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THE EFFECT OF THE BIRTH HOSPITAL AND THE TIME OF BIRTH ON THE OUTCOME OF FINNISH VERY PRETERM INFANTS

by

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To My Family and Kimmo

ABSTRACT

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The Effect of the Birth Hospital and the Time of Birth on the Outcome of Finnish Very Preterm Infants

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The purpose of this study was to evaluate the effect of the birth hospital and the time of birth on mortality and the long-term outcome of Finnish very low birth weight (VLBW) or very low gestational age (VLGA) infants.

This study included all Finnish VLBW/VLGA infants born at <32 gestational weeks or with a birth weight of ≤1500g, and controls born full-term and healthy. In the first part of the study, the mortality of VLBW/VLGA infants born in 2000–2003 was studied. The second part of the study consisted of a five-year follow-up of VLBW/VLGA infants born in 2001–2002. The study was performed using data from parental questionnaires and several registers.

The one-year mortality rate was 11% for live-born VLBW/VLGA infants, 22% for live-born and stillborn VLBW/VLGA infants, and 0% for the controls. In live-born and in all (including stillbirths) VLBW/VLGA infants, the adjusted mortality was lower among those born in level III hospitals compared with level II hospitals. Mortality rates of live-born VLBW/VLGA infants differed according to the university hospital district where the birth hospital was located, but there were no differences in mortality between the districts when stillborn infants were included. There was a trend towards lower mortality rates in VLBW/VLGA infants born during office hours compared with those born outside office hours (night time, weekends, and public holidays). When stillborn infants were included, this difference according to the time of birth was significant.

Among five-year-old VLBW/VLGA children, morbidity, use of health care resources, and problems in behaviour and development were more common in comparison with the controls. The health-related quality of life of the surviving VLBW/VLGA children was good but, statistically, it was significantly lower than among the controls. The median and the mean number of quality-adjusted life-years were 4.6 and 3.6 out of a maximum five years for all VLBW/VLGA children. For the controls, the median was 4.8 and the mean was 4.9. Morbidity rates, the use of health care resources, and the mean quality-adjusted life-years differed for VLBW/VLGA children according to the university hospital district of birth. However, the time of birth, the birth hospital level or university hospital district were not associated with the health-related quality of life, nor with behavioural and developmental scores of the survivors at the age of five years.

In conclusion, the decreased mortality in level III hospitals was not gained at the expense of long-term problems. The results indicate that VLBW/VLGA deliveries should be centralized to level III hospitals and the regional differences in the treatment practices should further be clarified. A long-term follow-up on the outcome of VLBW/VLGA infants is important in order to recognize the critical periods of care and to optimise the care. In the future, quality-adjusted life-years can be used as a uniform measure for comparing the effectiveness of care between VLBW/VLGA infants and different patient groups

Keywords: behaviour, centralisation, development, follow-up, health-related quality of life, hospital level, mortality, morbidity, organisation of care, preterm infant, QALY, regionalisation, time of birth

TIIVISTELMÄ

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Syntymäsairaalan ja syntymäajan vaikutus suomalaisten pikkukeskosten ennusteeseen
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Tämän tutkimuksen tavoitteena oli selvittää syntymäsairaalan ja syntymäajan vaikutusta suomalaisten pikkukeskosten kuolleisuuteen ja pitkäaikaisennusteeseen.

Tutkimuksessa olivat mukana Suomessa <32 raskausviikolla tai ≤1500g painoisina syntyneet pikkukeskoset sekä täysaikaisena ja terveenä syntyneitä verrokkeja. Ensimmäisen vuoden kuolleisuutta selvitettiin Suomessa 2000–2003 syntyneiden pikkukeskosten osalta ja viisivuotisennustetta 2001–2002 syntyneiden osalta. Tutkimus perustui viisivuotiaiden lasten vanhempien täyttämiin kyselylomakkeisiin sekä useisiin eri rekistereihin.

Elävänä syntyneistä pikkukeskosista menehtyi ensimmäisen vuoden aikana 11%, kaikista pikkukeskosista 22% ja verrokeista 0%. Vakioitu kuolleisuus oli pienempi yliopistosairaaloissa kuin keskussairaaloissa syntyneillä pikkukeskosilla sekä tarkasteltaessa elävänä syntyneitä että elävänä ja kuolleena syntyneitä pikkukeskosia. Kuolleisuudessa oli eroja myös yliopistosairaanhoitopiirien välillä, mutta nämä erot eivät tulleet esille vertailuissa, joissa olivat mukana myös kuolleena syntyneet pikkukeskoset. Lisäksi tutkimuksessa havaittiin trendi pienemmästä kuolleisuudesta virka-aikana syntyneillä verrattuna päivystysaikana (yöt, viikonloput ja juhlapyhät) syntyneisiin. Kun kuolleena syntyneet pikkukeskoset huomioitiin vertailussa, virka-aikana syntyneiden kuolleisuus oli merkitsevästi pienempi verrattuna päivystysaikana syntyneisiin.

Viisivuotisseurannassa pikkukeskosten sairastavuus, terveyspalvelujen käyttö sekä käyttäytymisen ja kehityksen ongelmat olivat yleisempiä kuin verrokeilla. Pikkukeskosten elämänlaatu oli hyvä, mutta tilastollisesti merkitsevästi matalampi kuin verrokeilla. Laatupainotteisten elinvuosien mediaani oli keskosilla 4.6 ja keskiarvo 3.6. Verrokeilla mediaani oli 4.8 ja keskiarvo 4.9 (maksimi on 5). Pikkukeskosten sairastavuus, terveyspalvelujen käyttö ja laatupainotteisten elinvuosien keskiarvo vaihteli syntymäsairaalan yliopistosairaanhoitopiirin mukaan verrattaessa. Syntymäaika, syntymäsairaalan luokitus (keskus- tai yliopistosairaala) tai yliopistosairaanhoitopiiri eivät kuitenkaan olleet yhteydessä eloonjääneiden elämänlaatuun, käyttäytymiseen tai kehitykseen viisivuotiaana.

Yhteenvetona voidaan todeta, että yliopistosairaaloiden pienempää kuolleisuutta ei saavutettu huonomman pitkäaikaisennusteen kustannuksella. Erot kuolleisuudessa viittaavat siihen, että pikkukeskosten synnytykset tulisi keskittää yliopistosairaaloihin ja että alueittaisia eroja hoitokäytännöissä tulisi selvittää laajemmin. Pikkukeskosten pitkäaikainen kehitysseuranta on tärkeää, jotta voitaisiin löytää hoidon tulosten kannalta kriittiset kohdat sekä löytää ja hyödyntää parhaat hoitokäytännöt. Laatupainotteisia elinvuosia voidaan jatkossa käyttää hoidon vaikuttavuuden mittarina myös eri potilasryhmien välillä.

Avainsanat: hoidon organisointi, kehitys, keskittäminen, kuolleisuus, käyttäytyminen, laatupainoitteiset elinvuodet, pikkukeskonen, sairaalataso, sairastavuus, seuranta, syntymäaika, terveyteen liittyvä elämänlaatu

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ABBREVIATIONS

AGA	Appropriate (± 2 SD) birth weight for GA according to the reference values from the Finnish population
BPD	Bronchopulmonary dysplasia
CI	95% confidence interval
CLD	Chronic lung disease
CP	Cerebral palsy
ELBW	Extremely low birth weight (<1000g)
ELGA	Extremely low gestational age
FTF	Five to Fifteen-questionnaire on the behaviour and development of five- to fifteen-year-old children
GA	Gestational age
HRQoL	Health-related quality of life
ICD-10	The International Statistical Classification of Diseases and Related Health Problems, 10th Revision
IQ	Intelligence quotient
IVH	Inraventricular haemorrhage
LGA	Large (>2 SD) birth weight for GA according to the reference values from the Finnish population
MBR	the National Medical Birth Register
NHDR	the National Hospital Discharge Register
NICU	Neonatal intensive care unit
OR	Odds ratio
OT	Occupational therapist
PT	Physiotherapist
QALY	Quality-adjusted life-years
ROP	Retinopathy of prematurity
RR	Risk ratio
SD	Standard deviation
SGA	Small (<-2SD) birth weight for GA according to the reference values from the Finnish population
VLBW	Very low birth weight (≤1500g)
VLGA	Very low gestational age (<32 gestational weeks)
17D	A questionnaire on the health-related quality of life of children that includes 17 dimensions

LIST OF ORIGINAL PUBLICATIONS

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

I Rautava L, Lehtonen L, Peltola M, Korvenranta E, Korvenranta H, Linna M, Hallman M, Andersson S, Gissler M, Leipälä J, Tammela O, Häkkinen U, for the PERFECT Preterm Infant Study Group. The Effect of Birth in Secondary- or Tertiary-Level Hospitals in Finland on Mortality in Very Preterm Infants: A Birth-Register Study. Pediatrics. 2007;119:e257–263, doi: 10.1542/peds.2006-1964

II Rautava L, Häkkinen U, Korvenranta E, Andersson S, Gissler M, Hallman M, Korvenranta H, Leipälä J, Peltola M, Tammela O, Lehtonen L, for PERFECT Preterm Infant Study Group. Health and the Use of Health Care Services in Five-Year-Old Very-Low-Birth-Weight Infants. Acta Paediatr. 2010 Mar 5. [Epub ahead of print]

III Rautava L, Andersson S, Gissler M, Hallman H, Häkkinen U, Korvenranta E, Korvenranta H, Leipälä J, Tammela O, Lehtonen L, for PERFECT Preterm Infant Study Group. Development and Behaviour of Five-Year-Old Very-Low-Birth-Weight Infants. Eur Child Adolesc Psychiatry. 2010 Mar 23. [Epub ahead of print]

IV Rautava L, Häkkinen U, Korvenranta E, Andersson S, Gissler M, Hallman M, Korvenranta H, Leipälä J, Linna M, Peltola M, Tammela O, Lehtonen L. Health-Related Quality of Life in Five-Year-Old Very-Low-Birth-Weight Infants. J Pediatr. 2009; 155:338–43.

In addition, some previously unpublished data are presented.

1. INTRODUCTION

Pre- and postnatal care in Finland is of a high quality, and the neonatal mortality rate is one of the lowest in the world (WHO. 2006, Richardus et al. 2003). Since infant mortality rates are low, preterm birth is the main cause of neonatal mortalities (Official statistics of Finland, Statistical Summary 30/2008) and a significant factor leading to morbidity and the need for health care services.

The reasons for preterm birth are not fully understood. The most common pathological processes behind preterm birth involve intrauterine infection or inflammation, cervical insufficiency, hormonal disorders, overdistension of the uterus related to multiple pregnancies, and abnormal allograft reactions related to pre-eclampsia (Romero et al. 2006). In developed countries, approximately 40-45% of preterm births follow spontaneous preterm labour, 20–25% follow a premature rupturing of the membranes, and 30–35% are iatrogenic due to maternal or foetal indications (Goldenberg et al. 2008). Of all preterm infants, 11% are born from multiple pregnancies (Morken et al. 2005).

The increased survival of infants at the limits of viability has raised concerns over the long-term outcome of this patient group, since a very low birth weight or a very low gestational age (GA) at birth has been associated with increased morbidity (Larroque et al. 2008, Gäddlin et al. 2007, Mai et al. 2003, Cooke et al. 2004, Costeloe et al. 2000), developmental and behavioural problems (Gäddlin et al. 2007, Arnaud et al. 2007, Hack et al. 2004, Weindrich et al. 2003), and a lower health-related quality of life (HRQoL) (Eiser et al. 2005, Chien et al. 2006, Theunissen et al. 2001). Due to rapid changes in care practices, the results for the follow-up studies on preterm infants born in the past decades are not fully applicable to preterm infants born in the present decade. Also, prior research has demonstrated significant inter-hospital variation in NICU practices and outcomes (Vohr et al. 2004, Lee et al. 2000). On the other hand, studies on other populations are not directly applicable to Finnish preterm infants because socioeconomic and cultural backgrounds and preterm birth rates differ between populations (Steer. 2005, Kramer et al. 2001). Therefore, up-to-date research on Finnish very preterm infants is needed.

This study was a part of the Performance, Effectiveness and Cost of Treatment Episodes (PERFECT) project, which aims at producing comparative data on the outcomes and the effectiveness of care, and at creating models for monitoring treatment episodes in specialized health care. In order to assess the effectiveness of care, data from extensive registers and questionnaires were used. The objectives of this thesis were: [1] to describe the outcome and the use of health care resources in very low birth weight or very low gestational age (VLBW/VLGA) infants born in the present decade in Finland, and; [2] to improve current understanding about the effects of organisational factors related to the time and place of birth on the five-year outcome of VLBW/VLGA infants.

2. REVIEW OF LITERATURE

2.1 Definitions and Epidemiology

Infants born before 37 weeks of gestation are considered preterm infants (Oh and Merenstein. 1997). Definitions in the literature vary, but the limit of very preterm birth is often set at <32 gestational weeks, whereas infants born at <28 gestational weeks are considered extremely preterm. There has been no general agreement between studies on the lower limit for the defining preterm infants. However, World Health Organisation has defined the perinatal period as starting from 22 completed gestational weeks (WHO 2001). This lower limit is used in collecting birth register data in many countries, including Finland (Macfarlane et al. 2003). In the following text, infants born with a birth weight of ≤1500g or a GA of less than <32 weeks are referred to as very low birth weight or very low gestational age (VLBW/VLGA) infants.

The prevalence of birth before the GA of 37 weeks in Finland is 5.7% (Official statistics of Finland, Statistical Summary 30/2008). This is low in comparison with the international prevalence of preterm births in developed countries; a preterm birth rate of 12.7% has been reported in the USA and the prevalence ranges from 8.2% to 13.6% in 10 regions of Europe (Field et al. 2009, Heron et al. 2010). A similar preterm birth rate to that of Finland has been reported in Sweden (5.6% in 2001) (Morken et al. 2005). In Finland, the prevalence of preterm births has remained relatively constant during the last twenty years (Official statistics of Finland, Statistical Summary 30/2008). The rate of VLBW births is 0.8% and of VLGA births is 0.9% (Official statistics of Finland, Statistical Summary 30/2008). This compares favourably to the rate of VLGA births in other parts of Europe, which varies from 0.8 to 1.4% (EURO-PERISTAT Project. 2008, Morken et al. 2005), and to the prevalence of VLBW infants in the USA, which stands at 1.6% (Mathews and MacDorman. 2008).

2.2 The Effect of Organisation of Care on the Outcome of VLBW/VLGA Infants Up to School Age

2.2.1 Mortality

Due to the development of care practices, the mortality of VLBW and VLGA infants has dramatically decreased during the past decades (Zeitlin et al. 2009, Platt et al. 2007, Cooke. 2006, Wilson-Costello et al. 2005, Fanaroff et al. 2003). However, of all perinatal deaths in Finland in 2007, 42% occurred in infants born before 32 weeks of gestation (Official statistics of Finland, Statistical Summary 30/2008). Similarly, Callaghan et al. (2006) have shown that 34% of all infants dying in the USA are VLBW/VLGA infants. The mortality rate of VLBW or VLGA infants has been reported to vary in the developed countries from 11% to 16% when including only live-born infants (Fanaroff et al. 2003, Draper et al.

2009, Fanaroff et al. 2007, Stoelhorst et al. 2005, Larroque et al. 2004, Horbar et al. 2002) and from 25 to 33% when including stillbirths (Larroque et al. 2004, Draper et al. 2007) in the late 1990s and early 2000. Mortality increases with decreasing GA (Wilson-Costello et al. 2005, EXPRESS Group et al. 2009, Lui et al. 2006, Johansson et al. 2004). However, even in the smallest infants, most of the infants surviving the first few days of life usually survive irrespective of GA (Field et al. 2008, Hintz et al. 2005b, Cooper et al. 1998).

Recent studies show that the decrease in the mortality rates of VLBW/VLGA infants has slowed down or even stopped. The mortality rates for VLBW infants born in the USA did not change significantly between the periods 1995–1996 (16%) and 1997–2000 (15%) (Fanaroff et al. 2007). In VLBW infants born in Vermont Oxford Network centres the decrease in the mortality rates stopped in the second half of the 1990s (Horbar et al. 2002). In contrast, recent European studies show a continuing decrease in the mortality of infants born at GA <27 weeks (EXPRESS Group et al. 2009) and <26 weeks (Field et al. 2008). Since significant differences in mortality rates have been shown between different populations, mortality rates from other countries are not necessarily applicable to Finnish VLBW/VLGA infants. In Finnish extremely low birth weight (ELBW) infants, no significant changes were seen between the periods 1996–1997 and 1999–2000 in prenatal (34% in 1996–1997 vs 34% in 1999–2000), perinatal (55% vs 52%), neonatal (38% vs 34%), or post-neonatal (2% vs 1%) mortality rates (Tommiska et al. 2007).

Several studies have shown that a higher birth hospital level is associated with lower mortality rates in VLBW (Phibbs et al. 2007, Warner et al. 2004, Samuelson et al. 2002) and VLGA infants (Empana et al. 2003), infants born with a birth weight <2000g (Cifuentes et al. 2002), and infants born at GA <28 weeks (Johansson et al. 2004). Among Finnish ELBW infants born in 1996–1997, the adjusted mortality rate was lower for those born in level III hospitals compared with level II hospitals (Tommiska et al. 2001), but the difference was not statistically significant for those born in 1999–2000 (Tommiska et al. 2007). The survival rate in level II hospitals was reported to increase in the latter study. However, the comparison of the hospital levels was not adjusted for any confounding variables. In a recent Swedish study, births at GA <27 weeks in level III hospitals were associated with a decreased mortality rate compared with births in level II hospitals according to a univariate analysis with adjustment for GA. The difference in mortality between hospital levels disappeared when adjustments were made for the use of tocolytic treatment, antenatal corticosteroids, and surfactant treatment within two hours after birth. This suggests that the lower mortality rates in Swedish level III hospitals compared with level II hospitals are explained by the more active use of these interventions. However, the methodology varies between these studies (See Table 1). For example, some studies have included malformed infants or a significant number of outborn infants and adjustments have been made for different confounding variables. In addition, some studies (Empana et al. 2003, Shah et al. 2005, Tucker and UK Neonatal Staffing Study Group. 2002) have attributed deaths to the centre receiving the transferred infants instead of attributing them to the birth hospital, even thought transporting infants after birth has been shown to increase mortality (Lee et al. 2003, Truffert et al. 1998, Obladen et al. 1994).

Table 1. Previous studies on the effect of hospital level on mortality in very preterm infants. The adjusted odds ratios (OR), or rate ratios (RR), and 95% confidence intervals (CI) or adjusted p-values, are shown when applicable. GA=gestational age, NICU=neonatal intensive care unit.

Study	Patients	Percentage of infants transferred to Level III after birth	Effect on mortality	OR or RR (95% CI) or p-value
Effect of birth hospital level				
EXPRESS Group et al. 2009	GA <27 weeks born in Sweden from 2004–2007	17% of all infants (=80% of those born in level II or I hospitals) were transferred to level III hospitals	Increased by birth in level II hospitals compared with level III hospitals, adjusted for GA	**OR 0.5 (0.3; 0.8)**
			NS in multivariate analysis	OR 0.8 (0.5; 1.4)
Phibbs et al. 2007	Infants born at 500-1500g without major malformations in California from 1991–2000	14% of all infants transferred between hospitals	Increased by birth in level II and ***IIIa*** hospitals with ≤25 VLBW deliveries per year compared with level IIIB-D hospitals with >100 deliveries	**OR 1.9 (1.6; 2.3)** ***OR 1.7 (1.9; 2.2)***
Tommiska et al. 2007	Infants born live at <1000g in Finland in 1996–7 and in 1999–2000	Number of transferred infants not reported	Increased by birth in level II hospitals compared with level III hospitals in 1996–1997 **(unadjusted)**	**p<0.01**
			NS in 1999–2000 **(unadjusted)**	p=0.22
Johansson et al. 2004	Singleton firstborn infants born at GA 24–31 weeks in Sweden from 1992–1998	Number of transferred infants not reported	NS in GA 24–31 group	OR 1.3 (0.9; 2.0)
			Increased in GA 24–27 group by birth in level II hospitals compared with level III	**OR 2.0 (CI 1.2; 3.5)**
Warner et al. 2004	Live births at 500–1499g without lethal malformations in Cincinnati from 1995–1997	20% of all infants (62% of all born in non-subspecialty centres) were transferred from non-subspecialty to subspecialty centres	Increased by birth in non-subspecialty centres compared with subspecialty centres	**OR 1.9 (1.02; 3.5)**
Cifuentes et al. 2002	Singleton infants born at 500–2000 g in California in 1992–1993	33 % of those born in intermediate NICUs and 4% of those born in community NICUs were transferred to regional NICUs after birth	Increased by birth in an intermediate NICUs and ***community NICUs*** with <15 of <2000g deliveries per year compared with regional NICUs	**OR 1.9 (1.4; 2.5)** ***OR 1.4 (1.1; 1.8)***
			NS by birth in community NICUs with ≥15 of <2000g deliveries per year compared with regional NICUs	OR 1.1 (0.9; 1.4)

Samuelson et al. 2002	Born at 500–1499g in Georgia from 1994–1996	Number of transferred infants not given	Increased by birth in basic and specialty care (normal and selected high risk) compared with regional centres	OR not given
Tommiska et al. 2001	Infants born live at <1000g in Finland in 1996–1997	Number of transferred infants not reported	Increased by birth in level II hospitals compared with level III hospitals	**P<0.001**
Effect of hospital level of the NICU the infants were transferred to				
Shah PS et al J Pediatr 2005	Singletons infants born without lethal malformations at GA 23–32 weeks in Canadian Neonatal Network units in 1996–1997, transferred within the first 4 days	Only outborn infants were included in the analyses, **deaths were attributed to the centre the infants were transferred to**	Increased in free standing pediatric hospitals compared with perinatal centres	**OR 2.3 (CI 1.2; 4.2)**
Empana et al. 2003	GA ≤32 weeks born without lethal malformations in Northern France in 1997, excluding delivery room deaths	35% of all infants were transferred after birth, **deaths were attributed to the centre providing the first 48 hours of consecutive care**	Increased in infants cared for in level I–II hospitals compared with level III teaching units	**OR 7.9 (2.2; 29.1)**
			NS in those cared for in level III non-teaching hospitals compared with level III teaching units	OR 0.8 (0.3; 2.1)
Tucker et al. 2002	Infants with birth weight <1500g or GA <31 weeks in Scotland in 1993–1994	**Number of transferred infants not reported, deaths were attributed to the centre providing the longer period of care between 12–72 hours from birth**	NS between level III and non-tertiary NICUs, a trend towards higher mortality in level III hospitals reported	OR not given

High VLBW patient volumes in the NICU have also been associated with lower mortality rates (Phibbs et al. 2007, Bartels et al. 2006, Rogowski et al. 2004), but the cut-off levels for beneficial unit size vary between studies. Rogowski et al (2004) analysed the mortality rate of inborn VLBW infants born in 332 NICUs belonging to the Vermont Oxford Network. They showed that with up to 50 patients per year, each additional 10 patients resulted in an 11-percent reduction in mortality. In California, where the number of NICUs and the range in the sizes of NICUs are large, mortality has been shown to decrease by increasing yearly volume, even up to 100 VLBW infant admissions per year (with adjustment for, e.g., neonatal transfers) (Phibbs et al. 2007). In Germany, the risk of death was reported to double for infants born in NICUs with less than 36 yearly admissions compared with larger NICUs (Bartels et al. 2006). It is possible that this study underestimates the cut-off levels since there are only a small number of large units in Germany. In addition, the study excluded delivery room deaths and attributed the deaths of outborn infants to the NICUs where the child was mostly cared for during the first four weeks of life, instead of attributing the deaths to the birth hospital. Interestingly, a more recent publication by Bartels et al. (2007) on the same year-cohorts showed that the delivery unit size (cut-off level 1000 deliveries annually) and the NICU size (cut-off level 36 VLBW infants annually) had no effect on mortality rates, while the inborn status remained a protective factor. In the region of Trent in the UK, Field and Draper (1999) did not find a difference between large and small units in the survival rates of inborn VLGA infants when using 500 days of ventilation per year as the cut-off level for categorising the units.

The risk of mortality has been shown to increase in full-term infants and in the general population born during the night (Gould et al. 2005, Stephansson et al. 2003, Luo and Karlberg. 2001, Heller et al. 2000, Stewart et al. 1998), and during the summer holiday season (Stewart et al. 1998). However, mortality has not varied according to the time of birth on weekends and during weekdays after adjustments for confounding factors (Gould et al. 2005, Luo et al. 2004, Gould et al. 2003). Among VLBW and VLGA infants, an increase in mortality has also been shown for those born at night compared with those born during the daytime (Gould et al. 2005, Stephansson et al. 2003). Other studies have not shown a significant increase in mortality for those VLBW (Gould et al. 2003) and VLGA (Luo et al. 2004) infants born on the weekends, or VLBW infants born at the beginning of the academic year when pediatric and neonatal housestaff are more inexperienced (Soltau et al. 2008). The selection of patients in the previous studies has varied (e.g. exclusion of elective births) and not all comparisons have been adjusted for confounding factors (see Table 2), which may affect the results considerably.

Table 2. Previous studies on the effect of the time of birth on mortality. The odds ratios (OR), or rate ratios (RR), and 95% confidence intervals (CI), or p-values, are shown with adjustments made for confounding variables when applicable. NICU=neonatal intensive care unit, GA=gestational age.

