, Ringborg et al. 2006, Gilbert et al. 2003, Bannwart Dde et al. 1999, Powell et al. 1992). In addition to the long initial hospitalisation, the use of hospital resources remained higher in early childhood compared to their full-term peers (Gray et al. 2006, Leijon et al. 2003, Elder et al. 1999, Rogowski 1998).

The economic consequences of very preterm birth to the society have not been sufficiently investigated. Only a few studies have explored the costs of hospitalisations of very preterm children after the first year of life, and other health-care costs have barely been evaluated. Moreover, there are no studies on the effect of prematurity-related morbidities, and more importantly, the absence of these morbidities on the use and costs of health-care services. Many treatments compete for limited health-care resources, and there are studies on the cost-effectiveness of many of these. However, to our knowledge, both quality of life and hospitalisation costs have not been assessed in the same study population in children born very preterm. To be able to justify the treatment of this patient group, it is important to evaluate the effects of very preterm birth on the society in terms of health-care-related costs and quality of life.

2 REVIEW OF THE LITERATURE

2.1 History and causes of very preterm birth

Preterm deliveries are those occurring before 37 weeks of GA and very preterm/very low birth weight (VLBW) deliveries occur before 32 weeks of gestation or at a birth weight under 1501g. Prior to the era of modern neonatal intensive care, virtually all very preterm infants died soon after birth, whereas most of them survive today. Assisted ventilation has increased the survival of especially those born before 28 weeks of gestation. Antenatal corticosteroids and the administration of pulmonary surfactant, which were introduced in the early 1990s, have increased the survival rate even more. Thus, advances in neonatology result in smaller and smaller infants surviving. However, prematurity is still the leading cause of perinatal mortality and morbidity. As also the care and prognosis of term infants with problems has improved, the role of prematurity in perinatal mortality and morbitidy is further emphasized.

A recent study by McElrath et al. (2008) divides preterm deliveries into two broad groups. The first group includes conditions associated with intrauterine inflammation, such as preterm labour, preterm premature rupture of the membranes, placental abruption, and cervical insufficiency, and is characterised by evidence of infection and inflammation. The second group consist of conditions associated with placental dysfunction, such as preeclampsia and fetal indication/intrauterine growth restriction, and is characterised by the relative absence of inflammation in the placenta (McElrath et al. 2008). In addition, multiple gestations are an important factor associated with preterm delivery, as 15-20% of all preterm births are such. Nearly 60% of all twins are born preterm. Also preterm labour induction, especially in moderate prematurity, can be associated with other maternal medical disorders such as thyroid disease, diabetes, asthma and hypertension (Goldenberg et al. 2008). Maternal stress (Copper et al. 1996) and depression (Hoffman et al. 1996), and the use of drugs (Reis et al. 2010, Almario et al. 2009), alcohol (O'Leary et al. 2009) and tobacco (Lanting et al. 2009, Simpson 1957) have been associated with preterm delivery. About 40-45% of preterm births follow spontaneous preterm labour, and about 23-30% occur due to preterm premature rupture of the membranes (Goldenberg et al. 2008, McElrath et al. 2008). Intrauterine infection has been shown to associate with 25-40% of preterm births (Goldenberg et al. 2000), the frequency increasing with decreasing GA (Mueller-Heubach et al. 1990).

2.2 Consequences of very preterm birth to the individual

2.2.1 Survival

The survival rates of very preterm infants have improved markedly in the last decades, in particular in the smallest gestational groups. In an Australian study, the survival of extremely low birth weight (ELBW; those born before 28 weeks of gestation or at a birth weight under 1001g) infants increased from 25% in the late 1970s to 73% in the late 1990s (Doyle et al. 2004). In Finland, the rates of ELBW survival remained at a stable level in the late 1990s, the survival rates being 40-44% including stillbirths, and 66-68% in those born alive (Tommiska et al. 2007). A recent national Swedish study on births before 27 weeks of gestation during 2004-2007 presented a one-year survival rate of 49% for all births including stillbirths. For those born alive, the survival rate was 70%, ranging from 10% at 22 gestational weeks to 85% at 26 weeks (EXPRESS Group 2009). According to a study by the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network, the survival of VLBW infants increased from 80% for those born in 1990-1991 to 85% for those born in 1997-2002 (Fanaroff et al. 2007). A study of 10 European regions in 2003 presented the survival rate in very preterm infants as ranging from 79% to 93%, indicating the variability of treatments provided in this population (Zeitlin et al. 2008).

There is an increasing amount of evidence that the odds of death (Phibbs et al. 2007, Rautava et al. 2007, Warner et al. 2004, Cifuentes et al. 2002) or major morbidity (Warner et al. 2004) are lower for VLBW infants who are born in hospitals with a high level of care and a high volume of preterm births. A large population cohort study by Warner et al. (2004) demonstrated that the effect of birth hospital type on death or major morbidity was greater for infants of 1000 to 1499 g (OR: 3.42; 95% CI: 2.0–6.1) than for infants of 500 to 999 g birth weight (OR: 2.1; 95% CI: 1.0–4.8). In a Swedish national study of ELBW births in 1990–92, infant mortality was 30% for infants born at level III (tertiary centres), 46% at level IIa (with full perinatal service), and 55% at level IIb (basic neonatal service) hospitals (Finnström et al. 1997). A Finnish study reported similar findings, where the perinatal survival of ELBW infants in tertiary-care and secondary-care hospitals in 1996–97 was 79% and 45%, and the neonatal survival 59% and 32% respectively (Tommiska et al. 2001). These findings support the centralization of very preterm births to tertiary-care centres.

2.2.2 Early complications

Preterm infants are at increased risk of early complications in different organ systems such as lungs, bowel, and central nervous system. Again, those born at the lowest gestations are at the greatest risk. In addition, infections commonly complicate the early hospitalisation of very preterm infants. Early complications are related to higher mortality (Fitzgibbons et al. 2009), prolonged length of stay (LOS) and increased costs during the first year of life (Russell et al. 2007). Early complications are also related to later morbidity in very preterm infants (Roze et al. 2009, Gäddlin et al. 2008, Quinn et al. 1998, Darlow et al. 1997, Schaubel et al. 1996).

Respiratory distress syndrome (RDS) is caused by the structural immaturity of the lungs, surfactant deficiency, and surfactant dysfunction, and is mainly seen in preterm infants. A total of 50-70% of VLBW infants develop RDS, the rates increasing with decreasing GA (Horbar et al. 2002, Lemons et al. 2001). Although most infants with RDS recover, from 3 to 43 % of them develop bronchopulmonary dysplasia (BPD) (Lemons et al. 2001). A Finnish study reported that 49% of VLBW infants with BPD had previous RDS (Korhonen et al. 1999). In a study comparing the outcomes of 10 European regions, the rate of BPD in very preterm infants surviving to discharge varied from 11% to 22% (Zeitlin et al. 2008). A US study has also presented variation in BPD rates of 27-38% in surviving infants born with birth weight less than 1,250g (Walsh et al. 2007).

Intraventricular haemorrhage (IVH) is an early complication of prematurity, as more than 50% of bleeding episodes occur during the first 24 hours of life (Vohr et al. 1996). Antenatal steroids and postnatal indomethacin are likely to be protective (Linder et al. 2003, Vohr et al. 1996). In a study comparing the outcomes of 10 European regions, the rate of severe IVH or cystic periventricular leukomalacy in very preterm infants surviving to discharge varied from 3% to 17% (Zeitlin et al. 2008). Similar figures have been found in the Vermont Oxford Network (VON) centres, where the rate of severe IVH in very preterm infants in 1991-1999 was 8-10%, the rate decreasing significantly over the nine-year study period (Horbar et al. 2002). IVH has been associated as a risk factor in mortality, seizures, periventricular leukomalacy, hydrocephalus and neurodevelopmental problems (Vohr et al. 1996).

Retinopathy of prematurity (ROP) is the main ophthalmologic problem in the neonatal period. It is initiated by delayed retinal vascular growth after premature birth. According to the literature, 21-34% of VLBW infants were diagnosed with ROP (Schalij-Delfos et al. 2000, Darlow et al. 1997). Recent studies indicate an increase in the incidence of ROP in VLBW (Hameed et al. 2004) and ELBW (Austeng et al. 2009) populations during the last two decades. The extremely preterm children are at the highest risk, a recent Swedish study on ROP in ELBW infants demonstrated a risk reduction of 50% for each increase of a week of GA at birth (Austeng et al. 2009). Those diagnosed with ROP are later at increased risk of ophthalmologic problems such as strabismus, poor distance acuity, amblyopia, and myopia (Quinn et al. 1998, Darlow et al. 1997, Page et al. 1993, Robinson et al. 1993).

The pathophysiology of necrotising enterocolitis (NEC) is poorly understood. Prematurity is the main risk factor for developing NEC; the risk is inversely related to birth weight and GA. The prevalence of NEC in very preterm infants in 2005-2006 in the VON centres was 3-12%, the risk increasing with a decreasing birth weight (Fitzgibbons et al. 2009). Similarly, the NICHD Neonatal Research Network presented a 7% rate of NEC in VLBW infants born in 1999-2001 (Guillet et al. 2006). NEC is associated with a15-30%

risk of death, and VLBW survivors of NEC are at increased risk of neurodevelopmental, neurosensory and functional disabilities (Lin et al. 2006).

Very preterm infants are relatively immunocompromised, which, together with the need for invasive treatments, put them at greater risk of infection. Early onset sepsis (starting below 72 hours of age) has been found in less than 2% of VLBW infants, whereas late onset sepsis (> 72 hours) developed in almost 25% of infants. Both early- and late-onset sepsis have been associated with increased risk of death, and for those surviving, a prolonged initial hospitalisation (Stoll et al. 2003). There is evidence that the rates of late-onset sepsis can be reduced with hygiene interventions (Horbar et al. 2001).

2.2.3 Long-term consequences

Preterm birth is associated with an increased risk of chronic morbidity and disability (Saigal et al. 2008, Hack et al. 2005, Marlow et al. 2005, Hack et al. 2002). In addition to early complications, many treatments of severe neonatal problems are associated with long-term adverse effects: prolonged oxygen supplementation is associated with retinopathy of prematurity (Silverman 2004) and BPD (Bancalari et al. 2003, Jobe et al. 2001), while postnatal steroid administration and prolonged ventilator treatment are associated with later neurological impairments and cerebral palsy (CP) (Vohr et al. 2005, Walsh et al. 2005, Halliday et al. 2003, Barrington 2001, Shinwell et al. 2000).

Recurrent respiratory symptoms requiring treatment are common in prematurely born children, especially in those who have had BPD (Dombkowski et al. 2008, Gross et al. 1998). In a cohort of school-aged children, 30% of very preterm children with BPD and 24% of those without BPD presented with wheezing, whereas only 7% of the full-term control group were affected (Gross et al. 1998). In a Finnish study, VLBW children with a history of BPD had more pulmonary obstruction and hyperinflation at seven years of age than those without BPD (Korhonen et al. 2005). The most severely affected suffer from airway obstruction even as adults (Vrijlandt et al. 2005, Northway et al. 1990), with women reporting more respiratory symptoms than men (Vrijlandt et al. 2005).

Severe problems in psychomotor development and sensory deficits (CP, blindness, and hearing loss) are diagnosed during the first years of life (Vohr 2007). According to previous research, 4-9% of the children born very preterm have cerebral palsy (CP) (Larroque et al. 2008, Gäddlin et al. 2007, Platt et al. 2007, Vincer et al. 2006). Although some studies have indicated an increase in CP prevalence with the falling neonatal mortality rate (Vincer et al. 2006, Hagberg 2001), and other studies have documented a stable CP rate (Mongan et al. 2006), an increasing number of more recent studies have presented a declining rate of CP in ELBW and VLBW children (Groenendaal et al. 2010, Platt et al. 2007, Robertson et al. 2007, Wilson-Costello et al. 2007, Surman et al. 2003).

Those diagnosed with ROP are later at increased risk of ophthalmologic problems such as poor distance acuity, strabismus, amblyopia, and myopia (Quinn et al. 1998, Darlow et al. 1997, Page et al. 1993, Robinson et al. 1993). According to the literature, a total of 56-64% of very preterm infants had at least one ophthalmologic problem (Schalij-Delfos et al. 2000, Darlow et al. 1997). In the study by Darlow et al, 2% of the VLBW children were blind (Darlow et al. 1997). Hearing impairments have been reported in around 3-5 % of VLBW subjects (Doyle et al. 2005, Hintz et al. 2005, Vohr et al. 2005).

Several studies have reported a poorer health status in adolescents or young adults born extremely or very preterm compared to their term-born peers, but not necessarily a lower self-perceived health (Gäddlin et al. 2009, Saigal et al. 2006, Dinesen et al. 2001, Bjerager et al. 1995). Parents of VLBW young adults reported more difficulties than parents of control young adults; thought problems in men and higher scores on the anxious or depressed, withdrawn, and attention scale in women than in men. (Hack et al. 2004). A recent Finnish study found that even in the absence of neurosensory impairments, VLBW birth constitutes a risk factor for slower psychomotor processing speed and impaired visual learning abilities in young adulthood (Strang-Karlsson et al. 2010). VLBW has been associated with a delay in leaving the parental home and starting sexual activity and partnerships in subjects (Kajantie et al. 2008). A few studies have shown young adults born very preterm to have slightly lower rates of educational achievement, employment, and independent living than normal birth weight controls (Moster et al. 2008, Cooke 2004, Hack et al. 2002). In contrast, a recent Swedish study did not find differences in the rate of graduating from high school, occupation, or way of living (Gäddlin et al. 2009).

2.2.4 Quality of life

The WHO defines health as ”a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” (WHO, 1949). Thus, an individual can perceive his or her health as good despite morbidities or other limiting health conditions. Indeed, there are an increasing number of studies assessing the health-related quality of life (HRQoL) in children/adolescents born preterm. The finding by Saigal et al. (1999) showing that health care professionals provided lower utility scores for hypothetical conditions of children compared to parents of ELWB infants underlines the importance of such studies. Despite a higher rate of neurosensory impairments and their associated long-term medical, surgical, and psychosocial problems of morbidities, a body of evidence suggests that the self-perceived health/quality of life in extremely and very preterm infants at adolescence or as young adults does not significantly differ from those born full-term (Gäddlin et al. 2009, Gray et al. 2007, Hack et al. 2007, Dinesen et al. 2001, Bjerager et al. 1995). In addition, studies have shown that very preterm infants as teenagers (Indredavik et al. 2005) or as young adults (Saigal et al. 2006) do not rate themselves as significantly different from their peers, despite the fact that their parents reported significantly lower scores for their child compared to parents of children in the control group. Similarily, a Finnish study on spinal cord injury patients shows that the HRQoL scores of patients who have had their injury since childhood were significantly higher than those of the newly injured patients (Kannisto et al. 1998). These examples demonstrate that the QALY is a subjective measure affected also by other factors than the severity of the disease.

2.3 Consequences of preterm birth to the society

2.3.1 Hospitalisations and the use of other health care resources

Very preterm infants need long initial hospitalisations, and the LOS has been shown to increase significantly with decreasing GA and birth weight (Phibbs et al. 2006, Ringborg et al. 2006, Gilbert et al. 2003, Bannwart Dde et al. 1999, Powell et al. 1992). In addition to increased costs and burdening of hospital bed capacity, a longer initial hospitalisation has multiple other disadvantageous consequences such as augmenting infant exposure to adverse environmental stimuli (Rivkees et al. 2004, Zahr et al. 1995), and impeding the developing parent–infant relationship (Flacking et al. 2006).

The mean LOS in very preterm infants has varied in different studies from 41 to 63 days (Phibbs et al. 2006, Ringborg et al. 2006, Gilbert et al. 2003, Leijon et al. 2003, Rogowski 1998, St John et al. 2000), the LOS decreasing with increasing GA (Table 1). The median LOS tended to be shorter than the mean LOS in most of the studies, indicating a small subset of longer stays that reflects an intense use of resources in the most complicated stays (Phibbs et al. 2006, Ringborg et al. 2006, Gilbert et al. 2003). Previous studies have explained 57-82% of the variability in the LOS of premature survivors (Bannwart et al. 1999, Powell et al. 1992), GA accounting for the greatest impact, with complications such as BPD and infections also being associated with a longer LOS (Powell et al. 1992). In contrast to survivors, the LOS of non-survivors was not related to GA at birth (St John et al. 2000).

