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Dissertation

ASSOCIATION OF APGAR SCORE AND POSTTERM DELIVERY WITH NEUROLOGIC MORBIDITY: COHORT STUDIES USING DATA FROM DANISH POPULATION REGISTRIES

by

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Dedication

Маме и папе

(To my parents)

Acknowledgments

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ABSTRACT

Antenatal and perinatal events are important for neurologic development, but the mechanisms involved are not fully understood. The three thesis studies examined the association of perinatal characteristics with subsequent neurologic outcomes by record linkage of birth data with medical and administrative population databases in Denmark. Study 1 and Study 2 sought to determine whether 5-minute Apgar score is associated with subsequent neurologic morbidity after accounting for its known determinants. In a cohort of >130,000 singleton births, neonates with an Apgar score <7 had 2- to 5-fold greater risk of epilepsy hospitalization before age 12 than did neonates with a 5-minute Apgar score ≥7. Study 2, based on examination of draft records of >17,000 Danish men, showed that 5-minute Apgar<7 score was weakly associated with worse intelligence test performance and worse sensory acuity. Study 3 examined the association of postterm (≥42 weeks) delivery with the risk of childhood epilepsy in a cohort of >250,000 live singleton births. Postterm delivery was found to be a risk factor for epilepsy with onset during the first year of life. We estimated a 1.2- to 2-fold increase in risk and a stronger effect was conferred by longer gestation. An enhanced effect was also found for neonates delivered with forceps or vacuum or by cesarean section. This was one of the first large cohort studies to explore long-term neurologic consequences of postterm delivery. All three studies point to an important role of prenatal and early neonatal period in neurologic development. Studies 1 and 2 suggest that antenatal and perinatal conditions set the stage for neurologic dysfunction or affect future susceptibility, while Study 3 offers a new insight in long-term repercussions of prolonged intrauterine stay.

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List of Abbreviations

AGA	Adequate for gestational age
BPP	Boerge Prien test (from Danish, Børge Prien Prøve)
CI	Confidence interval
CNS	Central nervous system
CPR	Central personal registry
HDR	Hospital discharge registry
HIE	Hypoxic-ischemic encephalopathy
ICD- 8	International classification of diseases, 8th revision
ICD-10	International classification of diseases, 10th revision
IQ	Intelligence quotient
LMP	Last menstrual period
MBR	Medical birth registry
MRI	Magnetic Resonance Imaging
PR	Prevalence ratio
RD	Risk difference
RR	Risk ratio
SES	Socioeconomic status
SGA	Small for gestational age

BACKGROUND AND RATIONALE

The idea that foundations of health and disease are present at or before birth has been recently explored in many disciplines. The 'developmental origins hypothesis' – the Barker's hypothesis – proposes that adverse antenatal exposures acting at certain periods of vulnerability may cause increased risk of adult disease by permanently altering physiology and metabolism.[1, 2] Early evidence came from studies of cardiovascular disease[3] and diabetes,[4] whose risk seems to be increased in adults after aberrant fetal growth. The aim of this thesis is to use epidemiologic evidence to gain insight into the role of prenatal and early neonatal period in developing neurologic disability.

Epidemiologic evidence

Recent epidemiologic studies provide evidence for the importance of antenatal and perinatal period in subsequent neurodevelopment. Many studies have focused on low birth weight as a potential predictor of neurologic outcomes ranging from cognitive impairment[5-7] to cerebral palsy.[8] Other prenatal factors implicated in the development of cerebral palsy include prematurity, asphyxia,[9] bilateral deviations from optimal birth weight,[8] and antenatal infections.[10] Large studies in Scandinavia have linked maternal bleeding during pregnancy and birth order to risk of schizophrenia[11] and autism.[12]

Molecular and biochemical mechanisms

Hypoxia (reduced oxygen supply) and ischemia (reduced blood flow) together cause asphyxia leading to brain damage - hypoxic-ischemic encephalopathy (HIE). HIE is a

major cause of neurologic dysfunction, and it occurs predominantly in term newborns. An interruption of placental blood flow hinders gas exchange, and HIE can continue even after a resuscitation, causing neuronal necrosis and apoptosis (programmed cell death). In cells, inadequate oxygenation initiates acidosis, free radical formation, accumulation of calcium ions, peroxidation of lipid membranes, and release of excitatory amino acids (e.g., glutamate and aspartate) and nitric oxide, which are neurotoxic.[13, 14] The reported incidence of HIE is 2-4 per 1000 live births; severe HIE is associated with up to 75% infant mortality. In surviving infants, there is dose-response relation between HIE severity and risk of long-term complications. As many as 80% of infants who survive severe HIE develop such serious complications as mental retardation, learning disabilities and cerebral palsy.[15] In particular, HIE accounts for about 20% of cerebral palsy cases,[16] but even if not attributable to HIE, an estimated 70-80% of cerebral palsy cases are thought to have antenatal origins. When CP is associated with mental deficits (about 50% of the cases), a peripartum etiology is hypothesized to be more likely.[16] Epilepsy, one of the outcomes examined in this thesis, commonly co-occurs with cerebral palsy, suggesting overlapping etiology, including that in the antenatal and neonatal periods.

Epidemiologic studies have shown that risk of newborn encephalopathy is raised with maternal disease, including pre-eclampsia, bleeding, infection, and placental abnormalities.[17-19] During labor and delivery hypoxic brain damage can occur from oxygen deprivation caused by placental abruption, rupture or winding of umbilical cord, or prolonged labor. Furthermore, neonates may sustain mechanical head injury during an instrument delivery.[20] A group of researchers in the Netherlands examined, with magnetic-

resonance imaging (MRI), 261 term infants with a clinical diagnosis of neonatal encephalopathy and found 80% of them to have acute lesions with characteristics of hypoxic-ischemic insult. Having found evidence of a chronic lesion in <1% of infants, the authors concluded that most of the hypoxic-ischemic damage occurs during the 'immediate perinatal period'.[21]

While HIE occurs predominantly among term infants, antenatal infections may play a more important role in causing brain damage among preterm neonates. Intrauterine infection triggers fetal inflammatory response, which can cause long-term neurologic consequences both independently from and mediated by prematurity. Fetal inflammatory response in preterm infants causes white matter damage, apoptosis, abnormal synaptogenesis and anomalies in neurotransmitters. Studies using ultrasound and MRI have shown that white matter damage is associated with lowered cognitive function, at least short-term. MRI-based studies have also shown that in preterm infants white matter damage is accompanied with gray matter involvement.[19,22] A recent meta-analysis of 44 studies demonstrated that intrauterine infection was associated with increased risk of cerebral palsy in term and preterm infants.[10] Additionally, there is emerging evidence – mainly from animal, but also from human studies – of the association between neurodevelopmental outcomes and maternal stress mediated by intrauterine exposure to stress hormones.[23, 24]

Epigenetic and evolutionary aspects

With the accumulation of multidisciplinary evidence, the naive "nurture versus nature" discourse is replaced by the more nuanced view of health as a product of complex

interactions of genetic substrate, epigenetic change and environmental influences. Epigenetic processes, defined as 'heritable changes in gene function that cannot be explained by changes in DNA sequence'[25] are interaction between genes and their cellular environment that bring about a particular phenotype. In a metaphor, genotype has been likened to a dictator and joint cellular, molecular, genetic – epigenetic – model of development to a more flexible, plastic 'democratic state'.[25] Genomic imprinting, which results in selective silencing of alleles depending on their parental origins, are thought to be involved in regulation of fetal metabolism and growth rate. DNA methylation and histone modification are known imprinting mechanisms. Aberrant methylation has been implicated as a mechanism by which inadequate folate supply affects myelination.[26] Indeed a recent large case-control study has demonstrated an association of periconceptual intake of folic acid antagonists with an increased risk of neural tube defects.[27] Evidence from animals suggests that imprinted genes also regulate postnatal behaviors of offspring and mother (including child rearing practices and availability of breast milk). However remotely, this suggests that some aspects of child-rearing practices that bear on behavior and cognition may be epigenetically determined. In newborns imprinted genes seem to impact homeostasis control and the ability to suckle.[28]

Related to imprinting is the evolutionary aspect of the mother-fetus interaction. What is referred to 'maternal disease' during pregnancy may be a manifestation of the so-called 'prenatal power plays'[29] whereby epigenetic aberrations in the developing fetus 'highjack' maternal metabolism for its own benefit to an abnormal degree. For example, such mechanisms might raise maternal blood glucose levels (in order to 'take a greater

share of each meal'[29]) or increase maternal blood pressure (to compensate for inadequate blood flow). Maternal regulatory mechanisms usually keep such 'claims' in check, but in some cases regulation breaks down, leading to gestational diabetes or preeclampsia.[29] Labor course and apparent characteristics of a newborn may be indicative of an existing neurologic damage; alternatively, some signs and symptoms may signal increased susceptibility to potential neurologic disability. In this thesis, I examined risks of several neurologic outcomes in relation to the 5-minute Apgar score and to postterm delivery. The former is a clinical index of infant's condition, while the latter is a little-studied biologic condition.

Apgar score

Apgar score[30] is a widely used method of evaluation of a newborn's condition. A delivery-attending medical professional assigns the score at 1 and 5 minutes of age. Five clinical signs are rated as 0, 1 or 2: heart rate, respiratory function, reflex irritability, muscle tone, and color. Apgar score thus ranges from 0 to 10, with a higher score indicating a better condition (Panel 1, Panel 2).

Panel 1. Apgar evaluation of a newborn[*]

Sign	**0**	**1**	**2**
Heart rate	Absent	< 100	≥ 100
Respiratory effort	Absent	Slow, irregular	Good, crying

[*] Modified from *Nelson Textbook of Pediatrics.* 15th ed. Philadelphia: W.B. Saunders Co.; 1996 (after Apgar V. A proposal for a new method of evaluation of the newborn infant. *Curr Res Anesth Analg.* 1953;32:260-267.)

Reflex irritability	No response	Grimace	Cough or sneeze
Muscle tone	Limp	Some flexion of extremities	Active Motion
Color	Blue, pale	Body pink, extremities blue	Completely pink

The 1-minute score is used to determine the need for resuscitation. At 5 minutes, an Apgar score below 4 is a good predictor of neonatal mortality[31] and it has been associated with an increased risk of cerebral palsy, mental retardation, poor academic performance, and autism (Panel 3). [9, 32-36]

A recent (2001) registry-based Swedish study of 1 million non-preterm infants born in 1988-1997 specifically examined both perinatal correlates of low (<7) 5-minute Apgar score and its neurologic consequences. The study found that increased risk of a low 5-minute Apgar score was associated with mother's older age and low parity and not only with lower but also with upper extremes of birth weight and gestational age (Panel 3). Presumably comparing 5-minute Apgar score of <7 to that of ≥7, the authors reported a 15- to 25-fold increased risk of cerebral palsy, 2- to 5-fold increase risk of epilepsy, and 3- to 10-fold increase risk of mental retardation. This study's estimates (odds ratios) are reasonably precise because of the large sample size, but they are difficult to interpret because reference groups were not clearly designated. For the neurologic outcomes, no range of follow-up time was explicitly given. From the dates of birth and study publication, one can estimate that the follow-up time ranged from 2 to 12 years.[37]

Currently an Apgar score of 0-3 is considered low (and is an indication for resuscitation at 1 minute); score of 4-6 intermediate; and score of 7-10, normal. The prevalence of Apgar scores <4 is very low, particularly at five minutes; because of that and due to the accompanying high neonatal mortality, scores <7 are defined as low for research purposes. Some studies have defined a low Apgar score as <8,[36, 38, 39] which, though arbitrary, but may complicate comparisons across studies and interpretation, provided that clinicians may be trained to assign the score with the guidelines' cut-off of <7.

Panel 2. Selected maternal and infant characteristics associated with suboptimal (<7) Apgar score[37, 40]

Mother	Child
Age	Prematurity
Primiparity	Low birth weight
Precipitous delivery	Extremes of gestational age
Epidural analgesia	Male gender
Maternal medication	Breech presentation
Smoking in pregnancy	Acute cerebral trauma
Preeclampsia	Intracranial hemorrhage
	Congenital neuropathy
	Spinal cord trauma
	Central nervous system anomaly
	Airway obstruction
	Congenital malformations

With the exception of a small proportion of infants whose resuscitation begins seconds after birth, one-minute Apgar score reflects a newborn's natural condition at 60 seconds after both head and feet emerge from the birth canal. The 5-minute Apgar score, however, reflects the response to resuscitation among infants in whom it was initiated in response to a depressed 1-minute score. Most, but not all, infants with a depressed 1-minute

score will have a normal 5-minute score. Lack of improvement of Apgar score in response to resuscitation and poor long-term neurologic prognosis may have common underlying causes.