Study	Patients	Effect on mortality	OR or RR or p-value
Birth during night-time			
Gould et al. 2005	General population without lethal malformations born in California in 1992–1999	Increased in those born during early night and ***late night***, (adjusted)	**OR 1.12 (1.05; 1.19)** **OR 1.16 (1.09; 1.23)**
	Birth weight 500–1499g		***OR 1.10 (1.02; 1.19)*** ***OR 1.18 (1.09; 1.28)***
Stephansson et al. 2003	Spontaneous full-term births in Sweden in 1991–1997	Increased in those born during the night-time (adjusted)	**RR 1.13 (1.01; 1.27)**
	GA <32 weeks		**RR 197.11 (187.54; 207.18)**
Luo and Karlberg. 2001	General live-born population born spontaneously and without considerable malformations in Sweden in 1990–1995	Increased in those born during the night-time (unadjusted)	**OR 1.31 (1.10; 1.57)**
Heller et al. 2000	Spontaneous live full-term births without malformations born in Hesse in 1990–1998	Increased in those born during the night-time (unadjusted)	**RR 1.89 (1.10; 3.13)**
Stewart et al. 1998	Births with weight >1499g without malformations in Wales in 1993–1995	Increased in those born during the night-time (unadjusted)	**RR 2.18 (1.37; 3.47)**
Birth during weekends			
Luo et al. 2004	Full-term births in Canada in 1985–1998	Increased in those born during the weekend (unadjusted)	**RR 1.11 (1.07; 1.16)**
		NS (adjusted)	OR 0.96 (0.91; 1.01)
	GA 22–27 weeks	NS (unadjusted)	OR 0.98 (0.94; 1.05)
	GA 28–31 weeks	NS (unadjusted)	OR 0.98 (0.89; 1.07)
Gould et al. 2003	General population born in California in 1995–7	Increased in those born during the weekend (unadjusted)	**OR 1.12 (1.05; 1.55)**
	Birth weight 500–1499g	NS (adjusted for birth weight)	OR 1.01 (0.95; 1.08)
		Marginally increased on weekends (unadjusted)	**OR 1.10 (1.00; 1.21)**
		NS (adjusted for birth weight)	OR 1.07 (0.96; 1.19)
Stephansson et al. 2003	Spontaneous full-term births in Sweden in 1991–1997	NS (adjusted)	RR 1.02 (0.88; 1.18)
Birth during the summer holiday season			
Stephansson et al. 2003	Spontaneous full-term births in Sweden in 1991–1997	NS (adjusted)	RR 0.93 (0.78; 1.11)
Stewart et al. 1998	Births with weight >1499g without malformations in Wales in 1993–1995	Mortality increased in those born during the summer holiday season (unadjusted)	**RR 1.99 (1.23; 3.23)**
Birth in the beginning of the academic year			
Soltau et al. 2008	VLBW infants with GA ≥24 weeks born in Birmingham Regional NICU in 1991-2004, delivery room deaths excluded	No difference according to month of birth (unadjusted)	p=0.49

There are some reports of regional differences in neonatal mortality among the general population (Tromp et al. 2009, Serenius et al. 2001, de Vonderweid et al. 1997). In the Netherlands, the risk of mortality for infants born at GA 26–31 weeks has been shown to vary between four geographical regions (Tromp et al. 2009). Similarly, mortality differences have been shown between the northern and the southern region of Sweden in infants born at GA 22–27 weeks (Hakansson et al. 2004). Among Finnish ELBW infants born in the 1990s, differences have been shown in mortality rates according to the university hospital district of birth (Tommiska et al. 2007, Tommiska et al. 2001). However, there are no previous reports on regional differences in the mortality rates of VLBW/VLGA infants born during the present decade in Finland.

2.2.2 Morbidity

2.2.2.1 Neurosensory Outcome

The risk of neurologic impairment in preterm infants increases with decreasing GA (Hack and Fanaroff. 2000) and birth weight (Fanaroff et al. 2007, Horbar et al. 2002). Cerebral palsy (CP) is a major clinical marker of brain injury, and the most common brain lesions causing it in preterm infants are periventricular haemorrhagic infarction and periventricular leukomalacia (Volpe. 1998). The incidence of CP was first reported to increase (Wilson-Costello et al. 2005, Hintz et al. 2005a, Vohr et al. 2000) due to a rapid decrease in the mortality of VLBW/VLGA infants and changes in the neonatal intensive care, such as the widespread use of postnatal corticosteroid therapy (Lodygensky et al. 2005). With the further developments in the care of most preterm infants, such as the administration of antenatal corticosteroids and the decrease in the use of postnatal corticosteroids (Vohr et al. 2005), the incidence of brain lesions has decreased (Hamrick et al. 2004, Cooke. 1999). Consequently, despite decreasing mortality, the most recent studies have shown either a decrease or no change in the rate of CP in VLBW/VLGA, ELBW, and ELGA infants (Groenendaal et al. 2010, Roberts et al. 2009, Platt et al. 2007, Wilson-Costello et al. 2007, Vohr et al. 2005, Robertson et al. 2007, Himmelmann et al. 2005). Scholars have reported a 4 to 10% prevalence of CP in VLBW (Platt et al. 2007) or VLGA (Larroque et al. 2008, Vohr et al. 2005, Himmelmann et al. 2005, Vincer et al. 2006) infants born during the second half of the 1990's.

Another marker of brain injury in preterm infants is seizure disorder. 3.6% of the VLBW/VLGA children have been reported to have seizures by 18 months of age (Amess et al. 1998), and preterm infants with cerebral haemorrhage are at an eightfold risk of having epilepsy at six months of age compared with those without cerebral haemorrhage (Pisani et al. 2004).

In addition to the increased incidence of CP and seizures, minor neuromotor dysfunctions are overrepresented in VLBW/VLGA children (de Kieviet et al. 2009). Among five-year-old VLGA children, 41% have been reported to have mild and 3% moderate minor neuromotor dysfunctions compared with the rates of 22% and 0.7% among full-term children (Arnaud et al. 2007). However, the reported incidence of neurologic impairment

varies due to both differences between populations and differences in the diagnostic criteria and study definitions. Of the five-year-old VLGA children participating in the EPIPAGE study, 61% were reported to be free of neurologic disability (Larroque et al. 2008). In other populations, no significant deviation in the neurologic outcome was reported in 85% of four-year-old VLBW children (Bylund et al. 1998), while a normal neurologic outcome was reported in 39% of five-year-old children born before 30 weeks (van Baar et al. 2005). In five-year-old Finnish ELBW children born in 1996–1997, scholars considered the neurological outcome normal in 57% (Mikkola et al. 2005).

Visual impairments are overrepresented in VLBW/VLGA infants compared with the general population. However, the risk of visual impairment associated with preterm birth has decreased over time (Bodeau-Livinec et al. 2007). A major cause of visual disability in this patient group is retinopathy of prematurity (ROP), a condition related to the immaturity of the retinal vasculature. The increasing severity of ROP has been associated with decreasing GA (Bodeau-Livinec et al. 2007). ROP of any severity has been reported in 51% of VLBW children (Cooke et al. 2004), while Finnish ELBW infants have been reported to have a 5% incidence of ROP stage 3-5 (Tommiska et al. 2007). Bilateral blindness has been reported in 0.8% of VLGA infants (Vohr et al. 2005). An incidence of 56% in strabismus, amblyopia, or refractive errors has been shown in five-year-old VLGA children, while the incidence of these conditions also increases with decreasing GA (Schalij-Delfos et al. 2000). Cooke et al (2004) showed that 13% of VLGA and 4% of full-term children wore eyeglasses at the age of seven years.

VLBW/VLGA infants are at greater risk of hearing impairment compared with their full-term peers (Cristobal and Oghalai. 2008), possibly because they are more often exposed to infections in utero and postnatally, assisted ventilation, hypoxia, hyperbilirubinaemia, noise, and ototoxic drugs. With the development of treatment strategies, the incidence of sensorineural hearing loss has also decreased (Cristobal and Oghalai. 2008). A recent study (Ari-Even Roth et al. 2006) showed that 3% of VLBW infants had hearing loss. However, only 0.3% of these consisted of bilateral sensorineural hearing loss, whereas the rest were attributable to conductive hearing deficits. Hearing impairment requiring amplification in both ears has been reported in 1.8% of VLGA children (Vohr et al. 2005).

Data on the effects of birth hospital level and region or the time of birth on the neurosensory outcome of VLBW/VLGA infants is scarce. A study on the long-term effects of birth hospital level and patient volume on VLBW infants showed no differences in neurosensory disabilities between hospitals of the same level, but visual function varied marginally between hospitals (Darlow et al. 2000). In addition, high patient volumes have been associated with a lower rate of severe intraventricular haemorrhages (IVH) in VLBW/VLGA infants (Synnes et al. 2006). In Finnish ELBW children born in 1996–1997, Mikkola et al. (2005) showed birth in the university hospital district with largest patient volumes (A) to be associated with lower rates of CP and minor neuromotor dysfunctions. Tommiska et al. (2001) also reported differences in ROP during this period

between the districts, but they no longer found morbidity differences between districts in infants born in 1999–2000 (Tommiska et al. 2007).

2.2.2.2 Cognition, Behaviour, and Development

School-aged preterm infants have poorer mean cognitive scores than full-term controls and the scores decrease with decreasing birth weight and GA (Bhutta et al. 2002). British VLGA children at six years of age have been shown to score about one standard deviation lower on cognitive measures than full-term controls (Wolke and Meyer. 1999). The EPIPAGE study reported severe intellectual impairment (mental processing composite index <55) in 2% of VLGA children at five years of age (Larroque et al. 2008), while milder intellectual impairment (mental processing composite index 55-84) was reported in 30%. Another study reported a mild or severe cognitive impairment (intelligence quotient [IQ] <85) in 22% of eight-year-old VLBW children compared with 11.5% in the general population in New Zealand (Horwood et al. 1998). However, there are studies from Finland and Sweden showing the mean IQ of VLBW children falling within the normal range (Munck et al. 2010, Bohm et al. 2002). The distribution of the scores has been close to normal but with a leftward shift towards the lower values, particularly in the performance scale measuring visual perception and spatial reasoning (Bohm et al. 2002). In addition, Ment et al. (Ment et al. 2003) have shown improvement with age in most VLBW children in IQ tests.

Preterm children have been reported to be at an increased risk of hyperactive, externalising, and internalising behaviour, and at a twofold risk of attention-deficit and hyperactivity disorder compared with full-term controls (Bhutta et al. 2002, Hoff et al. 2004). Consequently, VLBW children (Horwood et al. 1998), and children born at ELBW or at a GA <28 weeks (Davis et al. 2007, Bowen et al. 2002) have been reported to need more educational support and have poorer academic performance than the controls. Schraeder et al (1997) showed that VLBW children born in Philadelphia needed 2.8 times more special academic assistance than their normal birth-weight peers. Another study from Sydney reported that 8% of eight-year-old children born at <30 gestational weeks were in special education (Wocadlo and Rieger. 2006). The latter study did not have a controls group, which would have been important for evaluating the results, since the availability of and the criterion for admittance to special education programs may vary considerably between countries. No clear change in the rate of behavioural problems has been shown over time, but the proportion of VLBW/VLGA children recording an optimal performance in all tested developmental domains has been shown to be higher for those born in 1993 (43%) than for those born in 1983 (30%) (De Kleine et al. 2007).

There is one study that shows no differences in the behavioural and educational outcome of VLBW children at seven to eight years of age between birth hospitals categorised according to their level and size (Darlow et al. 2000). However, differences have been shown between the five Finnish university hospital districts in full-scale, verbal, and performance IQ, in the rate of cognitive impairment, and in the mean attention value for

ELBW children born in 1996–1997 (Mikkola et al. 2005). There are no studies on the effect of the birth hospital region and the time of birth on the behaviour and development of VLBW/VLGA children born during the present decade in Finland.

2.2.2.3 Respiratory Outcome

Preterm infants are prone to pulmonary symptoms because their lungs are immature and lack surfactant at birth. The saccular stage of lung development begins at about 24 weeks of gestation, whereas the alveolar stage begins after 30 weeks of gestation. In addition, the vascular development of the lungs is incomplete (Jobe and Bancalari. 2001, Jobe and Ikegami. 2001).

Chronic lung disease (CLD) or bronchopulmonary dysplasia (BPD) is a group of pulmonary disorders resulting from a neonatal respiratory disorder (Allen et al. 2003), characterized by fewer and larger alveoli and decreased pulmonary vasculature (Jobe and Bancalari. 2001). It is usually defined either as the need for supplementary oxygen at the age of 28 days or at 36 weeks of corrected gestational age. The development of treatments for respiratory distress, such as antenatal corticosteroids, surfactant replacement therapy, and continuous positive airway pressure replacing mechanical ventilation, have reduced CLD in preterm infants born at higher gestational weeks. However, because more immature infants survive, the overall incidence of CLD has not decreased recently (Baraldi and Filippone. 2007). The risk of CLD increases with decreasing GA; 75% of infants who need oxygen at the age of 28 days weigh less than 1000g at birth (Rojas et al. 1995). The reported incidence of a need for supplementary oxygen for at least 28 days after birth in VLBW or VLGA infants varies largely, from 12% to 30 %, between different studies and populations (Larroque et al. 2008, Zeitlin et al. 2009, Fanaroff et al. 2007, Stoelhorst et al. 2005). In Finland, 31% of VLBW infants born between 1990 and 1994 in Tampere have been reported to need supplementary oxygen at a postnatal age of 28 days, while the corresponding figure was 13% at 36 weeks of corrected age (Korhonen et al. 1999b). Another study has reported that 49% of the national cohort of ELBW infants born in 1999–2000 needs supplementary oxygen at a postmenstrual age of 36 weeks (Tommiska et al. 2007). However, in most VLGA infants with CLD, lung growth and remodelling during infancy result in the improvement of lung function and in the weaning from oxygen therapy by the age of two years (Greenough et al. 2006). Nevertheless, former preterm children who needed for supplementary oxygen at the age of 28 days can still be distinguished from other preterm children based on a pulmonary functions test at the age of three to eight years (Vrijlandt et al. 2007, Malmberg et al 2000).

Children born as VLBW/VLGA infants are prone to respiratory infections. VLGA children have been shown to experience more wheezing and chronic coughing at seven years of age than full-term controls (Gross et al. 1998). These symptoms and the use of bronchodilators increase for children with a neonatal diagnosis of CLD (Greenough et al. 2005). The incidence of severe disease and the need for hospitalisation due to respiratory

syncytial virus also increase in VLGA infants and have been shown to increase with decreasing GA in this patient group (Prais et al. 2003, Stevens et al. 2000).

A low birth weight (Bernsen et al. 2005) and a low GA (Gessner and Chimonas. 2007) at birth have also been associated with an increased incidence of asthma later in life. Bronchial obstruction and increased bronchial reactiveness in school-age children have been associated with a very low birth weight regardless of whether the children have had CLD or not (Kriemler et al. 2005, Pelkonen et al. 1997). Among VLGA children up to nine years of age, a two-fold risk of asthma has been shown compared with those born at a GA of ≥37 weeks (Gessner and Chimonas. 2007). Among five- to twelve-year-old VLGA or VLBW children, 20 to 34% have been reported to have asthma (Mai et al. 2003, Gross et al. 1998, Renard et al. 2008), compared with 9 to 21% of the full-term controls (Mai et al. 2003, Gross et al. 1998) and 9% of the general five-year-old population in South-West Finland (Kaila et al. 2009).

Scholars have shown that the rate of CLD among VLBW infants varies between level III hospitals in Columbia and Boston. They mainly attribute the increased risk of CLD to more frequent use and longer periods of mechanical ventilation (Van Marter et al. 2000). Differences in the rate of CLD were also seen between the five Finnish university hospital districts among ELBW infants born in 1996–1997, but not in those born in 1999–2000 (Tommiska et al. 2007). The national rates of CLD remained similar during the two study periods and the rate of oxygen dependency at 36 weeks of corrected age did not differ between level II and III hospitals. No previous studies have been published about the effect of the birth hospital level or the time of birth on the incidence of CLD, respiratory infections, or asthma in VLBW/VLGA infants born during the present decade in Finland.

2.2.2.4 Inguinal Hernia

The lower the GA of the infant is the more common the incidence of inguinal hernia (Lau et al. 2007, Kumar et al. 2002). In VLGA infants, a 9% incidence of inguinal hernia has been reported (Lau et al. 2007, Kumar et al. 2002), whereas in VLBW infants the reported incidence varies from 11% to 18% (Kumar et al. 2002, Rajput et al. 1992, Kitchen et al. 1991). There are no previous studies on the effect of the birth hospital level or region, or the time of birth on the incidence of inguinal hernia in VLBW/VLGA children.

2.2.3 Health-Related Quality of Life and Quality-Adjusted Life-Years

Interest in measuring the impact of chronic conditions on the HRQoL of the patients has increased recently. There are, however, relatively few previous publications on the HRQoL of former VLBW/VLGA infants before and during the early school-age years. In three studies on one- to four-year-old VLBW or VLGA infants, the parents estimated a lower HRQoL for their children than the parents of the controls (Eiser et al. 2005, Chien et al. 2006, Theunissen et al. 2001).

The quality-adjusted life-years (QALY) of preterm infants have only been reported as part of a cost-utility analysis on the care of ELBW infants in Victoria (Doyle and Victorian Infant Collaborative Study Group. 2004a, Doyle and Victorian Infant Collaborative Study Group. 2004b, Victorian Infant Collaborative Study Group. 1997), a cost-effectiveness analysis of technology of birth (Cutler and Meara. 1999) and a cost-effectiveness analysis of pre-discharge monitoring for apnea (Zupancic et al. 2003). These analyses have been based on assumptions of the QALY according to birth weight, estimated health status, or the severity of disability, instead of calculating QALY based on subjective HRQoL.

No comparisons of the HRQoL or QALY of former VLBW/VLGA children according to the time and place of birth have previously been reported.

2.3 The Use of Health Care Resources in VLBW/VLGA Infants Up to School Age

Very preterm infants need a long initial hospitalisation period (Russell et al. 2007), and the length of the initial hospitalisation period for VLBW or VLGA infants has been shown to increase with decreasing GA and birth weight (Phibbs and Schmitt. 2006, Klinger et al. 2005, Bannwart Dde et al. 1999). Similarly, previous studies have shown that VLBW or VLGA infants need to be rehospitalised more often during the first years of life than their full-term peers (Gray et al. 2006, Leijon et al. 2003, Korhonen et al. 1999a). Of all surviving VLBW or VLGA infants, scholars have reported that 30 to 42% need to be hospitalised at least once during the first year of life and 30% during the second year of life, compared with 12 and 15% of the full-term controls, respectively (Gray et al. 2006, Brissaud et al. 2005, Elder et al. 1999). Scholars have also shown that the increasing frequency of hospital readmissions is related to decreasing birth weight and GA among the VLBW/VLGA infants (Gray et al. 2006, Elder et al. 1999, Rogowski. 1998). Brissaud et al. (2005) and Rogowski (1998B) showed that VLGA infants need to be rehospitalised an average of two times during the first year of life. The length of stay for rehospitalisations during the first year of life has been shown to be longer for VLBW/VLGA infants than full-term infants (Jackson et al. 2001), with an average length of 11 days for VLBW/VLGA infants (Rogowski. 1998). During the first five years of life, Petrou et al. (Petrou et al. 2003) showed hospital stays (including the initial hospitalisation period) to be nearly eightfold longer for VLGA children than for controls born full-term. The total duration of admissions for infants born at <28 gestational weeks and at 28–31 gestational weeks increased a total of 85 and 16 times, respectively, compared with children born full-term. The lengths of hospital stays for each year were not reported separately, but the costs of hospitalisation periods were reported to decrease with increasing age.

VLBW/VLGA infants have been shown to visit general practitioners and health care centres as often as the full-term controls during the first two years of life (Gray et al. 2006, Jackson et al. 2001). However, scholars have shown that they undergo more outpatient hospital visits (Gray et al. 2006), particularly pediatric and ophthalmic outpatient visits

(Jackson et al. 2001), than full-term controls during the first years of life. VLGA infants born in eastern and northern Finland have been shown to visit special health care from one to twelve times (mean not given) during the first year of life. The most common reason for these visits was a follow-up assessment of growth (Korhonen A. 2003). Leijon et al. (Leijon et al. 2003) similarly showed that among Swedish VLGA children ranging from one to four years of age, the percentage of children who had visited a general practitioner was similar to that of the full-term controls, but VLGA children more often visited specialists. In the EPIPAGE study, 32% of five-year-old VLGA children were shown to use services by a physiotherapist (PT), speech therapist, occupational therapist (OT), psychologist, or psychiatrist compared with 16% of the full-term controls (Larroque et al. 2008). In Finland, two- to eight-year-old VLBW infants born in one of the level III hospitals in 1990–1994 have been shown to use more physiotherapy and occupational therapy than full-term controls (Korhonen et al. 1999a).

There are no studies on the effect of the birth hospital level, district, and the time of birth on the use of health care resources among Finnish VLBW/VLGA infants born during the present decade.

3. AIMS AND HYPOTHESIS OF THE STUDY

This study was a part of the Performance, Effectiveness and Cost of Treatment Episodes (PERFECT) project that was founded to produce comparative data on the effectiveness of care, and to create models for monitoring the effectiveness of treatment episodes in specialised health care. The general aim of this study was to describe the outcome and the need for health care services among VLBW/VLGA infants born in the present decade in Finland with reference to full-term controls. The main aim was to improve the current understanding about the effects of organisational factors related to the time and place of birth on the outcome and the need for health care services among VLBW/VLGA infants.

The specific aims of the study were:

1) To evaluate the effect of the birth hospital level on Finnish VLBW/VLGA infants in one-year mortality rates, behaviour, development, HRQoL, and the use of health care resources during the fifth year of life, as well as on the accumulated five-year morbidity rates and QALY.

2) To assess the association of the time of birth during or outside office hours with one-year mortality rates, behaviour, development, HRQoL, and the use of health care resources during the fifth year of life, as well as with the accumulated five-year morbidity rates and QALY in Finnish VLBW/VLGA infants.

3) To define whether there are differences in one-year mortality rates, behaviour, development, HRQoL, and the use of health care resources during the fifth year of life, as well as in the accumulated five-year morbidity and QALY in Finnish VLBW/VLGA infants according to the university hospital district that the birth hospital is a part of.

The corresponding hypotheses of the study were:

1) It was hypothesised that VLBW/VLGA births in level II hospitals compared with level III hospitals are associated with increased mortality, morbidity, problems in behaviour and development, and an increased use of health care resources, as well as decreased HRQoL and QALY.

2) The hypothesis was that VLBW/VLGA births outside office hours compared with births during office hours are associated with increased mortality, morbidity, and developmental and behavioural problems, as well as increased use of health care services and decreased HRQoL and QALY.

3) It was hypothesised that there are differences in mortality, morbidity, development and behaviour, HRQoL, and QALY, as well as in the use of health care services according to the university hospital district of birth for Finnish VLBW/VLGA infants.

4. MATERIALS AND METHODS

4.1. The Organisation of Care of VLBW/VLGA Infants in Finland

The public hospitals in Finland are categorised according to three types: local, central, and university hospitals. The local hospitals are small hospitals that usually provide care only in a few specialities. Central hospitals are larger hospitals that provide care in most specialities. The central hospitals have 24-hour emergency service, but are not required to have a pediatrician or a neonatologist in the hospital outside office hours. The largest and most specialized hospitals in Finland are university teaching hospitals located in Helsinki, Tampere, Turku, Kuopio, and Oulu. They have a paediatrician at the hospital 24 hours a day and a neonatologist on call as a backup. Scholars have previously used different definitions for categorising the level of neonatal care (Johansson et al. 2004, Cifuentes et al. 2002, Blondel et al. 2009). According to the definitions proposed by the American Academy of Pediatrics Committee on Fetus and Newborn (Table 3.) (Stark and American Academy of Pediatrics Committee on Fetus and Newborn. 2004), all five university hospitals in Finland have at least a level IIIB neonatal intensive care unit (NICU), all central hospitals caring for VLBW/VLGA infants have at least level IIB neonatal care, and local hospitals with deliveries have level I neonatal care. These hospitals are referred to in the text as level III, level II, and level I hospitals, respectively. There are no private delivery hospitals in Finland.

Finland is divided into 20 hospital districts. The districts are administrative units that organise and offer the residents special health care services that are not provided by the primary health care centres. They are also responsible for research, development, and educational activities in their region. Participating municipalities fund the districts. The Ministry of Social Affairs and Health can issue guidelines but the hospital districts have the authority to make decisions on treatment policies locally. The hospital districts are arranged into five university hospital districts that all consist of one level III hospital, and one or more level II or level I hospitals (Act on Specialized Medical Care).

In 2004, when the current study was initiated, there were no national guidelines on where VLBW/VLGA infants should be delivered. VLBW/VLGA infants were delivered in level II and level III hospitals, depending on the local policies. After initial intensive care, those infants whose delivery had been centralized to level III hospitals were often transferred back to level II hospitals closer to home. The distribution of hospitals with VLBW/VLGA deliveries between 2000 and 2003, and the hospital and university hospital districts are shown in Figure 1. The map demonstrates the geographical challenges to perinatal care in our country; most people live in the southern part of the country while the northern part has a low population density and long distances to the delivery hospitals.