In addition to the long initial hospitalisation, the need for hospital inpatient and outpatient care remains substantial during the first years of life in very preterm children. The literature presents rehospitalisation rates of 39-44% during the first year of life (Gray et al. 2006, Leijon et al. 2003, Elder et al. 1999, Rogowski 1998). In an Australian study, De Elder et al. (1999) found a readmission rate of 42% during the first year of life in a cohort of 560 VLBW infants born in 1990-1991. A total of 84% of the admissions were due to medical and 16% to surgical reasons. Acute respiratory problems were the most common medical reason (49% of medical admissions) and inguinal hernia repair was the most common surgical reason for admission (59% of surgical admissions). Male

Table 1 Initial length of stay from birth to discharge or death for very preterm infants according to different studies.

	Length of stay, days, mean (median)					
	Survivors			Survivors and non-survivors	Non-survivors	
Study	**St John 2000***	**Gilbert 2003****	**Phibbs 2006**	**Ringborg 2006 ****	**St John 2000***	**Phibbs 2006**
Study Design	**Regional cohort born in 1989-1992 (N=495)**	**Regional cohort born in 1996 (N=3 749)**	**Regional cohort born in 1998-2000 (N=7 956)**	**National cohort, born in 1998-2001 (N=1 554)**	**Regional cohort born in 1989-1992 (N=104)**	**Regional cohort born in 1998-2000 (N=777)**
GA (wk)						
22				100 (67)		
23				128 (138)		
24	99		110 (104)	108 (109)	8	17 (5)
25	97	92 (87)	102 (96)	106 (104)	8	21 (7)
26	77	76 (75)	90 (85)	86 (90)	6	28 (9)
27	71	67 (66)	80 (73)	85 (83)	15	26 (11)
28	58	52 (51)	69 (63.5)	73 (69)	5	25 (14)
29	50	40 (40)	58 (53)	63 (60)	43	28 (13)
30	38	30 (29)	49 (44)	53 (50)	8	26 (13.5)
31	27	22 (18)	39 (34)	41 (39)	89	37 (9)
32	19	15 (9)	28 (24)	34 (33)	2	20 (9)
All <32	56	41	63	65	14	24

*median not reported ** Singleton births only

sex, chronic lung disease (CLD), supplemental oxygen need at 36 and 40 weeks were associated with an increased risk of admission for medical reasons, while breast feeding > 1 months was associated with a decreased risk of admission. Low GA at birth, small for gestational age (SGA), supplemental oxygen need at 36 and 40 weeks, male sex and severe hyaline membrane disease (=RDS) were associated with an increased risk of surgical admissions (De Elder et al. 1999). A study by Gray et al. (2006) showed that 42% of the very preterm infants were admitted at least once during the first year of life and 30% during the second year of life, whereas the respective figures were 12% and 15% in full term controls. Gray et al. (2006) also found that the most common reason for rehospitalisations in the preterm group was respiratory problems (41% of admissions), including both infectious and non-infectious disorders.

Few studies evaluate the need of health-care resources other than hospitalisations beyond the first year of life. Two studies with rather small sample sizes indicate that that there were no significant differences in visits to a general practitioner (GP) between very preterm infants and full-term controls during the first two (Gray et al. 2006) and four years of life (Leijon et al. 2003). However, during the first year of life, 67% of very preterm infants had visits to specialists, versus 26% of full-term controls. Between one to four years of age, the respective figures were 74% vs. 45% (Leijon et al. 2003). In a Swedish study, children who were born before 26 weeks' gestation had, even at 10–12 years of age, a greater need of services, such as physician visits, occupational or physical therapy, nursing or medical procedures, and a greater need of special arrangements at school than did children of normal birth weight (Farooqi et al. 2006).

There are few studies on the health-care resource use reaching beyond childhood in the preterm population. Saigal et al. (2007) showed that the use of health-care resources in ELBW infants in young adulthood in terms of hospitalisations, surgical procedures, visits to specialists, or in the use of rehabilitative services were not significantly different compared with full-term controls. Special health-care needs and equipment were necessary only for a very few ELBW adults (Saigal et al. 2007). Similarly, a group of 20-year-old Swedish VLBW subjects did not differ significantly in reported frequency of hospital admissions and need of emergency treatment over the previous five years from their full-term peers (Gäddlin et al. 2009). However, those VLBW subjects with a handicap had a greater need of emergency treatments and more frequent regular medical treatment than full-term controls.

2.3.2 Economic consequences

The financial burden of prematurity to the society is significant. Several studies have demonstrated that preterm births contribute disproportionately to overall delivery costs, accounting for a small percentage of discharges, but approximately half of all costs (Russell et al. 2007, Schmitt et al. 2006, Marbella et al. 1998). An example is a study by Russell et al. (2007) where 8% of all births included a diagnosis of preterm birth or low birth weight, yet these stays accounted for 47% of the total costs. Thus, the costs of the initial hospitalisation in very preterm infants are high, and the costs along with the LOS increase with decreasing GA or birth weight (Phibbs et al. 2006, Ringborg et al. 2006, Gilbert et al. 2003, Petrou et al. 2003, St John et al. 2000, Rogowski 1999, Marbella et al. 1998).

There are several studies from both Europe and the United States on the costs of the initial hospitalisation of very preterm infants (Table 2 and Table 3). In a study by Rogowski (1998), the costs of initial hospitalisation of very preterm infants born in Californian hospitals covered by Medicaid in 1986-87 were $ 69 200 (in 1987 US dollars) for those surviving the initial hospitalisation and $ 22 500 for non-survivors. St John et al. (2000) studied very preterm infants born in 1989-92; the mean costs in survivors varied from $145,892 in those born at 24 weeks of gestation to $19,548 in those born at 32 weeks, while the respective figures for non-survivors were $20,597 and $37,287. In a large

Table 2 The cost of initial hospitalisation in very preterm survivors in different studies. USD have been converted to EUR according to mean currency rates valid in the year the studies were published (Year 2000: 1€=$0.92; year 2003, 1€=$1.13; year 2006, 1€=$1.26), and an annual discount rate of 3% has been applied to convert the costs to 2008 prices.

	Mean original costs, $			Mean costs in 2008 prices €		
Study	**St John 2000**	**Gilbert 2003**	**Phibbs 2006**	**St John 2000**	**Gilbert 2003**	**Phibbs 2006**
Study design	**Regional cohort, born in 1989-1992 (N=495)**	**Regional cohort, born in 1996 (N=3 749)**	**Regional cohort, born in 1998-2000 (N=7 956)**			
GA (weeks)						
24	145,892		297,627	200,099		251,475
25	121,181	202,700	272,730	166,207	207,731	230,439
26	99,362	146,600	222,425	136,281	150,238	187,935
27	80,264	119,600	186,894	110,087	122,568	157,913
28	63,714	86,200	149,101	87,387	88,339	125,981
29	49,540	62,600	115,975	67,947	64,154	97,991
30	37,569	46,400	92,662	51,528	47,552	78,293
31	27,629	29,800	65,963	37,895	30,540	55,734
32	19,548	18,900	45,710	26,811	19,369	38,622
All <32	65,007	69,026	137,506	89,160	70,739	116,184

Californian birth cohort from the year 2000, the mean cost of initial hospitalisation for those born at <33 weeks of gestation was $66,813 (median $25,454) (Schmitt et al. 2006). However, the study did not report survivors and non-survivors separately. The same authors have presented more detailed data for all very preterm births in California in 1998-2000, where the costs in survivors varied from $297,627 in those born at 24 weeks of gestation to $45,710 in those born at 32 weeks, while the respective figures for non-survivors were $71,036 and $71,011 (Phibbs et al. 2006). In a study on all live singleton births in Sweden in 1998-2001 including both survivors and non-survivors, the mean costs of initial hospitalisation in 2000 prices were 116,594 € for those born at 22 weeks to 21,029 € for those born at 31 weeks. The most recent study on the subject is a study conducted in England and Wales by Mangham et al. (2009) where very preterm survivors born <33 weeks cost an average of £ 57,726 in 2006 prices. The fact that the studies are from different time periods, presented in different currencies and some of them include non-survivors, while others do not, complicates the cost comparisons, but roughly, large differences do exist between the studies.

There is also evidence that prematurity-related complications such as infections and pulmonary problems prolong the initial hospitalisation, resulting in additional costs. Russell et al. (2007) studied the effects of prematurity and common prematurity-related complications on the costs of initial hospitalisation and first-year readmissions in a

Table 3 The cost of initial hospitalisation in very preterm survivors and non-survivors in different studies. USD have been converted to EUR according to mean currency rates valid in the year the studies were published (year 2006, 1€=$1.26), and an annual discount rate of 3% has been applied to convert the costs to 2008 prices.

	Mean original costs		Mean costs in 2008 prices €	
Study	**Ringborg, 2006 €**	**Phibbs , 2006 $**	**Ringborg 2006**	**Phibbs 2006**
Study design	**National cohort, born 1998-2001 (N=1 554)**	**Regional cohort, born 1998-2000 (N=11 469)**		
GA (weeks)				
22	116,594		123,695	
23	72,524		76,941	
24	73,121	222,563	77,574	187,395
25	65,071	233,538	69,034	196,635
26	58,272	207,637	61,821	174,827
27	54,530	178,080	57,851	149,941
28	40,494	146,121	42,960	123,032
29	31,526	115,801	33,446	97,503
30	23,607	92,882	25,045	78,205
31	21,029	68,446	22,310	57,630
32	19,034	46,117	20,193	38,830
All <32	36,438	112,704	38,657	94,895

nationwide study including 4.6 million infant stays in the United States (US) in 2001. The single costliest complication (average cost of initial LOS per discharge) for those born with birth weight under 2500 g was BPD at an average cost of $116 000, reported in 4.4% of cases, compared to $ 16,900 in those without BPD. The most common diagnosis was RDS, reported in 23.3% of cases at an average cost of $ 56,800, compared to $10,700 in those without RDS. In addition ROP, IVH and NEC added significantly to the first-year hospitalisation costs (Russell et al. 2007).

The need of health-care services in very preterm infants remains higher than in term infants in childhood (Gray et al. 2006, Petrou 2005, Petrou et al. 2003, McCormick et al. 1991). The presence of any morbidity, multiple pregnancy, and SGA status have been associated with higher total hospitalisation costs during the first five years of life (Petrou et al. 2003). Also Stevenson et al. (1996) showed in a small geographical cohort of low-birth-weight children that those who were disabled accounted for a disproportionate amount of the total expenditure (hospital inpatient and outpatient care, visits to GP, special education services) up to age 8-9 years.

There is evidence, however, that the total costs in premature individuals decrease with age, and that the initial hospitalisation, in particular, seems to comprise the biggest cost burden (Petrou et al. 2003, Rogowski 1998). For instance, Rogowski (1998) showed that the initial hospital stay comprised 90%, rehospitalisations 9% and outpatient care 1% of the total first year costs. Mangham et al. (2009) recently estimated, in a hypothetical cohort of individuals born very preterm, that 97.4% of the incremental costs occurring during the first 18 years of life consist of the costs from the first five years of life, 1.6% from primary school age (5–11 years), and only 1.1% from secondary school age (11–18 years).

Hospitalisations seem to contribute most to the total costs of prematurity, when looking at the very premature population as a whole. For example, Mangham et al (2009) estimated that of the costs occurring during the first 18 years of life, 96.7% of the total consist of hospital inpatient and outpatient costs, 0.9% of community health care and social care, and 2.4% of education costs. However, when looking at the individual level, those with prematurity-related morbidities not only consume more health-care resources, but also social costs and productivity costs are higher in these individuals. For example, in a recent Danish study on the life-time costs of CP it was shown that two thirds of individuals with CP never enter the labour market, and that the average life-time cost of CP was calculated as 860 000 € for men and 800 000 € for women, the social costs accounting for the largest proportion of the costs (Kruse et al. 2009).

2.4 Measuring costs of hospital care

2.4.1 Hospital pricing systems in Finland

In Finland, municipalities provide and finance health-care services for their residents. The municipal health-care system is organisationally divided into primary and specialised health services. Public specialised care is provided by 20 hospital districts, and these hospital districts are administratively federations of municipalities (Mikkola et al. 2003). The hospital districts own and run public hospitals, which are divided into three levels: university hospitals, central hospitals, and regional hospitals. The five university hospitals provide tertiary-level services for its surrounding districts and, for example, most very preterm infants are born in the five university hospitals. Municipalities purchase services for their citizens from hospitals. Various pricing structures are used: bed-day prices, a combination of procedural pricing and bed-day prices, and diagnostic-related group (DRG) based pricing (Mikkola et al. 2003). The hospital districts prospectively set the prices, which are confirmed by the district boards.

The DRG system was developed for somatic in-hospital care of adults in the United States during the 1970s by Fetter et al. (1980). It classifies hospital cases into groups that meet three requirements: (1) the discharges included in a DRG group have to be as homogeneous as possible with respect to the resources used from the start of the hospitalisation and until the discharge, (2) the grouping should be clinically meaningful, and (3) the number of DRG groups should be limited. Different versions of the system are in use in many European countries (Schreyogg et al. 2006); the Nordic countries have developed their own version of the classification, NordDRG.

The DRG based price expresses the average use or resources in relation to the care episode. It includes all services involved in inpatient care. In the combination of fee-for-service and bed-day prices, bed-days and other services (such as radiology and laboratory examinations, surgical procedures) are invoiced separately. The DRG-based pricing system is increasingly used in the Finnish hospitals, but the relatively small number of very preterm infants born in Finland each year creates a problem in applying DRG-based prices to very preterm infants. Thus, at the time of the study, the prices of care of very preterm infants were based on a combination of fee-for-service and bed-day prices and bed-days prices alone.

2.4.2 Challenges in measuring the costs of hospital care

It is problematic to define the costs of hospital care. Costs-to-charges ratios have been used in most of the US studies estimating the costs of prematurity (Phibbs et al. 2006, Schmitt et al. 2006, Gilbert et al. 2003, Rogowski 1999). The costs-to-charges method converts charges to costs using different mark-up rates. Charges, however, are not accurate measures of hospital costs, as hospital charges reflect different mark-ups for different services (Rogowski 1999). Using the costs-to-charges method is especially problematic when comparing the costs between different institutes due to different pricing policies. In a study of VLBW infants in California it was shown that the average charge for the initial hospitalisation overestimated treatment costs by 53% (Rogowski 1999). The Swedish study by Ringborg et al. (al. 2006) used DRG costs, and the costs were significantly lower than in the studies from the United States.

In addition to different pricing policies, there are several other factors complicating cost comparisons across different institutions. The cost of hospital inputs, such as labour and capital, vary widely across different regions and countries. The ways in which indirect labour and material costs and other overhead costs are allocated has an effect on the total costs. Teaching hospitals have higher costs than non-teaching hospitals, further complicating cost comparisons between different hospitals. The results of a Finnish study on the subject suggests that the average rate of teaching and research reimbursement should be approximately 14.6% of the total operating costs in university teaching hospitals (Linna et al. 2006). In addition, because of inflation, it is necessary to reflect differences in the year in which the costs were incurred. When drawing conclusions from international studies, the costs are incurred in different currencies, creating the problem of which currency rate to use, as the currency rates can vary greatly across different periods of time. When benchmarking costs across different institutions, the case-mix should also be adjusted for, as illness severity is most definitely associated with treatment costs. One solution to this problem is the DRG system. A benefit of the grouping is that patients can be compared in terms of their relative expected costs. The relatively small number of very preterm infants born in Finland each year, as mentioned above, creates a problem in applying DRG-costs to very preterm infants.

Thus, when interpreting cost comparisons, there are several possible factors that could explain the differences: 1) differences in the case-mix; 2) differences in costs of hospital inputs, such as labour and capital; 3) differences in the allocation of indirect labour and material costs and other overhead costs; 4) differences in the pricing systems; and 5) differences in the care policies and possible inefficiencies in resource use.