The 5-minute score was shown to correlate better with adverse neurologic events than the 1-minute score, probably because it marks a lingering hypoxia and/or an inadequate response to resuscitation. Despite the consistently reported strong associations of a low Apgar score with neurologic outcomes (Panel 3), its predictive value is limited, since the majority of those with low Apgar scores have no disability. This proposal will focus on the 5-minute Apgar score as a marker of a biologic risk profile that may predispose a newborn to a neurologic disease. We hypothesize that a low Apgar score may correlate with both observed and observed antenatal and intrapartum CNS insults.

Panel 3. Studies of the association between Apgar score and neurologic outcomes (in order of publication, by first author).

Study	Design (study population)	Exposure	Relevant outcome(s)	Exposure info. source	Outcome info. source	N	Follow-up, years	Findings
Nelson, 1981[32]	Cohort (new-borns at 12 US hosp.)	Apgar score <8	Cerebral palsy	Hospital re-cords	Exami-nation of children	39,000	7	RR†Apgar score 0-3 vs. 7-10: 24 RR Apgar score 4-6 vs.7-10: 5
Seidman, 1991[39]	Cohort (Israeli draftees)	Apgar score ≤7	Intelligence test scores	Hospital re-cords	Com-puterized records of Israel Defense Forces	1,937	17	1-min. low Apgar score: Se†=8%, PPV†=8% 5-min. low Apgar score: Se†=1.5%, PPV†=5% with respect to low IQ

Study	Design (study population)	Exposure	Relevant outcome(s)	Exposure info. source	Outcome info. source	N	Follow-up, years	Findings
Haddad, 2000[41]	Follow-up (infants born at U of Tennessee Hospital who were successfully resuscitated)	Apgar score of 0 at 1 and 5 minutes	Short-term: hypoxic encephalopathy; Long-term: neurologic status	Perinatal database	Chart review, mother interview	33	Up to 12	3 infants w/short follow-up had diagnostic signs of cerebral complications Of 4 infants followed to school age, 2 had normal neurologic status; 1 had quadriplegia, 1 was mentally retarded

Study	Design (study population)	Exposure	Relevant outcome(s)	Exposure info. source	Outcome info. source	N	Follow-up, years	Findings
Moster, 2001[33]	Population based cohort (Norwegian Birth registry)	5-min. Apgar score <7	Cerebral palsy Mental retardation	Birth registry	National registries	235,165	8-12 yrs	RR†(95%CI†) Apgar score 0-3 vs. 7-10 CP: 81(48-138), MR†:9.4(3-29) RR(95%CI) Apgar score 4-6 vs.7-10 CP†: 31(22-44), MR†:4.4(2.2-8.8)
Thorngren-Jerneck, 2001[37]	Population based cohort (Swedish Birth registry)	5-min. Apgar score <7	Cerebral palsy Epilepsy Seizures Mental retardation	Birth registry	National Hospital Discharge registry	1,028,705	1-10 yrs[#]	OR†(95%CI) Apgar score 0-6 vs. 7-10 CP†: 19.1(14.8-24.6) Epilepsy: 3.51(2.40-5.14) Seizures: 1.25(1.04-1.50) MR†: 5.87(3.43-10.0)

Study	Design (study population)	Exposure	Relevant outcome(s)	Exposure info. source	Outcome info. source	N	Follow-up, years	Findings
Krebs, 2001[42]	Population based follow-up (term breech infants: Danish Birth registry)	5-min. Apgar score <7	Cerebral palsy Speech/lang. prob. DAMP[†]	Birth registry	Question-naire	323	4-15 yrs	RR[†#]Apgar score 0-6 vs. 7-10 CP: 9.2 Speech/lang. problems: 3.3, p=0.02 DAMP: 'no difference'
Moster, 2002[34]	Population based cohort (Norwegian Birth registry)	5-min Apgar score <7 + SNE[†]	Poor academic performance	Birth registry	Question naire, discharge summaries	727	8-13 yrs	OR[†](95%CI[†]) Apgar score 0-3 vs. 7-10 Poor academic perform.:7.6(2.5-23.1) OR[†](95%CI) Apgar score 4-6 vs.7-10 Poor academic perform: 2.6 (0.8-8.8)

Study	Design (study population)	Exposure	Relevant outcome(s)	Exposure info. source	Outcome info. source	N	Follow-up, years	Findings
Lawlor, 2006[38]	Population-based birth-registry based cohort study in Australia	5-min Ap-gar score <9	Standard IQ scores	Birth registry	Question-naires, IQ testing	3794	14 years	Mean difference in IQ scores of –1.64 points (95% CI: -3.72-0.44)
Sun, 2006[43]	Registry-based nationwide study in Den-mark	1- and 5-minute Ap-gar scores	Incidence of epilepsy	Birth registry	Hosp. discharge registry	>1.5 mio.	25 years	Incidence rate ratios for term babies 4.41 (95% CI: 3.83-5.07) for Apgar 4-6 vs. 10; corresponding IRR for Apgar 1-3: 8.68 (95% CI: 6.73 – 11.18)

† Se=Sensitivity; PPV=Positive predictive value; RR=risk ratio; OR=odds ratio; CI=confidence interval; CP=cerebral palsy; MR=mental retardation; DAMP=deficits in attention, motor control and perception; SNE=symptoms of neonatal encephalopathy

Not explicitly stated; inferred from available information

Postterm delivery

While preterm birth received massive attention in the research community, effects of prolonged gestation and postterm delivery have not been extensively studied. Yet what happens when the fetus 'overstays its welcome'? How long is too long? Shea and Wilcox have called postterm delivery 'a challenge for epidemiologic research'[44]. Defined as delivery at or after 42 full weeks of gestation, as determined by last menstrual period (LMP), the estimated prevalence of postterm delivery is 5 percent of all births. About 20% of postterm infants suffer from the dysmaturity syndrome, characterized by peeling skin, malnourished appearance, and meconium staining. Postterm infants may suffer from abnormal heart rate, growth retardation, and placental insufficiency.[44] Infant mortality in this group is higher than among term neonates. Postterm delivery is a biologic condition, with evidence of genetic predisposition. Additionally, in some women it may be a marker of inadequate perinatal care, and by extension, of low socioeconomic status – a known risk factor for neurodevelopmental disorders[40]. A Danish registry-based study in 1998-2001 reported increased risk of prolonged pregnancy in nulliparous women and mothers with pre-pregnancy body mass index above 25 kg/m^2.[45]

Because postterm delivery is rare, its meaningful study is possible based on large amount of data provided by population registries. A 1999 study of more than half a million non-preterm singleton births in Nordic countries, found that 8% of them were classified as postterm. Compared with term AGA newborns, postterm newborns had 2.5- to 3.5-fold greater risks of meconium aspiration, 1.2- to 1.9-fold greater risk of neonatal convulsions,

and 1.5- to 2.5-fold greater risk of 5-minute Apgar score <4. The latter two risks were further increased in SGA postterm neonates.[46]

Most studies of morbidity associated with postterm delivery focused primarily on perinatal period, whereby postterm delivery was associated with such risk factors for neurologic morbidity as fetal distress[47-50], asphyxia[49], and cesarean delivery[51, 52]. Perinatal and maternal complications have been reported[53] in a Danish population similar to the one that will be examined here. Paper 3 of this thesis examines the association of postterm delivery with a long-term risk of epilepsy.

Neurodevelopmental outcomes

This thesis examines several neurologic outcomes of different severity: epilepsy, impaired cognitive function, and visual and hearing acuity. The mechanisms of neurodevelopment in general are not completely understood but are thought to be a product of complex interactions between social, genetic, epigenetic, and environmental causes.

Epilepsy

An estimated 40 to 50 million people worldwide, including two million people in the United States, suffer from epilepsy, making it the most common serious neurologic disorder.[54, 55] Forty percent of new epilepsy cases occur in children younger than 15 years. In Europe and North America the annual incidence of childhood-onset epilepsy is 41-50 per 100 000, with the highest incidence – 150 per 100 000 – in the first year of life.[56]

Epilepsy is "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social

consequences of this condition."[56] Epilepsies are broadly classified as generalized (involving both cerebral hemispheres) and partial (older term, focal), but the list of different subtypes of epilepsies and epileptic syndromes is long. Types of epilepsy vary with age at onset.[56] Many generalized epilepsies can be traced to single-gene mutations or chromosomal abnormalities, while partial epilepsies are more often triggered by external insults to central nervous system (CNS), including brain injury and CNS infection.[56] However, in many cases causes of epilepsy are unknown.[54,55] Prenatal risk factors for epilepsy include placental pathology, preeclampsia, low birth weight, preterm birth, congenital anomalies, infection in pregnancy. [57,58] For most forms of epilepsy, it is the interactions of a susceptible genotype with the 'sufficient environmental insult' that ultimately lead to epilepsy diagnosis.[55] History of seizures is a strong predictor of epilepsy,[54,55] and neonatal seizures strongly correlate with hypoxic-ischemic encephalopathy,[57] as does low Apgar score.

Psychometric intelligence

Few research topics have been as emotionally charged, and as socially and politically abused, as that of intelligence testing.[59] In its most recent consensus statement, titled *Intelligence: Knowns and Unknowns*,[60] the American Psychological Association Task Force emphasizes that no single definition of intelligence exists, but in general one can talk about the human abilities '…to adapt effectively to the environment, to learn from experience, to engage in various forms of reasoning, to overcome obstacles by taking thought' (ref. 60, page 77).

Psychometric intelligence of an individual is his so-called 'intelligence quotient' (IQ) – the score of an age-appropriate standardized IQ test. IQ measures some aspects of what is

considered intelligence, and most standard IQ score tests are highly correlated with education. Currently intelligence testing is accepted as a practical tool for assessing cognitive function. IQ tests are designed to be normally distributed in the population. The most commonly used adult IQ test, the Wechsler Standard Intelligence Scale (WAIS)[61] has a mean of 100 and a standard deviation of 15. An IQ <70 during childhood is one of the requirements of the clinical diagnosis of mental retardation.[62]

Intelligence testing was developed in the beginning of the 20th century by the Sorbonne psychologist Alfred Binet. Binet was commissioned by the French ministry of education to create an instrument for a narrow practical purpose: to identify children who could benefit from special education. Binet was aware that his score was easy to abuse. He noted: "The scale […] does not permit the measure of the intelligence, because intellectual qualities […] cannot be measured as linear surfaces are measured."(Binet quoted in ref. 59)

Presently, synthesized evidence from psychological, genetic, and neuroimaging studies has led to the emergence of the complex 'mechanistic model' of intelligence, according to which, intelligence is a trait, which is shaped, as any other trait, in each individual by genetically determined physical substrate (neural structure), and its interaction with external – environmental, social, nutritional stimuli.[63]

Low cognitive function may co-occur with somatic diseases and it has been linked to excess mortality,[64-67] prematurity,[68] low birth weight,[5, 6] breech presentation, maternal infection[69]; memory may be affected by prenatal lack choline.[70]

Sensory acuity

Relatively few studies have examined the association between perinatal risk factors and sensory acuity. Mercuri and co-workers studied 39 full-term infants with neonatal encephalopathy confirmed by MRI, and found signs of abnormal vision at school age in 16 of them, with evidence that more severe brain damage conferred worse visual impairment.[71] In a case-control study, in Houston, 110 neonates who failed the auditory screening examination were compared with 638 randomly selected neonates who passed the examination with respect to perinatal profile. The following factors were associated with failed screening: low birth weight, congenital infections, asphyxia, meconium aspiration, neurodegenerative and genetic disorders, maternal substance abuse during pregnancy and absence of prenatal care.[72] With respect to long-term effects, large studies of Danish (N=4300) and Swedish (N>240,000) draftees have found that hearing loss in adulthood was associated with indicators of insufficient fetal growth, such as birth weight, length and body mass index. [73, 74] The second study of this thesis examines the association of Apgar score at 5 minutes with subsequent psychometric intelligence and sensory acuity.