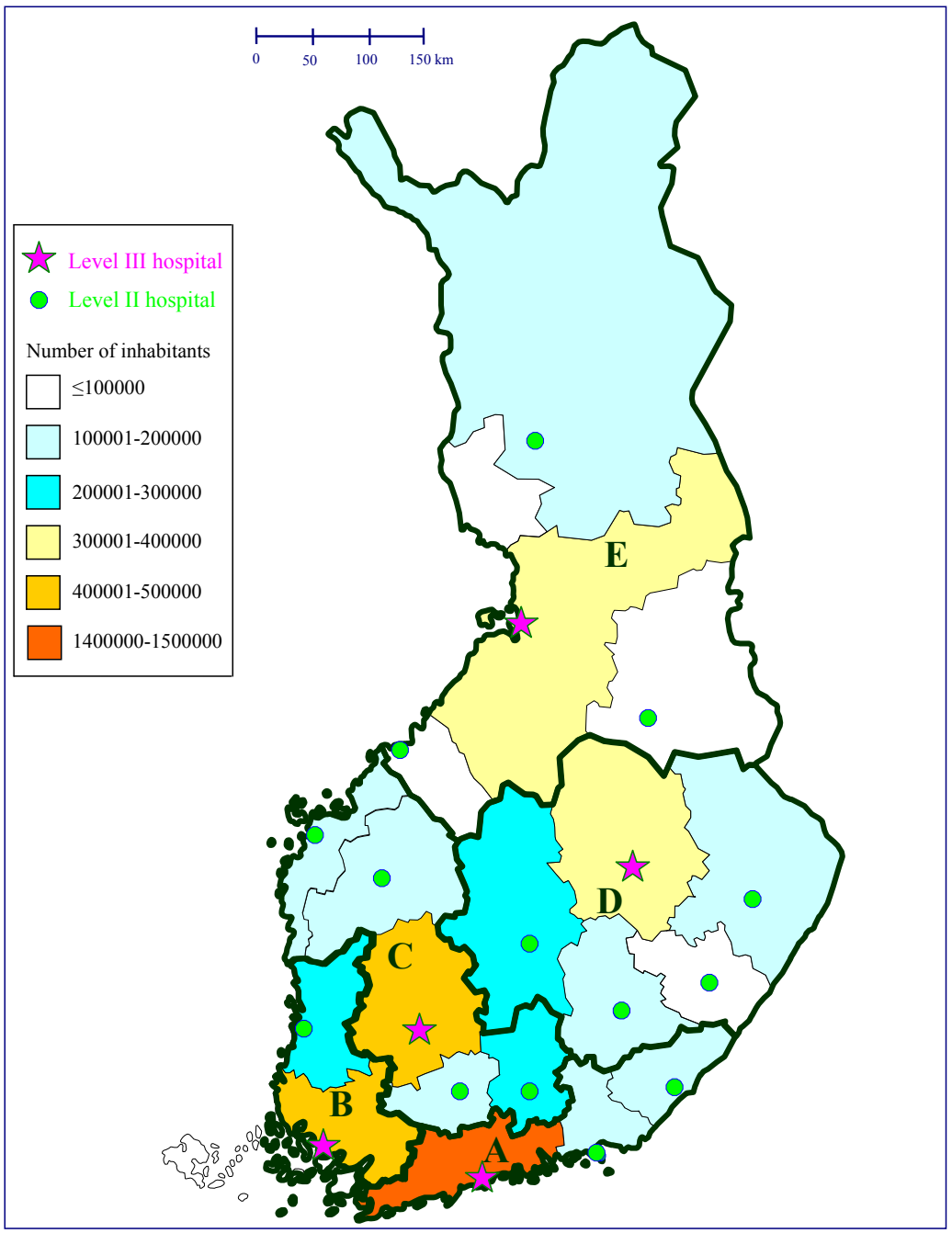

Figure 1. Map of Finland showing the 14 level II and five III hospitals with deliveries of VLBW/VLGA infants from 2000–2003. The borders of the five university hospital districts (A-E) as well as 20 hospital districts are shown, with colours indicating the number of inhabitants in the hospital districts.

Table 3. Definitions proposed by the American Academy of Pediatrics Committee on Fetus and Newborn for capabilities associated with the levels of neonatal care within an institution. The table is adapted from an article by Stark and the American Academy of Pediatrics Committee on Fetus and Newborn (2004).

Level I (basic) neonatal care
Well-newborn nursery: has the capabilities to - Provide neonatal resuscitation at every delivery - Evaluate and provide care for infants born at a GA of 35 to 37 weeks who remain physiologically stable - Stabilize newborn infants who are ill and those at GA <35 weeks until transfer to a facility that can provide the appropriate level of neonatal care
Level II (specialty) neonatal care
Level IIA has the capabilities to - Resuscitate and stabilize preterm and/or ill infants before transfer to a facility at which newborn intensive care is provided - Provide care for infants born at >32 weeks gestation and weighing ≥1500g (1) who have physiological immaturity such as apnea of prematurity, an inability to maintain body temperature, or an inability to take oral feedings or (2) who are moderately ill with problems that are anticipated to resolve rapidly and are not anticipated to need subecialty services on an urgent basis - Provide care for infants who are convalescing after intensive care
Level IIB has the capabilities of a level IIA nursery and the additional capability to provide mechanical ventilation for brief durations (<24h) or continuous positive airway pressure
Level III (subspecialty) neonatal care
Level IIIA has the capabilities to - Provide comprehensive care for infants born at >28 weeks gestation and weighing >1000g - Provide sustained life support that is limited to conventional mechanical ventilation - Perform minor surgical procedures such as the placement of a central venous catheter or an inguinal hernia repair
Level IIIB has the capabilities to - Provide comprehensive care for extremely low birth weight infants (≤1000g and ≤28 weeks gestation) - Provide advanced respiratory support such as high-frequency ventilation and inhaled nitric oxide for as long as required - Provide prompt and on-site access to a full range of pediatric medical subspecialists - Provide advanced imaging, with interpretation, on an urgent basis, including computed tomography, magnetic resonance imaging, and echocardiography - Provide pediatric surgical specialists and pediatric anesthesiologists on site or at a closely related institution to perform major surgery such as ligation of patent ductus arteriosus and repair of abdominal wall defects, necrotizing enterocolitis with bowel perforation, tracheoesophageal fistula and/or esophageal atresia, and myelomeningocele
Level IIIC has the capabilities of level IIIB and is also located within an institution that has the capability to provide extracorporeal membrane oxygenation and surgical repair of complex congenital cardiac malformations that require cardiopulmonary bypass.

4.2. Study Subjects

The first part of the study (original publication I), concerning one-year mortality rates, included all VLBW/VLGA infants (birth weight 500–1500 g or GA 22 weeks 0/7 days to 31 weeks 6/7 days at birth) born in Finnish level II and level III hospitals between 2000 and 2003. We excluded infants [1] with a major disparity between birth weight and GA

or who were missing data on either one of these variables, which suggested an entering error in the database (n=56), [2] with an incomplete social security number (n=3), and [3] with missing data on the initial hospitalisation period (n=9). [4] Infants born in level I (regional or local) hospitals (n=92), at home (n=3), or in hospitals with less than five deliveries during the four-year study period (n=23) were excluded because we did not want to deliberately include unplanned and generally unavoidable emergency deliveries in the study population. We also excluded infants [5] with lethal congenital malformations (n=95) to decrease the possibility that the differences in the outcome according to place or time of birth would be explained by differences in patient characteristics. In this first part of the study, the infants with the following congenital malformations were excluded: trisomy 13 or 18, triploidy, double-outlet right ventricle, double-outlet left ventricle, Taussig-Bing malformations, transposition of great arteries, hypoplasia of the heart, left-heart hypoplasia syndrome, hypoplasia of the left ventricle, univentricular heart, atresia of the pulmonary valve, anencephaly, bilateral agenesis of the kidneys, Potter syndrome, acrania, anencephaly, occipital encephalocele, holoprosencephaly, semilobar holoprosencephaly, cervical meningocele, large bilateral polycystic or microcystic kidneys, bilateral cystic dysplasia of the kidneys, bilateral severe hypoplasia of the lungs, bilateral rudimentary lungs, congenital tracheal stenosis, hypoplasia of the trachea, and agenesis of the diaphragm. After all the exclusions, 2291 infants (including stillborn) were included in the first part of the study, with 2021 of them being live-born infants.

The second part of the study concerned the five-year outcome and included VLBW/VLGA infants born in Finnish level II and level III hospitals in 2001–2002. The healthy full-term (GA 38 to 42 weeks) infants matched for gender and born in the same delivery hospital next in order after every third VLBW/VLGA were chosen for the control group. "Healthy" was defined as any infant not hospitalised during the first seven days of life, aside from the routine maternity ward stay. The inclusion and exclusion criteria differed slightly according to the original publications. The numbers of excluded infants for all original publications are presented in Figure 2 and the background data on the participants in Table 4.

In the part of the study that addresses morbidities and health care resource use (original publication II), and the behaviour and development (original publication III) of the children, all surviving VLBW/VLGA infants and their full-term controls were included. Children who died before the age of five years (n=122 VLBW/VLGA children and n=0 controls) were not included. The exclusion criteria included: [1] an incomplete personal identification number in the National Medical Birth Register (MBR), which prevented data linkage (n=6 in VLBW/VLGA infants and n=0 in controls); [2] a major and incongruous disparity between GA and birth weight or missing data on either one of these variables (n=29 VLBW/VLGA infants); [3] birth at a level I hospital or at a hospital with less than three deliveries of live-born VLBW/VLGA infants within the study period (n=4 VLBW/VLGA infants), and; [4] a lethal congenital malformation (n=19 VLBW/VLGA infants). Lethal congenital malformations were defined as trisomy 13 or 18, triploidy, severe

cardiac defects (acardia, univentricular heart, transposition of great arteries, interrupted aorta), severe cerebral malformations (anencephaly, holoprosencephaly), and other lethal conditions. Finally, [5] in original publication II, surviving VLBW/VLGA infants with an initial hospitalisation of <15 days, implying missing or incomplete data (n=12, some already excluded due to other exclusion criteria), were not included in the analyses.

The size of the study populations after the exclusions was 918 VLBW/VLGA infants in original publication II, 924 VLBW/VLGA infants in original publication III, and 381 controls in both original publications II and III.

When reporting the HRQoL and QALY of the VLBW/VLGA children (original publication IV), both live-born and stillborn VLBW/VLGA infants were included. VLBW/VLGA infants who died after birth were also included. None of the controls died during the follow-up period. The exclusion criteria included: [1] an incomplete personal identification number in the MBR, which prevented data linkage (n=134 stillborn, n=6 live-born VLBW/VLGA infants, and n=0 controls); [2] a major and incongruous disparity between GA and birth weight, suggesting erroneous data entry (n=27); [3] birth at a level I hospital or at a hospital with <3 live-born VLBW/VLGA deliveries during the study period (n=4), and; [4] at least one lethal congenital malformation (the criteria for lethal congenital malformation were the same as in original publications II and III) (n=19). Finally, [5] the surviving VLBW/VLGA infants hospitalised for less than five days during the first year of life (n=6) were not included in the QALY analysis because the data was assumed to be incomplete.

After the exclusion of infants for the above-mentioned criteria, a total of 902 live-born VLBW/VLGA infants and 378 controls were included in the study. Including live-born, non-surviving VLBW/VLGA infants and stillborn VLBW/VLGA infants, the size of the VLBW/VLGA population was 1171.

In addition, the questionnaires in original publications II-IV were not sent to families who were living abroad at the time the questionnaires were mailed, whose address was missing from the Central Population Register, or who would not let the register keepers release their address (n=23 VLBW/VLGA and n=13 controls).

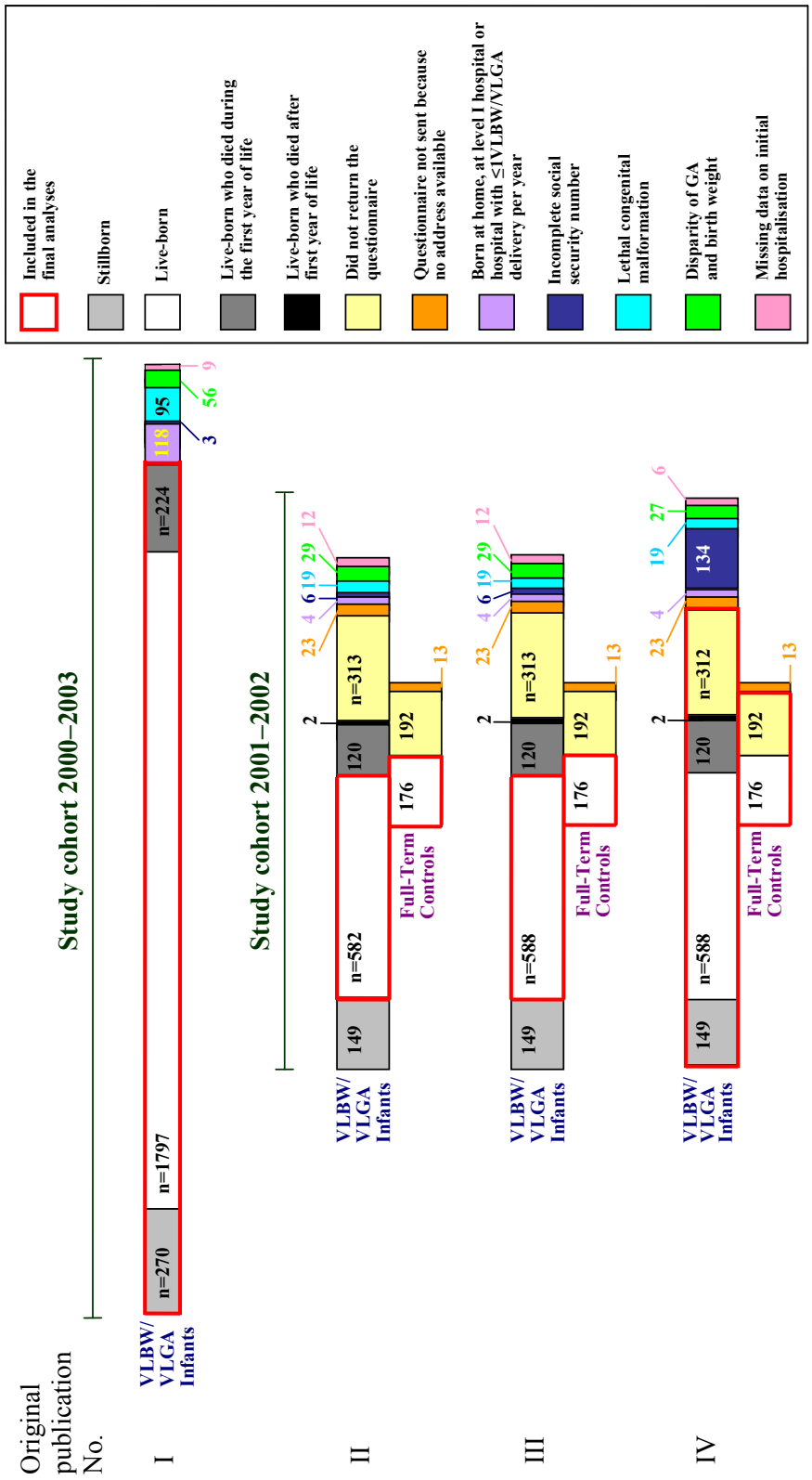

Figure 2. Participants of the four original publications are presented in the diagram, including the numbers of all excluded infants. VLBW/VLGA=very low birth weight or very low gestational age.

Table 4. Background data on the live-born VLBW/VLGA study population born from 2000–2003 (original publication I) and on the live-born VLBW/VLGA infants and full-term controls born in 2001–2002 (original publications II-IV) according to the National Medical Birth Register.

	VLBW/VLGA born 2000–2003 (n=2021)	**VLBW/VLGA born 2001–2002 (n=924)**	**Controls born 2001–2002 (n=381)**
Gestational age, weeks and days, mean (SD)	29 3/7 (2 6/7)	29 5/7 (2 3/7)	40 1/7 (1 1/7)
Percent born with GA <32 weeks	88%	88%	0%
Birth weight, g, mean (SD)	1229 (406)	1274 (394)	3636 (441)
Percent born with a birth weight ≤1500g	75%	73%	0%
Percent female	44%	44%	41%
Maternal age at delivery, years, mean (SD)	30.2 (6.0)	30.5 (6.0)	30.0 (5.5)
Previous pregnancies ending with foetal death, mean (SD)	0.6 (1.1)	0.7 (1.1)	0.5 (0.8)
Previous deliveries, mean (SD)	0.8 (1.3)	0.8 (1.3)	1.0 (1.3)
Mothers smoking during pregnancy	18%	19%	13%
Number of antenatal visits, mean (SD)	11.9 (8.2)	12.4 (8.8)	17.0 (5.1)
Number of visits at special health care maternity ward, mean (SD)	3.1 (2.9)	3.2 (2.9)	2.8 (2.8)
Multiple pregnancies (number of foetuses), mean (SD)	1.3 (0.5)	1.3 (0.5)	1.0 (0.1)

4.3 Study Design

Original publication I was a register-based study with a follow-up time of one year. Data from the MBR was used and linked to the Cause of Death statistics. The outcome was one-year mortality. The relation of the outcome to prematurity, the birth hospital level, and the university hospital district (presented in the thesis only), and the time of birth for VLBW/VLGA infants was studied. This part of the study included all VLBW/VLGA infants born between 2000 and 2003 in level II and III hospitals. The data was analysed including all VLBW/VLGA infants (n=2291) as well as focusing exclusively on live-born VLBW/VLGA infants (n=2021).

Original publications II-IV were prospective studies with a follow-up time of five years. They were based on parental questionnaires on five-year-old children. The data from the questionnaires were linked to register data.

In original publication II, data from the parental questionnaires was used to obtain information on visits to health care professionals during the last 12 months, on the chronic conditions of the children, and on background information related to family structure and socioeconomic status. The questionnaire data was linked to the MBR, the Cause of Death statistics, and the Register of Congenital Malformations for background information, the National Hospital Discharge Register (NHDR) for data on visits to special health care facilities and related diagnoses, and the Registers of the Social Insurance Institution of Finland for data on diagnoses related to special reimbursement payments and nursing subsidies. The association between the accumulated diagnoses from birth up to the age of five years and the use of different health care services from the fifth year of life to

prematurity, and the time of birth, birth hospital level, and university hospital district (the latter presented in the thesis only) among VLBW/VLGA infants was studied.

In original publication III, data from a parental questionnaire on the behaviour and development of the five-year-old children (Five To Fifteen questionnaire) was linked to background data from the MBR, the NHDR, the Register of Congenital Malformations, and the Cause of Death Register. In this part of the study, the association of the behavioural and developmental scores at five years of age with prematurity, and among the VLBW/VLGA infants, with the time of birth, birth hospital level and university hospital district was studied.

In original publication IV, parental 17D questionnaire data on HRQoL of five-year-old children was linked to the MBR for background information, the NHDR for data on initial hospitalisation, the Cause of Death statistics, and the Register of Congenital Malformations. The QALY were calculated for those who survived and those who were stillborn or died later on. The HRQoL and QALY were compared between the VLBW/VLGA children and the controls, and among just the VLBW/VLGA children according to the time of birth, birth hospital level and university hospital district.

4.4 Data Collection

4.4.1 Registers

Register data was acquired from the MBR, which is maintained by the National Research and Development Centre for Welfare and Health (currently merged into the National Institute for Health and Welfare). The data from the MBR was also linked to the Register of Congenital Malformations for information on any diagnosed malformations, and the NHDR for information on hospitalisations and other visits to special health care facilities. All special health care facilities in Finland are required to report all visits and the related diagnoses to NHDR, but health care centres and private practitioners do not report to NHDR. The diagnoses are reported according to the 10th Revision of International Statistical Classification of Diseases and Related Health Problems (ICD-10, ICD-10. 2007). Registers of the Social Insurance Institution were used to get data on the diagnoses that entitle the children to special reimbursement payments and a nursing subsidy. The addresses needed for the mailing the questionnaires were received from the Central Population Register.

4.4.2 Questionnaires

Questionnaires were sent to the home address of the child 0.5 to 1.5 months prior to his or her fifth birthday. Reminders were mailed 1.5 and 2.5 months later, if necessary. The questionnaire included three parts, which were filled in by 1) one or both parents, and 2) the mother and 3) the father separately.

The parents' questionnaire included the Five To Fifteen questionnaire (FTF), which is a validated instrument that includes 181 questions on development and behaviour

applicable to children aged 5–15 (Bohlin and Janols. 2004, Kadesjö et al. 2004, Korkman et al. 2004, Trillingsgaard et al. 2004). The parents were asked to compare their child with children of the same age and to circle one of the three alternatives that best described their child: 0=does not describe, 1=describes to some extent, and 2=describes well. After consulting one of the copyright holders (Dr. M. Korkman), questions 16, 48 to 51, 63 to 64, and 93 to 105 were removed because they are not fully applicable to children prior to school age. The removed items included sub-domains on time concepts, reading, writing, and mathematics. The individual items of the FTF have been listed in a previous publication (Kadesjö et al. 2004).

The second part of the parental questionnaire included questions on any long-term diagnoses for the child, the number of visits to different health care professionals during the last 12 months (including visits at health care centres and at private practitioners), the family structure, parental education and current employment situation. This part of the questionnaire is shown in the Appendix 1 of this thesis.

The third part of the parental questionnaire included the 17D (Apajasalo et al. 1996), which is an established instrument for measuring HRQoL (www.15d-instrument.net). It has one close-ended question on 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, where 0 corresponds to being dead, 0.0162 to being unconscious or comatose, and 1 to having no problems in any dimension or to experiencing a 'full' HRQoL. The 17D has been used as a self-administered questionnaire for 8- to 11-year-old children (Qvist et al. 2004, Apajasalo et al, 1997, Apajasalo et al. 1996, Apajasalo et al 1995). After consulting the copyright holders (H. Sintonen and M. Apajasalo), we modified the questions to allow for the parental evaluation of the HRQoL of their five-year-old child. Also, the question on vision was altered to enquire about the child's ability to watch TV and look at a picture book instead of his or her ability to read. The 17D total scores were analysed among all the responders who had completed all 17 questions. The analyses were performed using the importance weights developed for the 17D. The importance weights of the dimensions are based on a questionnaire for parents (Apajasalo et al. 1996). The parents have been asked to place the dimensions in order of importance for the quality of life of 8- to 11-year-old children. The 17D total scores were also used as a basis for calculating QALY. The translation of the modified 17D questionnaire is shown in Appendix 1 of original publication IV.

4.5 Statistical Analyses

All statistical analyses were performed using SAS for Windows, version 9 (SAS Institute, Cary, NC, USA). Differences were considered statistically significant if the p-value was below 0.05, unless otherwise mentioned. Logistic regression was used in the analysis of all dichotomous variables.

4.5.1 Analyses of Mortality

In the first part of the study on one-year mortality, the analyses were performed on live-born VLBW/VLGA infants alone and by including the stillborn VLBW/VLGA infants. When comparing level II and III hospitals, the outcome data was adjusted for maternal hospitalisation for hypertension during pregnancy, maternal age, smoking during pregnancy, primiparity, birth outside office hours, intrauterine growth, birth weight, categorised GA, and gender. The marital status of the mother, previous induced abortions, previous extrauterine pregnancies, previous miscarriages, the mode of delivery (Cesarean section or other), multiple pregnancies, and the year of birth were excluded as covariates in the models because they did not have a significant effect on the outcome. Smoking during pregnancy was included in the model because it was close to being significant and was considered a variable reflecting socioecomic status. Socioeconomic status of the mother based on register data on maternal occupation was not used as a covariate, because the information was not reliably available for young women of childbearing age. Births during public holidays, on weekends, or from 4:01 PM to 7:59 AM on weekdays were included in births outside office hours. Intrauterine growth was categorised as small (SGA), appropriate (AGA), or large (LGA) birth weight for GA, defined as birth weight below -2 SD, between -2 SD and 2 SD, and above 2 SD according to gender-specific reference values from the Finnish population, respectively.

One-year mortality between the five university hospital districts was first similarly analysed using logistic regression and adjusting for maternal hospitalisation for hypertension during pregnancy, maternal age, smoking during pregnancy, primiparity, intrauterine growth, birth weight, categorised GA, and gender. Thereafter, the same model was used with the birth hospital level and the time of birth added in the adjustments.

The potential number of lives saved if all the infants had been born in level III hospitals instead of level II hospitals was calculated. First, the parameters for all covariates were estimated. On the basis of these estimates and by hypothesising that all the infants were born in level III hospitals, the number of infants saved was calculated. It was defined as the difference between the actual number of observed deaths and the number of deaths predicted by the model.

The adjusted mortality indexes in different GA classes in level II and III hospitals, and in level II and III hospitals during and outside office hours (latter presented in this thesis only) were calculated as the ratio of observed mortality divided by expected mortality. The expected mortality for each unit was produced by taking the sum for the individual predictions for one-year mortality of logistic regression adjusted for gender, SGA, LGA, maternal age, maternal smoking, and maternal hospitalisation for hypertension. In addition to these variables, classified GA was included in the adjustment of the mortality indexes of hospitals.

4.5.2 Analyses of Morbidity and the Use of Health Care Resources

In original publication II, the ICD-10 diagnoses (without decimals) for VLBW/VLGA children up to five years of age, as recorded in the NHDR, were first compared with the controls without adjustments using Fisher's Exact Test. Diagnoses from the ICD-10 chapters Q, P (other than P27), R, and Z were not included in the comparisons (See Appendix 1 in original publication II for details on these groups). In these comparisons, a p-value of <0.01 was considered to be statistically significant. Those ICD-10 diagnoses that were overrepresented in the VLBW/VLGA children compared with the controls ($p<0.01$) were further analysed among the VLBW/VLGA children according to six groups of diagnoses: (1) CP; (2) ROP; (3) other ophthalmic problems; (4) respiratory infections; (5) asthma or CLD, and; (6) inguinal hernia. Diagnoses from the registers of the Social Insurance Institution were also included in the later analyses. In all the following analyses, a p-value of <0.05 was considered significant. The six groups of diagnoses were compared according to the time of birth, birth hospital level and university hospital district (the latter presented in this thesis only). The comparisons of the groups of diagnoses were adjusted for GA, birth weight, gender, intrauterine growth (SGA, AGA, or LGA), non-lethal congenital malformations, and multiple pregnancies (number of foetuses). Because none of the children born LGA had CP or ROP, the adjustment for intrauterine growth was categorised as "SGA or other" in the comparisons regarding CP or ROP.