2.5 Economic analyses of health care

Economic evaluation of health care aims to compare the costs and benefits of interventions. Cost-effectiveness analysis has become a standard method for comparing the expected benefits of an intervention with its net cost (Talmor et al. 2006, Coughlin et al. 2003, Hjelmgren et al. 2001, Gold et al. 1996). A cost effectiveness ratio is calculated by dividing the incremental cost, i.e changes in costs due to an intervention, compared with a specific alternative, by its incremental benefit. The most widely used approach is to measure clinical benefits in terms of number of life years saved. Thus, the typical cost-effectiveness expression is cost per life year saved. Cost-utility analysis goes further in the analysis of benefits as it examines the intervention by using the quality-adjusted life year (QALY) as its unit of effectiveness. The QALYs are based on HRQoL, preferably determined by generic preference-based instruments. Thus, when using QALY, both quality and quantity of life are taken into account. The purpose of this approach is to allow a direct comparison of the health benefits of interventions across different diseases and populations.

Measuring the quality of life is challenging. Although the severity of disease is an important determinant of the health of an individual, patient perception and adaptation largely define the overall quality of life. A number of instruments have been developed to assess HRQoL. HRQoL measures take into account some or all of the following aspects: physical function, psychological function, social role function, cognitive performance, perceptions of health, and symptoms. Generic preference-based instruments are recommended for calculating OALYs in cost-utility analyses of health interventions, as they reflect people’s values for different health states. In the preference-based instruments, health states are scaled from 0 (dead) to 1 (optimal health); states worse than death can be accounted for by assigning them negative scores. Preference scores are based on community-derived weights for the health states defined by the questionnaire. (Kopec et al. 2003, Gold et al. 1996). It is even more difficult to estimate the quality of life in small children, as most HRQoL tools have been designed for adults, and only modified for children. The HRQoL of small children must be done according to parental rating, and according to the existing literature, parental ratings may underestimate the HRQoL compared to children's own ratings (White-Koning et al. 2007, Sneeuw et al. 2002). In addition, children undergo dramatic changes in growth and function at different rates, which is an important confounding factor.

Whether a therapy is cost-effective or not is a subjective interpretation of the cost-effectiveness ratio. Although there is no absolute cut-off, a common internationally referred threshold for cost-effective treatment, established by the National Institute for Health and Clinical Excellence (NICE) in UK, has been £20,000 (29,000 €) (NICE 2008). In the United States, there tends to be general consensus that treatments with a cost-effectiveness ratio of \$50,000 to \$100,000 per year of life gained are acceptable (Talmor et al. 2006, Coughlin et al. 2003).

Only one study has evaluated the cost per QALY in preterm children. This study was based on estimations from different studies; it did not determine the costs or QALYs in an existing population of preterm infants. The study suggested a cost per QALY of \$6,101 for those born with BW below 1000g and \$1,290 in those weighing 1000 - 1500g at birth, when assuming that the children reach 50 years of age. The study indicated that the benefit of treatment of prematurity was so large that it dwarfed all the uncertainties inherent in the data (Cutler and Meara 1999).

Methodological issues such as cost estimation, discount rate used, time horizon, and the tool used for estimating QALYs, can have a major effect on the cost-effectiveness result. Problems with comparing costs across different studies have been presented above. In addition, there are studies demonstrating that QALY scores for identical conditions can vary substantially depending on the measure used (Conner-Spady et al. 2003, Kopec et al. 2003). Therefore, direct comparisons of cost-effectiveness ratios should be done with caution when there are differences in determining the costs and QALYs of the interventions.

2.6 Gaps in the current literature

Several studies have investigated the length and costs of the initial hospitalisation in very preterm infants, probably due to the extensive costs of these care episodes. Only a few studies, however, have explored the costs of hospitalisations of very preterm children after the first year of life, while the use and costs of other health care resources have barely been evaluated. In addition, there are few studies on the effect of prematurity-related morbidities on the later need and costs of health care resources. In addition, to our knowledge, there is only one study evaluating the cost-effectiveness of care of preterm infants, which is carried out on the basis of estimations of data from different studies; thus, no study has estimated the costs and QALYs in the same population.

3 AIMS OF THE STUDY

The aims of the study were:

1) to investigate the effect of maternal, infant, and birth hospital district -related factors on the length of initial hospital stay in very preterm infants (I).

2) to determine how the use of hospital resources during the first three years of life is associated with prematurity-related morbidity in children born very preterm (II).

3) to investigate the effects of very preterm birth and prematurity-related morbidities on the costs, QALYs and cost per QALY in children born very preterm during the first four years of life (III).

4) to assess the effects of very preterm birth and prematurity-related morbidities on the costs of in- and outpatient hospital care, primary care, therapies, and social welfare services during the fifth year of life (IV).

4 PATIENTS AND METHODS

4.1 Patients

4.1.1 Very preterm infants

This study was approved by the Ethics Committee of the National Institute for Health and Welfare (THL). The study population consisted of all surviving very preterm infants (GA less than 32 weeks or a birth weight less than 1 501g) born in Finland between 2000 and 2003. The length of gestation was based on the best clinical estimation at birth, usually based on ultrasound examination before the end of the 20th week of gestation or otherwise on the last menstrual period. Gestational age is a sound variable in the Finnish Medical Birth Register and its validity has been evaluated (Gissler et al. 1993).

During the study period there were 2 148 very preterm live births, and 295 stillbirths in 24 different hospitals. There are five University Hospitals in Finland which, according to definitions proposed by the American Academy of Pediatrics Committee on Fetus and Newborn (Stark et al. 2004), have level III neonatal intensive care units (NICU). In addition to the five hospitals with level III NICUs, very preterm infants were delivered in 19 hospitals with level I or II NICUs. A total of 18 infants born in level I or level II units were transferred to a level III unit after birth.

4.1.2 Full-term controls

Two full-term control groups were used in the study. A matched control group for the very preterm population born in 2000-2003 was formed of 395 infants born in 2001-2002 by adding the next healthy full-term infant of the same gender born in the same hospital after every third very preterm study infant. 'Full-term' was defined as GA from 37 0/7 to 41 6/7, and 'healthy' as no admission to hospital care within the first seven days of life. In addition, the whole population of full-term infants born in 2000-2003 was used as another control group (N=200 609).

4.1.3 Study samples

Study I included 2 031 live-born very preterm infants. Of the 2 148 infants born very preterm during the study period, 94 were excluded because of missing data on their first care episode, 20 because of incomplete Medical Birth Register data and three due to major disparities between GA and birth weight data.

Study II consisted of 1 796 very preterm survivors, 395 matched full-term controls, and the whole term born population (N=200 609). Of the 2 148 very preterm infants born alive during the study period, 264 were excluded as they did not survive to three years of age, and 88 were excluded because the Medical Birth Register data were incomplete, or the Hospital Discharge Register data were missing.

Study III included 1 752 very preterm survivors, after 129 infants with incomplete Medical Birth Register data or missing Hospital Discharge Register data, and three infants with major disparity between birth weight and GA had been excluded. The whole term born population (nN=200 609) was used as a control group.

Study IV included all very preterm children born alive during 2001-2002. The exclusion criteria were 1) incomplete Medical Birth Register or Hospital Discharge Register data (N=35), 2) birth in a hospital with fewer than three very preterm deliveries in 2001−2002 (N=4), and 3) at least one lethal congenital malformation (N=19), defined as trisomy 13 or 18, triploidy, severe cardiac defects (ie. acardia, univentricular heart, transposition of the great arteries, interrupted aorta), severe developmental disorders (ie. anencephaly, holoporsencephaly), and clearly defined lethal syndromes according to the Finnish Registry of Congenital Malformations. A total of 23 very preterm born children and 13 controls were excluded due to living abroad or a missing address. The final study population included 901 very preterm infants. In addition, study IV included 368 matched full-term controls as described above.

The sample characteristics are presented in Table 4. The small differences in the sample sizes are explained by different exclusion criteria, and data updates in the register.

4.2 Methods

4.2.1 Data collection

The register data used in this study were collected from the National Medical Birth Register, the Hospital Discharge Register, and the Finnish Registry of Congenital Malformations, all maintained by the National Institute for Health and Welfare (THL), and the Cause-of-Death Register (including stillbirths and infant deaths) at Statistics Finland. The Finnish National Medical Birth Register includes data on all live births, and stillbirths of infants with a GA of 22 weeks or more, or with a birth weight of 500g or more. The Hospital Discharge Register contains information on the utilization of inpatient and outpatient hospital care for all patients in Finland.

The individuals were defined as having a morbidity if the following diagnoses, known to be over-represented in preterm populations, occurred at least once in the Hospital Discharge Register by the end of 2006: CP (International classification of diseases (ICD-10) codes G80-83), seizure disorder (ICD-10 codes G40-47), later obstructive airway disease including asthma and other obstructive airway diseases (ICD-10 codes J44-J45),

Table 4: Summary of sample characteristics (very preterm infants)

	Study I	Study II	Study III	Study IV
Total number of live born	2148	2148	2148	1117
Non-survivors	253 (12%)	264 (12%)	264 (12%)	135 (12%)
Excluded due to missing data	117 (5%)	88 (4%)	132 (6%)	35 (3%)
Excluded due to other reasons (see text)				46 (4%)
No. of non-responders to the parental questionnaire(sent to 901 families)				313 (35%)
No of survivors included in the final analysis	1778	1796	1752	588
No. of non-survivors included	253			
Characteristics of survivors included in the final analysis				
Multiple birth				
Yes	511 (29%)	506 (28%)	490 (28%)	139 (24%)
No	1267 (71%)	1290 (72%)	1262 (72%)	449 (76%)
Birth weight for GA				
AGA	1228 (69%)	1255 (70%)	1240 (71%)	405 (69%)
SGA	501 (28%)	495 (28%)	471 (27%)	167 (28%)
LGA	49 (3%)	46 (3%)	41 (2%)	16 (3%)
Gender				
Male	978 (55%)	996 (55%)	978 (56%)	335 (57%)
Female [a]	800 (45%)	800 (45%)	774 (44%)	253 (43%)
Gestational age				
22-23	17 (1%)	17 (1%)	17 (1%)	5 (1%)
24-25	135 (8%)	135 (8%)	135 (8%)	54 (9%)
26-27	232 (13%)	234 (13%)	231 (13%)	74 (15%)
28-29	382 (21%)	391 (22%)	385 (22%)	149 (25%)
30-31	759 (43%)	771 (43%)	756 (43%)	231 (39%)
>31	242 (14%)	248 (14%)	228 (13%)	75 (13%)
Full term				
Birth hospital				
University Hospital 1	609 (34%)	606 (34%)	596 (34%)	192 (33%)
University Hospital 2	199 (11%)	199 (11%)	195 (11%)	94 (16%)
University Hospital 3	152 (9%)	158 (9%)	157 (9%)	46 (8%)
University Hospital 4	217 (12%)	228 (13%)	227 (13%)	67 (11%)
University Hospital 5	213 (12%)	213 (12%)	212 (12%)	74 (13%)
Other hospitals [a]	388 (22%)	392 (22%)	365 (21%)	115 (20%)
Full cost data available for the initial hospital stay			906 (52%)	

hearing loss (ICD-10 codes H90-91), visual disturbances or blindness (ICD-10 codes H53-54), and other ophthalmologic problems including disorders of ocular muscles, binocular movement, accommodation and refraction (ICD-10 codes H49-52). Diagnoses for both inpatient and outpatient visits were recorded. Psychiatric problems were not included, as most of them are diagnosed at a later age.

The cost data on the initial hospital stays for the very preterm infants were collected from hospital databases. Five hospitals, four with level III neonatal intensive care units (NICU) and one with a level II NICU, provided us with cost data on the initial hospitalisation of the very low-birth-weight infants born in their units. Cost data on the initial hospital stay were available for 997 infants, for 33% (N=91) of the non-survivors and 52% (N=906) of the survivors. The costs were calculated by the hospitals, two of the hospitals used bed-day pricing, and three of the hospitals used a combination of fee-for-service and bed-day prices. The background factors of those with and without cost data on the initial hospital stay are presented in Table 5. Those without costs had slightly higher GA and birth weight than those with costs. For the term infants, the cost of the initial hospital stay was calculated according to Diagnosis Related Groups (DRG), based on patient-level cost accounting. The DRG costing sample covers approximately 30% of all acute hospital care in Finland. Cost items include diagnostic tests, procedures, medical services, support services and overhead costs.

Table 5 Comparisons of the background factors of individuals with and without cost data on the initial hospital stay

Characteristics	Survivors			Non-survivors		
	With cost data (N=906)	Without cost data (N=846)	P Value	With cost data (N=91)	Without cost data (N=187)	P Value
Male N (%)	501 (55%)	427 (56%)	0.85	57 (63%)	110 (59%)	0.60
GA (mean days)	208	211	<0.01	180	190	<0.01
Birth weight (mean g)	1243	1317	<0.01	767	905	0.01
LOS (mean days)	67	61	0.01	18	11	0.21
Later morbidities N (%)						
Seizures	23 (3%)	30 (4%)	0.26			
Cerebral Palsy	52 (6%)	57 (7%)	0.43			
Other ophthalmologic problems	123 (14%)	117 (14%)	0.89			
Visual disorder	36 (4%)	32 (4%)	0.81			
Hearing loss	17 (2%)	28 (3%)	0.07			
Obstructive airway diseases	183 (20%)	175 (21%)	0.72			

The cost data for later outpatient and inpatient hospital visits were collected from the hospital databases of the largest hospital district in Finland, the Helsinki and Uusimaa Hospital district. The costs for non-emergency outpatient visits were received for 26% (N=10 053) of the total number of the studied visits of the very preterm infants and 29% (N= 144 847) of the visits of the controls; for emergency visits the figures were 30% (N=1 305) and 27% (N=46 220), respectively, and for inpatient visits 22% (N=1 534) and 24% (N=39 678), respectively.

The cost of the initial hospital stay was estimated for preterm survivors with missing cost data from the true costs of infants with similar background variables, which were survival status, sex, GA, multiple birth, intrauterine growth (classified as small (SGA), appropriate (AGA), or large birth weight for GA (LGA) defined as birth weight below -2.0 SD, between -2.0 SD and 2.0 SD, and above 2.0 SD, respectively according to reference values from the Finnish population), and LOS. For preterm non-survivors, the only factor associated with the costs was LOS according to a generalized linear model, and thus the costs of the initial LOS for those with missing cost data in non-survivors were based only on the LOS. The costs for later hospital stays were imputed for those with missing cost data based on the type of visit (emergency-outpatient visit, non-emergency outpatient visit and inpatient hospital visit) and the diagnosis of the visit. In 9% of the emergency outpatient visits and 26% of the non-emergency outpatient visits the diagnosis for the visit was missing, and in those cases we used the average cost of the emergency and non-emergency outpatient visits which were 286 € and 231 €, respectively. The costs for communal health and social services were calculated according to reference costs determined by THL (Hujanen et al. 2008). The reference costs per visit were: physician, public sector (including diagnostics) 115.1€; physician, private sector, 65.7 €; nurse practitioner, 52.5 €; physiotherapist (PT), 41.3 €; occupational therapist (OT), 95.6 €; psychologist, 206.1 €; speech therapist, 72.5 €; dietician, 61.3 €; family support clinic, 70.3 €; family adaptation course, 214.7 €; training in sign language, 72.5 €; home visits, 42.6 €; and use of communal transfer services, 17.7 €. The cost per day in an institution was 91.6 €.

A parental questionnaire was sent 0.5–1.5 months prior to the child's fifth birthday to the parents of all very preterm infants born in 2001-2002 and the matched control group (Rautava et al. 2009). Two reminders were sent 1.5 and 2.5 months thereafter if needed. The questionnaire asked parents about any long-term diagnoses of the child, the number of visits to different health care professionals during the previous 12 months, the family structure, and parental education and current employment situation. The parents of 588 (65% of all surviving) children born very preterm and 176 (46%) controls returned the questionnaire, the difference being statistically significant ($p<0.05$). A drop-out analysis showed that non-responders were more often maternal smokers during pregnancy and had more often multiple birth (Table 6).

The parental questionnaire also included the 17D, which is an established instrument for measuring HRQoL (Apajasalo et al. 1996). The 17D contains one closed-ended question addressing each of the following health dimensions: mobility, vision, hearing, breathing, sleeping, eating, speech, elimination, school and hobbies, learning and memory, discomfort and symptoms, depression, distress, vitality, appearance, friends, and concentration. The questionnaire provides a single HRQoL score on a scale from 0 to 1, with 0 corresponding to being dead, 0.0162 to being unconscious or comatose,

Table 6 Background variables of VLBW responders vs. non—responders.