Data Sources

Denmark, with its 80 medical and 120 demographic population databases is indeed "an epidemiologist's dream".[75] According to a review in *Science*,

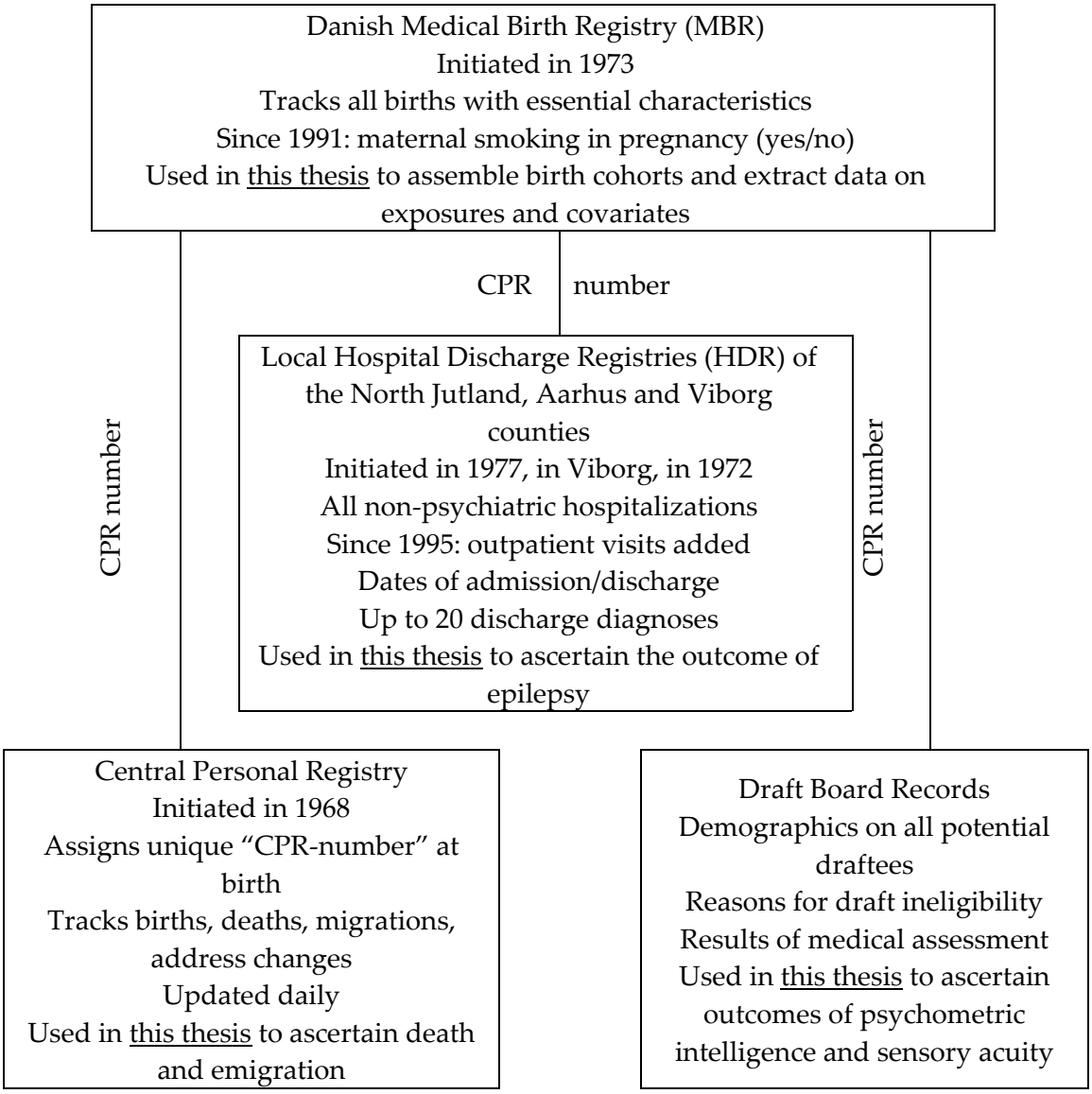
> *Other Scandinavian countries have created powerful database systems, but Denmark has earned a preeminent reputation for possessing the most complete and interwoven collection of statistics touching on almost every aspect of life […] from medical records to socioeconomic data […]. What makes the databases a plum research tool is the fact that they*

can all be linked by a 10-digit personal identification number, called the CPR, that follows each Dane from cradle to grave.[76]

The studies in this thesis use data linked from the Danish Medical Birth Registry (MBR[77]), the Hospital Discharge Registry (HDR) of respective counties,[78] and the Civil Registration System.[79] The pertinent registries will be described in each study. Panel 4 provides a general overview of these data sources.

To summarize, neurologic disability has been shown to have both genetic loci and physical substrate correlates, but its causes are often unknown. Neurologic well-being is important for the quality of life. The aim of this thesis was to study association of epilepsy and cognitive function with obstetric characteristics: five-minute Apgar score and postterm delivery in hope to make small steps in the direction of better understanding of the early origins of neurodevelopment.

Panel 4. Overview of Danish population registries used



Specific hypotheses

Apgar score below 7 at 5 minutes of age is associated with increased risk of epilepsy in childhood. (Paper 1: Ehrenstein V, Sorensen HT, Pedersen L, Larsen H, Holsteen V, Rothman KJ. Apgar score and hospitalization for epilepsy in childhood: a registry-based cohort study. BMC Public Health. 2006;6:23.)

Apgar score below 7 at 5 minutes of age is associated with worse performance on a group intelligence test and with worse visual and hearing acuity in young adulthood. (Paper 2: Five-minute Apgar score and neurologic outcomes among Danish draftees. To be submitted).

Postterm delivery is associated with increased risk of epilepsy in childhood (Paper 3: Ehrenstein V, Pedersen L, Holsteen V, Larsen H, Rothman KJ, Sorensen HT. Postterm delivery and risk for epilepsy in childhood. Pediatrics. 2007;119:e554-561.)

Justification for choosing effect measures and statistical models

In study 1 and study 3 we examined the risk of a rare outcome (epilepsy) in a cohort study, with variable and long follow-up time. Poisson regression is a suitable analytic approach in such situations, and the magnitude and the precision of relative effect estimates obtained from Poisson regression are very close to those obtained from the more often applied Cox's proportional hazards regression.[80]

In study 2, the measure of frequency of the dichotomous outcomes was prevalence, because, in contrast to studies 1 and 3, the cohorts were assembled not at the time of 'exposure' (Apgar score), but at the time of appearing before the draft board. This situation is analogous to studying birth defects in live-born infants. Just like some conceptuses are lost during gestation, some boys from the conscripts' birth cohort are lost during the time between the birth and the draft. Therefore prevalence seems to be an appropriate measure of outcome occurrence. We used log-binomial regression to model these outcomes because most of them were common (had a prevalence >10%), and therefore modeling them in a logistic model would yield odds ratio that would overestimate the association. According to a simulation study, log-binomial regression produced unbiased estimates of adjusted risk ratio and its interval coverage was similar to that obtained from the Mantel-Haenszel method.[81]

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APGAR SCORE AND HOSPITALIZATION FOR EPILEPSY IN CHILDHOOD: A REGISTRY-BASED COHORT STUDY

Abstract

BACKGROUND. A depressed Apgar score at 5 minutes is a marker for perinatal insults, including neurologic damage. We examined the association between 5-minute Apgar score and the risk of epilepsy hospitalization in childhood.

METHODS. Using records linked from population registries, we conducted a cohort study among singleton children born alive in the period 1978-2001 in North Jutland County, Denmark. The first hospital discharge diagnosis of epilepsy during the follow-up time was the main outcome. We followed each child for up to 12 years, calculated absolute risks and risk differences, and used a Poisson regression model to estimate risk ratios for epilepsy hospitalization. We adjusted risk ratio estimates for birth weight, gestational age, mode of delivery, birth presentation, mother's age at delivery, and birth defects.

RESULTS. One percent of the 131,853 eligible newborns had a 5-minute Apgar score <7. These children were more likely to be hospitalized with epilepsy during the follow-up than were children with an Apgar score of 7 or greater. The crude risk difference for epilepsy hospitalization was 2.5 cases per 100 (95% confidence interval [CI] 1.3 to 3.8). The risk difference estimates were greater in the presence of other perinatal risk factors. The adjusted risk ratio was 2.4 (95% CI 1.5 to 3.8). Half of the 12-year risk for epilepsy hospitalization in those with a depressed Apgar score occurred during the first year of life. The risk ratio during the first year of life was 4.9 (95% CI 2.0 to 12.3).

CONCLUSIONS. An Apgar score <7 at five minutes predicts an increase in the subsequent risk of epilepsy hospitalization. This association is amplified by other perinatal risk factors.

Background

Designed to assess infants' condition immediately after birth, Apgar score [1] is a cumulative ranking of five clinical signs – heart rate, respiratory effort, muscle tone, reflex activity, and color – each assigned a rating of 0, 1, or 2 with lower number corresponding to poorer condition [2]. Apgar scores take on integer values from zero to ten and are measured at one and five minutes of age. A prolonged Apgar score below four is a component of a diagnosis of asphyxia and is a stronger predictor of neonatal death than the pH of umbilical artery blood [3, 4]. A depressed five-minute Apgar score reflects a host of intrauterine and perinatal insults, some of which are also known or suspected risk factors for neurologic morbidity: hypoxic and mechanical brain trauma, birth defects, non-optimal birth weight or gestation, breech presentation, delivery complications, maternal age and smoking, as well as the newborn's poor response to resuscitation prompted by a low one-minute Apgar score [3-13]. Unknown prenatal causes of neurologic damage (e. g., subclinical in-utero infection [14]) may likewise contribute to the value of the Apgar score, making it a sign of increased general vulnerability of the infant.

The five-minute Apgar score correlates better with subsequent neurologic morbidity than the one-minute score [3]. Studies report associations of five-minute Apgar score with cerebral palsy, mental retardation, seizures, and with minor neurologic disability [15, 16]. The association of Apgar score with epilepsy – one of the most prevalent neurologic disorders [17] – was reported by a single study, in which epilepsy was not the primary

outcome [11]. Moreover, the statistical analysis was inappropriate for the varying follow-up, and modification of the effect of the Apgar score by other perinatal characteristics was not addressed.

Using data from Danish population registries, we conducted a cohort study to examine the relation between five-minute Apgar score and the risk of hospitalization for epilepsy. We also examined whether this relation depended on perinatal characteristics that are known or suspected risk factors for neurologic morbidity.

Methods

Study population and design

We conducted the study in the Birth Cohort of North Jutland County, Denmark, using routinely collected electronically stored data from the Danish Medical Birth Registry, North Jutland County Hospital Discharge Registry, and the Danish Civil Registration System [18]. In the Birth Registry, we identified all single live births from 1978 through 2001 and retrieved variables for five-minute Apgar score, birth weight, gestational age, mode of delivery, birth presentation, birth defects (defined here as malformations discovered during the birth hospitalization), mother's age at delivery, and mother's smoking in pregnancy.

From the Hospital Discharge Registry, we retrieved records of epilepsy hospitalizations. We used the International Classification of Diseases version 8 (ICD-8) codes 345.00-345.99 (before 1994), and ICD-10 codes G40.0-G40.9, G41.0-G41.9 (thereafter) to identify epilepsy cases. Whenever available, we also retrieved records on epilepsy hospitalizations for mothers and fathers of the newborns.

Data on emigration and death were from the Civil Registration System. Records

were linked using the National Civil Registration number, which is a unique identifier assigned to all Danish residents at birth and used in all public records. The follow-up time for each child was calculated from birth until the date of the first epilepsy hospitalization, emigration, death, 12th birthday, or December 31, 2002.

The informed consent was not required for this study, since it was conducted using public-domain records with the identifier removed from the analysis dataset.

Data analysis

From the incidence of epilepsy, we estimated the corresponding risk from birth to age 12 and calculated the risk difference associated with a depressed five-minute Apgar score, defined as a score below seven. We examined the extent to which the risk and risk difference varied according to birth weight in grams (≤2500, 2501-3000, 3001-3500, 3501-4000, ≥4001), gestational age in weeks (<28, 28 – 36, 37 – 42, >42), mode of delivery (spontaneous, assisted by vacuum or forceps, caesarean), birth presentation (cephalic vs. non-cephalic), birth defects (present/absent), mother's age at delivery in years (≤20, 21-30, ≥31 years), and when available, dichotomous variables for mother's smoking during pregnancy and parental epilepsy hospitalization.

We used Poisson regression [19, 20] to model the rate of epilepsy hospitalization and to estimate the risk ratio, while adjusting simultaneously for the effects of non-cephalic birth presentation, birth weight, gestational age, maternal age, birth defects, and mode of delivery. Maternal smoking in pregnancy became reportable to the Birth Registry after 1990. We repeated the adjusted analysis in a subcohort of children born after 1990, with a variable for maternal smoking in pregnancy added into the model. The Hospital Discharge Registry

was established in 1977 and thus contained only partial information on parental hospitalizations for our cohort. We estimated that the earliest parental hospitalizations would be recorded in the Hospital Discharge Registry for children who were born after 1994 and did the regression analysis separately for this subcohort, with an indicator variable for parental epilepsy hospitalization added to the model.