Next, an analysis was performed of the number of visits during the fifth year of life to the (1) physician, (2) nurse practitioner, (3) OT or PT, (4) psychologist, (5) speech therapist, and (6) dietitian based on parental questionnaire responses, (7) the number of inpatient days, and (8) the number of non-emergency and emergency outpatient visits to specialized health care facilities according to NHDR data. The covariates used in the adjustments were chosen by first testing the associations of each visit type with the background variables separately. This and subsequent analyses in original publication II were performed using a generalised linear model with a negative binomial as the response distribution. The tested background variables included family income, family structure ([1] two biological parents, [2] single parent or joint custody, [3] one biological parent and a step-parent, or [4] foster care or adoption), the number of minors in the family, the mother's and the father's years of education and current employment situation ([1] employed, [2] unemployed, or [3] at home taking care of a family member), and the day-care arrangements ([1] at home care, [2] in a day-care group including 4 to 8 children, or [3] in a larger day-care or pre-school group). The family income was analysed as the logarithm of monthly income taking the number of adult and minor family members into account according to the Organisation for Economic Co-operation and Development equivalence scale (http://www.oecd.org/dataoecd/61/52/35411111.pdf). The significant background factors for each visit type were then used as covariates in the comparisons between the VLBW/VLGA children and controls. None of the children whose father was unemployed visited the psychologist and none of those with foster or adoption families visited the nurse practitioner. These variables were thus not included in the adjustments of the two visit types. The visits of the VLBW/VLGA infants were then compared

according to the time of birth, birth hospital level and university hospital district (the latter presented in this thesis only). For the adjustments in VLBW/VLGA children, the significance of GA, birth weight, gender, intrauterine growth (SGA, AGA, or LGA), non-lethal congenital malformations, and multiple pregnancies (number of foetuses) was tested for each visit type. Again, the significant background variables for each visit type were used as covariates for the comparisons of the VLBW/VLGA children in addition to covariates used for the comparisons between the VLBW/VLGA children and the controls. All five university hospital districts were first compared in one model and thereafter in pair-wise comparisons. The proportion of infants that used different health care services during the fifth year of life was also analysed as dichotomous variables by using logistic regression with the adjustments described above.

Finally, the effect of each of the six groups of diagnoses in VLBW/VLGA children on each type of health care visit was tested. These comparisons were adjusted for the GA, birth weight, gender, intrauterine growth (SGA, AGA, or LGA), non-lethal congenital malformations, multiple pregnancies (number of foetuses), and the five other groups of diagnoses.

4.5.3 Analyses of the Behavioural and Developmental Scores

In original publication III, the FTF developmental and behavioural scores of five-year-old VLBW/VLGA children were compared with those of the controls. The relationships of the scores of the VLBW/VLGA children and the birth hospital level, university hospital district, and the time of birth was then assessed. The comparisons, which included both VLBW/VLGA children and controls, were adjusted for gender**,** the mother's and the father's years of education and current employment status [(1) employed, (2) unemployed, or (3) at home taking care of a family member]**,** and family structure [(1) two biological parents, (2) single parent or joint custody, (3) a biological parent and a step-parent, or (4) foster care or adoption family]. These adjustments were chosen because gender and parental education, the latter used as a measure of socioeconomic status, have been shown to be associated with FTF scores (Bohlin and Janols. 2004, Kadesjö et al. 2004). The same adjustments were used in the comparisons of the VLBW/VLGA children. In addition, comparisons within the VLBW/VLGA children were adjusted for intrauterine growth (SGA, AGA, or LGA), multiple pregnancies (number of foetuses), GA, birth weight, and non-lethal malformations.

The statistical analyses for the FTF scores were performed using generalised linear models. The response distribution for the sums of the FTF scores was a negative binomial and the link function was log. In the analysis of FTF scores, the logarithm of the number of answered questions was used as the offset variable. The results for these comparisons are given as rate ratios (RR) with 95% confidence intervals (CI) or as P-values. The results are also considered in relation to the normative values previously obtained from a sample of 5.0- to 5.5-year-old Finnish children (Korkman et al. 2005). The children

whose Domain Score exceeded the 98th percentile limit for normative children were regarded as having considerable difficulties in that particular domain area.

The effect of GA on the 8 main FTF domains was studied separately within the VLBW/VLGA children. The covariates included in the model were the same variables that were used in the adjustments for VLBW/VLGA children. However, birth weight was not included in the model, because of multicollinearity with GA and the categorised intrauterine growth.

4.5.4 Analyses of the Health-Related Quality of Life and Quality-Adjusted Life-Years

In original publication IV, the main outcomes were the HRQoL scores (17D) and the QALY at five years of age. These were first compared between the VLBW/VLGA children and the controls. Thereafter, focusing on VLBW/VLGA children alone, the relation of the outcomes to the time of birth, birth hospital level and university hospital district was assessed.

Comparisons of 17D total scores were performed using Tobit regression (Long. 1997). The background variables used in the adjustments were chosen by testing the associations of the 17D total score with the following variables: gender, mother's and father's years of education and current employment status, a logarithm of the family's monthly income, and the family structure [(1) two parents, (2) single parent or joint custody, (3) one biological parent and a step-parent, or (4) foster care or adoption family). The background variables significantly influencing the 17D total score in the univariate analyses were adjusted for in the comparisons between the VLBW/VLGA children and controls. The associations of the 17D total scores for VLBW/VLGA children with gender, mother's and father's years of education and current employment status, logarithm of the family's monthly income, the family structure, and to intrauterine growth (SGA, AGA, or LGA), multiple pregnancies (number of foetuses), GA, birth weight, and any non-lethal congenital malformation were tested similarly. The individual variables significantly influencing the 17D total score within the whole study population and the individual variables significantly affecting the 17D total score of VLBW/VLGA children were adjusted in the comparisons involving VLBW/VLGA children only.

Adjusted individual 17D dimension scores were compared using a generalised linear model. The response distribution of 17D scores was multinomial and the link function was a cumulative logit. If the assumption of proportional odds was not met in the analysis of 17D dimension scores, the most severe (and rarest) categories were combined until the assumption was met.

QALY at five years of age were calculated by defining a HRQoL score for each day of life and multiplying this by the number of days alive up to five years of age. The HRQoL was assumed constant for all days after discharge from the initial hospitalisation period. This "home score" was acquired from the parental 17D questionnaire at five years of

age. Separate HRQoL scores were estimated for the days of the initial hospitalisation period for VLBW/VLGA children. Immediately after birth, the VLBW/VLGA children were assumed to have an "all worst" HRQoL score. "All worst" means 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. Preceding the discharge home, the HRQoL scores linearly increased from "all worst" to "home score", which was reached on the day of discharge. If the infant died during the initial hospitalisation period, the "all worst" score linearly decreased to zero until the day of death. For stillborn infants, the QALY were directly assigned the value of 0. The healthy control infants had no hospitalisation periods during the first seven days of life, and were assigned the "home score" from birth. The later hospitalisation periods were not taken into account when calculating the QALY, because of the variation in the severity of reasons for later hospital stays and because the number of hospital days after the initial hospitalisation period of VLBW/VLGA children was low (mean 1.2 days per year after the first year, SD 6.5).

To calculate QALY, the HRQoL scores were estimated for non-responders in order to match the 17D scores of children with similar background variables. Multiple imputation was performed to estimate values for missing 17D observations, using the Markov Chain Monte Carlo method (Schafer. 1999). The imputation was performed using existing 17D scores and background data on the time of birth, birth hospital level and university hospital district, gender, GA, multiple pregnancies (number of foetuses), birth weight, and intrauterine growth (SGA, AGA, or LGA). Five complete data sets with different imputed values were generated by this method. Parallel analyses were performed on all sets. Results obtained from the analyses of each of the five data sets were combined using methods that accounted for the imputation process.

Associations between the QALY and independent variables were studied using a linear multiple regression analysis. The QALY in the VLBW/VLGA children and in the controls were compared using a multivariate model adjusted for gender. In the VLBW/VLGA children, the effects of time of birth, hospital level and district on QALY were studied, adjusting for gender, GA, multiple pregnancies (number of foetuses), birth weight, and intrauterine growth. QALY comparisons were not adjusted for congenital malformations because it is likely that non-lethal malformations are underreported for infants who die. Due to the bimodality of QALY distribution, the median quantile regression was also used (Koenker and Bassett. 1978).

4.5.5 Statistical Methods of the Drop-Out Analysis

A drop-out analysis was performed between the responders and non-responders to the questionnaire separately for the VLBW/VLGA children and the controls. The responders and non-responders in both study groups were compared regarding the number of all antenatal visits and of visits to the university hospital maternity ward during pregnancy, maternal age, smoking during pregnancy, the number of previous pregnancies with foetal death (including miscarriages, abortions, extrauterine pregnancies, and previous

stillbirths), the number of previous deliveries, GA, birth weight, gender, multiple pregnancies (number of foetuses), the number of days the child had been hospitalised or institutionalised, the number of emergency visits and other visits to special health care facilities during the first five years of life. In addition, the five-year incidence of CP, ROP, other ophthalmic problems, respiratory infections, asthma or CLD, and inguinal hernia were compared in univariate analyses using Fisher's exact test.

4.6 Ethics

The parents gave written informed consent to participation in the study. All the questionnaires were sent to the home addresses of the children. The questionnaires included an information letter signed by the head of neonatology of the level III hospital in the district of birth.

The Ethics Committee of the National Research and Development Centre for Welfare and Health approved the study protocol. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The register keeping organisations gave their permission for using the data for this study.

4.7 Drop-Out Analysis

588 (64%) parents of VLBW/VLGA children and 176 (46%) parents from the control group returned the questionnaire. There were more multiple pregnancies and previous pregnancies ending with foetal death in the VLBW/VLGA non-responder group than in the VLBW/VLGA responder group. Although the mothers for the non-responder group smoked more often during pregnancy and had fewer antenatal visits (although more special health care visits) than the mothers for the responder group, there was no significant difference in the birth weight and the GA between the groups. Furthermore, the number of emergency care visits or other special health care visits, the number of days spent hospitalised during the first five years of life did not differ between the responders and non-responders (Table 5). The five-year incidence of CP, ROP, other ophthalmic problems, and asthma or CLD did not differ between the responders and non-responders. The non-responders had more respiratory infections, while inguinal hernia was more common among the VLBW/VLGA responders (Table 6). In the control group, the GA was higher in the non-responder group than in the responder group and the mothers smoked more often during the pregnancy than the mothers of children in the responder group did, but no other significant differences were found between the responders and non-responders in the control group (Table 7 and 8).

Table 5. Comparison of the background variables for the VLBW/VLGA children whose parents responded (n=588) and for those whose parents did not respond (n=322) to the five-year questionnaire. The odds ratio (OR) and the confidence interval (95% CI) are given per increase of one unit unless otherwise mentioned. Previous pregnancies ending with foetal death represent the sum of the number of miscarriages, abortions, extrauterine pregnancies, and previous stillbirths. GA=gestational age; SD=standard deviation.

	Responders, mean (SD)	Non-responders, mean (SD)	OR (95% CI)
Maternal age (years)	30.7 (5.8)	30.2 (6.3)	0.98 (0.95; 1.01)
Previous pregnancies ending with foetal death	0.6 (1.0)	0.8 (1.3)	**1.26 (1.09; 1.46)**
Previous deliveries	0.8 (1.4)	0.9 (1.3)	1.02 (0.89; 1.15)
Maternal smoking during pregnancy (yes)	14%	24%	**1.93 (1.31; 2.83)**
No. of antenatal visits	13.0 (9.7)	11.3 (7.0)	**0.94 (0.91; 0.97)**
No. of visits at special health care maternity ward	3.1 (3.0)	3.2 (2.7)	**1.08 (1.004; 1.16)**
Multiple pregnancies (number of foetuses)	1.3 (0.5)	1.4 (0.6)	**2.10 (1.53; 2.82)**
Percent female	43%	53%	**1.36 (1.002; 1.85)**
Birth weight (g) (OR per increase of 100g)	1249 (382)	1307 (403)	1.05 (0.997; 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; 1.17)
No. of emergency visits at special health care facilities at age 0–5 years	2.4 (3.0)	3.1 (4.3)	1.04 (0.99; 1.09)
No. of other special health care visits at age 0–5 years	20.8 (19.9)	22.6 (23.0)	1.00 (0.999; 1.01)
Hospitalised at age 0–5 years (days)	68.4 (39.5)	76.3 (69.8)	1.00 (0.99; 1.01)

Table 6. Comparison of the five-year incidence of diagnoses for the VLBW/VLGA children whose parent responded (n=588) and for those whose parents did not respond (n=322) to the five-year questionnaire.

	Responders, incidence of diagnoses (%)	Non-responders, incidence of diagnoses (%)	Unadjusted P-value
CP	4.2	6.2	0.20
ROP	14.4	17.7	0.21
Ophthalmic problems	13.7	14.9	0.62
Respiratory infections	53.9	61.5	**0.03**
Asthma or CLD	33.2	32.6	0.88
Inguinal hernia	18.1	11.2	**<0.01**

Table 7. Comparison of the background variables for the full-term controls whose parents responded (n=176) and for those whose parents did not respond (n=202) to the five-year questionnaire. The odds ratio (OR) and the confidence interval (95% CI) are given per increase of one unit unless otherwise mentioned. Previous pregnancies ending with foetal death represents the sum of the number of miscarriages, abortions, extrauterine pregnancies, and previous stillbirths. GA=gestational age; SD=standard deviation.

	Responders, mean (SD)	Non-responders, mean (SD)	OR (95% CI)
Maternal age (years)	30.0 (5.6)	30.0 (5.5)	1.00 (0.96; 1.04)
Previous pregnancies ending with foetal death	0.4 (0.7)	0.5 (0.9)	1.27 (0.95; 1.70)
Previous deliveries	0.9 (1.1)	1.1 (1.5)	1.21 (0.98; 1.48)
Maternal smoking during pregnancy (yes)	9%	16%	**1.96 (1.004; 3.81)**
No. of antenatal visits	17.1 (5.2)	16.9 (5.0)	1.00 (0.94; 1.06)
No. of visits at special health care maternity ward	2.9 (3.1)	2.7 (2.5)	0.97 (0.87; 1.08)
Multiple pregnancies (number of foetuses)	1.0 (0.1)	1.0 (0.1)	2.50 (0.14; 42.05)
Percent female	41%	40%	0.97 (0.62; 1.54)
Birth weight (g) (OR per increase of 100g)	3570 (436)	3693 (438)	1.04 (0.98; 1.10)
GA (weeks and days) (OR per increase of 1 week)	40 0/7 (1 0/7)	40 2/7 (1 1/7)	**1.32 (1.04; 1.67)**
No. of emergency visits at special health care facilities at age 0–5 years	0.8 (1.4)	1.0 (1.5)	1.01 (0.86; 1.20)
No. of other special health care visits at age 0–5 years	2.6 (6.6)	3.0 (7.3)	1.00 (0.97; 1.04)
Hospitalised at age 0–5 years (days)	1.0 (2.7)	2.0 (9.0)	1.03 (0.98; 1.09)

Table 8. Comparison of the five-year incidence of diagnoses for the full-term controls whose parent responded (n=176) and for those whose parents did not respond (n=202) to the five-year questionnaire.

	Responders, incidence of diagnoses (%)	Non-responders, incidence of diagnoses (%)	Unadjusted P-value
CP	0	0	NA
ROP	0	0	NA
Ophthalmic problems	1.7	1.0	0.67
Respiratory infections	22.2	22.3	1.00
Asthma or CLD	6.3	4.5	0.49
Inguinal hernia	1.7	1.5	1.00

5. RESULTS

5.1 The Five-Year Outcome of VLBW/VLGA Infants and the Comparison to Full-Term Controls

5.1.1 Mortality

The five-year mortality was 12% (n=122) for the live-born VLBW/VLGA children and 0% for the controls. The median age of death for the VLBW/VLGA children was 2 days. Only two VLBW/VLGA children died after the first year of life, one of complications of Fallot's tetralogy at 1.8 years of age and the other of a brain tumour at 1.6 years of age.

5.1.2 Morbidity

Based on the NHDR data up to five years of age, 13 diagnoses were overrepresented in the VLBW/VLGA children compared with the controls, while one diagnosis, atopic dermatitis, was more common in the controls than in VLBW/VLGA children (Table 9). The number of VLBW/VLGA children with a diagnosis of epilepsy (n=10) or a hearing defect (n=8, all sensorineural or combined defects) did not significantly differ from the controls (0 and 2 children, respectively). Those ICD-10 diagnoses overrepresented in VLBW/VLGA children compared with the controls ($p<0.01$) were further analysed in the following six groups of diagnoses: 1) CP [ICD-10 code: G80]; 2) retinopathy [H35]; 3) other ophthalmic problems (including strabismus [H50], and disorders of refraction and accommodation [H52]); 4) upper or lower respiratory infections (including otitis media [H65-66], acute upper respiratory infections [J06], bronchitis [J20], or bronchiolitis [J21], and pneumonia [J18]); 5) asthma [J45], or chronic respiratory disease originating in the perinatal period [P27], and; 6) inguinal hernia [K40]. Linking the NHDR data to the diagnoses reported to the Social Insurance Institution yielded the following additional cases: one VLBW/VLGA child with CP, six with respiratory infections, and 13 with asthma or CLD.

Table 9. The number (and percentage) of study children with diagnoses (accumulated from birth up to five years of age) that differed significantly (p<0.01) between the VLBW/VLGA children and the controls according to data from the National Hospital Discharge Register. Unadjusted comparisons between the groups are shown. The roman numerals indicate the six diagnostic groups included in further analyses within the VLBW/VLGA group.

	ICD-10 diagnoses	ICD-10 code	VLBW/VLGA (n=582) n (%)	Controls (n=176) n (%)	P-value
I	Cerebral palsy (CP)	G80	23 (4.0)	0 (0)	**0.004**
II	Retinopathy of prematurity (ROP)	H35	85 (14.6)	0 (0)	**<0.001**
III	Strabismus	H50	51 (8.8)	1 (0.6)	**<0.001**
	Disorders of refraction and accommodation	H52	39 (6.7)	2 (1.1)	**0.002**
IV	Nonsuppurative otitis media	H65	80 (13.8)	9 (5.1)	**0.001**
	Suppurative and unspecified otitis media	H66	186 (32.0)	18 (10.2)	**<0.001**
	Acute upper respiratory infections	J06	140 (24.1)	10 (5.7)	**<0.001**
	Pneumonia	J18	49 (8.4)	3 (1.7)	**0.001**
	Acute bronchitis	J20	28 (4.8)	0 (0)	**<0.001**
	Acute bronchiolitis	J21	142 (24.4)	14 (8.0)	**<0.001**
V	Chronic respiratory disease originating in the perinatal period (CLD)	P27	115 (19.8)	0 (0)	**<0.001**
	Asthma	J45	110 (18.9)	8 (4.6)	**<0.001**
VI	Inguinal hernia	K40	105 (18.0)	3 (1.7)	**<0.001**
	Atopic dermatitis	L20	22 (3.8)	17 (9.7)	**0.005**

5.1.3 Behaviour and Development

Compared with the controls, the VLBW/VLGA children had significantly higher scores in all FTF domains, indicating more developmental and behavioural problems (Table 10).

The FTF Domain Scores were less optimal with decreasing GA (Figure 3). Among the VLBW/VLGA children, the scores of all eight main domains significantly decreased with an increasing GA. An increase of one week in the GA was associated with a 0.9-fold lower score in all main domains, i.e. motor skills (p<.0001), executive functions (p=0.0096), perception (p<.0001), memory (p=0.0007), language (p=0.0002), learning (p=0.0002), social skills (p=0.0007), and emotional and behavioural problems (p=0.0029).

Table 10. Developmental and behavioural scores from the Five To Fifteen questionnaire (FTF) in VLBW/VLGA children and full-term controls. The proportion of children within the normal range and the proportion having considerable difficulties according to Finnish normative values is given for the main domains. The rate ratio (RR) estimates and 95% confidence intervals (CI) describe how many times higher the scores of VLBW/VLGA children are in comparison with the controls after adjustments for gender, family structure, and the mother's and the father's years of education and employment status.

FTF domain	VLBW/VLGA children (n=588)			Controls (n=176)			Adjusted RR (95% CI)
	Unadjusted mean score	Proportion within the normal range	Proportion having considerable difficulties	Unadjusted mean score	Proportion within the normal range	Proportion having considerable difficulties	
Motor skills	0.38	66%	8.3%	0.18	86%	0.6%	**2.22 (1.83; 2.69)**
Gross motor skills	0.36			0.13			**2.89 (2.16; 3.86)**
Fine motor skills	0.40			0.22			**1.91 (1.59; 2.30)**
Executive functions	0.42	68%	7.8%	0.26	83%	0%	**1.53 (1.29; 1.82)**
Attention	0.44			0.23			**1.81 (1.47; 2.23)**
Hyperactive/Impulsive	0.47			0.35			**1.28 (1.07; 1.53)**
Hypoactive	0.26			0.10			**2.63 (1.88; 3.66)**
Planning/organising	0.40			0.30			**1.34 (1.07; 1.68)**
Perception	0.24	56%	3.9%	0.13	70%	0%	**1.92 (1.55; 2.39)**
Relation in space	0.24			0.11			**2.27 (1.68; 3.06)**
Body perception	0.22			0.13			**1.76 (1.34; 2.33)**
Visual perception	0.26			0.15			**1.83 (1.38; 2.43)**
Memory	0.32	59%	8.4%	0.26	61%	2.8%	**1.26 (1.01; 1.58)**
Language	0.30	68%	4.6%	0.18	82%	2.8%	**1.64 (1.33; 2.01)**
Comprehension	0.30			0.18			**1.61 (1.25; 2.07)**
Expressive language skills	0.29			0.18			**1.65 (1.31; 2.07)**
Communication	0.31			0.17			**1.76 (1.30; 2.38)**
Learning	0.39	NA	NA	0.22	NA	NA	**1.67 (1.35; 2.06)**
Coping in learning	0.41			0.25			**1.60 (1.30; 1.98)**
General learning	0.31			0.16			**1.91 (1.42; 2.56)**
Social skills	0.21	67%	4.3%	0.11	68%	0%	**1.83 (1.44; 2.34)**
Emotional/behavioural problems	0.16	65%	3.4%	0.11	77%	0%	**1.49 (1.20; 1.84)**
Internalising	0.13			0.08			**1.56 (1.19; 2.05)**
Externalising	0.23			0.17			**1.39 (1.09; 1.78)**
Obsessive compulsive	0.10			0.05			**1.79 (1.22; 2.62)**

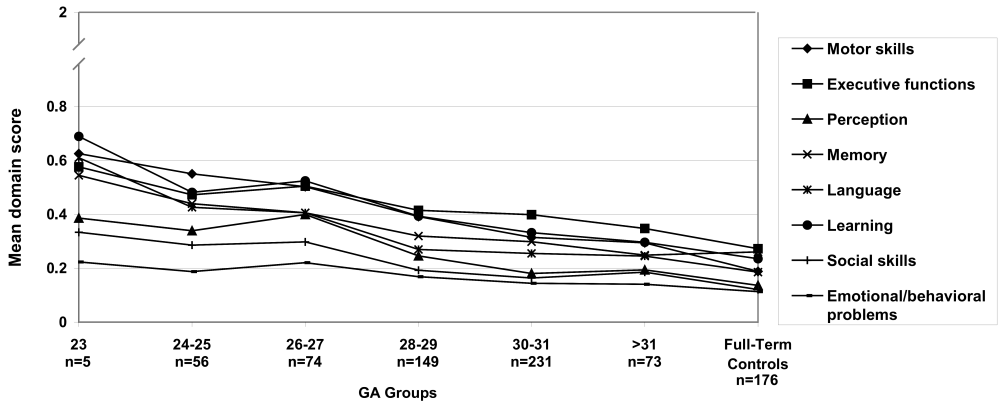

Figure 3. The developmental and behavioural scores according to the parental Five To Fifteen questionnaire. The main domain score means are presented according to GA groups in the VLBW/VLGA children and separately for the full-term controls. The scale ranges from 0 (=no problems) to 2.

5.1.4 The Use of Health Care Resources

The background variables significantly affecting the number of each type of health care visit are shown in Table 11. A larger proportion of VLBW/VLGA children than controls visited the OT/PT, psychologist, and speech therapist during the fifth year of life. Although the mean number of visits was low for the VLBW/VLGA children, they had on average more visits to the physician, nurse practitioner, and OT or PT, and had more visits to the special health care facilities and more inpatient days compared with the controls (Table 12). Among the VLBW/VLGA children, CP, asthma or CLD, and ophthalmic problems (other than ROP) were associated with increased contacts with health care professionals. CP, ophthalmic problems (other than ROP), respiratory infections, and asthma or CLD were associated with an increased number of outpatient visits at special health care facilities. However, only respiratory infections were associated with increased inpatient days (Table 13).

Table 11. Background variables significantly affecting the number of different visit types during the fifth year of life according to the univariate analysis. The direction of effect is indicated with + (positive correlation with increased number of visits/days) or – (negative correlation). OT=occupational therapist; PT=physiotherapist.

Visit type	Tested group	Background variables	Direction	P-value
Data from the parental questionnaires				
Physician	All study children	Family income†	+	**0.013**
		Number of minors	–	**<0.001**
		Day-care type (with respect to a large group)	At home –, Family day-care –	**0.012**
	VLBW/VLGA children	GA	–	**<0.001**
		Birth weight	–	**<0.001**
		Non-lethal malformations	+	**<0.001**
Speech therapist	VLBW/VLGA children	GA	–	**0.005**
		Birth weight	–	**0.016**
		Multiple pregnancies (number of foetuses)	–	**0.003**
OT/PT	VLBW/VLGA children	GA	–	**<0.001**
Dietitian	VLBW/VLGA children	Birth weight	–	**0.042**
		Intrauterine growth (with respect to AGA)	LGA + SGA +	**0.001**
		Non-lethal malformations	+	**0.019**
The sum of all abovementioned visits	All study children	Mother's years of education	–	**0.010**
		Day-care type (with respect to a large group)	At home –, Family day-care –	**<0.001**
	VLBW/VLGA children	Male gender	+	**0.008**
		GA	–	**<0.001**
		Birth weight	–	**<0.001**
Data from the Hospital Discharge Register on the use of specialized health care services				
Emergency visits	VLBW/VLGA children	GA	–	**0.015**
		Birth weight	–	**0.021**
		Non-lethal malformations	+	**0.037**
Non-emergency visits	All study children	Mother's employment situation (with respect to "at home")	Employed –, Unemployed –	**0.050**
		Day-care type (with respect to a large group)	At home –, Family day-care –	**0.008**
	VLBW/VLGA children	GA	–	**<0.001**
		Birth weight	–	**<0.001**
		Non-lethal malformations	+	**<0.001**
Days hospitalised	All study children	Mother's employment situation (with respect to "at home")	Employed – Unemployed +	**0.012**
		Day-care type (with respect to a large group)	At home +, Family day-care –	**0.028**
	VLBW/VLGA children	GA	–	**0.028**
		Birth weight	–	**0.002**
		Non-lethal malformations	+	**0.009**

†Family income with respect to the number of minor and adult family members. The income was divided by 1 for the first adult and by 0.75 for the next adult, and by 0.5 for each child.