	Responders, mean (SD) (N=588)	Non-responders, mean (SD) (N=313)	Odds ratio (OR)	95% CI
Maternal age, years	30.7 (5.8)	30.2 (6.3)	0.98	0.96 to 1.01
Maternal smoking during pregnancy (yes)	14%	24%	1.93	1.31 to 2.83
Multiple birth (number of children)	1.3 (0.5)	1.4 (0.6)	2.1	1.53 to 2.82
Female sex	43%	53%	1.36	1.002 to 1.85
Birth weight, g (OR per increase of 100 g)	1249 (382)	1307 (403)	1.05	0.997 to 1.11
GA, weeks and days (OR per increase of 1 week)	29 5/7 (2 3/7)	29 6/7 (2 4/7)	1.07	0.98 to 1.17
Number of emergency visits for special health care from birth to age 5 y	2.4 (3.0)	3.1 (4.3)	1.04	0.991 to 1.09
Number of other visits for special health care from birth to age 5 y	20.8 (19.9)	22.6 (23.0)	1.003	0.999 to 1.01
Hospitalized or institutionalized from birth to age 5 years, days to age 5 y	68.4 (39.5)	76.3 (69.8)	1.003	0.994 to 1.01
None of the studied morbidities	68%	65%	0.85	0.65 to 1.13

and 1 to having no problems in any dimension, or “full” HRQoL. The 17D has been used for 8- to 11-year-old children, and the questions were modified after consulting the copyright owners (H. Sintonen and M.Apajasalo) to allow for parental evaluation of HRQoL of 5-year old children (Rautava et al. 2009). QALYs by the age of four years were calculated by defining a HRQoL score for each day of life and then multiplying this by the number of days alive up to age four. The HRQoL was assumed to be constant for all days after discharge from the initial hospitalisation period. This “home score” was acquired from the parental 17D questionnaire at the age of five years. Separate HRQoL scores were estimated for the days of the VLBW infants’ initial hospitalisation period. Immediately after birth, the VLBW infants were assumed to have an “all worst” HRQoL score, meaning that the infants were given the worst score for each 17D dimension, and thus the total 17D score was 0.13 after appropriate weighting of each dimension score. Before discharge to home, the HRQoL scores increased linearly from “all worst” to “home score,” which was reached on the day of discharge. If the infant died during the initial hospitalisation period, then the “all worst” score linearly decreased to 0 until the day of death. The QALY was based on the HRQoL. The QALY was estimated for those with missing QALY according to morbidities and GA. All parents gave their written permission for participating in the study.

4.2.2 Statistical analysis

Data from the registers, parental questionnaires, and the cost data were linked with a unique anonymous ID code. Analyses were performed with LIMDEP 9.1 (Econometric software, inc, NY, USA), Stata 9 (StataCorp, Texas, USA), Statistical Package for Social Sciences for Windows version 13.0 (SPSS, Chicago, Illinois, USA), and SAS 9.1 (SAS Institute, Cary, NC, USA). χ^2 tests were performed on dichotomized variables and analyses of variance were used to compare means. $P < 0.05$ was considered as statistically significant. All costs are presented in 2008 prices, with a discount rate of 3% per year.

4.2.2.1 Factors associated with the initial length of stay (I)

The relationships between LOS and selected independent risk factors were studied using a generalized linear model (GLM). Based on a modified Park test (Manning et al. 2001), GLM with log link and Poisson distribution was used. Those with exceptionally long initial LOS were removed from the analysis. The high LOS outliers were defined by dividing the infants into subgroups by birth weight (<500, 500–749, 750–999, 1 000–1 249, 1 250–1 499 and 1 500 g or more), and the cases with LOS exceeding the geometric mean by 2 standard deviations N=45 (2.5%) were removed (Cots et al. 2003). Statistically significant factors ($p<0.05$) were entered in the model. To obtain sufficient sample sizes for all factors, we did not include binomial independent factors with a representation below 2% in the less frequent category in the analysis.

The maternal factors tested in the analysis included age, number of hospital antenatal visits, smoking during pregnancy, incidence of hospitalisation due to bleeding or high blood pressure during present pregnancy, nationality (Finnish or other), and dichotomized (yes/no) history of previous pregnancies, miscarriages, abortions, extrauterine pregnancies, deliveries, stillbirths, or Caesarean sections. Delivery-related factors included time of birth (office hours vs. outside office hours covering public holidays, weekends, and time between 4:01 pm and 7:59 am), mode of delivery (Caesarean section vs. vaginal), and the occurrence of the following diagnoses: placenta praevia, abruption placentae, eclampsia, and breech or other malpresentation. Infant-related factors included birth weight, GA, intrauterine growth, gender, multiple birth, Apgar score at 1 min, ventilator treatment within seven days of birth, and death as an endpoint of the care episode. Hospital-district-related factors included birth hospital district (five regions each covered by one university hospital), number of very preterm births per year in the hospital of birth, back-transfer before discharge, level of discharging hospital, and distance between home and discharging hospital. In addition, we tested the association between LOS and rehospitalisation within one year of initial discharge.

We also completed a collinearity analysis, which showed a significant correlation between birth weight and GA. Birth weight was removed from the multivariate model because analysis based on GA is clinically more relevant.

4.2.2.2 Morbidities and hospital resource use (II)

The LOS and the number of rehospitalisation days and outpatient visits within the first three years of life were calculated from the National Hospital Discharge Register. Both the matched control group and the whole population of full-term infants were included to compare the frequency of the diagnoses between the preterm and full-term populations.

The association between morbidities and the use of hospital resources was analyzed using a negative binomial model as was required on the basis of the results obtained from over-dispersion analysis. The results were presented as marginal effects, which were evaluated for each individual averaged over its sample. The marginal effects were presented as the number of days for the initial LOS and for other inpatient hospital stays, and as the number of outpatient visits. For continuous variables, the marginal effect demonstrates how a change of one unit in the independent variable affects the studied variable (ie. the increase or decrease in hospital days or number of visits). For discrete variables the change is presented as a comparison to the reference. The analyses were adjusted for GA at birth, gender, SGA, multiple birth and birth hospital. In addition, the year of birth was added as an explanatory factor, as the follow-up time of the morbidities differed among individuals (3–6 years). Birth weight was not added in the analysis due to its collinearity with GA and SGA.

4.2.2.3 Costs and QALY during the first four years of life (III)

The number of inpatient and outpatient visits and the number of hospital days during the first four years of life were presented as means and medians, and costs of hospitalisations were presented as means and standard deviation (SD). All analyses were made separately according to GA and morbidities. The costs were presented in 2008 prices, with a discount rate of 3% per year. In the cost per QALY analysis, the total costs of survivors and non-survivors were divided by the total QALYs of survivors and non-survivors when calculating the cost per QALY according to GA. The non-survivors were removed from the analysis when determining the cost per QALY according to morbidities. The 5% confidence intervals (CI) were calculated by bootstrapping simulation.

4.2.2.4 Costs during the fifth year of life (IV)

The parents of 588 (65% of all surviving) children born very preterm and 176 (46%) controls returned the questionnaire. The analysis included the number of visits during the fifth year of life to a 1) physician, 2) nurse practitioner, 3) PT or OT, 4) psychologist,

5) speech therapist, 6) dietician, and 7) for other services (family support clinic, family adaptation courses, training in sign language, home visits, and use of communal transfer services) based on the parental questionnaire responses. The number of inpatient days was received from the register data, as well as the number of non- emergency and emergency outpatient visits to specialized health care. The register data on hospital visits and the parental reports on contacts with other health and social care professionals and use of other municipal resources were combined with the cost data to obtain a net cost per child during the fifth year of life.

The costs and the number of visits were analyzed according to GA and the presence of morbidities in the very preterm population (no morbidities, one or more prematurity-related morbidity). In addition, we used a generalized linear model with gamma distribution to analyze the effect of morbidities on the costs of health-care use during the fifth year of life. The model was adjusted for sex, GA at birth, intrauterine growth (SGA, AGA, or LGA), and multiple pregnancy. The marginal effect describes how the presence of the studied morbidities affects the costs during the fifth year of life.

5 RESULTS

5.1 Survival of very preterm infants (I)

Altogether 295 stillborn and 2 031 live-born infants were included in the analysis. Of the live-born infants, a total of 87% (N=1767) survived to the age of one year. Of the non-survivors, 78.8% (N=208) died within five days of delivery. Of those surviving six days, 3.1% (N=56) died and the rest were discharged home. Table 7 presents the survival rates according to GA.

Table 7 Total survival rate according to GA

GA (weeks)	Number of still born infants	Number of live-born infants	Died before the age of 6 days	Died between the age of 6 and 365 days	Alive after first year
			N (% of live born)		
22	54	33	30 (90.9)	2 (6.1)	1 (3.0)
23	39	52	32 (61.5)	4 (7.7)	16 (30.8)
24	36	103	36 (35.0)	7 (6.8)	60 (58.3)
25	31	109	27 (24.8)	7 (6.4)	75 (68.8)
26	21	103	17 (16.5)	4 (3.9)	82 (79.6)
27	24	175	12 (6.9)	13 (7.4)	150 (85.7)
28	17	178	8 (4.5)	3 (1.7)	167 (93.8)
29	11	227	5 (2.2)	7 (3.1)	215 (94.7)
30	15	326	9 (2.8)	4 (1.2)	313 (96.0)
31	19	465	17 (3.7)	2 (0.4)	446 (95.9)
32 or more	28	260	15 (5.8)	3 (1.2)	242 (93.1)
All very preterm	295	2031	208 (10.2)	56 (2.8)	1767 (87.0)

5.2 Morbidities (II)

Of very preterm infants, 66% did not have any of the morbidities studied. The prevalence of morbidities diagnosed during the first 3–6 years of life classified by GA is presented in Table 8. The prevalence of morbidities generally decreased with increasing GA. The most common disease category was obstructive airway diseases. One tenth of the very preterm infants had more than one of the studied morbidities. The morbidity rates were similar in the matched full-term control group and in the total full-term population.

Table 8 The prevalence of major disorders during the first 3 to 6 years of life according to GA in very preterm infants surviving to the age of 3 years, in the full-term matched control group and in the full-term population.

GA (weeks)	N	CP %	Seizures %	Obstructive Airway Disease %	Hearing Loss %	Visual Disorder %	Other Ophtalmologic Problem %	No Morbidities %	2 Morbidities or more %
22-23	17	11.8	17.6	29.4	17.6	29.4	35.3	41.1	47.1
24-25	135	11.1	5.9	40.0	5.9	8.1	31.1	37.9	33.3
26-27	234	8.5	4.7	31.2	2.6	6.4	22.0	50.9	15.8
28-29	391	8.2	3.8	22.0	3.3	2.0	10.0	63.4	8.2
30-31	771	4.2	1.0	14.4	1.4	3.0	10.2	74.6	7.4
32 or more	248	3.2	3.2	12.1	1.6	2.4	8.9	75.9	5.6
All very preterm	1 796	6.1	3.0	20.0	2.5	3.8	13.4	66.2	10.4
Matched full-term controls	395	0.3	0.8	3.5	0.5	0.8	1.5	93.7	1.0
Full-term population	200 609	0.15	0.75	4.7	0.30	0.60	2.3	92.0	0.76

5.3 Initial LOS (I)

The mean initial LOS in very preterm survivors was 64 days and the median 55 days. The LOS of the surviving infants decreased with increasing GA, while there was no clear trend for the LOS of the non-survivors (Table 9). The median LOS for non-survivors was two days (i.e. died on the day following birth).

Table 9 Initial LOS of survivors according to gestational age.

GA (weeks)	Initial LOS in days					
	Survivors		Non-survivors		All	
	Mean (SD)	Median (Min, Max)	Mean (SD)	Median (Min, Max)	Mean (SD)	Median (Min, Max)
22	133	133 (133,133)	2 (3)	1 (1, 16)	6 (25)	1 (1, 133)
23	137 (20)	132 (99, 170)	3 (3)	1 (1, 18)	46 (64)	4 (1, 170)
24	132 (63)	123 (68, 517)	6 (13)	2 (1, 65)	78 (79)	95 (1, 517)
25	117 (89)	101 (69, 846)	5 (5)	3 (1,23)	81 (91)	89 (1, 846)
26	107 (57)	96 (62, 645)	18 (42)	3 (1, 156)	87 (73)	90 (1, 645)
27	87 (34)	79 (34, 400)	30 (65)	7 (1, 270)	77 (46)	79 (1, 400)
28	73 (20)	70 (30, 170)	20 (59)	1 (1, 208)	69 (29)	69 (1, 208)
29	64 (23)	60 (31, 261)	35 (60)	9.5 (1, 190)	62 (28)	59 (1, 261)
30	52 (18)	48 (20, 402)	58 (81)	5 (1, 286)	53 (32)	48 (1, 402)
31	44 (23)	40 (16, 332)	9 (17)	2 (1, 62)	43 (25)	39 (1, 332)
32 or more	41 (20)	35 (20, 340)	11 (24)	2 (1, 103)	40 (29)	36 (1, 340)
All very preterm	64 (42)	55 (16, 846)	14 (39)	2 (1, 286)	57 (46)	49 (1, 846)

The GA at discharge varied among the hospital districts. Those born at 28-32 weeks were discharged earlier compared with those born at GA of less than 28 weeks or more than 32 weeks. The GA at discharge according to hospital district, GA at birth, and BW are presented in Table 10.

Table 10 Gestational age at discharge according to birth hospital district (all non-survivors and LOS-outliers excluded).

Hospital district	Gestational age at discharge according to gestational age at birth (median, IQR)			Gestational age at discharge according to birth weight (median, IQR)	
	<28 weeks	**28-32 weeks**	**>32 weeks**	**<1000 g**	**≥1000 g**
1	39+6 (38+2;42+4)	37+2 (36+2;38+6)	38+1 (37+3;39+3)	40+6 (39+0;44+1)	37+3 (36+6;40+0)
2	38+0 (37+2;40+0)	36+4 (35+5;38+1)	38+0 (36+6;39+1)	39+0 (37+6;40+0)	36+5 (35+5;38+0)
3	38+4 (37+6;40+2)	37+4 (36+3;38+6)	38+6 (38+2;40+3)	39+4 (36+3;41+0)	37+5 (36+4;39+6)
4	39+2 (38+4;41+4)	37+6 (36+5;39+0)	39+3 (38+2;40+2)	40+3 (38+7;42+3)	37+6 (36+6;39+2)
5	41+6 (39+5;44+0)	38+3 (37+2;39+5)	38+6 (38+1;39+2)	41+5 (39+4;44+4)	38+3 (37+2;39+2)
All	39+5 (38+1;42+2)	37+3 (36+3;38+6)	38+5 (37+5;39+6)	40+2 (38+4;42+6)	37+4 (36+3;38+6)

When estimating factors associated with the initial LOS, the model that fitted the LOS data best is presented in Table 11. According to the model, a one-day increase in GA decreased LOS by one day. LOS was 35.8 days shorter if the infant died before discharge home. Back-transfer increased LOS by 1.7 days, and those infants who were discharged from a level III NICU had 1.3 days longer LOS compared to infants discharged from a level I or II NICU. Those who were not rehospitalized within one year after the initial discharge had 4.1 days shorter LOS compared to those with at least one rehospitalisation.

In addition, the birth hospital district affected LOS markedly as we found that the LOS was 10.5 days longer in the hospital district with the longest LOS compared to the

Table 11 Multivariate generalized linear model for LOS. The effects of the individual factors are presented as marginal effect and 95% CI. The marginal effects were calculated at the means of the independent variables. For continuous variables the marginal effect describes how change in one unit affects the LOS. For discrete variables the change is from 0 to 1.