For 69 randomly selected children hospitalized with epilepsy in 1998-2000, we compared Hospital Discharge Registry records with paper medical records in order to estimate positive predictive value of the registered discharge diagnosis. For the paper records, we defined an epilepsy case as a physician-recorded epilepsy diagnosis, based on two or more unprovoked seizure episodes or on electroencephalography findings, or both [21]. Febrile seizures were excluded.

We analyzed the data with version 8.02 of SAS® software (SAS Institute, Cary, NC).

Results

From the 132,932 neonates who had records in the Birth Registry and met our entry criteria, we excluded 1,079 (0.8%) with a missing five-minute Apgar score. Of the remaining 131,853 newborns, 476 (0.4%) had a five-minute Apgar score below four, 847 (0.6%) had Apgar scores between four and six; the rest of the newborns had Apgar scores of seven or above. Table 1 shows prevalence of depressed Apgar score according to perinatal characteristics. Infants with low birth weight, short gestation, non-cephalic birth presentation, non-spontaneous delivery, birth defects, and notably, a parent who had been hospitalized for epilepsy, were more likely to have five-minute Apgar score below seven compared with the cohort as a whole.

There were 815 cases of epilepsy hospitalization, corresponding to a 12-year risk of 0.8% (Table 2). Twenty-seven cases occurred among those with five-minute Apgar score below seven, including eight cases among those with Apgar score below four. The latter group had the shortest median follow-up time of 8.4 years.

Table 3 shows risks and risk differences related to having a depressed Apgar score in categories of perinatal characteristics. Risks were consistently greater in children with Apgar scores below seven compared with children with Apgar score of seven or greater. The overall excess risk related to having a depressed Apgar score was 2.5 cases per 100 persons (95% confidence interval [CI] 1.3 to 3.8 cases per 100 persons). The absolute risk increase was greater among children with either low or elevated birth weight (respectively, 4.5 and 3.2 per 100); birth defects (4.2 per 100); maternal smoking in pregnancy (5.3 per 100), gestation beyond 42 weeks (18.6 per 100); and a history of parental epilepsy hospitalization (36.1 per 100), though the latter two estimates were based on few cases.

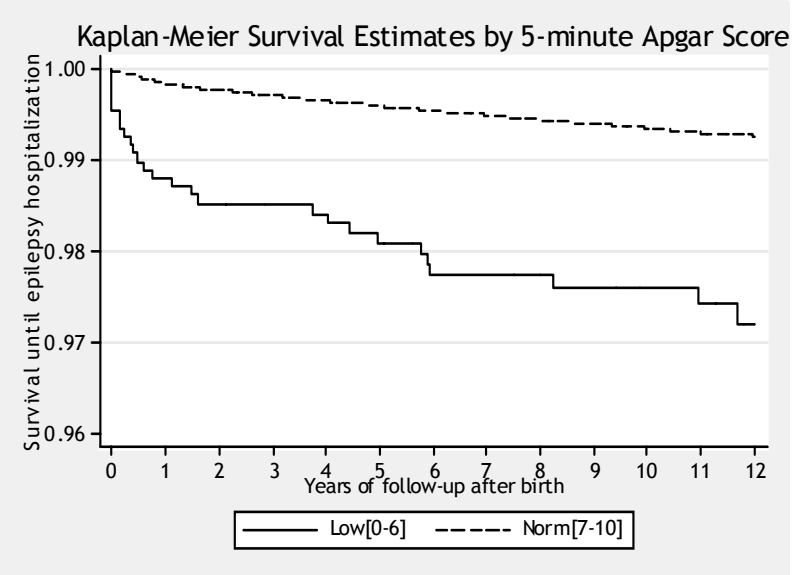
Risks of epilepsy hospitalization in Apgar score categories 0-3 and 4-6 were similar (Table 2) and the categories were combined for the further analyses. The crude risk ratio for epilepsy hospitalization was 4.3 (95% CI 2.0 to 6.3) for an Apgar score below seven vs. an Apgar score of seven and above, and the adjusted risk ratio was 2.4 (95% CI 1.5 to 3.8).

In the subcohort of infants born in 1991-2001 with added maternal smoking information, the adjusted risk ratio was 3.8 (95% CI 1.9 to 7.5), and in the subcohort of births with added information on parental hospitalization for epilepsy (1995-2001), the adjusted risk ratio was 5.2 (95% CI 2.1 to 13.0) (Table 4). Removing maternal smoking or parental epilepsy variables, or both, from these analyses of the restricted cohorts, however, did not

substantially change the adjusted estimates, suggesting that larger risk ratio estimates resulted from the subcohort having a shorter follow-up rather than from better control of confounding. Adjusted risk ratios for epilepsy hospitalization were 1.6 (95% CI 1.1 to 2.5) for maternal smoking in pregnancy and 1.8 (95% CI 0.6 to 5.8) for having a parent hospitalized with the disease.

Half of the epilepsy hospitalizations among those with Apgar score below seven occurred during the first year of life. Restricting the analysis to that period yielded an adjusted risk ratio estimate of 4.9 (95% CI 2.0 to 12.3). There was an association also beyond the first year of life. Crude risk ratio was 2.77 (95% CI: 1.60 – 4.80); after including the other predictors, risk ratio was 1.79 (95% CI: 0.94 – 3.38). The Kaplan-Meier survival curves stratified by 5-minute Apgar score category are presented below.

Figure 1. Survival until epilepsy hospitalization, by 5-minute Apgar score



The epilepsy diagnosis validation of the 69 cases recorded in the Hospital Discharge Registry showed that 52 of them also had a diagnosis of epilepsy recorded in the paper chart. Of the 17 unconfirmed epilepsy diagnoses, two were coding errors; five were seizures without a definite diagnosis of epilepsy; five were suspected seizures; one was asphyxia; one was mental retardation; one was an unspecified neurologic problem; and two were heart failure diagnoses. Thus, while 75 percent of validated cases fulfilled strict clinical criteria for epilepsy, a further seven to 14 percent had seizures without being given an epilepsy diagnosis. Coding errors occurred in three percent of the examined records. None of the children with epilepsy whose diagnosis was validated had a depressed five-minute Apgar score.

Compared with the analysis cohort, the small (<1%) group of infants with a missing 5-minute Apgar score had a lower median birth weight, higher prevalence of birth defects, and were more likely to be in a non-cephalic birth presentation. The risk of epilepsy among them was 0.6 percent (6 cases). Under the hypothetical extreme assumption that all these newborns actually had a 5-minute Apgar score below seven, the 12-year risk of epilepsy hospitalization in the exposed group would have decreased slightly but would still be about twice the risk among infants with Apgar score of seven or greater. Such an extreme distribution of missing Apgar score values would of course be unlikely, given their observed distribution in the analysis cohort and median follow-up time of 12 years.

Discussion

In this large population-based study with prospectively collected data, having a depressed five-minute Apgar score was consistently associated with increased risk of epilepsy hospitalization in the first 12 years of life. It is often noted that the overwhelming majority of babies with a depressed Apgar score grow up healthy [3, 15]. Nevertheless, the two- to four-fold increase in the risk of epilepsy hospitalization that we found is substantial. We observed a greater absolute effect of Apgar score on risk of epilepsy hospitalization among children delivered with the assistance of forceps or a vacuum extractor. The absolute effect was also amplified by having a low birth weight and by maternal smoking in pregnancy. These characteristics alone were not strong risk factors for epilepsy in our data, but combined with a depressed Apgar score, predicted a large increase in risk. This finding is consistent with the current opinion that epilepsy can result from the gradual accumulation of environmental insults to the central nervous system [17].

Five of the 8 cases in the 0-3 group were registered before the age of 1 year (3 focal symptomatic epilepsies; 1 West syndrome; 1 unspecified); 1 at age 3 years (focal asymptomatic epilepsy); 1 at age 4 years; and 1 at age 5 years (both unspecified). This could imply that certain types of epilepsy (eg, those with early onset) are more likely to be triggered by Apgar score correlates than others, but we refrain from making a conclusion given the uncertainty of the electronically registered diagnosis and the small number of cases.

The risk of epilepsy hospitalization was somewhat greater among babies with Apgar scores between four and six than in babies with scores below four. We offer two

possible explanations for this observation. First, because babies with a low Apgar score face a high mortality, epilepsy and death are, for them, competing outcomes and some children will not survive long enough to develop epilepsy [22]. We obtained mortality data for babies born in North Jutland County in 1980-2001 and found that 30% of the newborns with a five-minute Apgar score below four died within the first year of life, compared with 14% and 0.4% among those with scores of 4-6 and 7-10 (the high mortality is also a possible explanation for the shorter follow-up time in among those with Apgar scores <7). Second, epilepsy due to perinatal complications is likely to have an early onset. We found that all epilepsy cases occurring among those who fell into the lowest Apgar score group (0-3) were diagnosed before the age of six. Between ages 6 and 12, these children had zero risk of new-onset epilepsy in these data, contributing to a comparatively low 12-year risk estimate in this group.

The association between perinatal history and neurologic morbidity has been shown in a number of studies: low birth weight and prematurity are risk factors for neonatal seizures [5]; in-utero nicotine exposure has been implicated in occurrence of cerebral hemorrhage [6]; breech presentation affects cognitive function [10]; and inadequate intrauterine growth increases risk of cerebral palsy [7]. We found that the association between depressed Apgar score and epilepsy remained strong even after removing the effect of low birth weight, preterm and postterm birth, birth defects, non-spontaneous delivery, and non-cephalic birth presentation.

The outcome of interest of this study was a diagnosis of epilepsy that resulted in hospitalization. Not all children diagnosed with epilepsy are hospitalized, and the risk of

epilepsy diagnosed among outpatients may exhibit a different relation to five-minute Apgar score. Registration of outpatient visits in North Jutland County started after 1993. Based on a portion of these data, we estimate that about 20 percent of epilepsy diagnoses are made among outpatients, with an incidence of 3/1000 person-years for those with Apgar score below 7 and 0.2/1000 person-years among those with Apgar score of 7 and above. Based on 32 outpatient epilepsy cases observed in these data, we estimated the adjusted risk ratio for outpatient epilepsy to be 9.8 (95% CI 2.6 to 36.6) over six years of follow-up.

Epilepsy develops by a number of mechanisms, many still unknown [17, 23, 24] and its association with Apgar score may or may not reflect a causal connection. Insofar as the value of five-minute Apgar score is a rough composite measure of neurologic vulnerability, it may reflect the action of a set of prenatal and perinatal factors that cause epilepsy or increase individual's susceptibility to developing it. The stronger associations seen for shorter follow-up times support the notion of the importance of perinatal factors in determining epilepsy risk in early childhood.

Despite the large size of our cohort and the long follow-up, the number of epilepsy cases observed among the children with a 5-minute Apgar score<7 was very small. Therefore in this study we could not examine in detail the effects of age or calendar time and had to resort to dichotomizing exposure and averaging incidence estimates.

Danish Birth Registry data have been validated and found to have high quality [25]. Hospital discharge diagnoses, however, are not always accurate [26]. Our validation of a small sample of cases suggests that roughly 25% of epilepsy records in the hospital discharge registry do not correspond to strict epilepsy diagnoses; this proportion of false-

positive diagnoses is an important limitation of these data. Validated ascertainment of all cases was not logistically possible for the countywide long-term data used here. Since birth data are entered before and independently of discharge data, however, the rate of false positive diagnoses are not likely to differ much by Apgar score, unless the conditions that constitute the false positive cases are themselves related to Apgar score [27].

Registry data inherently lack clinical detail. Thus, we did not have information on head trauma or neonatal seizures – important precursors of epilepsy [17, 28, 29]. Nevertheless, the complex causal constellations for both Apgar score and epilepsy suggest that these are unlikely to entirely explain away the observed association. The ability to differentiate between elective and emergency caesarean delivery and between different types of non-cephalic birth presentations would elucidate the role of these characteristics in affecting neurologic morbidity and in determining the predictive value of the Apgar score.

Conclusions

We found that neither prematurity nor low birth weight was associated with epilepsy hospitalization as strongly as was a low Apgar score. The Apgar score, which is an easily and routinely collected correlate of a host of perinatal events, may be a useful addition to birth weight and gestational age in predicting epilepsy morbidity among infants.

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Appendix

Unknown to me at the time of publication, but reported later in a larger Danish paper on the same topic, some children may have "*arbitrarily received an Apgar score of zero if they were transferred to another department [intensive care unit] immediately after birth*" (Sun Y, Vestergaard M, Pedersen CB, Christensen J, Olsen J. Apgar scores and long-term risk of epilepsy. *Epidemiology.* 2006;17:296-301.) In our cohort, two of the 238 newborns with recorded Apgar score of zero at 5 minutes received a discharge diagnosis of epilepsy at ages 4 and 6 during the follow-up.