Table 12. The percentage of children using different health care services during the fifth year of life, and the mean number of visits and hospital days for all live-born VLBW/VLGA children and controls born in 2001–2002. The adjusted odds ratios (OR) and incidence rate ratios (RR) and 95% confidence intervals (CI) describe how much the percentage of children using the services and the mean number of visits or days has increased in VLBW/VLGA children in comparison with the full-term controls. Adjustments were made for those background variables that had a significant effect on the univariate analyses for each visit type (See Table 11). OT=occupational therapist; PT=physiotherapist.

Type of visit	Percentage of children using the services during the fifth year of life			Number of visits/days, mean (SD)		
	VLBW/VLGA (n=582)	Controls (n=176)	Adjusted OR (95 % CI)	VLBW/VLGA (n=582)	Controls (n=176)	Adjusted RR (95 % CI)
Data from the parental questionnaires						
Physician	90%	84%	1.62 (0.95; 2.75)	4.9 (5.2)	3.5 (4.1)	**1.37 (1.15; 1.63)**
Nurse practitioner	59%	54%	1.26 (0.98; 1.77)	1.0 (1.7)	0.8 (1.2)	**1.33 (1.05; 1.69)**
OT/PT	21%	5%	**5.41 (2.59; 11.31)**	6.8 (25.5)	0.7 (8.0)	**9.50 (4.01; 22.48)**
Psychologist	14%	7%	**2.65 (1.34; 5.23)**	0.3 (1.1)	0.2 (1.1)	1.66 (0.85; 3.27)
Speech therapist	18%	7%	**3.08 (1.65; 5.74)**	2.1 (9.2)	1.6 (9.8)	1.37 (0.61; 3.08)
Dietitian	2%	1%	2.00 (0.45; 8.94)	0.04 (0.4)	0.02 (0.2)	2.53 (0.46; 14.07)
The sum of all abovementioned visits	93%	90%	1.53 (0.83; 2.81)	15.1 (30.2)	6.7 (18.8)	**2.23 (1.78; 2.78)**
Data from the Hospital Discharge Register on the use of specialized health care services						
Emergency visits	15%	9%	**1.83 (1.04; 3.21)**	0.2 (0.5)	0.1 (0.3)	**2.06 (1.18; 3.61)**
Non-emergency visits	47%	13%	**5.82 (3.63; 9.34)**	1.9 (3.8)	0.4 (1.9)	**5.87 (3.90; 8.82)**
Days hospitalised	10%	4%	**2.67 (1.19; 6.01)**	0.4 (1.9)	0.1 (1.0)	**2.85 (1.17; 6.98)**

Table 13. The effect of the six groups of diagnoses (accumulated since birth) on the use of health care services during the fifth year of life by VLBW/VLGA children (n=582). The rate ratio (RR) and the 95% confidence interval (CI) indicate how each group of diagnoses affected the number of visits to health care professionals or the number of days hospitalised. The RR for each group of diagnoses is adjusted for GA, birth weight, sex, intrauterine growth (SGA, AGA, or LGA), non-lethal congenital malformations, multiple pregnancies, and for the five other groups of diagnoses. CP=cerebral palsy; ROP=retinopathy of prematurity; CLD=chronic lung disease; OT=occupational therapist; PT=physiotherapist.

Number of visits/days	**CP** (n=24)	**ROP** (n=85)	**Ophthalmic problems** (n=79)	**Respiratory infections** (n=312)	**Asthma or CLD** (n=192)	**Inguinal hernia** (n=105)
	RR (CI)	RR (CI)	RR (CI)	RR (CI)	RR (CI)	RR (CI)
Data from the parental questionnaires						
Physician	1.19 (0.82; 1.73)	0.82 (0.65; 1.05)	1.25 (1.00; 1.55)	**1.36 (1.15; 1.60)**	**1.32 (1.10; 1.58)**	1.00 (0.82; 1.22)
Nurse	1.05 (0.60; 1.84)	0.75 (0.51; 1.09)	1.01 (0.72; 1.42)	1.09 (0.86; 1.38)	1.05 (0.80; 1.39)	0.83 (0.61; 1.12)
OT/PT	**76.52 (13.91; 420.94)**	**0.23 (0.08; 0.71)**	**4.17 (1.43; 12.12)**	1.30 (0.65; 2.63)	**2.62 (1.18; 5.79)**	0.93 (0.41; 2.13)
Psychologist	1.19 (0.28; 5.09)	0.71 (0.28; 1.77)	1.15 (0.46; 2.87)	0.97 (0.47; 2.00)	2.05 (0.95; 4.43)	0.48 (0.20; 1.14)
Speech therapist	0.69 (0.11; 4.51)	2.99 (0.88; 10.20)	**4.48 (1.16; 17.27)**	0.75 (0.33; 1.74)	1.19 (0.44; 3.24)	0.49 (0.17; 1.41)
Dietitian	0.40 (0.01; 19.20)	0.42 (0.04; 4.35)	0.84 (0.09; 7.65)	3.23 (0.54; 19.30)	1.31 (0.22; 7.92)	0.32 (0.04; 2.43)
The sum of all abovementioned visits	**8.38 (5.40; 13.03)**	1.02 (0.75; 1.37)	**1.60 (1.22; 2.11)**	1.16 (0.96; 1.42)	**1.52 (1.21; 1.91)**	0.84 (0.66; 1.07)
Data from the Hospital Discharge Register on the use of specialized health care services						
Emergency visits	1.69 (0.75; 3.83)	0.98 (0.51; 1.88)	1.44 (0.83; 2.52)	**2.38 (1.41; 4.03)**	1.44 (0.86; 2.41)	0.76 (0.42; 1.38)
Non-emergency visits	**4.83 (2.60; 8.98)**	1.02 (0.67; 1.54)	**1.76 (1.23; 2.53)**	**1.36 (1.02; 1.83)**	**2.03 (1.47; 2.80)**	1.16 (0.82; 1.65)
Days hospitalised	2.87 (0.54; 15.27)	0.70 (0.21; 2.42)	2.48 (0.87; 7.09)	**2.65 (1.06; 6.59)**	0.68 (0.25; 1.86)	0.47 (0.16; 1.32)

5.1.5 Health-Related Quality of Life and Quality-Adjusted Life-Years

Among all study children the 17D total score for the HRQoL independently decreased according to low family income, being male as opposed to female, the mother's unemployment, and when the child lived in a family with a step parent or in a single-parent home. The mother's and the father's years of education and the father's employment situation did not have an effect on the 17D total score. Among VLBW/VLGA children only, the 17D total score independently increased according to multiple pregnancies and increasing GA and birth weight, and decreased according to the presence of congenital malformations. Intrauterine growth (SGA, AGA, or LGA) had no effect on 17D total score in VLBW/VLGA children.

VLBW/VLGA children had a lower adjusted total 17D score than the controls (Regression Coefficient -0.02, 95% confidence interval [CI] -0.03 to -0.01). Several dimensions contributed to the difference in the total score (Figure 4). The distribution of the 17D total score in live-born VLBW/VLGA children is shown in Figure 5 and the 17D total score in relation to GA in Figure 6. GA was not significantly associated with the 17D total score in VLBW/VLGA children, when the analysis was adjusted for all the variables that independently affected 17D total score (p=0.11). However, when birth weight was excluded from the adjustments, an increase of one week in GA was associated with an increase of 0.004 points in the 17D total score (p<0.001).

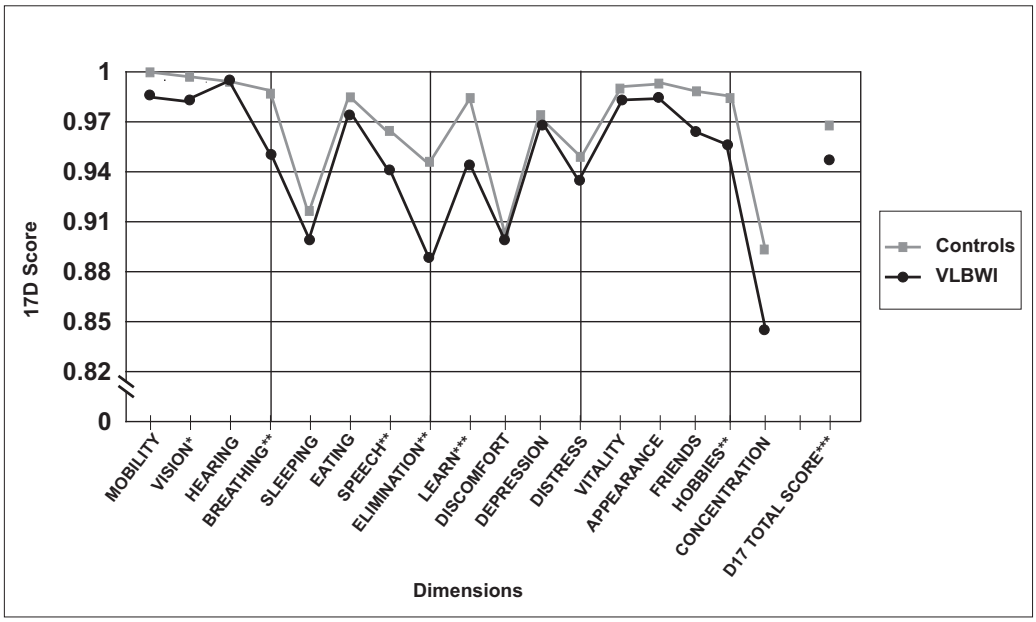

Figure 4. Health-related quality of life of five-year-old VLBW/VLGA children (n=568) and full-term controls (n=173) according to the parental 17D questionnaire. The scale ranges from 0 to 1 (0=dead, 1=perfect health). The comparisons were adjusted for gender, family income, mother's current employment situation, and family structure. Significant differences between the groups are indicated as * for p<0.05, ** for p<0.01, and *** for p<0.0001.

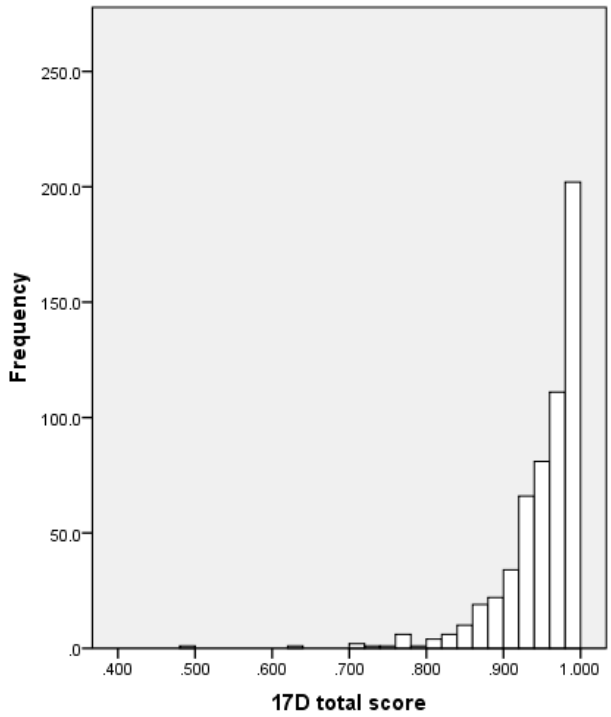

Figure 5. The distribution of the 17D total score in live-born VLBW/VLGA children (n=568).

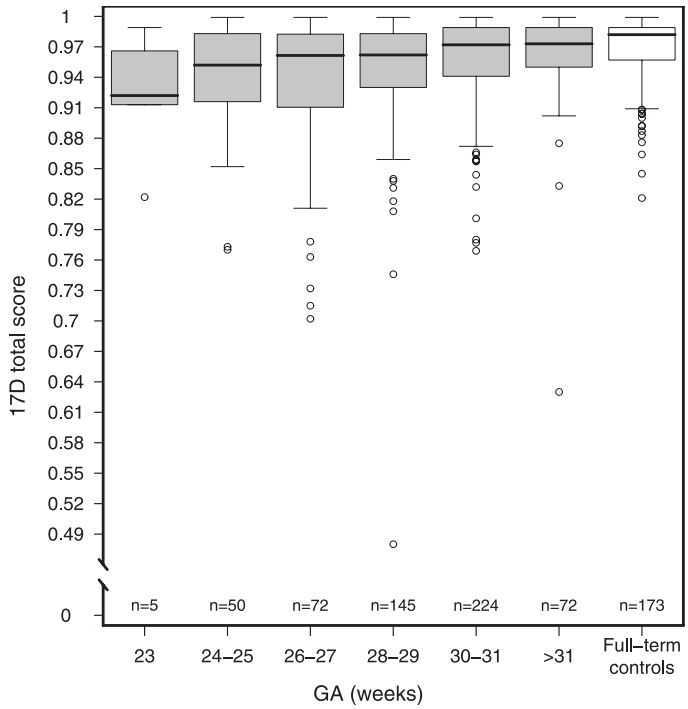

Figure 6. Health-related quality of life for VLBW/VLGA children and controls at five years of age from the parental 17D questionnaire is shown according to gestational age groups in VLBW/VLGA children and separately for the full-term controls.

The median for the QALY for all VLBW/VLGA children (including stillbirths) was 4.6 (mean 3.6) out of a maximum 5, and 4.8 (mean 4.9) for the controls. The differences between the group medians ($p<0.0001$) and means ($p<0.0001$) were significant when adjusted for gender. In live-born VLBW/VLGA children, the median for the QALY was 4.7 ($p=0.0001$ in adjusted comparison with the controls) and the mean was 4.1 ($p<0.0001$ in adjusted comparison with the controls).

5.2 Comparison among the VLBW/VLGA Infants According to the Birth Hospital Level

5.2.1 Mortality

The total one-year mortality of VLBW/VLGA infants born between 2000 and 2003 was 21.6% (494 of 2291 infants) when stillbirths were included. Of the live-born infants, 11.1% (224 of 2021) died during the first year of life. The median age of death for the live-born infants was 2 days (range: 0–336 days). The risk of total one-year mortality (including stillbirths) was significantly increased by birth in a level II hospital, a low birth weight and a low GA, inappropriate intrauterine growth (SGA or LGA), male gender, decreasing maternal age, and birth outside office hours. The independent effect of maternal smoking during pregnancy was of statistically borderline significance. Maternal hospitalisation for hypertension and primiparity decreased the risk of total mortality. The one-year mortality of live-born infants was significantly affected by the same variables with two exceptions; birth outside office hours and maternal smoking did not have a statistically significant effect (Table 14).

Table 14. The one-year mortality of both stillborn and live-born, and of live-born VLBW/VLGA infants born in Finland from 2000–2003.

	Stillborn and Live-Born Very Preterm Infants				Live-Born Very Preterm Infants			
	N Born	1-y Mortality		Adjusted 1-y Mortality	*N* Born	1-y Mortality		Adjusted 1-y Mortality
		n	%	OR (95% CI)		*n*	%	OR (95% CI)
Hospital level								
III	1746	324	18.6	1.0	1601	179	11.2	1.0
II	545	170	31.2	3.8 (2.8–5.2)	420	45	10.7	2.1 (1.3–3.3)
Birth weight (per increase of 100 g)				0.8 (0.7–0.8)				0.7 (0.7–0.8)
Gestational age, wk								
22–23	165	148	89.7	13.4 (4.9–36.7)	78	61	78.2	10.9 (2.9–41.6)
24–25	257	121	47.1	1.9 (0.9–4.2)	208	72	34.6	2.0 (0.7–5.9)
26–27	330	93	28.2	1.5 (0.8–2.8)	278	41	14.8	1.3 (0.6–3.1)
28–29	456	61	13.4	1.1 (0.6–1.7)	416	21	5.1	0.7 (0.3–1.5)
30–31	829	53	6.4	1.0	798	22	2.8	1.0
≥32	254	18	7.1	0.6 (0.3–1.1)	243	7	2.9	0.6 (0.3–1.6)
Time of birth								
Office hours	860	134	15.6	1.0	800	74	9.3	1.0
Non–office hours	1431	360	25.2	1.8 (1.3–2.3)	1221	150	12.3	1.3 (0.9–1.9)
Gender								
Male	1280	285	22.3	1.4 (1.1–1.8)	1135	140	12.3	1.7 (1.2–2.4)
Female	1011	209	20.7	1.0	886	84	9.5	1.0
Fetal growth								
SGA	641	155	24.2	1.7 (1.1–2.8)	534	48	9.0	1.1 (0.6–2.2)
AGA	1585	323	20.4	1.0	1427	165	11.6	1.0
LGA	65	16	24.6	6.6 (3.0–14.7)	60	11	18.3	9.2 (3.4–24.6)
Maternal smoking								
Yes	562	157	27.9	1.3 (1.0–1.8)	467	62	13.3	1.2 (0.8–1.8)
No	1729	337	19.5	1.0	1554	162	10.4	1.0
Maternal age (per increase of 1 y)				0.97 (0.95–0.99)				0.96 (0.93–0.99)
Parity								
Primiparity	1267	224	17.7	0.5 (0.4–0.7)	1151	108	9.4	0.6 (0.4–0.8)
Multiparity	1024	270	26.4	1.0	870	116	13.3	1.0
Mother hospitalized for hypertension								
Yes	332	23	6.9	1.0	323	14	4.3	1.0
No	1959	471	24.0	3.8 (2.3–6.4)	1698	210	12.4	2.1 (1.1–3.9)

Mortality was adjusted for maternal hospitalization for hypertension during pregnancy, maternal age, smoking status, primiparity, birth during non–office hours, birth weight, SGA, LGA, categorized gestational age, and gender.

VLBW/VLGA deliveries occurred in five level III and 14 level II hospitals between 2000 and 2003. The distribution of the VLBW/VLGA deliveries is shown according to the hospital type in Table 15. Depending on the university hospital district, the proportion of very preterm infants born in level III hospitals varied from 55% to 95% (See 5.4.1). Only 17 infants (0.8% of all live-born VLBW/VLGA infants) were transferred from level II to level III hospitals during their first week of life. Among the transferred infants, the mean GA was 28 weeks 4 days and the mean birth weight 1103g. Of the transferred VLBW/VLGA infants, four died during the first year of life.

Table 15. The number of VLBW/VLGA infants born at 14 level II and five level III hospitals in Finland from 2000–2003 according to gestational age at birth. The percentage of VLBW/VLGA infants born at each hospital level at the corresponding gestational age is given in parenthesis.

Gestational age, weeks	Stillborn and live-born VLBW/VLGA infants, n (%)		Live-born VLBW/VLGA infants, n (%)	
	Level III hospitals	Level II Hospitals	Level III hospitals	Level II Hospitals
22–23	109 (66.1)	56 (33.9)	64 (88.5)	14 (11.5)
24–25	219 (85.2)	38 (14.8)	184 (88.5)	24 (11.5)
26–27	282 (85.5)	48 (14.5)	254 (91.4)	24 (8.6)
28–29	363 (79.6)	93 (20.4)	342 (82.2)	74 (17.8)
30–31	604 (72.9)	225 (27.1)	593 (74.3)	205 (25.7)
>31	169 (66.5)	85 (33.5)	164 (67.5)	79 (32.5)
Total (22–39)	1746 (76.2)	545 (23.8)	1601 (79.2)	420 (20.8)

In theory, delivery of all VLBW/VLGA infants (including stillbirths) in level III instead of level II hospitals translated into an annual prevention of 69 of the 170 total deaths and prevention of 18 of the 45 deaths of live-born infants. When the VLBW/VLGA infants were divided into subgroups, the subgroup of VLBW/VLGA infants born at a GA of 22 to 28 weeks had a higher adjusted one-year mortality including stillbirths (OR 4.7, CI 3.0; 7.5) and a higher adjusted one-year mortality of live-born infants (OR 3.3, CI 1.8; 6.1) in level II hospitals compared with level III hospitals. At 29 to 33 gestational weeks, the adjusted mortality was higher when stillbirths were included (OR 3.3, CI 2.1; 5.4), but the mortality rate of live-born infants did not differ between level II and level III hospitals (OR 1.2, CI 0.5; 2.6). The distribution of one-year mortality rates according to birth hospital level and GA groups is shown in Figures 7 and 8.

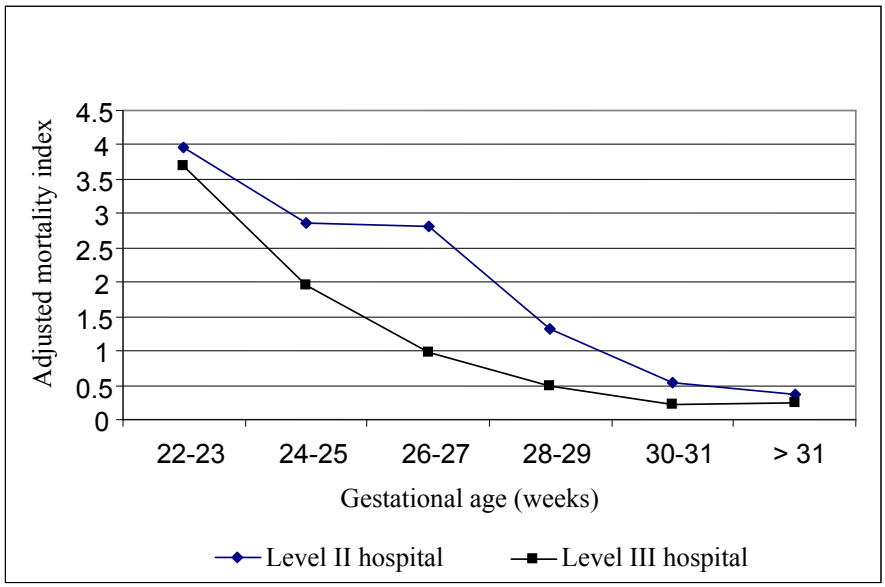

Figure 7. Total one-year mortality (including stillbirths) of VLBW/VLGA infants significantly differed between level II and level III hospitals when adjusted for maternal age, smoking, hospitalisation for hypertension, primiparity, SGA, LGA, and gender (OR 4.5, CI 3.4; 6.1). Mortality differences between hospital levels were not significant when assessed in two-week gestational-age subgroups.

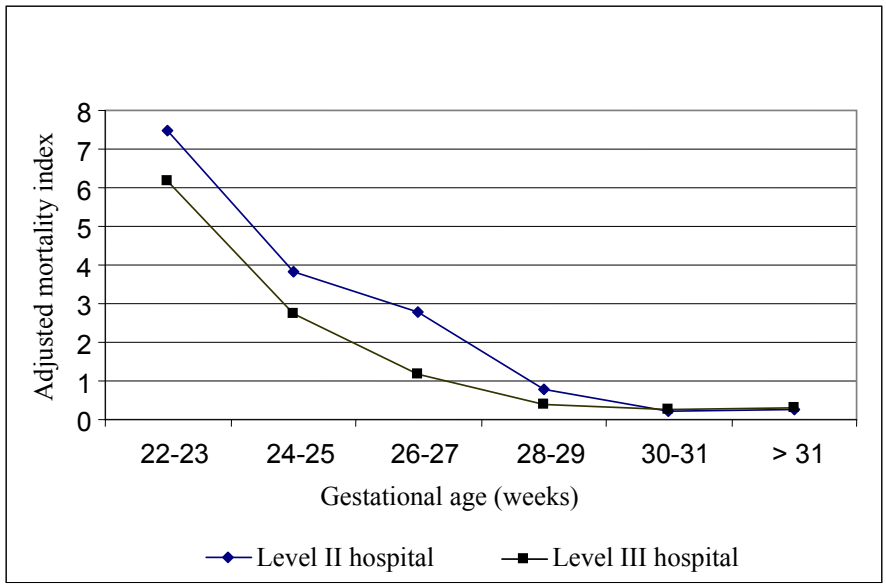

Figure 8. One-year mortality of live-born VLBW/VLGA infants was significantly different between level II and level III hospitals (OR 1.9, CI 1.2; 3.0) when adjusted for maternal age, smoking, hospitalisation for hypertension, primiparity, SGA, LGA, and gender. Mortality differences between hospital levels were not significant when assessed in two-week gestational-age subgroups.

The median number of VLBW/VLGA deliveries was 7.5 (range 1–29) per year in level II hospitals and 68.5 (range 45–211) per year in level III hospitals in 2000–2003. The association between the VLBW/VLGA birth rate and mortality is shown in Figures 9 and 10.

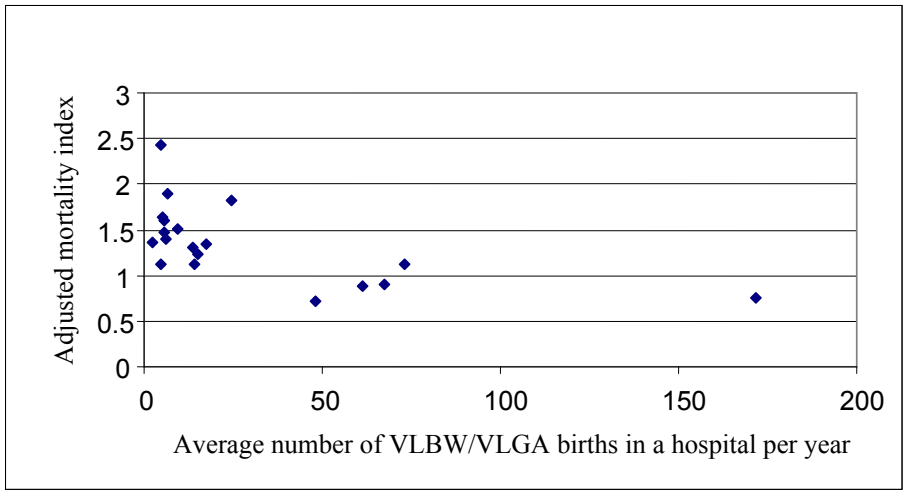

Figure 9. Mortality ratio of stillborn and live-born VLBW/VLGA infants according to the average number of VLBW/VLGA births in delivery hospitals per year from 2000–2003. It has been adjusted for maternal age, smoking, hospitalisation for hypertension, primiparity, gender, SGA, LGA, and classified gestational age.