Factor		N	Marginal effect		
			Days	95% CI	
Mode of delivery: Caesarean –sectio	no*	588			
	yes	1190	2.9	2.1	3.6
Gestational age at birth (increase of one day)			-1.07	-1.10	-1.05
Apgar score at 1 min (increase of one point)			-0.7	-0.9	-0.5
Sex	female*	800			
	male	978	1.7	1.0	2.4
Multiple pregnancy	no*	1267			
	yes	511	2.6	1.8	3.4
Ventilator treatment within 7 days of birth	no*	776			
	yes	1002	5.0	4.3	5.8
Birth weight for GA	AGA*	1228			
	SGA	501	13.7	12.7	14.6
	LGA	49	-7.6	-9.5	-5.6
Mode of separation	home*	1729			
	death	49	-35. 8	-36.9	-34.6
Back-transferred before discharge home	no*	1188			
	yes	590	1.7	0.7	2.7
Discharge from a level III hospital	no*	908			
	yes	870	1.3	0.4	2.3
Distance between home and hospital (100km)			1.8	1.1	2.4
Hospital district					
#1 (93.7 % born in level III hospital)		650	-4.6	-5.6	-3.5
#2 (77.4%)		257	-10.5	-11.5	-9.3
#3 (64.2%)		332	-4.7	-5.8	-3.5
#4 (53.1%)		294	-2.3	-3.6	-1.1
#5* (88.6%)		245			
Rehospitalisation	no*	939			
	yes	839	4.1	3.3	4.8

* reference

hospital district with the shortest LOS. There were no distinct differences among the five university hospital districts in the factors reflecting biological (birth weight, GA at birth), and socio-economic status (age of the mother, smoking during pregnancy) of the cases. The average distance between the discharging hospital and home varied in the districts from 16km to 44km.

5.4 Other hospitalisations during the first four years of life (II, III)

The number of outpatient visits and inpatient hospital days during the first four years of life classified by GA is presented in Table 12 and Table 13. The need for inpatient care and the number of outpatient visits decreased with increasing GA. An exception to this was a higher rate of rehospitalisations and a higher number of outpatient visits during the second, third and fourth year of life in very preterm infants born at or after 32 weeks of gestation compared to the those born at 30 to 31 gestational weeks.

Table 12 Outpatient visits during the first four years of life (very preterm N=1 752, full-term N=200 609).

GA (wk)	Number of non-emergency outpatient visits – mean (median)				Number of emergency outpatient visits – mean (median)			
	1. year	**2. year**	**3. year**	**4. year**	**1. year**	**2. year**	**3. year**	**4. year**
23	21.8 (22)	9.7 (8)	7.4 (6)	5.1 (3)	1.5 (1)	0.7 (0)	0.7 (0)	0.3 (0)
24	18.5 (17)	12.6 (6)	8.1 (5)	6.4 (3.5)	1.6 (1)	1.2 (1)	0.9 (0)	0.4 (0)
25	17.1 (15)	8.4 (6)	5.3 (4)	3.7 (3)	1.3 (1)	1.2 (0)	0.7 (0)	0.4 (0)
26	16.9 (13)	7.3 (5)	4.7 (3)	2.3 (1)	1.2 (1)	1.4 (1)	0.7 (0)	0.3 (0)
27	14.5 (13)	6.9 (5)	4.6 (3)	3.3 (2)	1.8 (1)	1.2 (0)	0.7 (0)	0.5 (0)
28	15.2 (12)	6.8 (4)	4.1 (2)	3.1 (1)	1.5 (1)	0.8 (0)	0.5 (0)	0.2 (0)
29	12.9 (11)	5.2 (3)	2.8 (2)	2.2 (0)	1.2 (1)	0.5 (0)	0.3 (0)	0.2 (0)
30	11 (9)	3.8 (2)	2.4 (1)	1.8 (0)	1 (0)	0.5 (0)	0.3 (0)	0.2 (0)
31	8.6 (7)	3.4 (2)	1.8 (1)	1.2 (0)	1 (0)	0.5 (0)	0.3 (0)	0.2 (0)
>31	8.7 (7)	4.4 (2)	2.5 (1)	1.6 (0)	1 (0)	0.5 (0)	0.3 (0)	0.2 (0)
All	11.9 (9)	5.2 (3)	3.1 (1)	2.2 (0)	1.2 (0)	0.7 (0)	0.4 (0)	0.2 (0)
Full-term	0.9 (0)	0.6 (0)	0.5 (0)	0.5 (0)	0.3 (0)	0.3 (0)	0.2 (0)	0.1 (0)

Table 13 Inpatient hospitalisations during the first four years of life (very preterm N=1 752, full term N=200 609)

GA (wk)	Rehospitalisation rate				Rehospitalisation days – mean (median)			
	1. year	2. year	3. year	4. year	1. year	2. year	3. year	4. year
23	65%	41%	47%	35%	12.2 (6)	8.7 (5)	3.9 (3)	3.7 (3.5)
24	59%	44%	44%	30%	9.3 (6)	7.3 (6)	4.4 (3)	3.7 (2)
25	67%	34%	30%	21%	11.6 (6)	6.7 (5)	5.0 (4)	4.1 (3)
26	51%	41%	21%	9%	7.2 (4)	4.4 (3)	4.2 (4)	11.3 (3)
27	59%	35%	28%	20%	8.7 (5)	6.7 (4)	3.8 (3)	4.1 (2)
28	52%	33%	25%	16%	10.6 (5)	8.4 (4)	8.2 (2)	4.5 (3)
29	49%	25%	16%	15%	7.8 (4)	4.7 (3)	3.2 (1.5)	4.0 (3)
30	40%	21%	16%	12%	8.1 (3)	7.0 (3)	4.1 (2)	11.4 (3)
31	43%	16%	13%	10%	7.0 (4)	6.4 (3)	4.6 (3)	3.5 (2)
>31	38%	24	13%	12%	8.9 (4)	4.3 (2)	3.5 (3)	5.0 (3)
All	47%	26%	19%	14%	8.5(4)	6.2 (3)	4.6 (3)	5.4 (3)
Full-term	20%	16%	11%	9%	5.5 (3)	2.7 (1)	2.5 (1)	2.8 (1)

5.5 The effect of morbidities on the hospitalisations (II, III)

Hospital resource use in association with later morbidities is presented in Table 14. GA had the greatest effect on the initial LOS. In addition, SGA infants had 18 days longer initial LOS compared to non-SGA infants, and infants born from multiple pregnancies had three days longer initial LOS compared to infants born from singleton pregnancies. The infants who later in life were diagnosed with CP, later obstructive airway disease, hearing loss, visual disturbances or blindness, or other ophthalmologic problems had a mean of 7, 8, 12, 17, and 3 days longer initial LOS, respectively, compared with infants without these morbidities. When the child had one (23.4%) or more (10.4%) of the studied morbidities, the median initial hospital stay was 14 ($p<0.001$) and 32 ($p<0.001$) days longer, respectively.

Two of the six studied diagnoses (seizures and obstructive airway disease) and multiple birth were associated with an increased number of rehospitalisation days during the first year of life (Table 14). Gestational age was not significantly related to the number of rehospitalisation days during the first year of life. CP and later obstructive airway diseases were related to an increased number of rehospitalisation days during the second and the third year of life. In addition, all but one morbidity group were associated with an increased number of outpatient visits during either the second or the third year of life compared with infants without these morbidities.

Table 14 The association between gender, SGA, multiple birth, gestational age, morbidities, birth hospital, and the year of birth on the use of hospital resources during the first three years of life is presented. The marginal effects describe how the given variable associates with the number of days/visits compared with the reference group.

			Marginal effects						
		N	**Initial LOS (no. of days)**	**Other hospital stays (no. of days)**			**Outpatient visits (no. of visits)**		
				1. year	**2. year**	**3. year**	**1. year**	**2. year**	**3. year**
Initial LOS			.	***0.03***	.	.	0.002	.	.
Multiple birth	**Yes**	506	**2.6**	**1.6**	0.2	0.2	-0.2	0.4	-0.1
	No *	1290							
SGA	**Yes**	495	***18.3***	0.7	***2.3***	**0.6**	***1.1***	***1.9***	***1.4***
	No *	1301							
Gender	**Male**	996	**2.9**	0.3	***1.3***	**0.4**	0.4	0.01	0.3
	Female *	800							
Gestational age	**22-23**	17	***81.8***	-1.1	2.0	0.8	2.8	**4.0**	**2.8**
	24-25	135	***77.9***	1.3	**3.3**	**1. 5**	***3.4***	***4.0***	***2.5***
	26-27	234	***61.0***	0.02	***2. 9***	0.7	***3.2***	***3.5***	***2.4***
	28-29	391	***41.3***	1.4	***2.3***	0.5	***3.3***	***2.5***	***1.5***
	30-31	771	***19.9***	0.9	**1.5**	0.4	**1.6**	**0.8**	0.3
	32 or more	248							
CP		109	**6.9**	1.0	**2.9**	**1.7**	***2.9***	***5.0***	***3.1***
Seizures		53	3.5	***7.1***	1.8	0.8	***2.7***	***2.4***	***2.0***
Obstructive airway disease		359	***8.2***	***6.1***	**3.6**	**1.3**	***2.2***	***2.9***	***2.4***
Hearing loss		45	***12.1***	1.7	2.1	**1.4**	***6.0***	***4.8***	***4. 3***
Visual disorder		68	***17.3***	0.04	**2.5**	0.8	0.1	0.4	0.3
Other ophthalmologic problems		240	**2.7**	1.3	0.3	0.5	**0.9**	***1.8***	***2.0***
Birth hospital	**University Hospital 1**	606	-0.7	**-1.8**	-0.8	-0.3	***-1.1***	***-1.4***	-0.3
	University Hospital 2	199	***-8.3***	**-1.8**	-0.7	**-1.3**	0.4	-0.6	0.4
	University Hospital 3	158	**5.0**	-0.5	1.0	0.2	**1.1**	-0.3	**1.0**
	University Hospital 4	228	***7.4***	**-2.4**	0.2	-0.3	***-2.9***	**-1.0**	0.03
	University Hospital 5	213	1.3	-0.7	0.3	0.2	-0.5	-0.4	0.2
	Other hospitals *	392							
Year of birth	**2003**	399	**2.82**	**2.60**	**1.01**	***0.82***	***1.44***	0.27	**0.84**
	2002	450	**3.15**	-0.34	-0.21	0.32	**0.68**	-0.22	**0.53**
	2001	467	0.85	-0.19	0.03	0.41	0.52	0.19	0.37
	2000 *	480							

* Reference group, bold $p < 0.05$, bold and italic $P < 0.001$,

5.6 Reasons for inpatient and outpatient visits during the first four years of life

Prematurity-related neurosensory and other prematurity-related follow-up were the most common diagnoses for outpatient visits during the first year of life. Later, neurosensory impairments and CP were the most common diagnoses. During the first years of life, allergies dominated the outpatient visits in the controls, comprising 13-15% of the visits. Other common diagnoses in the controls were related to diabetes mellitus type I, follow-up of otitis media and later asthma. Respiratory infections and gastroenteritis were the most common reasons for outpatient emergency hospital visits for both preterm children and controls during the first four years of life.

In the very preterm population, prematurity related complications were the dominating reasons for hospitalisations during the first year of life. Later, upper respiratory infections and spastic diplegia were common diagnoses, comprising 43% and 6% of the hospital visits respectively. For controls, the most common reasons were related to upper respiratory and gastrointestinal infections.

5.7 Costs of hospitalisations (III, IV)

The mean cost of initial hospitalisation in the very preterm population was 54,104 € in the surviving infants, and 49,916 € when also non-survivors were included. The mean cost of initial hospitalisation in very preterm non-survivors was 18,217 €. The total costs of hospitalisations decreased with increasing GA in survivors (Figure 1). The initial hospital stay comprised 76-88% and the total first-year costs comprised 89-96% of the total four-year costs in the very preterm survivors. Figure 1 demonstrates that the majority of the hospital costs accumulated during the first year of life in all GA groups. The hospitalisation costs decreased with age in all GA groups (Figure 2), and in all morbidity groups (Figure 3 and Figure 4). The annual costs according to GA and morbidities are presented in Appendices 1-5.

Prematurity-related morbidities were associated with increased costs in the very preterm population (Figure 3 and Figure 4). The mean total costs in a very preterm child without any of the studied morbidities was 49% of the mean total costs of a child with multiple morbidities. Hearing loss and CP were associated with higher costs for non-emergency outpatient visits, whereas obstructive airway diseases were associated with the highest costs for emergency outpatient visits. The 10% of very preterm born with two or more prematurity-related morbidities comprised 19% of the total four-year costs, whereas the respective figure was 52% in those 66% without morbidities.

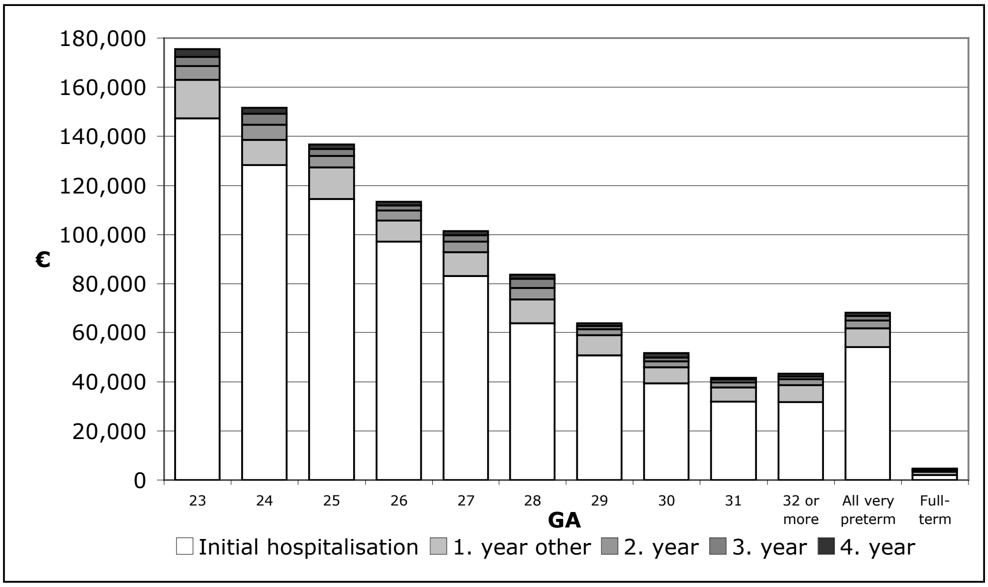

Figure 1 Mean hospital costs during the first four years of life according to gestational age in the very preterm and full-term control populations.

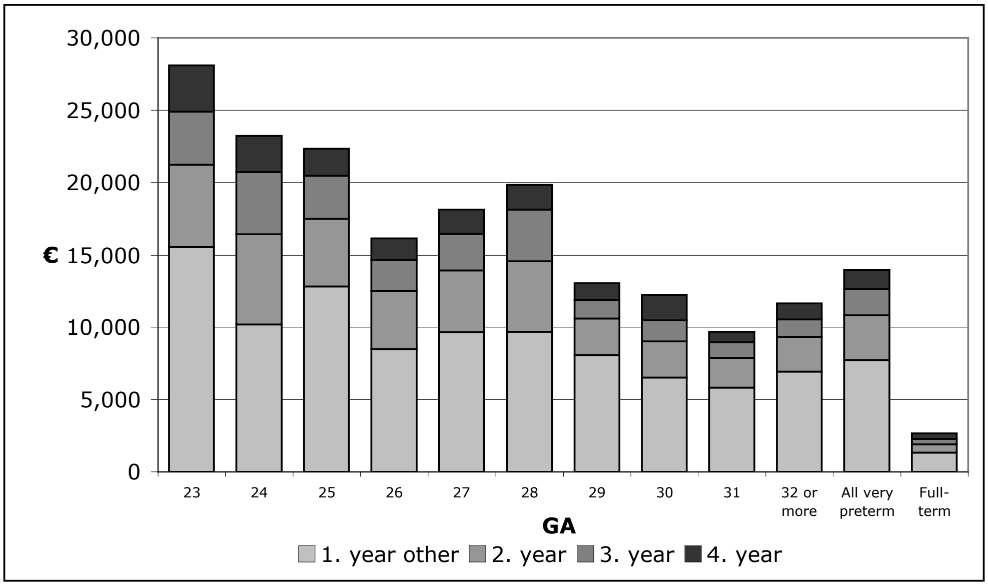

Figure 2 Mean hospital costs after the initial hospital stay during the first four years of life according to gestational age in the very preterm and full-term control populations.