This has implications for the estimates of risk and estimates of effect, since the true Apgar score of these children was probably not zero. From the available data, it is not possible to establish which newborns truly had a 5-minute Apgar score of zero, and which did not (although infants transferred to the intensive care unit are more likely to have a low Apgar score) Removing all those with Apgar score of zero from the analysis mainly decreases the denominator used to calculate the incidence rate of epilepsy among those with scores <7, thus increasing the value of the rate the magnitude of the effect. With zero values removed, the incidence rate of epilepsy in the 1-3 Apgar score category was 4.8 per 1000 person-years, and the 12-year risk, 5.8 per 100. The crude overall risk ratio for Apgar 1-6 versus 7-10 was 4.94 (95% CI: 3.32 – 7.35); after adding all other predictors, the risk ratio became 2.59 (95% CI: 1.60 – 4.80). The rate, risk and risk ratio have changed substantially for the lowest Apgar score category, but the estimates associated with the broader Apgar <7 group were less affected and the interpretation did not change. (This finding explains and

removes the counter-intuitive observation of the epilepsy incidence rate in the lowest Apgar score category (0-3) being lower than that in the intermediate category (4-6)).

Table 1. Birth characteristics and 5-minute Apgar score of 131,853 Danish newborns

Characteristic	N	Five-minute Apgar score < 7	
		Frequency	Prevalence, %
Entire cohort	131,853	1,323	1.0
Birth weight			
≤2500 g	5,633	334	5.9
2501-3000 g	17,043	163	1.0
3001-3500 g	44,381	289	0.6
3501-4000 g	43,779	296	0.7
≥4001 g	20,860	165	0.8
No record	157	76	48.4
Gestational age			
<28 weeks	179	55	30.7
28-36 weeks	5,258	265	5.0
37-42 weeks	116,527	847	0.7
>42 weeks	3,866	45	1.2
No record	6,023	111	1.8
Mode of delivery			

Spontaneous	106,449	708	0.7
Assisted	10,007	213	2.1
Caesarean	15,350	401	2.6
No record	47	1	2.1
Birth presentation			
Cephalic	109,724	813	0.7
All other	14,837	420	2.8
No record	7,292	90	1.2
Any birth defect			
Absent	122,274	1,087	0.9
Present	9,579	236	2.5
Mother's age at delivery			
≤20 years	7,509	87	1.2
21-30 years	89,986	879	1.0
≥31 years	34,358	357	1.0
Mother smoked in pregnancy*			

No	43,375	485	1.1
Yes	17,804	191	1.1
No record	1,620	45	2.8
Parental epilepsy hospitalization[#]			
No	38,332	356	0.9
Yes	439	8	1.8

[*] Births after 1990, N=62,799. [#] Births after 1994, N=38,771

Table 2. Incidence of epilepsy hospitalization by 5-minute Apgar score

	Five-minute Apgar score			Total
	0-3	4-6	7-10	
Cases	8	19	788	815
Total births	476	847	130,530	131,853
Median years of follow-up	8.4	9.8	12.0	12.0
Person-years	3,193	6,559	1,215,045	1,224,797
Incidence, per 1000 person-years	2.5	2.9	0.6	0.7
12-year risk, per 100 persons	3.0	3.5	0.8	0.8

Table 3. Risks and risk differences for epilepsy hospitalization according to 5-minute Apgar score and other characteristics

Characteristic	Risk per 100 persons (no. of cases)			Risk difference, cases per 100 (95% CI)
	Overall	Apgar score <7	Apgar score ≥7, reference	
Entire cohort	0.8 (815)	3.3 (27)	0.8 (788)	2.5 (1.3 to 3.8)
Birth weight				
≤2500 g	1.7 (70)	3.2 (5)	1.6 (65)	1.6 (-1.2 to 4.5)
2501-3000 g	1.0 (133)	5.5 (6)	0.9 (127)	4.5 (0.1 to 8.9)
3001-3500 g	0.8 (275)	3.7 (7)	0.8 (268)	2.9 (0.2 to 5.6)
3501-4000 g	0.7 (228)	1.4 (3)	0.7 (225)	0.8 (-0.9 to 2.4)
≥4001 g	0.7 (106)	3.8 (4)	0.7 (102)	3.2 (-0.6 to 6.9)
Gestational age				
<28 weeks	1.6 (1)	0 (0)	1.9 (1)	-1.9 (-5.5 to 1.8)
28-36 weeks	1.4 (55)	2.9 (4)	1.3 (51)	1.6 (-1.3 to 4.4)
37-42 weeks	0.7 (684)	2.5 (14)	0.7 (670)	1.7 (0.4 to 3.0)
>42 weeks	0.9 (20)	5.5 (4)	0.7 (16)	18.6 (-0.3 to 37.6)
Mode of delivery				
Spontaneous	0.7 (621)	3.0 (13)	0.7 (608)	2.2 (0.6 to 3.9)
Assisted	0.9 (68)	4.4 (6)	0.8 (62)	3.6 (0.1 to 7.1)
Caesarean	1.1 (125)	2.9 (7)	1.1 (118)	1.9 (-0.3 to 4.0)
Birth presentation				
Cephalic	0.7 (662)	3.0 (16)	0.7 (646)	2.3 (0.8 to 3.8)

All other	1.1 (129)	3.7 (9)	1.1 (120)	2.6 (0.2 to 5.0)
Birth defects				
Absent	0.7 (639)	2.8 (20)	0.7 (619)	2.2 (0.9 to 3.4)
Present	2.3 (176)	6.5 (7)	2.2 (169)	4.2 (-0.6 to 9.0)
Mother's age at delivery				
≤20 years	1.1 (72)	3.4 (2)	1.1 (70)	2.3 (-2.4 to 7.1)
21-30 years	0.8 (572)	3.1 (17)	0.8 (555)	2.3 (0.9 to 3.8)
≥31 years	0.7 (171)	3.9 (8)	0.7 (163)	3.2 (0.5 to 5.9)
Mother smoked in pregnancy*				
No	0.6 (141)	2.4 (6)	0.6 (135)	1.8 (-0.1 to 3.7)
Yes	1.0 (99)	6.3 (6)	0.9 (93)	5.3 (0.3 to 10.4)
Parental epilepsy hospitalization#				
No	0.8 (122)	5.9 (7)	0.8 (115)	5.1 (0.7 to 9.4)
Yes	1.9 (3)	37.4 (1)	1.3 (2)	36.1 (-37.1 to 109.4)

* Births after 1990, N=62,799. # Births after 1994, N=38,771

Table 4. Crude and adjusted risk ratios for epilepsy hospitalization

Analysis cohort	N	Risk ratio for 5-minute Apgar score<7 (95% CI)	
		Crude	Adjusted
All births (up to 12 years of follow-up)	131,853 (815 cases)	4.3 (2.0 to 6.3)	2.4 (1.5 to 3.8)*
All births with follow-up restricted to the first year of life	131,853 (217 cases)	8.4 (4.9 to 14.4)	4.9 (2.0 to 12.3)*
Births 1991-2001 (maternal smoking data complete)	62,799 (249 cases)	4.9 (2.8 to 8.7)	3.8 (1.9 to 7.5)#
Births 1995-2001 (maternal smoking and parental epilepsy data complete)	38,771 (125 cases)	8.1 (4.0 to 16.7)	5.2 (2.1 to 13.0)†

* Rate ratios, modeled by Poisson regression, are reported as estimates of risk ratios because epilepsy is a rare condition. Adjusted for birth weight, gestational age, mode of delivery, birth presentation, mother's age at delivery, and birth defects

Adjusted for all of the above plus maternal smoking

† Adjusted for all of the above plus parental epilepsy

FIVE-MINUTE APGAR SCORE AND NEUROLOGIC OUTCOMES AMONG DANISH DRAFTEES

Abstract

BACKGROUND**.** A low 5-minute Apgar score is associated with increased risk of epilepsy or cerebral palsy, but its association with long-term cognitive and sensory function is unclear.

METHODS**.** We conducted a population-based cohort study based on birth registry data and linked conscript records of 19843 men born in 1978-1983 in a well-defined Danish conscription district. The men underwent medical evaluation and took the Boerge Prien intelligence test (BPP). We examined BPP scores and prevalence of hearing and visual impairment, according to 5-minute Apgar score (<7, 7-9, 10 [reference]). Among men exempt from the draft evaluation, we examined the occurrence of neurologic disability as a recorded reason for being exempt.

FINDINGS**.** 106 (0.6%) draftees had 5-minute Apgar score <7; 998 (5.8%) had a score between 7 and 9. Prevalence ratios (95% confidence interval, CI) comparing conscripts with 5-minute Apgar score <7 with the reference group were 1.32 (0.98 to 1.78) for having a low BPP score; 1.56 (0.83 to 2.91) for unilateral visual impairment; 1.26 (0.76 to 2.10) for bilateral visual impairment; 1.25 (0.96 to 1.63) for hearing impairment; and 2.19 (1.44 to 3.32) for a neurologic disability among the exempt men. These changed slightly after taking into consideration other perinatal characteristics. The associations seemed stronger among offspring of mothers of high parity or young age.

INTERPRETATION**.** Though associations were modest, our findings offer some support for the hypothesis that there are biologic indicators of adult neurologic function that are present at birth and are measurable the Apgar score.

Introduction

Apgar score,[1] used to evaluate neonatal status, is a sum of ratings (0, 1 or 2) of five clinical signs at one and five minutes of age: heart rate, respiration, reflex irritability, muscle tone, and color. The final score ranges from 0 to 10, corresponding to the 'worst' and the 'best' possible conditions. Low 5-minute Apgar score is associated with neonatal mortality,[2] and increased risks of mental retardation,[3] cerebral palsy,[3,4] and epilepsy.[3,5,6] Data on the association between Apgar score and changes in cognitive function are limited and conflicting,[7,8] and, to our knowledge, no epidemiologic study has examined the association between 5-minute Apgar score and long-term sensory acuity.

Studies have indicated that impairment of adult cognitive function may be associated with adverse perinatal conditions,[8-12] including poor growth,[9,12,13] breech presentation,[10] birth defects,[14] or maternal medication use.[15] One population-based study has shown an association between suboptimal fetal growth and reduced visual and hearing acuity.[16] Although it is a non-specific clinical shorthand for a newborn's condition, a low Apgar score reflects poor prenatal development and labor complications.[3] We aimed to examine the association of low Apgar score at 5-minutes with cognitive function and sensory acuity in young adulthood and to potentially identify susceptible subgroups defined by characteristics of mother, neonate, and labor course.

Methods

Population

We examined records of men who were born in 1978-1983 and at draft age resided in the northern Danish region under the jurisdiction of the Fifth Conscription District. At

the time of their mandatory registration with the draft board, the conscripts complete a health questionnaire, in which they report chronic health problems that may preclude military service. The draft board verifies such reports with health care providers, and exempts men who are deemed ineligible from further examination. Whenever the diagnosis is uncertain, draftees are referred to medical specialists for evaluation and those with severe chronic diseases are excused from the draft (hereafter "non-presenters"). The reasons for being exempt are recorded in the conscripts' files according to the International Classification of Diseases 10th revision.[17] The draft suitability of the remaining men (hereafter "examinees") is determined by a routine draft board evaluation, consisting of a medical evaluation and an intelligence test. We computerized data from the paper-based draft records and linked them with the corresponding records in the Danish Medical Birth Registry (MBR).[18] The unambiguous linkage is possible via a personal registration number, which is assigned to Danish residents at birth and is used in all administrative and health databases.[19]

Birth Registry data

Since 1973 the MBR electronically tracks all births in Denmark.[18] The data, entered from birth certificates filled out by attending midwives, contain information on maternal and newborn characteristics and labor course. From the MBR we extracted relevant variables recorded in the registry during the study period: maternal age at delivery, marital status, parity, and newborns' gestational age, fetal presentation, mode of delivery, and five-minute Apgar score. We considered only singleton births in this study.

Draft board records

Cognitive function

The Danish draft board has been using the Boerge Prien test (Danish, *Børge Priens Prøve*, BPP) since 1957. It is a 78-item group intelligence test with four subscales (letter matrices, verbal analogies, number series, and geometric figures) and a single score recorded as the number of correctly answered items.[20] The correlation coefficient (*r*) between BPP and the standard Full Scale WAIS (Wechsler Adult Intelligence Scale[21]) is 0.82. Psychology studies have shown patterns of BPP similar to those seen with traditional IQ tests.[22,23] We examined distributions (mean, quartiles) of the BPP score also examined a dichotomous 'low BPP' outcome (defined as a score below <37, or in the bottom quartile).