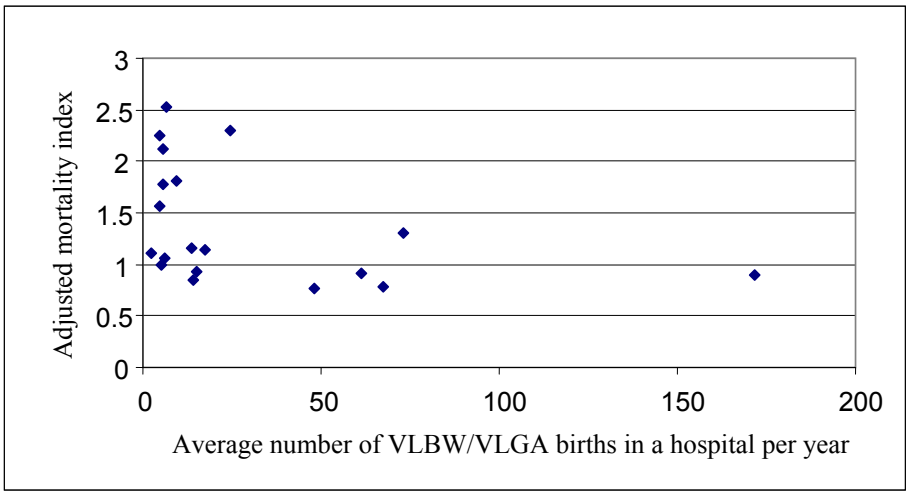

Figure 10. Mortality ratio of live-born VLBW/VLGA infants according to the average number of VLBW/VLGA births in delivery hospitals per year from 2000–2003. It has been adjusted for maternal age, smoking, hospitalisation for hypertension, primiparity, gender, SGA, LGA, and classified gestational age.

5.2.2 Morbidity

In the adjusted analyses for VLBW/VLGA children born in 2001–2002, the birth hospital level was not associated with the five-year incidence of any of the six groups of diagnoses overrepresented in the VLBW/VLGA children up to five years of age (Table 16). This result remained unchanged after including the diagnoses from the parental questionnaires (one additional case of CP, 9 additional cases of respiratory infections, and 9 of asthma or CLD).

Table 16. The five-year accumulated incidence of diagnoses in the six diagnostic groups among the VLBW/VLGA children is presented according to birth hospital level. The odds ratio (OR) and 95% confidence interval (CI) was adjusted for intrauterine growth (SGA, AGA, or LGA), multiple pregnancies (number of foetuses), gestational age, birth weight, gender, and non-lethal malformations. CP=cerebral palsy; ROP=retinopathy of prematurity; CLD=Chronic lung disease.

Group of diagnoses	Level II hospital, Incidence of diagnosis (%) in VLBW/VLGA children (n=116)	Level III hospital, Incidence of diagnosis (%) in VLBW/VLGA children (n=466)	Adjusted OR (95% CI)
CP (n=24)	1.7	4.7	1.75 (0.38;7.99)
ROP (n=85)	4.7	16.7	0.82 (0.31; 2.11)
Opthalmic problems (n=79)	8.6	14.8	1.05 (0.50; 2.21)
Respiratory infections (n=312)	43.1	56.2	1.28 (0.82; 2.00)
Asthma or CLD (n=192)	24.1	35.2	0.79 (0.46; 1.37)
Inguinal hernia (n=105)	18.1	18.0	0.58 (0.31; 1.08)

5.2.3 Behaviour and Development

There were no significant differences in the behavioural and developmental domain scores among the five-year-old VLBW/VLGA children according to the birth hospital level (Table 17).

Table 17. Developmental and behavioural scores of VLBW/VLGA children born in level II (n=116) and III (n=466) hospitals according to the Five To Fifteen questionnaire (FTF). The rate ratio (RR) estimates of birth in level III hospitals are adjusted for intrauterine growth, multiple pregnancies, gender**,** gestational age, birth weight, non-lethal malformations, the mother's and the father's years of education and employment status**,** and family structure.

FTF domain	Level II (unadjusted mean)	Level III (unadjusted mean)	Adjusted RR (95% CI)
Motor skills	0.34	0.39	1.04 (0.83; 1.30)
Executive functions	0.42	0.42	1.13 (0.91; 1.39)
Perception	0.23	0.25	1.22 (0.94; 1.57)
Memory	0.28	0.33	1.04 (0.78; 1.37)
Language	0.26	0.30	1.04 (0.82; 1.34)
Learning	0.34	0.39	1.03 (0.79; 1.33)
Social skills	0.18	0.21	0.93 (0.69; 1.26)
Emotional/behavioural problems	0.15	0.17	0.92 (0.71; 1.21)

5.2.4 The Use of Health Care Resources

Among VLBW/VLGA children during the fifth year of life, the proportion of VLBW/VLGA children who had visited the OT or PT was higher for those born in level II hospitals than level III hospitals. However, the birth hospital level was not associated with the mean number of visits to the OT/PT, any other health care professionals or the total number of visits reported by the parents. The birth hospital level did not affect the number of outpatient visits to specialized health care facilities or the number of inpatient days either (Table 18).

Table 18. The percentage of children using different health care services during the fifth year of life, and the mean number of visits and hospital days for all participating VLBW/VLGA children born in 2001–2 is shown according to the level of birth hospital. The odds ratios (OR) and incidence rate ratios (RR) and 95% confidence intervals (CI) for the percentage of service use and the mean number of visits were adjusted for background factors that are described in Table 11. PT=physiotherapist; OT=occupational therapist.

Type of visit	Percentage of children using the services during the fifth year of life			Number of visits/days, mean (SD)		
	Level II (n=116)	Level III (n=466)	Adjusted OR (95 % CI)	Level II (n=116)	Level III (n=466)	Adjusted RR (95 % CI)
Data from the parental questionnaires						
Physician	82%	92%	**0.50 (0.26; 0.97)**	3.9 (6.7)	5.2 (4.9)	0.92 (0.74; 1.15)
Nurse practitioner	58%	60%	0.96 (0.63; 1.47)	1.1 (1.8)	1.0 (1.7)	1.12 (0.86; 1.46)
OT/PT	23%	20%	**2.25 (1.29; 3.91)**	5.2 (19.7)	7.2 (26.8)	1.21 (0.47; 3.11)
Psychologist	18%	13%	1.55 (0.89; 2.67)	0.4 (1.3)	0.3 (1.1)	1.42 (0.71; 2.85)
Speech therapist	19%	18%	1.26 (0.72; 2.21)	1.4 (6.3)	2.3 (9.8)	0.78 (0.31; 1.96)
Dietitian	2%	2%	0.72 (0.16; 3.30)	0.1 (0.8)	0.03 (0.2)	2.25 (0.44; 11.57)
The sum of all abovementioned visits	91%	94%	0.77 (0.34; 1.73)	11.9 (19.9)	15.9 (31.2)	1.14 (0.86; 1.49)
Data from the Hospital Discharge Register on the use of specialized health care services						
Emergency visits	8%	17%	0.48 (0.23; 1.01)	0.1 (0.4)	0.2 (0.6)	0.56 (0.28; 1.10)
Non-emergency visits	40%	49%	1.28 (0.79; 2.06)	1.5 (3.9)	2.0 (3.8)	1.35 (0.91; 2.00)
Days hospitalised	9%	11%	1.33 (0.60; 2.93)	0.3 (1.6)	0.4 (2.0)	0.95 (0.32; 2.81)

5.2.5 Health-Related Quality of Life and Quality-Adjusted Life-Years

Among five-year-old VLBW/VLGA children, there was no difference in the adjusted 17D total score according to the birth hospital level. However, birth at a level III hospital was associated with an increase of 0.03 in the median QALY compared with birth at a level II hospital ($p= 0.036$ in adjusted comparison) when all VLBW/VLGA (including stillbirths) children were included. Similarly, the mean was increased by 0.5 QALY by birth at a level III hospital in all VLBW/VLGA children (including stillbirths) ($p<0.0001$ in adjusted analysis). However, when only live-born VLBW/VLGA children were included, there were no significant differences in the median or mean QALY according to the birth hospital level.

5.3 Comparison among the VLBW/VLGA Infants According to the Time of Birth

5.3.1 Mortality

As shown in Table 14, birth outside office hours increased the adjusted total one-year mortality when stillbirths were included (OR 1.8, CI 1.3; 2.3), and there was a trend towards increased mortality outside office hours for live-born VLBW/VLGA infants (OR 1.3, CI 0.9; 1.9). The effect of the time of birth on total one-year mortality (including stillbirths) and on the mortality of live-born VLBW/VLGA infants born in level II and III hospitals are shown according to two-week gestational age groups in Figures 11 and 12, respectively.

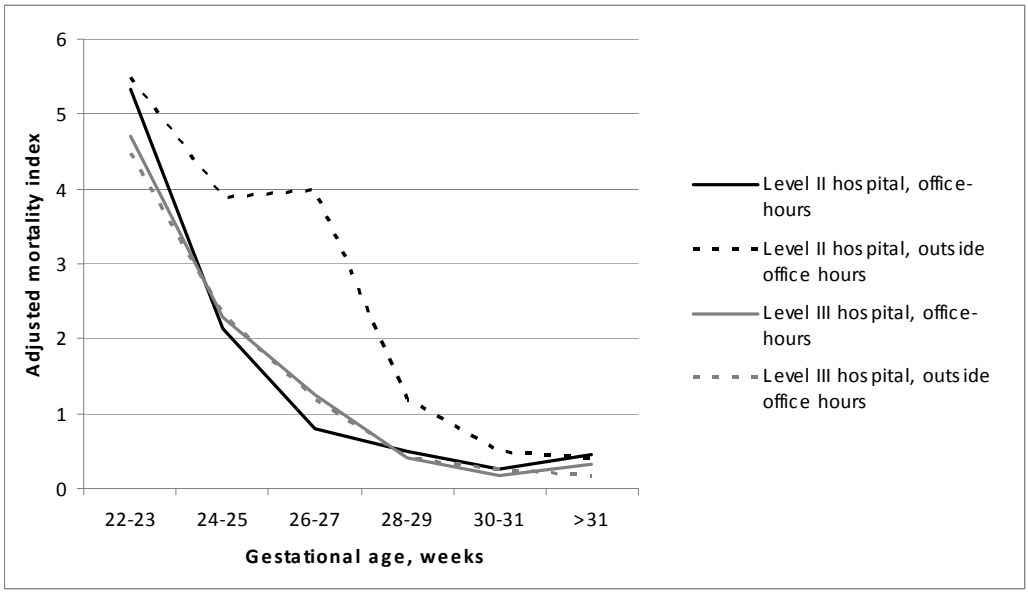

Figure 11. One-year mortality index of all VLBW/VLGA infants (including stillborn) born from 2000–2003 presented according to the birth hospital level and the time of birth. Mortality index was adjusted for maternal hospitalisation for hypertension during pregnancy, maternal age, smoking during pregnancy, primiparity, intrauterine growth, birth weight, categorised gestational age, and gender.

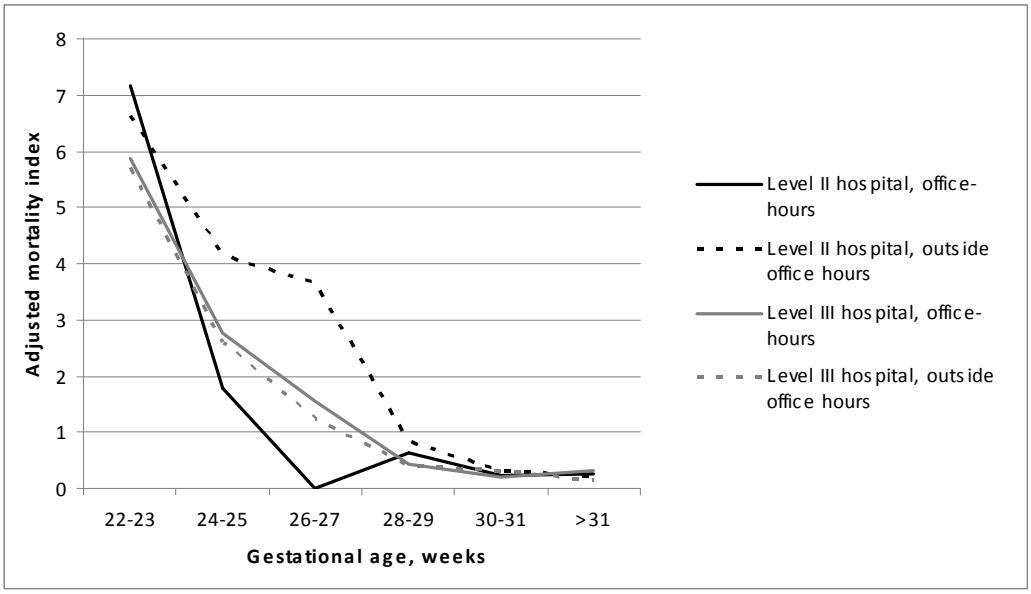

Figure 12. One-year mortality index of live-born VLBW/VLGA infants born from 2000–2003 presented according to the birth hospital level and the time of birth. Mortality index was adjusted for maternal hospitalisation for hypertension during pregnancy, maternal age, smoking during pregnancy, primiparity, intrauterine growth, birth weight, categorised gestational age, and gender.

5.3.2 Morbidity

The background characteristics of the VLBW/VLGA infants according to the time of birth are presented in Table 19.

Table 19. The background characteristics of the VLBW/VLGA infants born in 2001–2002 whose parents returned the questionnaire are presented according to the time of birth.

	VLBW/VLGA infants born outside office hours (n=352)	VLBW/VLGA infants born during office hours (n=230)
Gestational age, weeks and days, mean (SD)	29 3/7 (2 3/7)	29 6/7 (2 3/7)
Birth weight, g, mean (SD)	1262 (380)	1214 (371)
Frequency of birth weight ≤1000g (%)	28	30
Mothers smoking during pregnancy (%)	17	12
Frequency of SGA at birth (%)	22	38
Multiple pregnancies (number of foetuses), mean (SD)	1.3 (0.5)	1.2 (0.5)
Number of visits at special health care antenatal clinic, mean (SD)	2.7 (2.7)	3.6 (3.3)

In the adjusted analyses for the VLBW/VLGA children, the time of birth (during vs. outside office hours) was not associated with the five-year incidence of any of the six groups of diagnoses overrepresented in the VLBW/VLGA group (Table 20). This result remained unchanged after including the diagnoses from the parental questionnaires (one additional case of CP, 9 additional cases of respiratory infections, and 9 of asthma or CLD).

Table 20. The five-year accumulated incidence of diagnoses for VLBW/VLGA children according to the time of birth. The odds ratio (OR) and 95% confidence interval (CI) was adjusted for intrauterine growth (SGA, AGA, or LGA), multiple pregnancies (number of foetuses), gestational age, birth weight, gender, and non-lethal malformations.

Groups of diagnoses	VLBW/VLGA children born outside office hours (n=352), Incidence of diagnosis (%)	VLBW/VLGA children born during office hours (n=230), Incidence of diagnosis (%)	Adjusted OR (95% CI)
CP (n=24)	4.0	4.3	1.56 (0.65; 3.71)
ROP (n=85)	16.5	11.7	0.64 (0.35; 1.18)
Opthalmic problems (n=79)	15.7	10.4	0.73 (0.43; 1.26)
Respiratory infections (n=312)	54.1	52.8	1.01 (0.71; 1.43)
Asthma or CLD (n=192)	33.1	32.9	1.11 (0.73; 1.68)
Inguinal hernia (n=105)	19.1	17.4	1.20 (0.75; 1.93)

5.3.3 Behaviour and Development

There were no significant differences in the behavioural and developmental domain scores for VLBW/VLGA children according to the time of birth (Table 21).

Table 21. Developmental and behavioural scores of five-year-old VLBW/VLGA children from the Five To Fifteen questionnaire (FTF) according to time of birth. The rate ratio (RR) estimates for birth outside office hours are adjusted for intrauterine growth, multiple pregnancies, gender, gestational age, birth weight, non-lethal malformations, the mother's and the father's years of education and employment status, and family structure.

FTF domain	VLBW/VLGA children born outside office hours (n=351) (unadjusted mean)	VLBW/VLGA children born during office hours (n=231) (unadjusted mean)	Adjusted RR (95% CI)
Motor skills	0.38	0.38	0.88 (0.74; 1.05)
Executive functions	0.43	0.40	1.05 (0.89; 1.24)
Perception	0.25	0.23	0.97 (0.79; 1.18)
Memory	0.34	0.29	1.15 (0.93; 1.44)
Language	0.30	0.28	1.02 (0.84; 1.24)
Learning	0.40	0.35	1.10 (0.90; 1.34)
Social skills	0.21	0.19	1.08 (0.85; 1.37)
Emotional/behavioural problems	0.16	0.17	0.88 (0.71; 1.09)

5.3.4 The Use of Health Care Resources

Among the VLBW/VLGA children, the time of birth (during vs. outside office hours) was not associated with the proportion of children using any of the health care services, the mean number of all visits reported by the parents, the number of visits to the physician, OT or PT, psychologist, or dietitian during the fifth year of life. However, among VLBW/VLGA children born outside office hours, the mean number of visits to the nurse practitioner was decreased whereas the mean number of visits to the speech therapist increased compared with those born during office hours. The number of emergency or non-emergency visits and inpatient days did not differ according to the time of birth (Table 22).

Table 22. The percentage of children using different health care services during the fifth year of life, and the mean number of visits and hospital days for all participating VLBW/VLGA children born in 2001–2002 is shown according to the time of birth. The odds ratios (OR) and incidence rate ratios (RR) and 95% confidence intervals (CI) for the percentage of service use and the mean number of visits were adjusted for background factors that are described in Table 11. PT/OT=physiotherapist or occupational therapist.

Type of visit	Percentage of children using the services during the fifth year of life			Number of visits/days, mean (SD)		
	Outside office hours (n=352)	Office hours (n=230)	Adjusted OR (95 % CI)	Outside office hours (n=352)	Office hours (n=230)	Adjusted RR (95 % CI)
Data from the parental questionnaires						
Physician	89%	90%	0.88 (0.48; 1.61)	4.9 (5.7)	4.9 (4.7)	0.97 (0.82; 1.14)
Nurse practitioner	57%	62%	0.81 (0.57; 1.15)	0.9 (1.3)	1.2 (2.2)	**0.77 (0.62; 0.96)**
OT/PT	21%	21%	0.87 (0.56; 1.34)	7.0 (25.6)	6.5 (25.5)	1.64 (0.74;3.64)
Psychologist	14%	13%	1.17 (0.72; 1.91)	0.3 (1.2)	0.3 (0.9)	1.25 (0.69;2.26)
Speech therapist	18%	19%	0.94 (0.60; 1.47)	2.8 (11.2)	1.1 (4.7)	**2.22 (1.09;4.52)**
Dietitian	2%	3%	0.76 (0.25, 2.29)	0.1 (0.5)	0.03 (0.2)	1.68 (0.39;7.31)
The sum of all abovementioned visits	93%	94%	0.89 (0.44; 1.78)	15.8 (31.8)	14.0 (17.8)	1.06 (0.86;1.32)
Data from the Hospital Discharge Register on the use of specialized health care services						
Emergency visits	16%	14%	1.10 (0.68; 1.77)	0.2 (0.5)	0.2 (0.6)	0.99 (0.64;1.55)
Non-emergency visits	47%	48%	0.88 (0.61; 1.28)	1.9 (3.7)	2.0 (4.0)	0.88 (0.65;1.18)
Days hospitalised	13%	7%	1.67 (0.88; 3.14)	0.5 (2.3)	0.2 (1.0)	1.82 (0.82;4.03)

5.3.5 Health-Related Quality of Life and Quality-Adjusted Life-Years

There was no difference in the adjusted 17D total score for five-year-old VLBW/VLGA children according to the time of birth. Birth outside office hours had no influence on the adjusted median or mean QALY either in all VLBW/VLGA infants (including stillbirths) or in live-born VLBW/VLGA infants.

5.4 Comparison among the VLBW/VLGA Infants According to the University Hospital District of Birth

5.4.1 Mortality

When comparing the adjusted mortality rate between the five university hospital districts of birth, the one-year mortality of live-born VLBW/VLGA infants born in district C was increased in comparison with district E (OR 1.91; CI 1.06, 3.43). This difference did not reach statistical significance when both stillborn and live-born infants were included in the model (OR 1.34; CI 0.89, 2.04). Adjusted mortality rates between other districts and district E did not differ for either live-born or all VLBW/VLGA infants. When the birth hospital level and the time of birth were included as covariates in the model, the mortality differences between districts were no longer significant. The proportion of very preterm infants born in level III hospitals was 95%, 79%, 66%, 56%, and 85% within districts A, B, C, D, and E, respectively.

5.4.2 Morbidity

Among VLBW/VLGA children born in 2001–2002, there were differences in the adjusted comparison of the incidence of ROP and inguinal hernia up to five years of age between the five university hospital districts (see Table 23).

Table 23. Comparison of the five-year incidence of diagnoses for VLBW/VLGA children according to the university hospital district of birth. The comparisons were adjusted for gestational age, birth weight, gender, non-lethal malformations, multiple pregnancies (number of foetuses), and intrauterine growth (SGA, AGA, or LGA).

Groups of diagnoses	District A (n=203), Incidence of diagnosis (%)	District B (n=112), Incidence of diagnosis (%)	District C (n=108), Incidence of diagnosis (%)	District D (n=89), Incidence of diagnosis (%)	District E (n=76), Incidence of diagnosis (%)	Adjusted p-value
CP (n=24)	3.0	8.1	1.9	4.6	4.0	0.41
ROP (n=85)	17.5	7.2	9.4	18.2	21.1	**<0.01**
Opthalmic problems (n=79)	12.5	11.7	9.4	20.5	17.1	0.05
Respiratory infections (n=312)	51.0	53.2	48.6	58.0	63.2	0.17
Asthma or CLD (n=192)	35.0	27.0	31.8	39.8	30.3	0.08
Inguinal hernia (n=105)	17.0	27.0	15.0	22.7	6.6	**<0.01**

5.4.3 Behaviour and Development

There were no significant differences in the behavioural and developmental domain scores for VLBW/VLGA children according to the university hospital district of birth (Table 24).

Table 24. Developmental and behavioural scores of VLBW/VLGA children born in the five different university hospital districts according to the Five To Fifteen questionnaire (FTF). Comparisons are adjusted for intrauterine growth, multiple pregnancies, gender**,** gestational age, birth weight, non-lethal malformations, the mother's and the father's years of education and employment status**,** and family structure.

FTF domain	District A (n=200), (unadjusted mean)	District B (n=111), (unadjusted mean)	District C (n=107), (unadjusted mean)	District D (n=88), (unadjusted mean)	District E (n=76), (unadjusted mean)	Adjusted p-value
Motor skills	0.38	0.40	0.35	0.41	0.38	0.84
Executive functions	0.40	0.42	0.42	0.44	0.43	0.87
Perception	0.24	0.25	0.22	0.26	0.25	0.62
Memory	0.31	0.37	0.25	0.32	0.38	0.06
Language	0.27	0.30	0.28	0.31	0.34	0.44
Learning	0.36	0.42	0.34	0.41	0.41	0.54
Social skills	0.20	0.19	0.19	0.22	0.23	0.98
Emotional/ behavioural problems	0.16	0.16	0.16	0.17	0.18	0.97

5.4.4 The Use of Health Care Resources

The sum of all visits to health care professionals according to parental reports and the number of non-emergency visits and days hospitalised during the fifth year of life differed between the birth hospitals in the five university hospital districts for VLBW/VLGA children. However, the district was not associated with the number of visits to the physician, the nurse practitioner, the OT or PT, the dietitian, or the speech therapist, according to the parental report, or the number of emergency visits, according to register data, when all groups were compared (Table 25).

Table 25. The unadjusted mean numbers of visits to different health care professionals during the fifth year of life for VLBW/VLGA children according to the university hospital district where the birth occured and the adjusted comparison of the five districts. The comparisons were adjusted for the background factors that are described in Table 11. OT/PT=Occupational therapist or physiotherapist.

Type of visit	District A (n=203), mean (SD)	District B (n=112), mean (SD)	District C (n=108), mean (SD)	District D (n=89), mean (SD)	District E (n=76), mean (SD)	Adjusted p-value
Data from the parental questionnaires						
Physician	5.0 (4.8)	5.2 (5.7)	5.3 (7.1)	4.5 (3.5)	4.1 (4.8)	0.58
Nurse practitioner	1.0 (1.6)	0.9 (1.3)	1.1 (1.6)	1.0 (1.0)	1.2 (3.1)	0.41
OT/PT	5.5 (21.4)	9.1 (30.2)	4.1 (19.4)	7.0 (22.0)	10.4 (37.0)	0.64
Psychologist (unadjusted comparisons)	0.4 (1.5)	0.1 (0.4)	0.4 (1.0)	0.4 (1.2)	0.2 (0.6)	0.02
Speech therapist	1.5 (6.2)	0.9 (3.9)	1.4 (5.8)	2.6 (8.2)	6.2 (19.7)	0.19
Dietitian (unadjusted comparisons)	0.04 (0.2)	0.01 (0.1)	0.1 (0.8)	0 (0)	0.1 (0.4)	0.07
The sum of all abovementioned visits	13.2 (24.0)	16.1 (33.1)	12.3 (25.7)	15.8 (26.3)	21.6 (46.2)	**<0.01**
Data from the Hospital Discharge Register on the use of specialised health care services						
Emergency visits	0.2 (0.5)	0.2 (0.4)	0.3 (0.7)	0.2 (0.6)	0.2 (0.6)	0.17
Non-emergency visits	2.1 (4.3)	1.8 (3.7)	1.7 (4.3)	2.6 (3.3)	1.1 (1.7)	**<0.01**
Days hospitalised	0.3 (1.0)	0.2 (0.7)	0.6 (3.0)	0.4 (1.4)	0.8 (3.0)	**<0.01**

In the pair-wise comparisons, the sum of all visits during the fifth year of life reported by the parents was increased in district E compared with all other districts. The VLBW/VLGA children born in district B visited the psychologist less than in district A (RR 0.22, CI 0.09; 0.55), district C (RR 0.25, CI 0.09; 0.69), and district D (RR 0.22, CI 0.08; 0.87), but the difference was not significant in comparison with district E. The VLBW/VLGA children born in district D had more non-emergency visits during the fifth year of life compared to those born in district E and in district B (RR 0.75, CI 0.28; 1.23). The VLBW/VLGA children born in district C had more emergency visits in comparison with those born in district B (RR 2.34, CI 1.56; 4.74). Compared with district E, VLBW/VLGA children born in districts A and B spent less days hospitalised during the fifth year of life. The VLBW/VLGA children born in district D also had significantly more hospital days during the fifth year of life than those born in districts A (RR 4.48, CI 1.38; 14.60) and B (RR 4.63, CI 1.25; 17.10). The RR for the pair-wise comparisons to district E are presented in Figure 13.