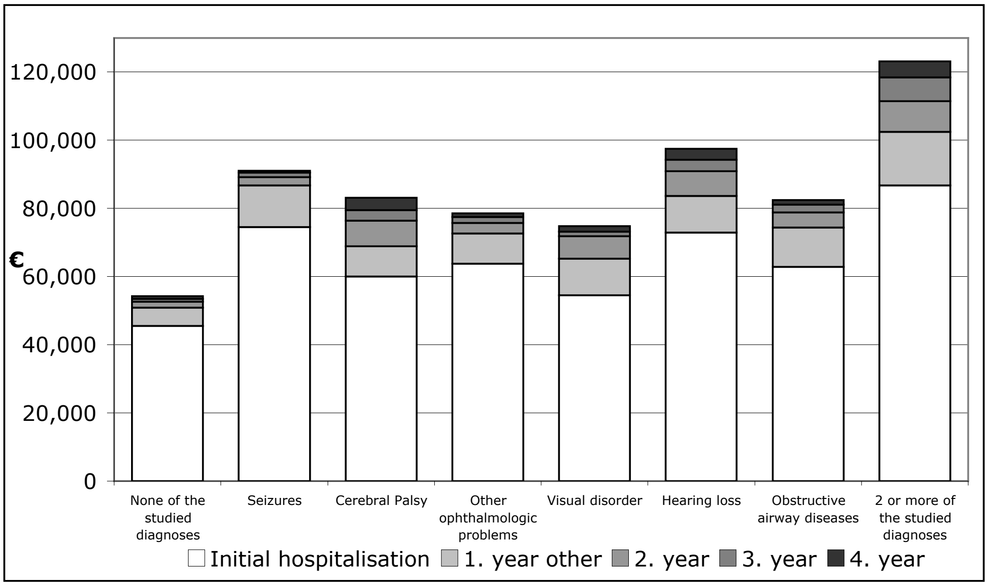

Figure 3 Mean hospital costs during the first four years of life according to morbidities in the very preterm population.

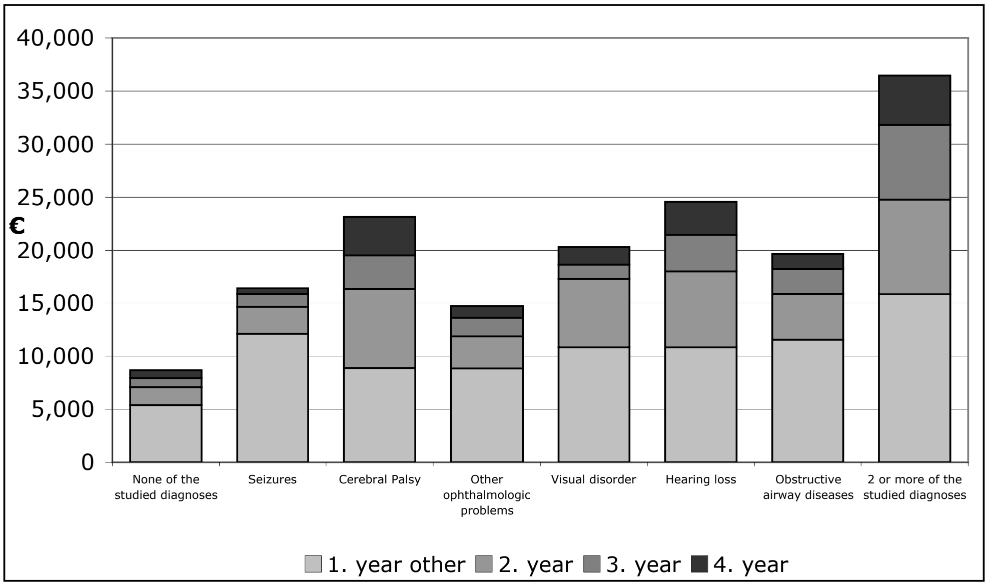

Figure 4 Mean hospital costs after the initial hospital stay during the first four years of life according to morbidities in the very preterm population.

5.8 Costs per QALY at four years of age (III)

The QALY and cost per QALY according to GA and morbidities are presented in Table 15. No significant differences were found in the cost per QALY between males and females. The total hospital cost per QALY was 1,181 € for term controls at four years of age. The cost per QALY decreased with increasing GA (Figure 5). In the preterm group, the mean cost per QALY was 19,245 €, ranging from 11,824 € for those born at 32 weeks of gestation or later to 54,324 € for those born at 23 weeks of gestation. The cost per QALY was 14,368 € for those without any of the studied morbidities, and 36,110 € for those with two or more morbidities (Table 15).

Table 15 QALY and costs per QALY during the first four years of life according to gestational age in the very preterm survivors and non-survivors and full-term controls and QALY and costs per QALY according to morbidities in the very preterm survivors.

GA (weeks)	QALY at four years of age		Total cost per QALY in survivors and non-survivors € (N=2 030)		
	Survivors only (N=1 752)	Survivors and non-survivors (N=2 030)	Mean	95 % CI Low	95 % CI High
23	3.61	1.20	54,324	32,600	83,012
24-25	3.63	2.87	41,166	35,793	46,981
26-27	3.67	3.00	31,074	28,631	33,601
28-29	3.71	3.50	20,378	19,146	21,670
30-31	3.76	3.58	12,840	12,102	13,583
32 or more	3.77	3.47	11,824	10,717	13,046
	QALY at four years of age		**Total cost per QALY € Mean**	95 % CI Low	95 % CI High
Full-term control group	3.88		1,181	1,166	1,195
Morbidity	**QALY at four years of age (N=1 752)**		**Total cost per QALY € (N=1 752) Mean**	95 % CI Low	95 % CI High
None of diagnoses below	3.79		14,368	13,843	14,849
Seizures	3.87		23,868	14,920	36,020
Cerebral Palsy	3.69		22,546	20,014	25,383
Other ophthalmologic problems	3.75		21,073	18,931	23,262
Visual disorder	3.50		21,469	16,688	25,942
Hearing loss	3.53		27,588	21,354	34,038
Obstructive airway diseases	3.64		22,850	20,884	24,985
2 or more of the above diagnoses	3.48		36,110	32,733	39,579

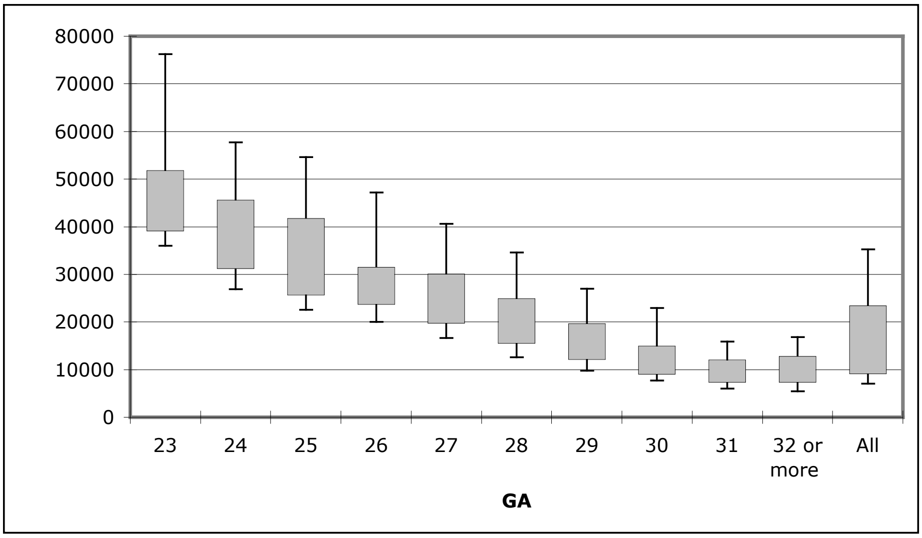

Figure 5 Cost per QALY at four years of age according to gestational age in very preterm born (the boxes present the IQR and the whiskers present the 10th and 90th percentiles).

5.9 Health-care-related costs during the fifth year of life (IV)

The average total health care costs during the fifth year of life amounted to 749 € in controls, 1,023 € in very preterm children without prematurity-related morbidities, and 3,265 € in those with one or more of these morbidities (Table 16 and Figure 6). Thus, the costs of preterm children without prematurity-related morbidities were 1.4-fold higher than the costs of term controls. On the other hand, the costs of the preterm children with morbidities were 4.4-fold compared to those of the term controls. They comprised 61% of the total costs in the very preterm population. The mean costs of all cost categories except the visits to the nurse practitioner were lower in very preterm children without than with prematurity-related morbidities.

The costs of hospital care comprised only 33% of the total costs in the very preterm population. The costs for therapies (PT/OT, psychologist, speech therapy) comprised 44% of the total costs in the very preterm born children with morbidities, 27% in those born very preterm without morbidities, and 30% in the controls. The hospital in- and outpatient costs comprised 37% of the total costs in very preterm infants with morbidities, 34% in those without morbidities, and 17% in the controls. The costs decreased with increasing GA (Figure 7).

Table 16 Mean and median costs of visits to hospitals and health-care professionals during the fifth year of life according to morbidities in the very preterm population and the full-term control population.

	Costs € - Mean (Median)			Significance	
	No morbidities (N= 400)	1 or more morbidities (N=188)	Full term (N=176)	1 or more morbidities vs. no morbidities P Value	No morbidities vs. controls P Value
Emergency outpatient	18 (0)	48 (0)	12 (0)	0.0005	NS
Non-emergency outpatient	157 (0)	814 (524)	73 (0)	<.0001	<.0001
Hospitalisation	170 (0)	356 (0)	41 (0)	0.0055	NS
Other physician	332 (244)	443 (356)	296 (237)	0.0007	NS
PT/OT	103 (0)	1108 (0)	67 (0)	0.0001	0.0063
Psychologist	46 (0)	109 (0)	40 (0)	<.0001	NS
Nurse	55 (54)	52 (54)	42 (54)	NS	NS
Speech therapist	124 (0)	233 (0)	117 (0)	0.0194	0.0070
Other	18 (0)	103 (0)	62 (0)	<.0001	NS
Total	1023 (423)	3265 (1368)	749 (291)	<.0001	0.0008

NS=Not significant

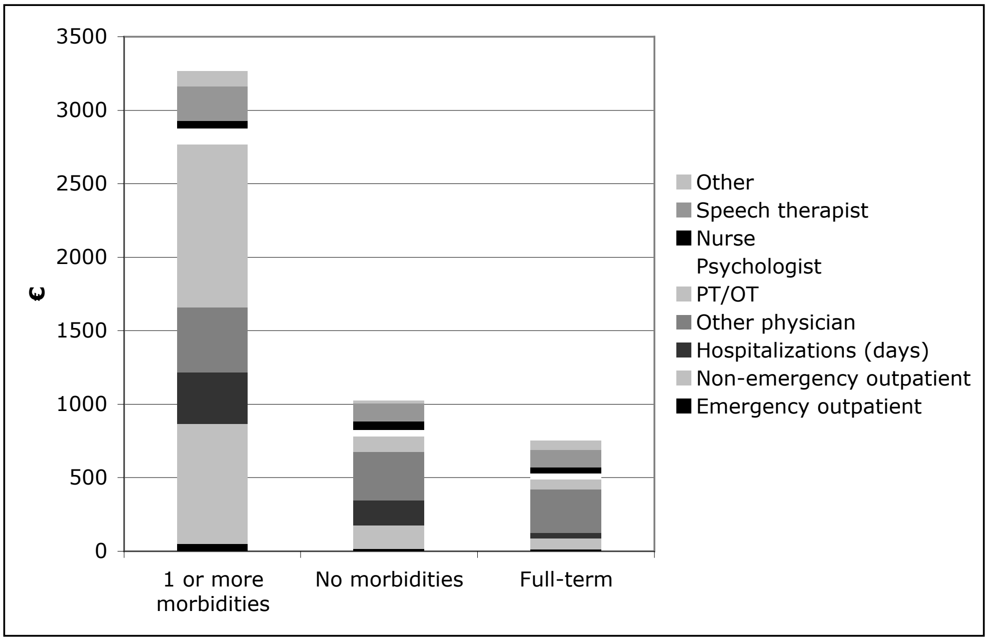

Figure 6 Mean health-care-related costs during the fifth year of life in very preterm infants with and without prematurity-related morbidities, and in the full term control population.

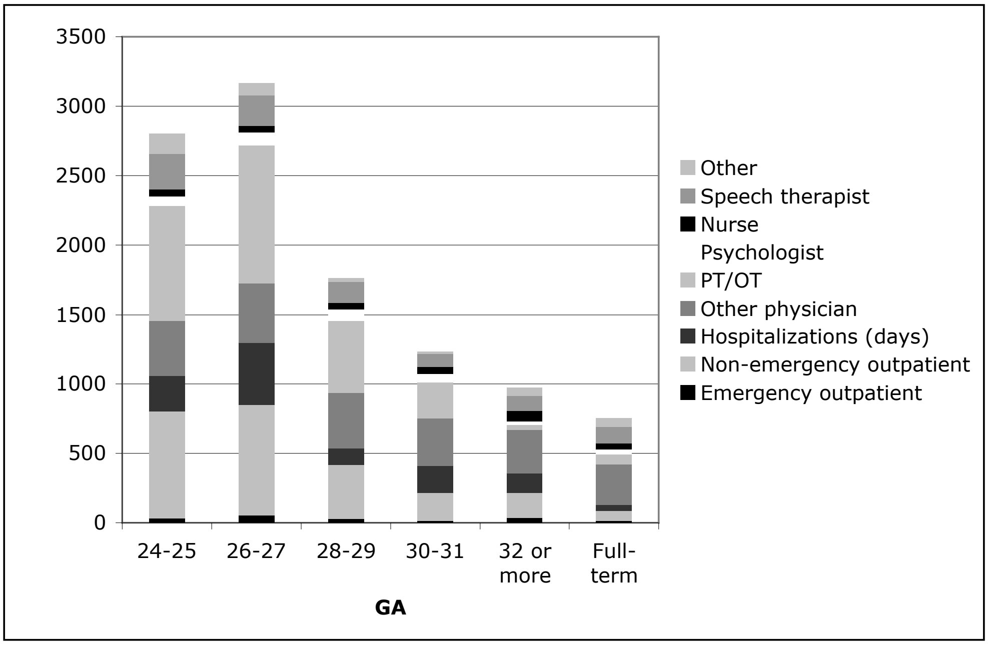

Figure 7 Mean health care –related costs during the fifth year of life according to gestational age (Those born at 23 weeks of gestation were excluded from the figure due to the small number (5) of individuals).

Among children born very preterm, CP was associated with 5,125 € higher costs, whereas later obstructive airway diseases increased the costs by 819 € compared with individuals without these morbidities. The cost increases attributed to each disease group according to the generalized linear model are presented in Table 17. In addition, the average cost for boys was 450 € higher than for girls (p=0.019).

Table 17 The results of a generalized linear model on the effect of morbidities on the total costs of care during the fifth year of life in very preterm infants

Morbidity	N	Marginal effect (€)	95% CI		P Value
Other ophthalmologic problems	81	464	-312	1241	0.187
Visual disturbances or blindness	26	1217	-613	3047	0.079
Hearing loss	8	167	-1785	2118	0.859
Later obstructive airway disease	115	819	148	1490	0.004
Seizure disorder	16	907	-1125	2939	0.264
Cerebral palsy	26	5127	711	9543	<0.001

6. DISCUSSION

6.1 Strengths and limitations

As a full four-year national cohort study of very preterm children, the present study makes an important contribution to the existing literature. The Finnish health care system is unique compared to many other countries as the national social security system covers all Finnish citizens, and municipalities are responsible for providing and financing health care services for their residents. In consequence, a great majority of specialized care occurs in public hospitals, and there are only few private hospitals in Finland. Moreover, there are no private children's hospitals in Finland, so all hospital care for premature infants is given in public hospitals, which report all inpatient and outpatient contacts comprehensively to the national registers in Finland (Gissler et al. 2004). This provided a unique opportunity to study morbidities and all hospitalisations in a national four-year cohort of very preterm infants, compared to earlier studies where the data have been collected from smaller geographic regions or limited populations. In addition, the register data distinguished inpatient care from outpatient care and emergency visits from non-emergency visits, thus providing an opportunity to further detail the characteristics of hospitalisations in the preterm population.