Sensory acuity

Uncorrected visual acuity was evaluated, for each eye, according to Snellen's method.[24] As in the earlier study with these data,[16] we defined impaired vision as an acuity worse than 6/9. Unilateral and bilateral visual impairment were examined separately. Hearing function was assessed using a screening value of 20 decibels, in 20-dB increments, and converted to a six-point scale of 0 to 5, from worst to best function, and recorded as a single variable averaged for both ears. Earlier study with these data used all values below 5 to indicate impaired hearing.[16] We excluded men who wore contact lenses from the analyses of visual impairment.[16]

Neurologic outcome among the non-presenters

Since cognitive and sensory functions among the non-presenters were not evaluated, we examined among them the occurrence of a neurologic outcome, which we defined as having a record of either a neurologic (ICD-10 codes G) or a mental/behavioral (ICD-10 codes F) disorder in the draft file.

Data analysis

We examined the 5-minute Apgar score in categories <7, 7-9, and 10 (reference).We examined all neurologic outcomes according to 5-minute Apgar score alone and in subgroups defined by prenatal characteristics recorded in the birth file: maternal marital status (married, unmarried), age at delivery (≤20, 21-35, >35 years); parity (0, 1, ≥2); mode of delivery (unassisted vaginal, forceps or vacuum-assisted [instrument-assisted], cesarean section), fetal presentation (cephalic, non-cephalic), gestational age (preterm or <37 weeks, term or 37-41 weeks, postterm or ≥42 weeks) and being small for gestational age (SGA), defined as having birth weight in the bottom decile of all infants born in the same gestational week.

In order to see whether any observed association between Apgar score and the neurologic outcomes was explained by known characteristics, we modeled each dichotomous outcome as a function of all above-mentioned variables, using log-binomial regression (the GENMOD procedure in SAS).[25]

Missing data

Although data on most variables were complete, gestational age was missing in 17% of birth records. To avoid loss of both observed and unobserved data in the regression

analyses, we used multiple imputation[26] to fill in the missing values by predicting them from the observed data. The imputation model included all study variables plus birth year. We created five imputed datasets and averaged the results for each outcome into a single estimate.

Results

There were 19 843 men born as singletons from 1978 to 1983 in the conscription district who were subject to being drafted in the district in 1996-2003. Twelve percent (2 374) of them were exempt from the draft board examination for health reasons (non-presenters). The non-presenters were more likely to have been born preterm, small for gestational age, and with a five-minute Apgar scores <7 (Table 5).

The median age of the 17 469 examinees was 19 years (interquartile range, 19-20 years, range, 18-24 years). One hundred and six (0.6%) examinees and 30 (1.3%) non-presenters had a five-minute Apgar score <7. Compared with draftees with a 5-minute Apgar score of 10, those with a score <7 were more likely to have a mother who was nulliparous or who was younger than 21 or older than 35 years at the time of their birth. They were also more likely to have a non-cephalic presentation, to be delivered with instrumental or surgical assistance, and to be born preterm or small for gestational age (Table 6).

Prevalence of low BPP, prevalence of impaired sensory acuity among the examinees and prevalence of a neurologic outcome among the non-presenters all decreased with increasing 5-minute Apgar score (Table 7).

Among the examinees, 6.2% had unilateral visual impairment, 10.9% had bilateral visual impairment, and 27.4% had hearing impairment. Prevalence of all sensory outcomes showed an inverse association with the 5-minute Apgar score. Stronger associations were seen for draftees born to mothers of high parity or young age.

Twenty-one percent (492/2 374) of the non-presenters were exempt with a mental/behavioral or neurologic disorder. The two most frequently recorded diagnoses were epilepsy (88/492, 18%) and developmental disorder of scholastic skills (56/492, 11%). Prevalence of the neurologic outcome increased with decreasing 5-minute Apgar score. Of all eligible men (examinees and non-presenters combined), unfit for military service were 45% of those with 5-minute Apgar score of 0-6; 40% of those with scores of 7-9 and 36% of those with the score of 10. Table 8 shows crude prevalence ratios associated with 5-minute Apgar scores and prevalence ratios obtained from regression models that included Apgar score and the other perinatal characteristics. After accounting for other characteristics, the prevalence ratios for all outcomes tended to decrease slightly. Results of complete data analysis (done without imputation, not shown) did not differ materially from those in Table 8.

Discussion

In this large cohort of male draftees, increasing prevalence of low cognitive function, impaired sensory acuity, and of severe neurologic disorder were associated with decreasing 5-minute Apgar score. The association of Apgar score with cognitive and hearing impairment was more pronounced in subgroups defined by maternal high parity and young age. After taking into account measured perinatal characteristics, the observed

association of 5-minute Apgar scores with the neurologic tended to decrease, but it did not disappear. The likelihood of being unfit for the military service likewise increased with decreasing Apgar score.

As far as we know, only two studies to date have examined the association between a low Apgar score and cognitive function.[7,8] Seidman and colleagues reported no association between the 5-minute Apgar score and mean intelligence quotient (IQ) score based on the examination of 1 942 Israeli draftees.[7] Lawlor and colleagues reported a -1.64-point (95% CI: -3.7 points to 0.4 points) mean difference in a standard (mean=100, SD=15) IQ test score at age 14 among 3 794 persons.[8] To examine comparability of those results with ours, we transformed the BPP score variable to the same distribution and calculated means according to the 5-minute Apgar score. We found the mean differences of –2.57 points (95%CI: -5.44 to 0.29) and –1.00 point (95% CI: -1.95 to –0.03) associated with Apgar score categories <7 and 7-9 each compared with the maximum score. The more pronounced mean difference could be explained by more restrictive definitions of a low Apgar score (<7 vs. <8) and the reference group (10 vs. 8-10) in our study. Both earlier studies used <8 to define low Apgar score. Under this definition, the majority of the scores in the group are likely to be 7 and they influence the results the most, masking any possible associations with lower scores. By using the cutoff of <7, we conformed to the clinical definition and reduced potential misclassification of the Apgar score, while allowing for a reasonable sample size in the low-Apgar group.

The observed association of 5-minute Apgar score with neurologic outcomes in our study likely reflects many heterogeneous underlying mechanisms, both social and biologic.

Low Apgar scores among babies of young mothers may be a consequence of poor birth outcome and prognosis associated with socioeconomic instability, low education, stress, absence of partner (in our cohort, mothers who were 20 year or younger were nearly three times more likely to be unmarried than mothers aged 36 years or older).

Being clinical shorthand, non-specific to any particular condition (e.g., asphyxia), the Apgar score is generally a poor predictor of long-term neurologic morbidity. Still, persisting association between the 5-minute Apgar score and neurologic outcomes after taking into consideration other perinatal variables supports the hypothesis of Apgar score correlating with unobserved antenatal causes of neurologic morbidity present at birth. Such causes could include, for example, silent intrauterine infections causing fetal inflammatory response, which could ultimately damage brain tissue.[27] Unlike infection-induced preterm labor, which is observed, brain damage triggered by a silent intrauterine infection may manifest at birth only as a low Apgar score. Postnatal events, which we did not examine (eg, early cerebral trauma), may also cause neurologic impairment.[28] In some newborns a low Apgar score may signal an in increased susceptibility to traumatic injury causing impaired cognitive and sensory function.

We conducted the largest study to date, with prospective, routine data collection, of the association between low 5-minute Apgar score and mild neurologic morbidity among conscripts. Still, our results, particularly those in subgroups are based on few events and must therefore be interpreted with caution. One must also be aware of multiple comparisons potentially leading to spurious associations.

Apgar score measurements in the electronic birth file are subject to inevitable data

entry errors, and, according to one small study, Apgar scores may have a high inter-rater variability.[29] Nor can one rule out a biased representation of the actual cognitive function by BPP test scores. For example, it is not clear how motivated potential draftees are to perform well on this test. (For this reason we avoided comparing mean BPP scores, and examined entire distributions instead).

The modest associations reported here are far from being compelling indicators of any intense association between Apgar score and neurologic damage. Nevertheless, in the context of Apgar score's association with severe neurologic diseases, shown in recent studies (references 3-6), our findings are consistent with the hypothesis that certain biologic indicators of adult neurologic function are present at birth and that these indicators are at least indirectly measurable even with a crude index such as the Apgar score.

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Table 5. Selected maternal and perinatal characteristics of examinees and non-presenters

Characteristics	Examinees (N=17469)	Non-presenters	
		All (N=2374)	Exempt with a record or a neurologic condition* (N=492)
Mother younger than 20 years	1626 (9.3%)	255 (10.7%)	60 (12.2%)
Mother unmarried	5755 (32.9%)	752 (31.6%)	189 (38.4%)
Parity of 2 or more	3298 (18.9%)	481 (20.3%)	111 (22.6%)
Preterm birth (<37 weeks)	610 (3.5%)	120 (5.1%)	37 (7.5%)
Small for gestational age	1441 (8.2%)	233 (9.8%)	61 (12.4%)
Cesarean delivery	1761 (10.1%)	278 (11.7%)	65 (13.2%)
Apgar score at 5 minutes <7	106 (0.6%)	30 (1.3%)	13 (2.6%)

* International Classification of Diseases (10^{th} revision) codes F and G

Table 6. Perinatal characteristics of the 17 461 examinees according to five-minute Apgar score

	Five-minute Apgar score		
	<7	**7-9**	**10**
	N=106	N=992	N=16 117
Mother unmarried	45 (42.5%)	364 (36.7%)	5271 (32.7%)
Mother's parity			
0	62 (58.5%)	507 (51.1%)	6879 (42.7%)
1	22 (20.8%)	324 (32.7%)	6180 (38.3%)
≥2	22 (20.8%)	161 (16.2%)	3058 (19.0%)
Mother's age at delivery			
≤20 years	10 (9.4%)	102 (10.3%)	1495 (9.3%)
21-35 years	89 (84.0%)	852 (85.9%)	13990 (86.8%)
36-46 years	7 (6.6%)	38 (3.8%)	632 (3.9%)
Non-cephalic presentation	17 (16.3%)	96 (9.9%)	771 (4.8%)
Delivery by an instrument	27 (25.5%)	200 (20.2%)	1466 (9.1%)
Delivery by Cesarean section	28 (26.4%)	200 (20.2%)	1495 (9.3%)
Preterm birth (<37 weeks)	22 (24.2%)	108 (12.7%)	462 (3.5%)
Postterm birth (≥42 weeks)	12 (13.2%)	90 (10.6%)	1168 (8.7%)
Small for gestational age	14 (15.4%)	111 (13.2%)	1292 (9.7%)

Missing data: gestational age 2988 (17%); birth presentation 237 (1.4%); five-minute Apgar score 246 (1.4%); birth weight 137 (0.8%). Percentages may not round up to 100 due to rounding

Table 7. Prevalence of neurologic outcomes among Danish draftees (%) according to 5-minute Apgar score and selected birth characteristics

Characteristic		Examinees					Non-presenters	
	Apgar at 5 min	N	BPP score <37	Unilaterally impaired vision*	Bilaterally impaired vision*	Impaired hearing	N	Neurologic outcome
Overall	<7	106	29.2	9.5	13.7	34.3	30	43.3
	7-9	992	24.6	7.2	10.9	27.0	151	29.8
	10	16117	22.1	6.1	10.8	27.4	2151	19.8
Mother's civil status								
Married	<7	61	27.9	9.1	16.4	29.5	17	52.9
	7-9	628	23.1	7.5	10.9	28.0	99	27.3
	10	10846	20.5	6.0	10.6	27.0	1479	17.7
Unmarried	<7	45	31.1	10.0‡	10.0	40.9	13	30.8‡
	7-9	364	27.2	6.7	11.0	25.3	52	34.6
	10	5271	25.5	6.3	11.2	28.1	672	24.4
Mother's parity								
0	<7	62	29.0	8.9	14.3	29.5	20	50.0
	7-9	507	20.1	6.5	10.4	24.7	63	31.8