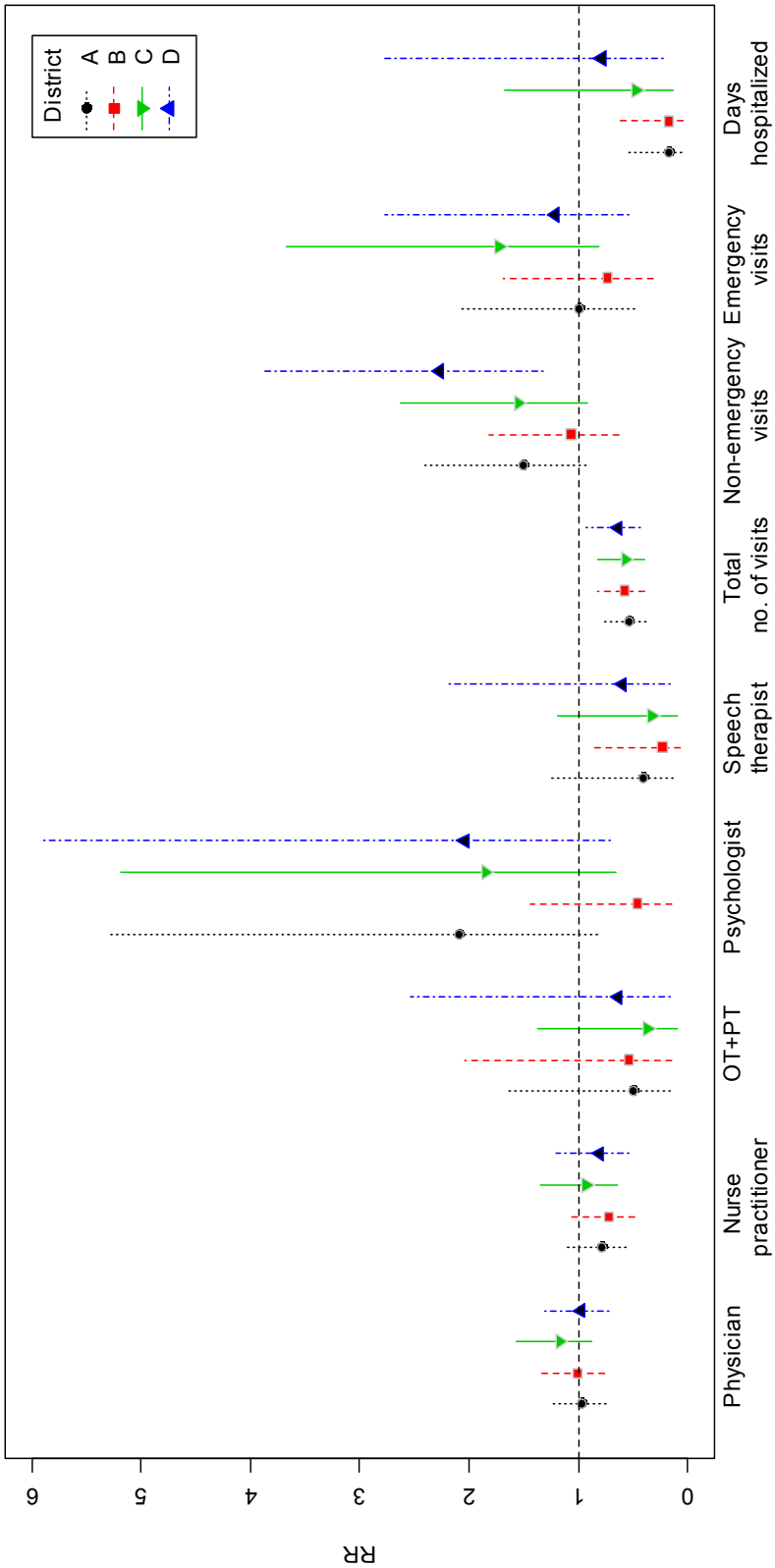

Figure 13. Comparison of the number of visits by VLBW/VLGA infants to different health care professionals between district E (reference line) and other districts. The rare ratios (RR) and 95% confidence intervals (CI) are shown with adjustments made for those background factors described in Table 11.

5.4.5 Health-Related Quality of Life and Quality-Adjusted Life-Years

The university hospital district for each birth hospital did not affect the adjusted 17D total scores in VLBW/VLGA children. However, the university hospital district where the birth occurred was associated with the adjusted mean QALY for all VLBW/VLGA infants (including stillbirths) ($p<0.001$) and for live-born infants ($p=0.011$), but it was not associated with the median QALY. Similarly, in the pair-wise comparisons the adjusted medians did not differ between the five districts. However, birth in district C compared with district E was associated with -0.4 lower mean QALY for all VLBW/VLGA infants (including stillbirths) and -0.5 lower mean QALY for live-born infants. These differences in means were significant in adjusted comparisons between districts C and E, both with the stillborn infants included ($p=0.002$) and excluded ($p=0.001$). Other districts did not differ significantly from district E. The effects of time of birth, birth hospital level and district, as well as the covariates used in QALY adjustments are shown in Table 26.

Table 26. Multiple regression analysis of QALY scores for stillborn and live-born VLBW/VLGA children (n=1171) and for live-born VLBW/VLGA children (n=1018). *=reference; b=regression coefficient; CI=confidence interval; GA=gestational age; SGA, AGA, and LGA=small, appropriate, and large birth weight for GA.

	Stillborn and live-born VLBW/VLGA children	**Live-born VLBW/VLGA children**
	b (95% CI)	**b (95% CI)**
Birth hospital level		
III	**0.72 (0.48; 0.96)**	0.18 (-0.05; 0.42)
II	*	*
Time of birth		
During office hours	0.15 (-0.05; 0.35)	-0.05 (-0.22; 0.13)
Outside office hours	*	*
Hospital district		
A	0.03 (-0.27; 0.32)	-0.16 (-0.42; 0.11)
B	-0.001 (-0.35; 0.35)	-0.19 (-0.50; 0.13)
C	**-0.36 (-0.68; -0.03)**	**-0.46 (-0.76; -0.16)**
D	0.04 (-0.31; 0.39)	-0.15 (-0.47; 0.16)
E	*	*
Gender		
Female	0.18 (-0.02; 0.37)	**0.20 (0.03; 0.38)**
Male	*	*
Multiple pregnancies		
Gemini or triplet (per increase of one child)	0.15 (-0.04; 0.35)	0.04 (-0.13; 0.21)
Single birth	*	*
Birth weight (per increase of 100g)	**0.09 (0.05; 0.14)**	0.007 (-0.04; 0.06)
GA (per increase of one week)	**0.26 (0.20; 0.33)**	**0.28 (0.21; 0.36)**
Intrauterine growth		
SGA	**-0.43 (-0.73; -0.14)**	**-0.44 (-0.75; -0.13)**
AGA	*	*
LGA	**-1.02 (-1.61; -0.43)**	**-0.62 (-1.16; -0.08)**

6. DISCUSSION

6.1 Strengths and Limitations of the Study

In the current study, register data was used from the MBR, which includes a large set of data that has been shown to be reliable (Gissler et al. 1995). MBR enjoys practically one hundred percent coverage, because it receives missing data from the Central Population Register (live births) and the Cause of Death statistics at Statistics Finland (stillbirths and deaths).

The data on diagnoses and health care visits were collected from several sources to ensure the coverage of all diagnoses and health care visits. The NHDR data on specialized health care visits and the related diagnoses proved in this study to be virtually complete, since the registers of the Social Insurance Institution and parental questionnaires added only a very few diagnoses to those collected from the NHDR. This enabled the use solely of register data when comparing the diagnoses.

The analyses of one-year mortality included a national four-year cohort of very preterm births, thus avoiding a selection bias typical of hospital-based studies. The data was analysed both by excluding and including stillbirths. Better coverage of births at each gestational week was therefore achieved in comparison with studies that do not include stillbirths. The relation between the time of foetal death and the time of birth, however, remains unknown in the present study. Therefore, it is not known whether the larger proportion of stillborn infants in level II hospitals reflects a lower referral rate for dead foetuses or a difference in the level of obstetric care.

The extensive background information enabled adjustments for several confounding variables, which made it possible to perform accurate and reliable comparisons. Adjusting for confounding variables was necessary in order to control for the differences in patient selection between level II and III hospitals, and for the differences between the university hospital districts, as well as to reduce bias caused by elective Caesarean sections mainly taking place during office hours instead of outside office hours.

Excluding the infants with lethal malformations (i.e. those VLBW/VLGA infants who would have died irrespective of the quality of the care) decreased the possibility that the differences in mortality would have been explained by differences in patient characteristics between hospitals. Malformations that were defined as lethal were separately chosen based on clinical consideration of their clear fatality in VLBW/VLGA infants, although some of these malformations (transposition of great arteries) may not always be lethal in full-term infants. Infants with non-lethal malformations or malformations with variable degrees were not excluded in order to avoid selection bias since there were regional differences in the reporting of non-lethal malformations. There

is no general agreement among different studies on the criteria for malformations that should be excluded (Johansson et al. 2004, Phibbs et al. 2007, Empana et al. 2003).

There were, however, some important prenatal variables that were not reliably available in the registers and which, thus, could not be used in the adjustments. One of these variables was the use of antenatal glucocorticoids. There will always be a small proportion of unavoidable emergency deliveries. Such emergency deliveries may comprise a larger proportion of very preterm deliveries in level II hospitals than in level III hospitals. There may be more potential disadvantages for the infant in these deliveries, such as missing the benefit of antenatal glucocorticoids. In addition, data on the presence and the severity of pre-eclampsia and chorionamnitis could not reliably be adjusted for. Adjustments were, however, made for maternal hospitalisation for hypertension in the analyses of one-year mortality, because this data was more comprehensively available in the NHDR.

A detailed drop-out analysis ruling out significant attrition bias concerning child health could be performed based on the background information. Drop-out analyses are necessary in the follow-up studies of VLBW/VLGA children since the incidence of adverse outcomes has previously been underestimated when the follow-up is incomplete, and since boys, and those with low maternal education have participated less often (Hille et al. 2005b, Hille et al. 2005a). In our study, the parents of VLBW/VLGA boys responded marginally more often than the parents of VLBW/VLGA girls did. The mothers in the non-responder group had more previous pregnancies ending with foetal death, more multiple pregnancies, and smoked more often during the pregnancy. Understandably, large family size may decrease the response rate for time-consuming questionnaires. Because of the higher maternal smoking rate in lower socioeconomic groups (Jaakkola et al. 2001), it is possible that a greater proportion of white-collar workers compared with those of a lower socioeconomic status participated in our survey. In addition, adolescents exposed to smoking during pregnancy have been shown to have more externalising and internalising psychiatric symptoms compared with non-exposed adolescents (Indredavik et al. 2007). Thus, it is possible that the FTF scores in the current study are somewhat more positive than what could have been expected of the non-responders. However, this was the case for both the VLBW/VLGA group and the controls. Importantly, the mean birth weight and gestational age for the non-responder group did not differ from that of the responder group, and there were no significant differences in the number of emergency or non-emergency visits to special health care facilities, or the number of days spent in the hospital during the first five years of life compared with the responders. Only the five-year accumulated incidence of respiratory infections was increased among the non-responders while inguinal hernia was more common in the responders. The other four diagnostic groups did not significantly differ between the non-responders and the responders. This indicates that the follow-up to the current study did not favour the healthier VLBW/VLGA children. Therefore, it is unlikely that morbidity was underestimated in the present study.

Since the mothers of full-term infants have been less willing to participate in trials than the mothers of preterm infants (Maayan-Metzger et al. 2008), the response rate for the controls was expectedly lower than for the VLBW/VLGA children. The parents of VLBW/VLGA children are likely to regard this type of study as more important than the parents of the controls. Whether the parents of VLBW/VLGA children are more sensitive to problems and more likely to report concerns about their children is not known. This could be controlled for by using a third party assessment, for example an assessment by teachers after the children have started school.

The FTF has been shown to be a sensitive instrument suitable for the screening of developmental and behavioural problems (Bohlin and Janols. 2004, Kadesjö et al. 2004, Korkman et al. 2004, Trillingsgaard et al. 2004). The sensitivity of the FTF among five-year-old children from the general population was 93%, although the specificity was only 63% when compared with the NEPSY neuropsychological assessment instrument (Korkman et al. 2004). Among VLBW/VLGA children, the neuropsychological performance as assessed by a psychologist with NEPSY II domains on *Executive Functioning*, *Language* and *Motor Skills has been shown to associate* significantly with the corresponding FTF domains (Lind et al. 2009). When using the FTF, the children are evaluated by proxy, not with clinical tests. Therefore, it is not possible to assess the influence of the parents' subjective opinion on the results and this may lower the diagnostic accuracy of the results. On the other hand, parental assessment can provide a more complete assessment from a long-term perspective on the behaviour and development of the child than that perceived through a clinical examination. While the clinical examination is often based on a one-time observation of the child and is dependent on the mood of the child that day, parents are familiar with the long-term average performance of their child. In this study, the parental FTF detected differences between VLBW/VLGA children and healthy controls, as well as gestational age-related differences in VLBW/VLGA children. Like in any study on young children, however, some problems of behaviour and development may not be detected in five-year-old children because they might manifest later in life.

Determining the quality of life for small children is difficult. The available instruments have shortcomings, such as concentrating on only one disease-group, being overly long, or being targeted only at adolescents (Wallander et al. 2001). There is no general agreement on which instrument should be used for five-year-old children. The 17D was used in our study because it is a generic and comprehensive instrument. It allows for comparisons between VLBW/VLGA children and the general population, instead of being limited to a certain disease group (www.15d-instrument.net). 15D and 17D have been widely used in Finland and are suitable for comparing HRQoL between different patient groups. At the time the study was initiated, 17D was to my knowledge the only instrument for assessing the HRQoL of children available in Finnish. Small modifications to the 17D questionnaire enabled the use of parental ratings of the HRQoL for five-year-old children. However, it is possible that parental ratings underestimate the HRQoL compared with the children's own ratings of it, as family members tend to underrate a

patient's HRQoL (Ingerski et al. 2010, White-Koning et al. 2007, Sneeuw et al. 2002, Rothman et al. 1991). Family members' ratings concerning observable HRQoL domains and physical functions, however, are shown to agree well with the patients' own ratings (Rothman et al. 1991, Verrips et al. 2000). As most 17D dimensions concern physical functions, it is likely that parental ratings in this study do not deviate much from the child's own perspective.

Importantly, the inclusion of background factors also enabled us to estimate the QALY for the children whose parents did not respond to the questionnaire by using multiple imputation. Both analyses, those based on the mean and those on the median QALY, are presented because the QALY distribution is bimodal. The results which are based on the median QALY are more robust than the results based on the mean QALY. However, the values are different and means provide additional information on the phenomenon.

6.2 The Effect of the Birth Hospital Level

The current study showed that the adjusted one-year mortality of Finnish VLBW/VLGA infants was increased for those born in level II hospitals compared with those born in level III hospitals. Among the surviving VLBW/VLGA infants, the birth hospital level was not associated with morbidity, behavioural and developmental scores, HRQoL, or QALY at five years of age, or the use of health care resources during the fifth year of life.

The current findings on the increased survival at level III hospitals parallel the results of studies from different populations of VLBW (Phibbs et al. 2007, Warner et al. 2004, Samuelson et al. 2002), and VLGA infants (Empana et al. 2003), of infants born at GA 24 to 27 weeks (Johansson et al. 2004) and at GA <27 weeks (EXPRESS Group et al. 2009), and the results of a previous study of Finnish ELBW infants born in 1996–7 (Tommiska et al. 2001). However, in contrast to our findings, differences in mortality rates between Finnish level II and III birth hospitals seemed to have levelled off among the smallest infants at the end of the 1990s; the differences in mortality rates between hospital levels were not significant for ELBW infants born in 1999–2000 due to an increase in survival rates at level II hospitals (Tommiska et al. 2007). However, these comparisons were unadjusted. In the current study, the survival advantage gained at level III hospitals seemed to be greatest among infants born at a GA of 26–27 weeks. Among the smallest infants, mortality rates were high irrespective of the level of the birth hospital. Parallel to this, Warner et al. (2004) have shown that the protective effect of birth in subspecialty centres on mortality rates is greater for infants with a birth weight between 1000 and 1499 grams than for infants born with a birth weight between 500 and 999 grams compared with non-subspecialty centres in Cincinnati, Ohio. This is most likely explained by the relatively high mortality rates of the smallest infants irrespective of the quality of initial care, while the effective initial care of slightly more mature infants may result in a more apparent decrease in mortality rates.

In comparison with previous studies that also show decreased mortality rates at level III hospitals (EXPRESS Group et al. 2009, Phibbs et al. 2007, Warner et al. 2004, Empana et al. 2003, Cifuentes et al. 2002), the current study showed that a smaller proportion of VLBW/VLGA infants was transferred after birth from level II to level III hospitals (0.8% of all VLBW/VLGA infants born between 2000 and 2003). The differences in the outcomes attributed to the hospital level in the previous studies may be confounded by the dangers of transfer between hospitals after birth, since outborn status has been shown to cause an increase in mortality rates (Lee et al. 2003, Truffert et al. 1998, Obladen et al. 1994). Among studies that attribute the deaths of outborn infants to the referring centre (EXPRESS Group et al. 2009, Phibbs et al. 2007, Warner et al. 2004, Cifuentes et al. 2002), a large number of transported infants would naturally favour the receiving centre in the comparisons, whereas attributing deaths to the receiving centre favours the referring centre (Empana et al. 2003, Shah et al. 2005). Some previous studies have not reported the number of outborn infants (Johansson et al. 2004, Tommiska et al. 2007, Samuelson et al. 2002), which makes it more difficult to evaluate the impact of their results. Although there is no separate neonatal transport service in Finland, the number of transported infants in the current study was so small that it does not change the results on the effects of the birth hospital level.

In the current study, a higher rate of preterm births per year seemed to be associated with a lower mortality rate (Figures 9 and 10), which is in line with the findings of previous studies (Phibbs et al. 2007, Bartels et al. 2006, Rogowski et al. 2004). Parallel to this, a previous study has also shown an association between higher patient volumes in the birth hospital and lower rates of severe IVH in VLGA infants (Synnes et al. 2006). However, in the current study, the effect of preterm birth rates could not be evaluated independently from the birth hospital level since all Finnish hospitals with more than 44 very preterm deliveries per year between 2000 and 2003 were level III university hospitals, while all those with less than 30 very preterm births were level II hospitals.

In addition to the higher patient volumes, the explanations for survival advantage in level III hospitals may be related to a more experienced and highly trained staff, better coverage outside office hours, and more up-to-date patient management styles and equipment. There might also be differences in how actively infants with borderline viability are resuscitated. Antenatal transfer and resuscitation practices of preterm infants have been shown to differ in Australia (Gooi et al. 2003) and in European countries (De Leeuw et al. 2000), and obstetricians in level II hospitals have been shown to underestimate the chances of survival for extremely preterm infants (Gooi et al. 2003). In the current study, there was a large variation between level II hospitals in mortality rates, suggesting differences in the care of VLBW/VLGA infants according to individual hospital policies.

Despite the differences in mortality rates, the birth hospital level was not associated with developmental and behavioural scores, HRQoL at five years of age, the five-year incidence of prematurity-related morbidities, or with the use of health care services by

VLBW/VLGA children during the fifth year of life. When analysing the effect of the birth hospital level on the use of health care services, only the proportion of VLBW/VLGA children visiting the OT or PT was higher for those born at level II compared with level III hospitals. This finding is likely to be attributed to chance, since the mean number of visits at the OT or PT and visits to any other health care professional were not increased among those born at level II hospitals. These results are in line with the work by Darlow et al. (2000) showing no differences in long-term sensorineural disability and behavioural or educational outcome between birth hospitals categorised according to their level and size. In the current study, however, birth at a level III hospital was associated with a gain in QALY compared with a birth at a level II hospital for all VLBW/VLGA infants, but not when focusing on live-born VLBW/VLGA infants alone. Since the level of birth hospital did not affect the HRQoL total score, the difference in QALY was mostly explained by differences in mortality rates between hospital levels.

6.3 The Effect of the Time of Birth

The majority of VLBW/VLGA births during the study period occurred outside office hours, which was associated with increased adjusted total mortality and a trend towards increased mortality in live-born VLBW/VLGA infants. However, morbidity, behavioural and developmental scores, HRQoL, and the QALY at the age of five years, as well as the use of health care resources during the fifth year of life did not differ according to the time of birth.

The current results showing increased mortality in all VLBW/VLGA infants (including stillbirths) and a trend towards increased mortality in live-born VLBW/VLGA infants born outside office hours parallel the results by Gould et al. (2005), showing increased mortality in infants born on weekends in intermediate, community, or regional neonatal intensive care. However, other studies have shown no differences in the mortality rates of VLBW or VLGA infants related to the time of birth (Stephansson et al. 2003, Luo et al. 2004, Gould et al. 2003, Soltau et al. 2008). In the current study, the difference in mortality rates during and outside office hours was largely explained by increased mortality rates outside office hours in level II hospitals. This indicates that it is difficult to maintain adequate resources for effective management of the deliveries and the initial care of VLBW/VLGA infants 24 hours a day in level II hospitals.

Despite differences in mortality, the possible differences in the quality of initial care according to the time of birth were not reflected in the five-year outcome for the surviving VLBW/VLGA children. Similarly, previous studies found no association between birth outside office hours and severe IVH or ROP, necrotizing enterocolitis, patent ductus arteriosus, or BPD in VLGA infants (Soltau et al. 2008, Abdel-Latif et al. 2006). However, their studies included only infants born in level III hospitals, which are likely to have a larger allocation of resources for care outside office hours than the Finnish level II hospitals do.

6.4 The Effect of the University Hospital District of Birth

This study showed that there are differences according to the university hospital district of birth in one-year mortality, the incidence of ROP and inguinal hernia up to five years of age, QALY, and the use of health care resources during the fifth year of life in VLBW/VLGA children. However, the university hospital district was not associated with HRQoL, or behavioural and developmental scores at the age of five years. There were significant regional differences between the districts in the proportion of infants born in level III hospitals.

Differences in mortality rates according to geographical regions, comparable to those found in the current study, have previously been shown for ELBW and VLGA infants (Tromp et al. 2009, Tommiska et al. 2007, Tommiska et al. 2001). Tommiska et al. (2007, 2001) showed that the mortality rates of ELBW infants born in the 1990s varied between the five Finnish university hospital districts. Parallel to this, inter-hospital variation in the mortality rates of ELBW infants has been shown between 12 centres participating in the National Institute of Child Health and Human Development Neonatal Network in the USA (Vohr et al. 2004). In addition, scholars have shown the mortality of Swedish infants born at a GA of 22–27 weeks from 1985–1999 to be significantly lower in the northern region compared with the southern region (Hakansson et al. 2004). The authors attributed the lower mortality rates of the northern region to the more proactive treatment practices, including the more active centralization of deliveries to level III hospitals (85% in the northern vs. 56% in the southern region). In the Netherlands, the comparison of four geographical regions showed that the risk of mortality for infants born at a GA of 26–31 weeks between 2000 and 2004 was lower in the northern region than in the western region (Tromp et al. 2009). In contrast, no regional differences prevailed in the mortality rates of those born at a GA of <26 weeks. Parallel to the current study, the differences in the mortality risk between regions in the latter study were not explained by regional variation in demographic risk factors like maternal age, and parity. Only a small part of the elevated risk in their study could be explained by the socio-economic status and urbanisation grade. Similarly, although the incidence of VLGA deliveries has been shown to increase in deprived areas of the UK, no differences in the mortality rates of VLGA infants were shown according to the most or least deprived areas of residence (Smith et al. 2009).

Parallel to the differences found in the morbidity rates between the university hospital districts in the current study, Darlow et al. (2000) found some inter-hospital differences in the rates of visual problems and the risk of myopia that were not fully explained by the hospital level or size. However, they did not find other differences in morbidity between hospitals of the same level. In addition, no inter-hospital differences in behaviour, school performance, or the need for special education were shown. This is in line with the current results showing no differences in the behavioural and developmental scores of VLBW/VLGA children according to the district of birth. The differences between the university hospital districts of birth shown in the current study and the inter-hospital

variation in NICU practices and outcomes shown in other countries (Vohr et al. 2004, Lee et al. 2000) warrant benchmarking between the Finnish university hospital districts and between hospitals to further optimise the care of VLBW/VLGA infants.

In addition to the possible differences in the treatment policies between the regions, the differences in the outcomes may partly be explained by differences in the centralisation of the deliveries of VLBW/VLGA infants. The current study showed that the proportion of VLBW/VLGA infants born in level III hospitals was 85% in the university hospital district with the largest geographical distances (district E). This indicates that a higher degree of centralisation of the deliveries of VLBW/VLGA infants to level III hospitals could be achieved nationally.