In addition to the length of hospital visits, the diagnoses of the visits are documented in the registers. ICD-10 is used in reporting the diagnoses. Thus, the prevalence of prematurity-related morbidities requiring hospital visits could be studied through the register data. All of the inpatient hospitalisations had at least one diagnosis recorded, and there was a diagnosis for 91% of the emergency outpatient visits and 74% of the non-emergency outpatient visits. There may be regional differences in how actively very preterm infants are being followed up. Despite the ICD-10, there might be some regional differences in applying the diagnostic criteria. However, the prevalence of later problems does not suggest under-reporting as, for example, the prevalences of CP and obstructive lung diseases were in accordance with previous studies, as described below. Another factor supporting the validity of the data was that the morbidities documented by the parents were in accordance with the morbidities from the registers. In addition, it is highly likely that the studied conditions have required hospital visits within the first four years of life in addition to routine controls in primary care.

There are some data-source-related limitations to this study. Firstly, the birth-register data were collected on day seven of life, which excluded prematurity-related complications occurring after the seventh day of life from the analysis. Thus, the effect of such complications on later morbidities and resource use could not be studied. Despite a large set of included factors, the Finnish National Medical Birth Register does not thoroughly cover antenatal, socio-economic and socio-demographic background factors. However, in the case of the latter two, the population of Finland is homogenous compared with many other countries. Neuropsychiatric diagnoses, such as mental retardation, ADHD, feeding disorders, and autism, have been reported to be over-represented in very preterm children. These conditions are usually diagnosed at school age, thus their prevalence could not be reliably estimated in this study. Not being able to include these diagnoses most likely underestimates neuropsychiatric morbidity in the very preterm population. In addition, the data on the use of therapies and social welfare services during the fifth year of life obtained from the questionnaires rely on parental recall. However, as the study period was only one year, it can be assumed that the parents remembered the health-care contacts quite well, especially when there were only a few contacts in most cases.

Another limitation could be that the hospitalisation costs were calculated according to data from five hospitals; thus, actual cost data on all of the hospitalisations were not received. In addition, the detailed way in which the prices of hospitalisations were determined varied among the hospitals, as some hospitals used solely bed-day prices and others used a combination of procedural pricing and bed-day prices. As the initial LOS accounted for the great majority of costs, it was particularly important to assess possible confounders when imputing costs of initial LOS for those without original cost data. According to the drop-out analysis, the frequencies of the studied morbidities were identical in those with and without original cost data. Those without original cost data had, on average, slightly higher GA and birth weight, which is explained by the fact that a greater proportion of those with original costs were born in hospitals with level III NICUs. As hospitals with level III NICUs, due to their case-mix, have higher treatment costs than lower level units, it can be assumed that the imputed costs of the initial LOS were not under-estimated in this study. When estimating the costs of the later hospitalisations and outpatient visits, the costs were imputed according to the type of visit and the diagnosis of the visit. As the care in the public hospitals can be considered similar, the accuracy of the used imputing method should be adequate. Due to the lack of original cost data for the whole very preterm population, a cost-comparison between the hospital districts could not be done.

Comparing the costs of this study with costs from previous studies was challenging in several ways. Firstly, cost analyses including several years require discounting the costs to a chosen time period. Different discounting and prolonging strategies can lead to quite different figures for the same cost data. Some studies have discounted the future costs to the price level of the birth year of the children, while others prolong them to the year in which the study ends, as was done in this study. Another problem in comparing costs in different studies is which currency rates to use. Although the costs in this study were compared in 2008 prices, the currency rates between the US dollar and the Euro have fluctuated a lot during the last decade, and today are different from the rates used in this study. It is important to bear these challenges in mind when interpreting the comparisons of costs in different studies.

Finally, an incremental cost-effectiveness analysis, which is a standard method for evaluating the effectiveness of medical treatments, could not be conducted. This approach was not applicable, as incremental cost-effectiveness analysis compares two or more treatment strategies or technologies. In this context, the only "alternative" treatment strategy would be to withhold active treatment, which most likely would result in death or severe morbidities. Theoretically, if the "not to treat" option would lead to death of all infants, the added QALY would be zero and also the cost would be close to zero. The resulting incremental cost per QALY would be very close to the true cost per QALY presented in our study. However, in real life the "not to treat" strategy would probably lead to increased number of severe morbidities with increasing costs. Therefore, although violating the standard methodology, we decided to use only the cost per QALY ratio when evaluating the cost-effectiveness of care.

6.2 Survival and morbidities

The suvival rate of 87% in the present study is in accordance with previous studies from this decade with survival rates from 77 to 93% (Zeitlin et al. 2008, Fanaroff et al. 2007, Schmitt et al. 2006). As mortality is highest in the lowest GA, decisions on whether to treat the infants in the lowest GAs have an important effect on the total survival rate. The lowest GA group included in our study was 22 full weeks, wereas the lower limit in other studies varied from 22 full weeks (Ringborg et al. 2006) to 25 full weeks (Gilbert et al. 2003). As the current study also included the tiniest very preterm born, the survival rate can be considered to be at a high level in Finland. Of the non-survivors in this study, 79% died within five days of the delivery. The median LOS for the non-survivors was one day, demonstrating that those who do not survive die early and therefore they constitute a small fraction of the total costs.

Two out of three of the children in the very preterm population did not have any of the studied morbidities that are common in this high-risk population. However, the prevalence of one or more of the six diagnoses was 4- to 10-fold higher in the preterm population than among the term-born children. Morbidity was strongly related to GA. The prevalence of five of the six morbidities was clearly highest in those born at 23 weeks of gestation, decreasing thereafter with increasing GA. An exception was later obstructive airway disease, which was most common in children born at 24 to 27 gestational weeks, suggesting that the infants with severe pulmonary problems born at 23 weeks of gestation die early. The incidences of most neurological problems decreased rapidly with increasing GA, in particular, the prevalence of seizures, visual disorder or blindness, and hearing loss was reduced to more than half already in those born at 24-25 weeks. Obstructive airway diseases were the most common diagnoses in the older gestations.

The morbidity rates reported in this study were similar to previous studies for both very preterm and control children. For example, in a cohort of school-aged children, 30% of very preterm children with BPD and 24% of those without BPD presented with wheezing, whereas only 7% of the full term control group were affected (Gross et al. 1998). In the present study 20% of the very preterm children and 5% of the full-term controls had a diagnosis of obstructive airway disease. The CP rate of 6% in this study was also in accordance with recent studies, showing a CP prevalence of 4-9% in the very preterm population (Larroque et al. 2008, Gaddlin et al. 2007, Platt et al. 2007, Vincer et al. 2006). Similarly, the full-term controls had a CP rate of 0.15% in this study, whereas other studies have reported rates around 0.10-0.12 % (Surman et al. 2009, Andersen et al. 2008, Hjern et al. 2008). Hearing impairments have been reported in around 3-5 % VLBW subjects (Doyle et al. 2005, Hintz et al. 2005, Vohr et al. 2005), and in this study 2.5 % of the very preterm infants had a diagnosis related to hearing loss. Blindness rates of 2% have been presented in VLBW children (Darlow et al. 1997), while 3.8% of children in this study had some kind of visual disorder or blindness. Although the definitions of the morbidities in the different studies probably vary to some extent, we can assume that the presence of morbidities are at a relatively low level in Finland, as we also included the lowest GA groups with clearly highest morbidity rates.

6.3 Initial LOS

The initial LOS was longer in this study compared to previous studies from the United States and Great Britain (Phibbs et al. 2006, Gilbert et al. 2003, St John et al. 2000, Powell et al. 1992). Higher survival rates in this study and in the study by Phibbs et al. (2006) are likely to contribute to the longer hospital stays at all gestational ages. Consistently with the findings of others (Phibbs et al. 2006, Beeby 2003), death was significantly associated with shorter LOS and, as in other previous studies (Ringborg et al. 2006, Powell et al. 1992), GA and birth weight had the greatest effect on the LOS of the survivors.

Several organizational factors influenced the LOS. Back-transfer to another hospital before discharge prolonged the LOS. Successful early discharge requires intensive teaching of infant care to the parents, and it is possible that back-transfer disturbs this process. In addition, there were variations in the LOS among birth hospital districts even after the distance between home and the discharging hospital had been adjusted for. Differences in patient management styles and discharge criteria are likely to explain some of the variation. For example, approaches to advancing oral feeding of the infant may differ, leading to different time to reach full oral feeding (Simpson et al. 2002), which is the most common infant skill postponing discharge (Eichenwald et al. 2001). Differences in discharge criteria may partly explain the differences, as using physiological discharge criteria shortens the LOS compared to fixed discharge criteria based on weight or postmenstrual age (Kotagal et al. 1995, Brooten et al. 1986).

Those with no rehospitalisations within one year from the initial discharge had a shorter LOS compared with infants who were hospitalized at least once within the same time period. This suggests that a short LOS has no disadvantageous effects in this population in regard to later need for hospital care. In contrast, increased LOS was associated with later morbidities. Those who later in life were diagnosed with CP, later obstructive airway disease, hearing loss, vision disturbances or blindness, or other ophthalmologic problems had a longer initial LOS. It can be speculated that the children developing later morbidities are more vulnerable from the very beginning, and therefore require longer and more intensive initial hospital care.

6.4 Use of hospital resources after the initial discharge

The rehospitalisation rate of 49% during the first year of life was slightly higher compared to previous studies with similar populations, where the rates were around 42 - 44% (Gray et al. 2006, Leijon et al. 2003, Elder et al. 1999). The need for inpatient and outpatient hospital care decreased with postnatal age. The rehospitalisation rate decreased from 49% during the first year to 28% during the second year and to 21% during the third year of life. This is in line with the findings of Gray et al. (2006), showing a rehospitalisation rate of 30% during the second year of life, and of Leijon et al. (2003), showing a rate of 21% between 1 and 4 years of age.

The effect of morbidities on the use of hospital resources after the initial hospitalisation has, to our knowledge, not been studied before to the same extent as we did. Later obstructive airway diseases and CP were the most resource-demanding morbidities as they were related to an increased number of both in- and outpatient visits throughout the whole study period. Interestingly, hearing loss was associated with the highest number of outpatient visits during the first three years of life. In addition, seizure disorders and other ophthalmologic problems were associated with an increased number of outpatient visits during one or more of the follow-up years. Overall, very preterm children surviving without morbidities required relatively little hospital care after the initial discharge, the rates approaching those of controls each year. Although the children with morbidities had consistently higher numbers of inpatient and outpatient hospital visits compared with children without diagnoses, the number of visits also decreased with age in the group of children with morbidities each year.

During the first year of life, the very premature children had several outpatient visits, of which most were related to routine follow-up to diagnose neurosensory and other prematurity-related conditions. After the first year of life, prematurity burdened the hospitals mainly through outpatient controls of children with morbidities. In contrast, although higher in number, the reasons for emergency outpatient and inpatient visits were similar after the first years of life in the preterm born to those born full term, and the number of these visits decreased with age close to the figures for full-term children.

6.5 Costs

Hospitalisations occurring during the first year of life, in particular the initial hospitalisation, accounted for the vast majority of the total four-year cost of hospital care. In relation to previous studies, our costs for the initial hospital stay were at the lower end, especially compared with studies from the United States (Phibbs et al. 2006, Gilbert et al. 2003, St John et al. 2000). In particular, the costs for non-survivors were markedly lower in our patients, and the fact that the LOS in non-survivors was a lot shorter in our patients is likely to explain most of the differences. A Finnish study on the costs of the initial hospitalisation of 50 ELBW survivors born in one tertiary-care unit during 1996-1997 presented a total cost of 67,375 €, which is in line with our study (Tommiska et al. 2003). Interestingly, a recent Swedish study on all very preterm singleton births in Sweden between 1999-2001, including both survivors and non-survivors, presented somewhat lower costs than this study (Ringborg et al. 2006). Including only singleton births might have led to underestimating the costs in the studies by Gilbert et al. (2003) and Ringborg et al. (2006), as, for example, this study presented shorter initial LOS for singletons. Probable explanations for the differences between the Nordic and the US costs include real wage differences and structural differences in the organization of health care. In addition, the costs in the US studies are mostly based on costs-to-charges ratios, and charges are not accurate measures of hospital costs. Hospital charges reflect different mark-ups for different services and, for example, a study of VLBW infants in California demonstrated that the average charge for the initial hospitalisation overestimated treatment costs by 53% (Rogowski 1999).

In contrast to the initial hospitalisation, the costs of later hospitalisations have not been widely studied. There is one study presenting higher hospitalisation costs during five years following preterm birth in children with any childhood disease (Petrou et al. 2003), but, to our knowledge, there are no studies on the association of prematurity-related morbidities with costs of hospitalisations. This study demonstrated that the hospitalisation costs decreased markedly with age. More importantly, the two-thirds of the very preterm population without prematurity-related morbidities had only slightly higher inpatient and outpatient hospital costs after the first year of life compared to full-term controls, and the differences disappeared by the fourth year of life. Although the costs were consistently higher in those with a lower GA at birth and those with morbidities, the hospitalisation costs decreased significantly with age in all GA groups as well as in all morbidity groups.

Morbidities were associated with higher costs in all types of visits. Non-emergency outpatient costs were particularly high for those with CP, hearing loss and individuals with more than one morbidity. Quite logically, obstructive airway diseases and seizures were associated with the highest emergency outpatient costs. Those with two or more morbidities clearly had the highest costs for later inpatient hospitalisations. The standard deviations of the costs were high in all types of visits in all GA and morbidity groups. In particular, the standard deviations of non-emergency and emergency outpatient visit costs and later hospitalisation costs were high in relation to the mean costs. This indicates that the cost distribution was skewed to the right with a few individuals with especially high costs in all groups.

Acknowledging that hospitalisation costs only form a part of the total costs of prematurity, we studied all health-care-related costs during the fifth year of life. Again, the two-thirds of very preterm infants surviving without prematurity-related long-term morbidities incurred only a slightly more health-care-related costs compared to their full-term peers. On the other hand, prematurity-related morbidities were still associated with a significant cost burden during the fifth year of life. These costs were created especially by PT/OT visits, non-emergency outpatient hospital visits, and inpatient hospital care. This is in accordance with the findings of Stevenson et al. (1996), which showed, in a small regional cohort of low-birth weight children, that disabled children accounted for a disproportionately high amount of the total expenditure (hospital inpatient and outpatient care, visits to GP, special education services) up to age 8–9 years. As Finnish children start school at 7 years of age, the special education costs do not exist yet at five years of age, and could not be included in this study. Although early intervention is included, it is likely that special education will add to the cost burden in later childhood, as prematurity has been shown to be associated with increased need for special education (Johnson et al. 2009).

An important finding was that the costs for therapies, primary care, and visits to private practitioners during the fifth year of life exceeded the costs for hospitalisations, both in the very preterm population and in the full-term controls. Thus, it seems that while the costs of hospitalisations decrease with age in children born very preterm, other health-care-related costs such as costs for social welfare services, and therapies increase, and thereby become more considerable. Consequently, it is likely that measuring only hospitalisation costs will underestimate the later costs of prematurity.

6.6 Costs per QALY

Defining whether a therapy is cost-effective requires a judgment about society's willingness to pay for a life year or QALY gained. To our knowledge, there are no Finnish studies evaluating an acceptable cost-effectiveness threshold for care. Results from international studies propose thresholds varying between 29,000 € and 70,000 € (NICE 2008, Talmor et al. 2006, Coughlin et al. 2003). There are several Finnish studies on the cost effectiveness of care of different treatments. For example, the costs per QALY gained from primary hip and knee replacements were 6,710 € and 13,995 €, respectively (Räsanen et al. 2007), for severe sepsis 2,139 € (Karlsson et al. 2009), for intensive care 2,143-4,185 € (Kaarlola 2007) and for routine cervical and lumbar neurosurgical spinal surgery 2,274 € and 1,738 €, respectively (Räsanen et al. 2006). The methodological differences in these studies, however, complicate direct comparisons of the cost-effectiveness ratios as how both costs and QALYs are calculated have a profound effect on the cost per QALY ratio (Conner-Spady et al. 2003, Kopec et al. 2003). The problems with comparing costs across different studies have been discussed above. In addition, comparing cost per QALY ratios, when the QALYs have been calculated with different tools, should be made with caution. The above-mentioned thresholds can, however, be used as rough comparisons given the lack of identically calculated ratios. It should also be kept in mind that the subjective QALY of similar disease seems to be higher in individuals who have had the disease since childhood compared with those in who the disease occur later, lowering the subjective cost per QALY in the first mentioned.