	10	1431	20.8	6.1	11.5	26.4	905	20.3
1	<7	22	22.7	5.0‡	10.0‡	31.8	7	28.6‡
	7-9	324	29.3	7.4	13.1	31.4	51	23.5
	10	6180	21.9	5.9	10.3	27.7	815	18.2
≥2	<7	22	36.4	15.8‡	15.8‡	50.0	3	33.3‡
	7-9	161	29.2	9.1	8.4	25.2	37	35.1
	10	3058	25.5	6.3	10.4	28.9	431	21.8
Mother's age at delivery								
≤20 years	<7	10	60.0	22.2‡	0.0	50.0	4	25.0‡
	7-9	102	35.3	7.3	8.3	36.6	17	35.3
	10	1495	32.4	5.6	9.9	29.3	229	22.7
21-35 years	<7	89	24.7	7.6	13.9	32.9	26	46.2
	7-9	852	23.5	7.3	10.7	25.6	121	28.1
	10	13990	21.1	6.1	10.8	27.2	1838	19.3
>35 years	<7	7	42.9‡	14.3‡	28.6‡	28.6	0	--
	7-9	38	21.0	5.6‡	22.2	31.6	13	38.5
	10	632	19.6	7.8	13.6	26.7	84	23.8
Fetal presentation at birth								
Cephalic	<7	87	25.6	7.5	13.8	33.7	24	41.7

	7-9	884	24.8	7.3	10.2	27.1	142	28.9
	10	15177	22.1	6.1	10.8	27.5	1995	19.8
Non-cephalic	<7	17	29.4	23.1‡	15.4‡	32.3	6	50.0‡
	7-9	97	22.7	5.4	18.3	29.5	8	50.0‡
	10	771	23.3	6.0	12.3	26.1	131	17.6
Mode of delivery								
Spontaneous	<7	51	23.5	6.4‡	8.5‡	35.3	18	33.3
	7-9	592	26.5	7.7	11.2	28.7	89	25.8
	10	13156	22.3	6.1	10.6	27.6	1731	19.9
Instrument	<7	27	40.7	11.5‡	15.4‡	33.3	6	50.0‡
	7-9	200	19.0	7.0	8.6	24.2	28	21.4
	10	1466	18.8	6.3	10.4	28.0	190	20.0
Cesarean	<7	28	28.6	13.6‡	22.7	33.3	6	66.7‡
	7-9	200	24.5	5.7	12.5	25.0	34	47.1
	10	1495	23.8	6.2	12.8	24.7	230	18.7
Gestation								
Preterm (<37 weeks)	<7	22	36.4	15.8‡	10.5‡	33.3	6	50.0‡
	7-9	108	34.3	8.2	14.3	34.3	24	33.3
	10	462	24.0	8.0	10.3	25.4	81	24.7

Term (37-41 weeks)	<7	57	31.6	7.4‡	16.7	33.3	17	41.2
	7-9	651	21.9	7.4	11.0	25.0	88	26.1
	10	11738	21.8	6.0	10.7	27.1	1511	19.7
Postterm (≥42 weeks)	<7	12	16.7‡	18.2‡	0.0	33.3‡	2	50.0‡
	7-9	90	33.3	7.0	10.5	24.1	17	41.2
	10	1168	20.0	5.3	10.9	29.4	170	22.4
Size for dates								
SGA	<7	14	35.7	15.4‡	7.7‡	50.0	4	25.0‡
	7-9	111	36.0	7.5	14.0	20.2	18	44.4
	10	1292	28.0	5.7	12.4	26.7	206	24.3
AGA	<7	77	29.8	8.5	14.6	31.9	26	46.1
	7-9	729	23.1	7.1	10.7	28.0	131	28.2
	10	11990	21.0	6.1	10.7	27.5	1938	19.3

*Restricted to examinees not wearing contact lenses

†Defined, for non-presenters only, as a record of a neurologic disorder (ICD-10 codes F or G)

‡ Based on fewer than 5 events

Table 8. Prevalence of neurologic outcomes among Danish draftees (%) according to 5-minute Apgar score and selected birth characteristics

		Examinees		Non-presenters	
Five-minute Apgar score	Low BPP score	Unilateral visual impairment*	Bilateral visual impairment*	Hearing impairment	Neurologic outcome†
		Crude prevalence ratios			
<7 vs. 10	1.32 (0.98 to 1.78)	1.56 (0.83 to 2.91)	1.26 (0.76 to 2.10)	1.25 (0.96 to 1.63)	2.19 (1.44 to 3.32)
7-9 vs. 10	1.11 (0.98 to 1.25)	1.16 (0.90 to 1.50)	0.98 (0.80 to 1.20)	0.98 (0.88 to 1.10)	1.16 (1.04 to 1.29)
		Prevalence ratios after accounting for the perinatal characteristics			
<7 vs. 10	1.20 (0.88 to 1.63)	1.51 (0.80 to 2.83)	1.23 (0.74 to 2.05)	1.29 (0.98 to 1.69)	1.95 (1.28 to 2.96)
7-9 vs. 10	1.10 (0.98 to 1.23)	1.11 (0.87 to 1.41)	1.04 (0.86 to 1.25)	1.00 (0.9 to 1.12)	1.41 (1.10 to 1.82)

* Restricted to examinees not wearing contact lenses. † Defined, for non-presenters only, as a record of a neurologic disorder (ICD-10 codes F, G)

Figure 2. Box-and-whisker plots for BPP test scores by categories of five-minute Apgar score among Danish conscripts born in 1978-1983

The cross marks the median, and the borders of the *box* mark top and bottom quartiles. The *whiskers* extend from the quartiles to observations not farther than 1.5 times the interquartile range. Beyond the whiskers, extreme observations are plotted individually. Dashed line is drawn through the sample's median (BPP=44)

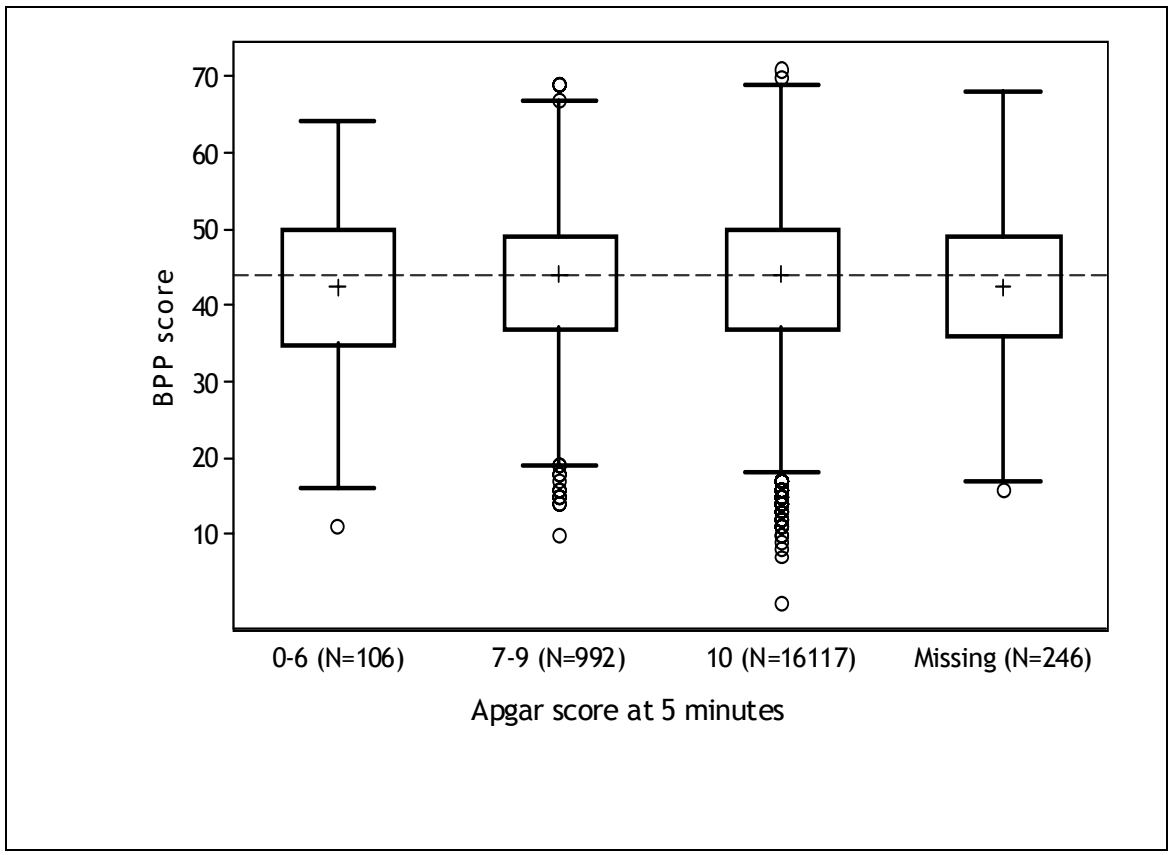
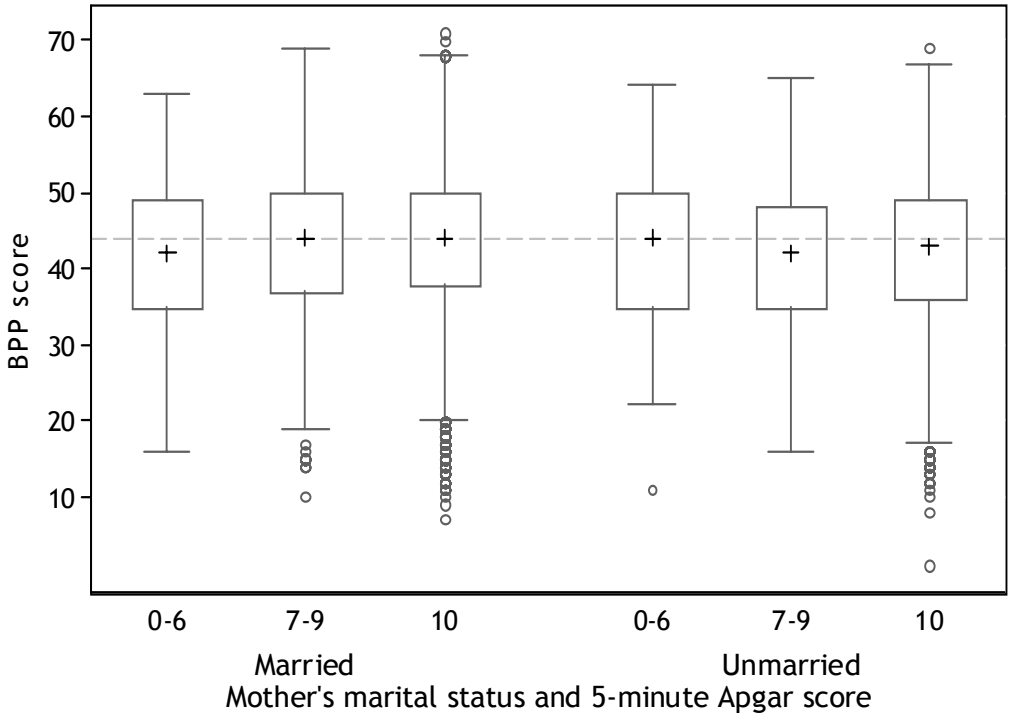
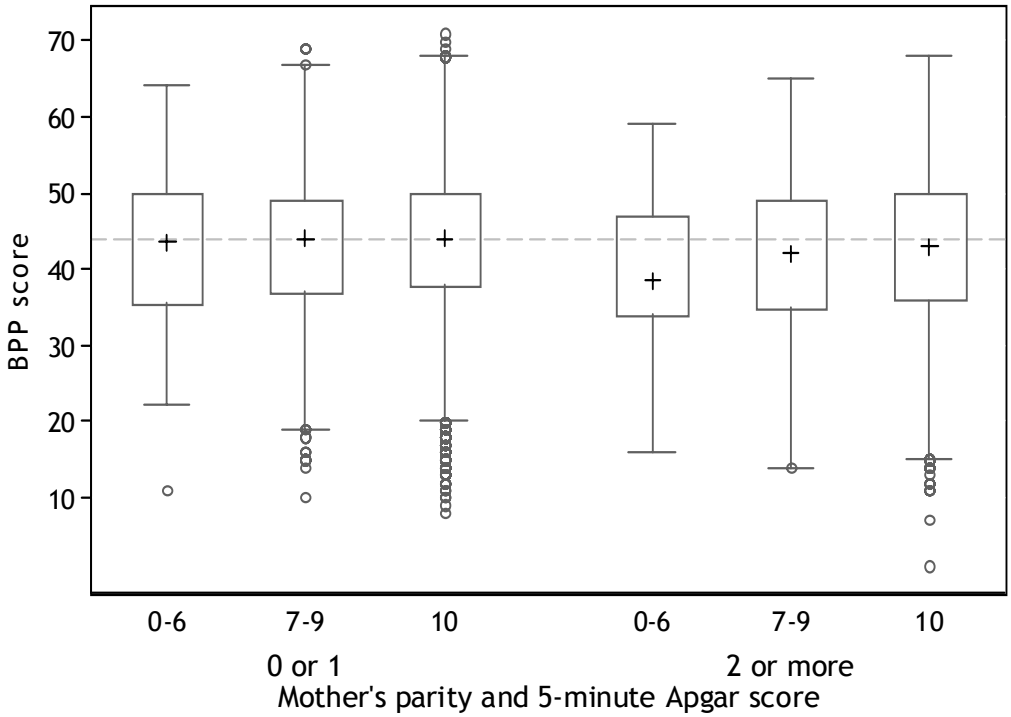


Figure 3. Box-and-whisker plots for BPP test scores by categories of five-minute Apgar score and other characteristics

Mother's marital status (a.); parity (b); age at delivery (c); mode of delivery (d); gestational age (e); and size for gestational age (f). Dashed line is drawn through the sample's median (BPP=44).