6.5 The Outcome for Finnish VLBW/VLGA Infants with Reference to Full-Term Controls

Although increased in comparison with the full-term controls, the mortality rate for Finnish VLBW/VLGA infants in the current study was relatively low compared with that reported from other countries for VLBW (Fanaroff et al. 2007) or VLGA (Zeitlin et al. 2009,Draper et al. 2009,Malloy. 2008) infants during the present decade. In the current study, all the controls survived up to five years of age, which also reflects the low infant and child mortality rate in Finland. A mortality rate comparable to the current study has recently been reported on live-born infants born at a GA of <27 weeks in Sweden (31% vs. 30%, respectively) (EXPRESS Group et al. 2009).

Among VLBW/VLGA children, the current study showed more problems in behaviour and development, more frequent use of health care resources during the fifth year of life and increased morbidity up to five years of age compared with the full-term controls. However, in comparison with other populations, the present study showed a low incidence of CP (4% vs. 5–17%) (Larroque et al. 2008, Platt et al. 2007, Vohr et al. 2005, Vincer et al. 2006, Hagberg et al. 2001), ROP (15% vs. 42–51%)(Cooke et al. 2004, Schalij-Delfos et al. 2000), and other ophthalmic problems (14% vs. 56%) (Schalij-Delfos et al. 2000), and a relatively high incidence of asthma (19% vs. 12%) (Dombkowski et al. 2008), and inguinal hernia (18% vs. 11%) (Kumar et al. 2002) for the Finnish VLBW/VLGA children. Some of these differences may be due to differences in the diagnostic criteria. However, the differences may indicate international differences in population characteristics, treatment strategies, and health service systems, and therefore highlight the importance of a national long-term follow-up on VLBW/VLGA infants.

Despite the low five-year incidence of CP and epilepsy shown in the current study, the incidence of major neurologic conditions is not likely to increase with age, since children with major neurologic impairment such as CP are mainly diagnosed during the first years of life (Gäddlin et al. 2007). Compared with the 4% of VLBW/VLGA children with CP in our study, a higher 7% to 10% prevalence of CP has been reported on VLBW adults (Hack and Fanaroff. 2000, Ericson and Kallen. 1998). However, treatment strategies

have changed considerably since these VLBW adults were born. Similarly, Hille et al. (2007) previously reported relatively high rates of moderate or severe hearing problems for 1.8%, vision problems for 1.9%, and problems with neuromotor functions for 8.1% of 19-year-old former VLBW/VLGA infants compared with the current results on infants born during the present decade. Men born as VLBW infants have been shown to be at three times the risk for blindness, 1.4 times the risk for lowered vision, 2.5 times the risk for deafness, and 1.5 times the risk for impaired hearing at the age of 19 years compared with males from the general population (Ericson and Kallen. 1998).

On the other hand, pulmonary function in most preterm BPD survivors has been shown to improve over time and permit normal activity, although abnormalities in pulmonary function testing, such as increased airway resistance and reactivity, can remain through adolescence (Koumbourlis et al. 1996). Previous studies have reported that 12% to 19% of former VLBW/VLGA infants in adolescence (Dombkowski et al. 2008, Anand et al. 2003), and 8% to 11% at the age of 19 to 20 years (Hack and Fanaroff. 2000,Vrijlandt et al. 2005) have asthma. These percentages are lower than in the current study five-year-old VLBW/VLGA children (19%), which could be explained by improvement of pulmonary function with increasing age. However, not all studies agree, since a recent study has shown a decline in the lung function of VLBW infants over time from 8 to 18 years of age (Doyle et al. 2006). In any case, due to the rapid development of care practices, the results from the pre-surfactant era should be interpreted with caution since they are not directly applicable to infants born in this decade. In addition, the overall incidence of asthma has been shown to have risen during the last twenty years (Rudd and Moorman. 2007). It is also possible that differences in diagnostic criteria partly explain the higher incidence of asthma in the current study. However, the full-term controls in the current study did not have a higher incidence of asthma (5%), compared with that reported in a study on the general population of South-West Finland (9% at five years of age and 5% at 18 years of age) (Kaila et al. 2009), and on other populations of full-term controls (5% to 6% at 19 to 20 years of age) (Hack and Fanaroff. 2000, Vrijlandt et al. 2005).

Interestingly, despite having more asthma, the VLBW/VLGA children in the current study had less atopic dermatitis than the full-term controls. Previous studies have similarly shown that prematurity is associated with a decreased incidence of atopy (Mai et al. 2003, Vrijlandt et al. 2005, Pekkanen et al. 2001, Siltanen et al. 2001), which could be explained by the abundant microbial exposure of the preterm infants during the neonatal period. The longer exposure to Th2 cytokines during a full-term pregnancy has also been suggested as a mechanism that could modify the immune system of the infant in the direction of the Th2 dominance associated with atopy (Pekkanen et al. 2001). The higher incidence of asthma in preterm children may thus be related to mechanisms other than atopy. A previous study (Siltanen et al. 2001) showed the incidence of atopic asthma to be equal in preterm and full-term children, whereas asthma without atopy was more common in preterm children. It has also been argued that the asthma-like symptoms of former VLBW/VLGA infants with BPD may sometimes be imprecisely labelled as

asthma and treated ineffectively with inhaled corticosteroids (Baraldi and Filippone. 2007). Contrary to the central role of eosinophil-driven inflammation in childhood asthma, exhaled nitric oxide levels have been reported normal among school-age VLGA survivors of BPD (Baraldi et al. 2005).

The VLBW/VLGA children in this study had significantly higher five-year accumulative incidence of upper respiratory infections and pneumonia compared with the full-term controls, indicating that VLBW/VLGA children are more susceptible to respiratory infections. However, it is possible that the parents of VLBW/VLGA children have a lower threshold for taking their child to a physician due to respiratory symptoms. Smoking in the home can also partly explain the increased five-year accumulative incidence of asthma and other respiratory conditions. The mothers of the VLBW/VLGA infants in the current study smoked more often during pregnancy (14%) than the mothers of the controls (9%), and they are thus also more likely to have continued to smoke after pregnancy. These results are in line with previous studies showing that maternal smoking during pregnancy is associated with low birth weight and an increased risk for preterm delivery (Fantuzzi et al. 2007, Windham et al. 2000).

In the current study, the mean duration of hospitalisation was short (0.4 days) for the VLBW/VLGA children during the fifth year of life, although, statistically it was significantly longer than for those in the control group (0.1 days). Parallel to the current findings, previous studies have shown increased hospital admissions and inpatient days for VLBW/VLGA children during the first year of life (Leijon et al. 2003, Jackson et al. 2001) and up to five years of age (Petrou. 2005, Xu et al. 1998) compared with full-term or normal birth weight controls. For Swedish VLGA infants, the risk of hospitalisation has been shown to still be increased at 12 to 23 years of age (Selling et al. 2008). However, contradictory results have also been published recently, which show no increase in admissions for VLBW or VLGA children between one to four years of age (Gäddlin et al. 2007, Leijon et al. 2003). While Gäddlin et al. (2007) showed increased admissions for VLBW boys during the first year and from four to nine years of life, the number of readmissions for VLBW girls during the first 15 years of life did not differ from full-term girls, nor did the readmissions for the VLBW boys at age 9 to 15 years. Similarly, a 24-year follow-up study on Northern Finnish VLBW children showed an increased rate of rehospitalisation during the first year of life and an increased length of stays during the first four years of life, but later in life the admission rates and the length of stays did not differ when compared with normal birth weight children (Xu et al. 1998). Our study group has previously shown that the need for hospitalisation decreases with increasing postnatal age among VLBW/VLGA children during the first three years of life (Korvenranta et al. 2009). The mean number of hospital days for the VLBW/VLGA children after the initial hospitalisation period was nine, eight, and five days during the first, second, and third year of life, respectively. The results of the current study showed that the need for hospital care for Finnish VLBW/VLGA children continues to decrease up to five years of age.

In the current study, the use of outpatient services by the VLBW/VLGA children was associated with CP, ophthalmic problems (other than ROP), asthma or CLD, and respiratory infections. Although there was a trend towards increased hospital days for those VLBW/VLGA children having CP or ophthalmic problems (other than ROP), these conditions and asthma or CLD were no longer associated, to a statistically significant degree, with hospital inpatient days during the fifth year of life. Hospital inpatient care for five-year-old VLBW/VLGA children was increased only by the presence of respiratory infections. Our study group has previously shown CP, obstructive airway disease, and visual disorders to be associated with increased hospital days for VLBW/VLGA children up to three years of age (Korvenranta et al. 2009). Since these conditions were no longer associated with hospital inpatient days during the fifth year of life, the impact of prematurity-related morbidities on resource-demanding inpatient care also seems to decrease with increasing age. The current results are consistent with previous findings showing upper respiratory infections to be the predominant causes for the readmissions of VLBW children up to 15 years of age (Gäddlin et al. 2007, Gray et al. 2006). However, a recent study by Walter et al. showed that after adjustments for other risk factors, respiratory infections were no longer associated, to a statistically significant degree, with hospitalisation among 18- to 27-year-old VLBW adults (Walter et al. 2009).

Parallel to the current results, an increased number of outpatient hospital visits has previously been reported for VLGA children during the first two years of life compared with full-term controls (Gray et al. 2006). Similarly, two- to eight-year-old Finnish VLBW infants born in one level III hospital between 1990 and 1994 were shown to use more occupational therapy and physiotherapy than full-term controls (Korhonen et al. 1999a). Compared with the five-year-old VLGA children participating in the EPIPAGE study (Larroque et al. 2008), the current results showed a similar use of OT and PT services. However, the current study showed more frequent use of the services of speech therapists and less frequent use of the services of psychologists than those reported in the EPIPAGE study. The high proportion of children that visited the nurse practitioner and the physician in the current study is explained by the fact that the Finnish child welfare clinic system offers at least one free visit to a nurse practitioner, a physician, or both during the fifth year of life. In the future, it is important to determine whether the national differences in morbidity and the use of health care services are due to genuine differences in health status, or whether they are due to different diagnostic criteria, different policies for following up VLBW/VLGA children, or to differences in the availability, supply, and demand for health care services for VLBW/VLGA children.

The current study showed VLBW/VLGA children to have significantly less optimal developmental and behavioural scores compared with the controls in all FTF domains. Among VLBW/VLGA children, the scores were less optimal the lower the gestational age. These findings are in agreement with earlier publications showing increased difficulties related to development and behaviour for preterm infants at five years of age (Hoff et al. 2004) and school age (Bhutta et al. 2002, Anderson et al. 2003) compared

with full-term or normal birth weight controls. Parallel to these results, parents have also reported former VLBW infants to have more social problems during adolescence (Dahl et al. 2006), and more attention problems throughout adolescence and young adulthood (Hack et al. 2004, Dahl et al. 2006) than controls. Increased problems with learning, language, and perception have also been found among 7−14-year-old ELBW children (<750g) compared with full-term controls (Taylor et al. 2004). These problems may lead to poorer academic readiness and achievement (Weindrich et al. 2003, Finnström et al. 2003, Hagen et al. 2006), and to the need for special education (Wocadlo and Rieger. 2006, Saigal et al. 2003). School problems in 10-year-old VLBW children have been shown to be most evident in mathematics (Hagen et al. 2006).

On the other hand, the proportion of five-year-old VLBW/VLGA children with considerable difficulties in the behavioural and developmental domains was not very alarming in the current study. The more moderate neurodevelopmental problems may, however, manifest themselves later on in life. Adolescents and adults born at as VLBW infants have been shown to have on average a lower IQ than full-term or normal birth weight controls, and to be at a disadvantage with more specific cognitive processes such as visual processing, visual memory, learning, problem solving, and arithmetic (Ericson and Kallen. 1998, Gäddlin et al. 2008, Hack et al. 2002, Rickards et al. 2001). They have also been reported having more social and attention problems and less school competence than the normative adolescents (Dahl et al. 2006, Walther et al. 2000). A Dutch study showed that twice as many 19-year-old former VLBW/VLGA infants were poorly educated compared with the 19-year-old general population, and three times as many were unemployed (Hille et al. 2007). Similar results on increased unemployment have been seen for ELBW adolescents, but these differences disappeared when participants with disabilities were excluded (Saigal et al. 2006b). There is also some evidence of increased psychopathology among VLBW adults; this includes mainly internalising behaviour among the women and problems of attention among the men (Hack et al. 2004). Gäddlin et al. (2007) reported that 5.8% of VLBW adolescents (all boys) have attention deficit and hyperactivity disorder, compared with 1.2% of the full-term controls. Although, there are contradictory findings showing less depression among VLBW adults than the controls (Räikkonen et al. 2008), continuous follow-up for VLBW/VLGA infants up to adolescence and adulthood is needed.

Although the HRQoL and QALY at five years of age were statistically significantly lower for the VLBW/VLGA children compared with the full-term controls in the current study, the difference in the HRQoL was small. While most VLBW/VLGA children seemed to have a good HRQoL, the distribution was bimodal, meaning that, though only a minority of children had a low HRQoL, this nonetheless lowered the group mean. The current results showing lower HRQoL for VLBW/VLGA children compared with the controls are in agreement with previous studies on the HRQoL of one- to four-year-old VLBW and VLGA infants (Eiser et al. 2005, Chien et al. 2006, Theunissen et al. 2001), and of adolescent ELBW infants (Saigal et al. 2000, Saigal et al. 1996). A Finnish study has also

shown delays among former VLBW infants in early adulthood in leaving the parental home and cohabiting with an intimate partner later compared with those born full-term (Kajantie et al. 2008). However, the difference in the 17D total score between VLBW/VLGA children and controls in the current study did not exceed 0.03 points, which has been regarded as the threshold of clinical significance when studying the HRQoL in adults using the 15D questionnaire (Sintonen. 1994).

There are also several studies showing no difference in HRQoL in adolescence and adulthood among prematurely born infants compared with the controls. A follow-up study on infants born in the 1970s showed a lower HRQoL in VLBW adults with mental and physical handicaps compared with normal birth weight controls, but this difference was not seen between VLBW adults free of handicaps and the controls (Bjerager et al. 1995). Another study showed the perceived quality of life for VLBW adults born in the 1980s to be similar to full-term controls in all other domains except physical functioning (Cooke. 2004). Despite the lower HRQoL assessed by others, the former VLBW and VLGA infants seem to have adapted to the situation and often estimate their subjective quality of life similar to normal birth weight controls (Walther et al. 2000, Indredavik et al. 2005, Dinesen and Greisen. 2001). Similarly, despite poorer health, the majority of children born at a GA <29 weeks or as ELBW infants rate their HRQoL similar to the full-term controls in adolescence and adulthood (Gray et al. 2007, Saigal et al. 2006a, Saigal et al. 2006b, Saigal et al. 1996). Former VLBW infants have also been shown to use less alcohol and illicit drugs (Hack et al. 2002, Cooke. 2004) and smoke less often, and to have similar rates of sexual intercourse compared with those born full-term (Cooke. 2004). Furthermore, one study showed former ELBW infants to be married or cohabiting, to have children, or live independently at the age of 22 to 25 years as often as the controls (Saigal et al. 2006a). Interestingly, differences in the HRQoL have been found between cohorts of adolescent ELBW infants from three different countries, which were not explained by birth weight, GA, or cerebral palsy (Verrips et al. 2008). This further speaks in favour of national long-term follow-up programs, as the results of studies on the HRQoL of different populations are not necessarily applicable to the Finnish VLBW/VLGA infants.

This study provides a way of applying QALY to an evaluation of the care of VLBW/VLGA infants. The yield of QALY for VLBW/VLGA infants could be used for a comparison of different treatment strategies and for a comparison with other patient groups. For example, the mortality rates in adult intensive care are comparable with the mortality rates for VLBW/VLGA infants. However, compared with the group of VLBW/VLGA infants in which most non-surviving infants die during the very first days of intensive care (Korvenranta et al. 2007, Meadow et al. 2003), the non-survivors in adult intensive care are often hospitalised for longer periods than the survivors (Meadow et al. 2003), which increases individual suffering and the costs of care. Furthermore, VLBW/VLGA infants have much lower mortality rates after discharge. Elderly Finnish ICU patients had a three-year survival rate of only 43% (Kaarlola et al. 2006). Graf et al.

(2005) showed a five-year survival rate of 73% after discharge from the adult intensive care, while all VLBW/VLGA children in the current study who were discharged home survived to the age of five. The same study (Graf et al. 2005) showed that the quality of life of the survivors, as described by a health status index, was 88% of that found among the age-matched healthy population. In adult intensive care, most other studies have also shown a significantly lower HRQoL after discharge compared with the general population (Dowdy et al. 2005). Since few VLBW/VLGA infants die after discharge, extrapolating the QALY for VLBW/VLGA children, e.g. up to 70 years of age, would most likely decrease the difference between their QALY and the QALY for the full-term population.

6.6 Current Trends in Centralisation of VLBW/VLGA Deliveries

The proportion of VLBW/VLGA deliveries centralized to level III hospitals has dramatically increased during the last fifteen years in Finland. In 1996–1997, it was reported that ELBW infants were born in 33 out of the 44 maternity hospitals in Finland (Tommiska et al. 2001). Of live-born ELBW infants, 82% were born in level III hospitals. In the current study between 2000 and 2003, the comparable rate was 89% for live-born ELBW infants (data not shown). The rate of live-born VLBW/VLGA infants born in level III hospitals was 79%, but varied from 55% to 95% between the university hospital districts. Between 2000 and 2003, VLBW/VLGA infants were delivered in 19 hospitals. The place of birth for VLBW/VLGA infants was affected by locally adopted policies and was also dependent on individual hospital policies. After this, in 2006, the Finnish Ministry of Social Affairs and Health proposed that all five university hospital districts should come up with a consensus for the examinations, operations, and treatments of conditions that should be managed in level III hospitals. In 2007, after the start of the public discussion, the proportion of live-born VLBW/VLGA infants born in level III hospitals had increased to 88%. The differences in centralisation practices between the five university hospital districts had narrowed, as the rate of VLBW/VLGA infants born in level III hospitals varied from 76% to 94% (According to the MBR). In 2008, the Ministry of Social Affairs and Health gave an ordinance that the delivery of infants born at less than 30 gestational weeks be centralized to level III hospitals.

The centralisation of VLBW/VLGA deliveries in Finland has been an active process, since 88% of live-born VLBW/VLGA infants compared with only 45% of all live-born infants (Official statistics of Finland, Statistical Summary 30/2008) were born in university hospitals in 2007. There are large differences between countries in the proportion of VLBW/VLGA deliveries centralized to level III hospitals (Zeitlin et al. 2004). In comparison, VLBW/VLGA deliveries in Sweden, a country with an equally low infant mortality rate, have been less efficiently centralized than in the Finnish health care system. In Sweden, only 70% of live-born singleton deliveries at a GA of <27 weeks and 41% at a GA of 24 to 31 weeks occurred in level III hospitals between 1992 and 1998 (Johansson et al. 2004). However, the centralisation rate has been increasing

also in Sweden, since 79% of live-born infants born at a GA of <27 weeks between 2004 and 2007 were delivered in level III hospitals (EXPRESS Group et al. 2009).

Parallel increases in the centralisation rate of VLBW or VLGA births have been reported for other populations. In New South Wales in Australia, improvement was reported on the centralisation of deliveries of live-born infants born at GA 23–28 weeks from 80% to 85% (Lui et al. 2006) and from 76% to 83% for VLGA infants (Roberts et al. 2004) born between 1992 and 2002. The mortality rate for infants born at GA 23–28 simultaneously decreased significantly from 27% to 24% (Lui et al. 2006). Similarly, the percentage of live-born VLGA infants born in level III hospitals increased in three health regions in the Netherlands from 32% in 1983 to 62% in 1996–97 (Stoelhorst et al. 2005) and from 67% to 77% between 1997 and 2003 in the region around Paris in France (Zeitlin et al. 2009). In the French study, a simultaneous decrease in mortality rates and the incidence of severe IVH was shown.

The centralisation of deliveries has also encountered opposition and even the concept of decentralisation has been brought up (Hein. 2004). Because of financial reimbursement systems, some smaller hospitals may be reluctant to refer the initial care of VLBW/VLGA infants into larger hospitals. Some hospitals also argue that the initial care of this patient group is needed to maintain adequate skills of the staff for acute situations. Some studies have reported no improvement in the rate of centralisation. For example, in Colorado in the USA, no differences were seen at the centralisation rate of deliveries for infants born at <750g between the periods 1991–1996 and 1997–2003 (Kamath et al. 2008). In a study from the metropolitan region of Germany, in the city-state of Berlin, Jochum et al. (2008) suggested that birth in larger hospitals would not be beneficial compared with birth in smaller hospitals in terms of avoiding mortality and morbidity. However, they did not have statistical power because the small hospitals (n=6) included in their study altogether delivered only 21 ELBW infants. They did not present any statistical comparisons to support their conclusion and their conclusion did not take the different patient selection and illness severity within the hospitals into account.

The current study showed that a good centralisation rate can be achieved despite geographical challenges. Finland is a scarcely populated country with distances up to 650km to the nearest level III hospital in the North, and the archipelago in the South poses special geographical challenges. It may be argued that centralisation of deliveries will lead to longer travel distances and increased inconvenience for the family, and to an increased workload for level III hospitals. However, these problems can be minimized without compromising survival by transferring the infants back to the hospital closest to home after the initial intensive care period. This back-transfer practice levels the workload between level II and III hospitals. This practice also provides experience in the care of stable VLBW/VLGA infants in level II hospitals. In the future, research on the economic consequences of centralisation is needed.

7. CONCLUSIONS

Despite the high overall survival rate for Finnish VLBW/VLGA infants, the current study confirmed the hypothesis stating that the chances for survival are higher for those born in level III hospitals compared with those born in level II hospitals. The decreased mortality in level III hospitals was not gained at the expense of long-term problems. However, contrary to our hypothesis, VLBW/VLGA children born in level II hospitals did not significantly differ from those born in level III hospitals in behaviour and development, the use of health care resources, HRQoL, QALY, and the five-year accumulated morbidity.

As hypothesised, there was a trend towards increased mortality for live-born VLBW/VLGA infants born outside office hours, particularly in level II hospitals. When stillborn VLBW/VLGA infants were included in the analyses, mortality was significantly increased for those born outside office hours. However, against the second hypothesis of the current study, the time of birth did not reflect in the five-year outcomes.

As hypothesised, mortality rates, the use of health care resources, and QALY differed according to the university hospital district where the birth occurred. However, there were no significant differences between the university hospital districts in development and behaviour, HRQoL, and the five-year accumulated morbidity of the survivors.

These results indicate that the deliveries of very preterm infants should efficiently be referred to level III hospitals to ensure the best chances of survival around the clock. In addition to the guidelines newly created for the centralisation of the deliveries of infants at a GA of <30 weeks, national consensus concerning treatment strategies, such as the resuscitation policy for infants at the border of viability, and the transfer of infants back to level II hospitals after intensive care, would contribute to the development of more equal care for VLBW/VLGA infants.

In the current study, the differences according to the birth hospital and the time of birth were more manifest in mortality rates than in the five-year outcome. This suggests that mortality works as a good indicator of the quality of initial care among VLBW/VLGA infants in Finland. Mortality rates may be more easily applicable in examining the effect of the initial care on VLBW/VLGA infants than later outcomes are, since the effect of initial care on mortality is confounded to a lesser extent by differences in care the infants receive later during the neonatal period. Since the QALY combine mortality and later outcome, QALY are important in providing a uniform measure for the comparison of effectiveness of care among VLBW/VLGA infants and also between different patient groups.

The differences in the outcomes for VLBW/VLGA infants between university hospital districts indicate that there are regional differences in the treatment strategies.

Benchmarking is one means to addressing this problem and to enhancing an equitable level of care throughout the entire country. In order to be able to evaluate the impact of therapeutic changes within units on VLBW/VLGA infants and of different organisational factors at the national level, continuous assessment of the long-term outcome of this patient group is also needed. This study, as a part of the PERFECT Preterm Infant study project, has produced and validated outcome measures available in the registers, which are now used in continuous performance surveillance between hospitals and districts.

APPENDIX 1

The translation of the parts of the study questionnaire that are not presented in the original publications

Questions for One or Both Parents:
Has the child visited any of the following physicians during the last 12 months:

1) A pediatrician or other physician at a health centre:
   □ no
   □ yes => a total of _____ times
2) A pediatrician or other physician at a hospital out-patient ward:
   □ no
   □ yes => a total of _____ times
3) A pediatrician or other physician at the private sector
   □ no
   □ yes => a total of _____ times
4) A pediatrician or other physician anywhere else:
   □ no
   □ yes => a total of _____ times

Has the child visited any of the following professionals during the last 12 months:

5) A nurse
   □ no
   □ yes => a total of _____ times
6) A physiotherapist
   □ no
   □ yes => a total of _____ times
7) A psychologist
   □ no
   □ yes => a total of _____ times
8) A speech therapist
   □ no
   □ yes => a total of _____ times
9) An occupational therapist
   □ no
   □ yes => a total of _____ times
10) A dietitian
    □ no
    □ yes => a total of _____ times
11) Does the child have any chronic conditions or permanent injuries (lasted over 6 months)?
    □yes □ no
    If yes, describe_____

12) Please, check the alternative that best describes the kind of day-care your child participates in
    - father takes care of the child at home
    - mother takes care of the child at home
    - a nanny takes care of the child at home
    - day-care centre
    - family day care/children's private day care in a group of 4-8 children
    - pre-school
    - special day-care
    - other _____
13) Does the child live
    - with both parents
    - with the mother
    - with the father
    - joint custody, takes turns in living with the mother and the father
    - with one biological parent and a step-parent
    - in foster care
    - with adoption parents
14) How many minors (<18 years of age) are included in your family?
    _____ minors
15) How many adults are included in your family?
    _____ adults
16) What is the combined monthly salary of your family members before taxes?
    _____ € per month

Questions Answered Separately by the Mother and the Father:

17) How many years have you studied?
    _____ years

18) Please, check the alternative that best describes your principal activity during the last 12 months. Principal activity is the activity, that you use most of your working time to or that you make most money from.
    - full-time job
    - part-time job
    - studying
    - retired
    - unemployed or temporarily dismissed
    - taking care of a family member at home
    - a draftee or a conscientious objector
    - other, what?_____

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Liisi Rautava

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