In this study, the average cost per QALY in very preterm children at four years of age was 19,245 € (ranging from 11,824 € to 54,324 €). The cost per QALY was in all GA groups beyond 28 weeks below the NICE limit. Taking into account the dramatic decrease in costs after the first year of life, the cost per QALY is likely to decrease with each additional follow-up year, supporting the cost-effectiveness of care in this population. Although an incremental cost-effectiveness analysis was not possible in this case, as discussed earlier, the assumption that the "not to treat" strategy would probably lead to severe morbidities with lower QALYs and increasing costs, further supports the active treatment of these infants. A weakness in the calculations is that only hospital costs were taken into account, as data on other costs during the first four years of life were not available. These other health care costs exceeded the hospitalisation costs during the fifth year of life. However, as the total four-year hospital costs, mainly due to the expensive initial hospitalisation, were substantially higher than other health-care-related costs during the fifth year of life, adding these costs would most likely not change the conclusions of this study.

Finally, cost-effectiveness studies often also take into account future costs and QALYs, assuming, for example, that the study individuals reach the age of 70 years. This study showed that the two-thirds of the very preterm population without prematurity-related morbidities had few hospital stays and outpatient visits after the first year of life, and that the need for health care resources decreased significantly even in those with morbidities. Therefore, it is unlikely that adding an estimation of the future visits would increase the cost per QALY ratio; instead, it can be assumed that the cost per QALY will decrease each year as the highest costs for most very preterm infants accumulate during the first year of life. Thus, speculations about the future were not added into this study, as they would most likely not have had any effect on the conclusions.

6.7 Summary and conclusions

The present study showed that most very preterm infants born in Finland survived without prematurity-related morbidities requiring hospital care during the first years of life. However, a minority of children born very preterm developing later morbidities had a long initial LOS and more re-admissions and outpatient visits during the five-year follow-up period. In particular, the number of non-emergency outpatient visits was considerable in individuals with chronic morbidities.

Substantial differences in the initial LOS were observed among hospital districts, leading to speculations that more optimal treatment strategies reducing complications which prolong hospital stay, more effective parental teaching and the use of physiological discharge criteria might shorten the LOS. Benchmarking the hospital districts reaching the shortest LOS could promote practices favouring earlier discharge. Earlier discharge is beneficial to the developing parent–infant relationship and it protects the infant from several environmental risks, including hospital-acquired infections. In addition, a reduced LOS is likely to result in cost savings and thus improve the cost-effectiveness of care.

The first-year hospitalisations, and the initial hospitalisation in particular, accounted for a clear majority of the hospitalisation costs. The costs of the initial hospitalisation were at the lower end compared to previous studies. The hospitalisation costs clearly decreased with each follow-up year, even in individuals with morbidities. During the fifth year of life, the health-care-related costs in very preterm children without prematurity-related morbidities did not differ greatly from the costs of children born full-term. However, the costs of the very preterm children with prematurity-related morbidities, especially CP, were 4.4-fold higher compared to those of the very preterm children without morbidities. Further prevention of morbidities such as CP would thus significantly reduce the long-term costs of prematurity. In addition, our study indicates that when estimating the costs of prematurity after the first year of life, one should not only calculate the hospitalisation costs, but also other costs for social welfare services, primary care, and therapies, as these exceed the hospitalisation costs in very preterm infants during the fifth year of life. Besides the costs studied here, it is likely that special education will add to the cost burden in later childhood.

The cost per QALY was already at an acceptable level by four years of age in the very preterm population as a whole. Prematurity-related later morbidities and decreasing GA increased the costs per QALY. As the initial hospital stay accounted for a great majority of the total four-year costs, and the costs of hospitalisation decreased with each follow-up year, the cost per QALY will most certainly decrease with age. The majority of costs arising after the initial hospitalisation were associated with morbidities related to prematurity. Therefore, offering high-quality neonatal care to prevent later morbidities in very preterm survivors has a long-term impact on the cost per QALY. Finally, estimating the cost-effectiveness of care of all very preterm infants as one group can be misleading, as there is now evidence that children born very preterm without prematurity-related morbidities do not cause significant additional costs for public services after the initial hospitalisation compared with infants born healthy at term.

6.8 Future research

Several studies have evaluated the length and costs of initial hospitalisation in very preterm children. In addition, there are a few studies quantifying the hospitalisations in this population during childhood and early adulthood. However, the use and costs of health-care resources other than hospitalisations have not been widely studied. Our finding that during the fifth year of life costs for social services and therapies exceed the costs of hospitalisations underline the importance of studying also other costs than hospitalisations. For example, the costs of special education will probably be an important factor at school age. These costs were not included in our study, as Finnish children begin school at the age of seven years.

We studied the effect of prematurity-related morbidities on the health-care resource use, as the most severe problems in psychomotor development and sensory deficits (CP, blindness, and hearing loss) are diagnosed during the first years of life (Vohr 2007). However, many of the adverse consequences of preterm birth, such as cognitive and behavioural problems are likely to be diagnosed later, and consequently, the effect of these on later costs should be studied at an older age. In the future, reliable measures of cognition should be included in the registers to study factors associated with cognitive and school performance.

Another interesting issue, which was not possible in the present study, would be to study the association of early complications with later morbidities and use of health-care resources. The findings of such studies could further underline the importance of effective perinatal care to prevent chronic morbidities, especially CP, which was associated with the highest costs at five years of age. Thus, the cost-effectiveness of primary prevention of CP in perinatal care should be carefully evaluated in order to attain optimal use of resources.

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Appendix 1 Costs of hospital care during the first four years of life according to gestational age in the very preterm survivors and full-term control populations.

GA (weeks)	N	Hospital costs during the first four years of life - € Mean (SD)				
		Total costs	**Initial hospitalisation**	**Outpatient visits - non-emergency**	**Outpatient visits - emergency**	**Other hospital stays**
23	17	175,490 (58,028)	147,398 (28,200)	11,156 (5,747)	1,183 (1,528)	15,753 (30,742)
24	62	151,655 (65,202)	128,409 (57,286)	11,999 (10,914)	1,406 (1,406)	9,840 (13,489)
25	73	136,813 (87,623)	114,465 (75,905)	9,535 (6,854)	1,297 (1,393)	11,516 (28,584)
26	81	113,412 (57,907)	97,270 (46,782)	8,386 (6,936)	1,133 (1,278)	6,623 (11,989)
27	150	101,429 (50,101)	83,285 (38,163)	8,263 (6,934)	1,493 (2,110)	8,389 (15,894)
28	165	83,694 (53,838)	63,852 (24,332)	8,443 (10,386)	1,050 (1,612)	10,350 (35,538)
29	220	63,883 (30,930)	50,816 (22,888)	6,586 (6,488)	833 (1,325)	5,648 (14,274)
30	316	51,580 (40,787)	39,362 (22,332)	5,565 (6,203)	699 (1,268)	5,953 (20,715)
31	440	41,559 (29,415)	31,897 (20,243)	4,252 (4,737)	699 (1,058)	4,711 (11,347)
32 or more	228	43,325 (37,250)	31,702 (22,193)	5,297 (8,918)	756 (1,193)	5,570 (17,994)
All preterm	1 752	68,073 (55,045)	54,087 (42,346)	6,412 (7,406)	900 (1,384)	6,675 (19,409)
Live-born non- survivors	278	18,217 (40,505)	18,217 (40,505)			
Full-term control group	200 609	4,580 (12,905)	1,334 (1,743)	720 (2,117)	251 (502)	2,275 (11,275)

Appendix 2 Costs of hospital care during the first four years of life according to morbidities in the very preterm survivors and full-term control populations.

Morbidity (very preterm survivors)	N	Hospital costs during the first four years of life - € Mean (SD)				
		Total costs	Initial hospitalisation	Outpatient visits - non-emergency	Outpatient visits - emergency	Other hospital stays
None of diagnoses below	1 157	54,232 (36,534)	45,551 (30,150)	4,525 (4,986)	559 (842)	3,597 (12,540)
Seizures	9	91,020 (80,901)	74,579 (73,742)	6,461 (5,411)	1,532 (1,355)	8,447 (8,139)
Cerebral Palsy	31	83,131 (35,053)	59,969 (25,262)	14,272 (10,241)	611 (647)	8,278 (11,863)
Other ophthalmologic problems	104	78,520 (51,123)	63,815 (42,644)	8,045 (8,269)	787 (915)	5,874 (14,393)
Visual disorder	8	74,770 (29,790)	54,464 (24,302)	8,942 (8,191)	871 (824)	10,493 (11,782)
Hearing loss	20	97,449 (61,084)	72,860 (43,925)	166,06 (14,083)	1,067 (1,683)	6,916 (14,520)
Obstructive airway diseases	241	82,500 (68,382)	62,864 (57,455)	7,353 (6,215)	1,797 (1,852)	10,486 (18,959)
2 or more of the above diagnoses	182	123,156 (85,709)	86,690 (61,388)	13,560 (11,800)	1,933 (2,352)	20,972 (41,209)

Appendix 3 Inpatient hospitalisation costs according to gestational age and morbidities during the first four years of life in very preterm children (initial hospitalisation excluded).

GA (weeks)	N	Inpatient hospitalisation costs € 1. year			2. year			3. year			4. year		
		Mean	Med	SD	Mean	Med	SD	Mean	Med	SD	Mean	Med	SD
23	17	9,442	2,551	22,950	3,148	0	6,090	1,639	0	2,717	1,524	0	3,412
24	62	4,634	1,265	7,577	2,467	0	6,183	1,928	0	5,403	811	0	2,036
25	73	7,536	2,102	25,556	1,938	0	5,021	1,311	0	3,006	731	0	2,008
26	81	3,444	626	7,258	1,757	0	5,645	712	0	1,673	711	0	4,681
27	150	4,749	1,086	10,804	1,972	0	5,144	1,049	0	3,135	619	0	1,910
28	165	4,818	637	10,826	2,639	0	11,021	2,197	0	16,095	695	0	2,707
29	220	3,878	0	13,071	893	0	2,451	386	0	1,574	490	0	1,541
30	316	2,887	0	7,758	1,226	0	6,555	693	0	4,787	1,147	0	11,114
31	440	2,955	0	8,050	931	0	4,385	522	0	2,190	302	0	1,252
32 or more	228	3,708	0	15,022	931	0	2,968	425	0	1,468	506	0	2,229
All	1 752	3,824	0	11,666	1,387	0	5,713	829	0	5,740	635	0	5,090
Morbidities													
None of diagnoses below	1157	2,240	0	8,249	642	0	3,302	309	0	1,433	406	0	5,811
Seizures	9	7,199	3,061	8,750	622	0	1,507	525	0	834	100	0	301
Cerebral Palsy	31	3,279	0	6,157	2,412	890	3,829	995	0	1,965	1,592	0	2,758
Other ophthalmologic problems	104	4,450	998	13,885	869	0	1,964	369	0	1,029	186	0	593
Visual disorder	8	5,231	1,898	7,814	4,248	1,176	6,826	353	0	494	662	0	1,228
Hearing loss	20	1,404	0	2,986	3,352	0	10,570	1,196	0	2,457	964	0	1,904
Obstructive airway diseases	241	6,794	2,528	13,104	2,084	0	6,220	1,085	0	5,827	524	0	2,032
2 or more of the above diagnoses	182	9,671	2,528	21,573	4,986	1,268	12,548	4,008	1,020	15,672	2,307	0	4,954

Appendix 4 Non-emergency outpatient costs according to gestational age and morbidities during the first four years of life in very preterm children.

GA (weeks)	N	Non-emergency outpatient visits, €											
		1. year			2. year			3. year			4. year		
		Mean	Med	SD	Mean	Med	SD	Mean	Med	SD	Mean	Med	SD
23	17	5,420	5,156	2,798	2,386	1,894	1,611	1,805	1,408	1,143	1,546	968	1,467
24	62	4,954	4,462	2,432	3,374	1,641	5,564	2,103	1,113	3,043	1,567	816	1,956
25	73	4,767	4,239	2,913	2,309	1,543	2,273	1,439	905	1,947	1,021	789	1,237
26	81	4,545	3,525	3,622	1,914	1,178	2,077	1,241	808	1,288	686	376	961
27	150	4,148	3,623	2,816	1,947	1,343	2,610	1,270	723	1,768	899	368	1,280
28	165	4,294	3,243	3,730	2,000	1,132	3,095	1,214	550	2,647	935	310	2,009
29	220	3,698	2,980	3,077	1,448	887	2,644	804	515	1,194	636	0	1,316
30	316	3,251	2,417	3,152	1,109	628	1,565	666	275	1,337	539	0	1,175
31	440	2,480	1,996	2,160	950	562	2,016	489	152	1,207	333	0	713
32 or more	228	2,818	1,916	5,592	1,290	626	3,064	676	271	2,070	514	0	1,240
All	1 752	3,438	2,612	3,464	1,471	792	2,616	865	333	1,749	638	146	1,285
Morbidities													
None of diagnoses below	1157	2,861	2,280	3,098	909	608	1,404	460	251	1,109	295	0	725
Seizures	9	3,946	3,381	3,363	1,654	1,066	1,614	564	361	596	298	0	420
Cerebral Palsy	31	5,239	3,838	4,291	4,962	3,013	5,879	2,049	1,921	1,512	2,022	1,585	2,025
Other ophthalmologic problems	104	3,965	2,990	3,554	1,972	1,236	3,841	1,272	702	2,196	836	551	1,197
Visual disorder	8	5,251	2,721	4,552	1,967	842	2,482	755	807	744	970	459	1,050
Hearing loss	20	9,097	6,539	8,684	3,412	1,982	3,881	2,058	1,694	1,802	2,039	1,571	1,753
Obstructive airway diseases	241	3,801	3,061	2,784	1,791	1,235	2,546	1,015	670	1,270	745	349	1,175
2 or more of the above diagnoses	182	5,266	4,212	3,852	3,466	2,245	4,463	2,671	1,475	3,344	2,156	1,385	2,286

Appendix 5 Emergency outpatient costs according to gestational age and morbidities during the first four years of life in very preterm children.

GA (weeks)	N	Emergency outpatient visits, €											
		1. year			2. year			3. year			4. year		
		Mean	Med	SD	Mean	Med	SD	Mean	Med	SD	Mean	Med	SD
23	17	678	282	945	179	0	272	228	0	384	98	0	221
24	62	599	396	645	395	240	562	274	0	591	138	0	298
25	73	538	342	710	437	0	655	210	0	409	111	0	194
26	81	475	262	717	385	206	582	193	0	374	81	0	210
27	150	756	379	1,178	376	0	597	215	0	564	145	0	367
28	165	567	113	1,163	248	0	453	153	0	343	82	0	196
29	220	470	219	838	188	0	456	99	0	268	75	0	229
30	316	365	0	930	171	0	354	96	0	230	67	0	192
31	440	384	0	637	155	0	406	93	0	225	68	0	217
32 or more	228	411	0	763	175	0	388	91	0	237	78	0	371
All	1 752	465	0	864	224	0	461	127	0	326	83	0	256
Morbidities													
None of diagnoses below	1157	300	0	535	127	0	308	78	0	211	53	0	220
Seizures	9	979	645	1,138	243	0	355	176	0	401	135	0	172
Cerebral Palsy	31	378	164	490	130	0	225	74	0	173	29	0	97
Other ophthalmologic problems	104	409	0	566	209	0	360	106	0	255	62	0	167
Visual disorder	8	339	114	429	305	0	475	227	145	261	0	0	0
Hearing loss	20	306	0	489	430	0	904	196	0	291	135	0	246
Obstructive airway diseases	241	977	592	1,252	470	288	616	201	0	450	148	0	291
2 or more of the above diagnoses	182	876	421	1,506	505	280	731	350	0	582	202	0	398