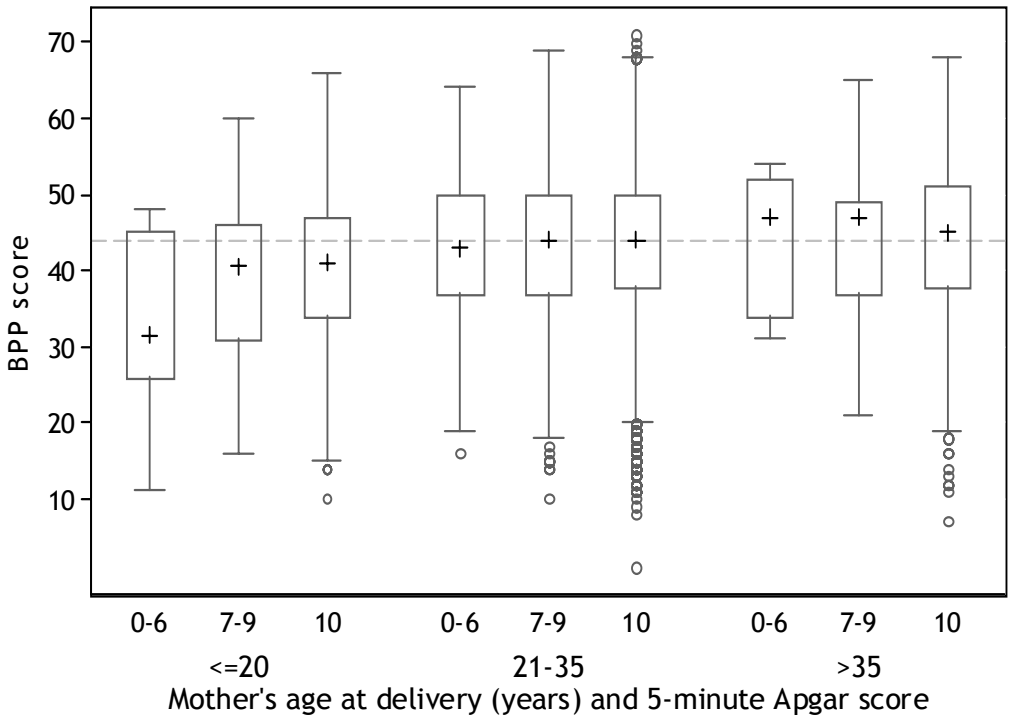


a.

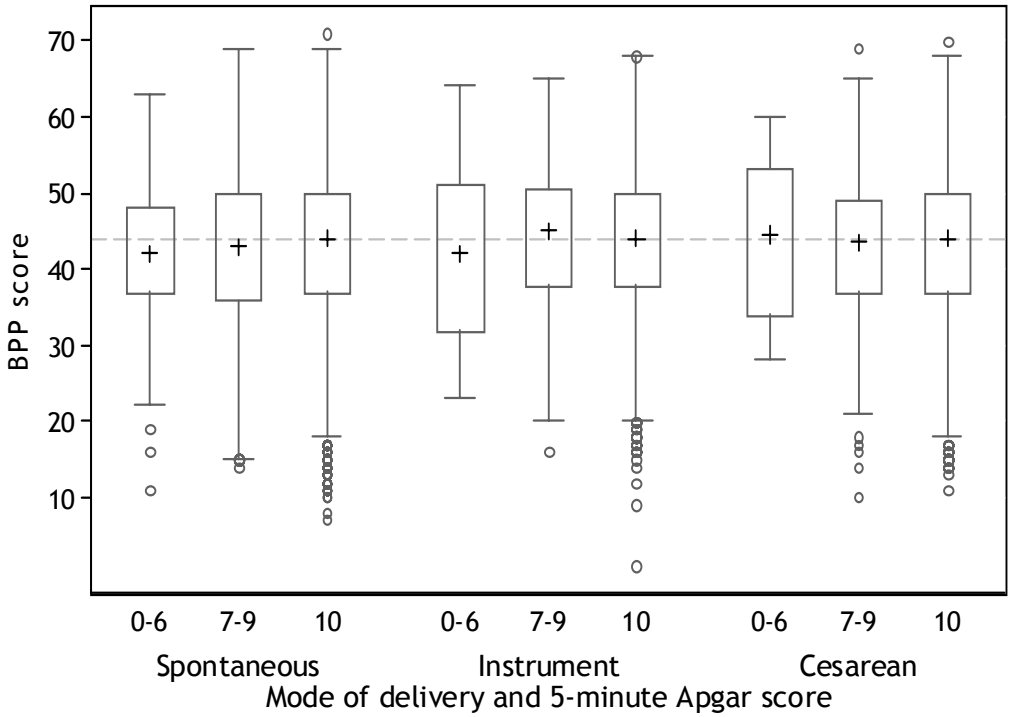

BPP score
70
60
50
40
30
20
10
0-6
7-9
10
0-6
7-9
10
0 or 1
2 or more
Mother's parity and 5-minute Apgar score

b

.

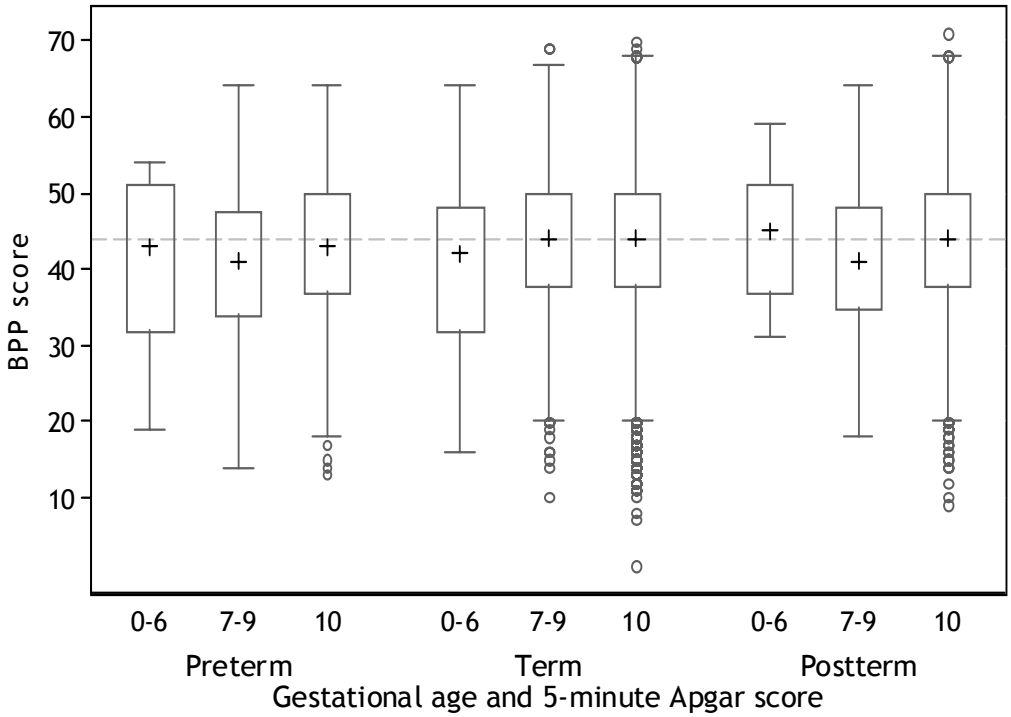

BPP score
70
60
50
40
30
20
10
0-6
7-9
10
0-6
7-9
10
0-6
7-9
10
<=20
21-35
>35
Mother's age at delivery (years) and 5-minute Apgar score

c.

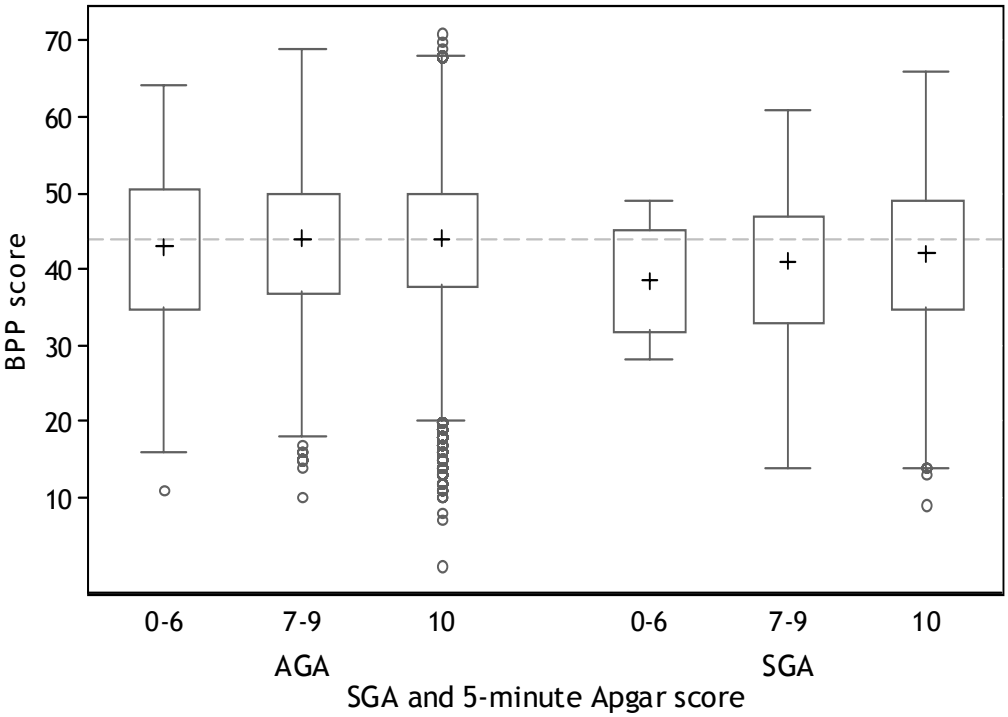

BPP score
70
60
50
40
30
20
10
0-6
7-9
10
Spontaneous
Instrument
Cesarean
Mode of delivery and 5-minute Apgar score

d

.


BPP score
70
60
50
40
30
20
10
0-6
7-9
10
Preterm
Term
Postterm
Gestational age and 5-minute Apgar score

e.


70
60
50
40
30
20
10
BPP score
0-6
7-9
10
0-6
7-9
10
AGA
SGA
SGA and 5-minute Apgar score

f.

POSTTERM DELIVERY AND RISK OF EPILEPSY IN CHILDHOOD

Abstract

OBJECTIVE. Postterm delivery is a risk factor for perinatal complications, some of which increase risk for neurologic morbidity. We aimed to examine the association between postterm delivery and risk for epilepsy in childhood.

METHODS. We conducted a cohort study of singleton children who were born in 3 Danish counties from 1980 to 2001. Birth registry data were linked with hospital records to identify cases of epilepsy in the first 12 years of life. We included children who were born at ≥39 gestational weeks and computed crude, age-specific, and birth weight standardized incidence rates of epilepsy. We estimated adjusted incidence rate ratios according to mode of delivery by Poisson regression.

RESULTS. Among the 277435 nonpreterm births, 32557 were at ≥42 weeks, including 3396 at ≥43 weeks. Nearly one fourth of the 2805 epilepsy cases occurred in the first year of life. In that period, birth weight standardized incidence rate ratios for epilepsy were 1.3 for birth at 42 weeks and 2.0 for birth at ≥43 weeks, compared with birth at 39 to 41 weeks. Among children who were delivered by cesarean section, incidence rate ratios adjusted for birth weight, presentation, malformations, and county were 1.4 for birth at 42 completed weeks and 4.9 for birth at 43 weeks, compared with term vaginal births. There was a similar tendency among children who were delivered with the assistance of instruments. We found

no evidence for the association between postterm delivery and risk for epilepsy beyond the first year of life.

CONCLUSIONS. Prolonged gestation is a risk factor for early epilepsy; the added increase in risk for instrument-assisted and cesarean deliveries could be attributable to factors that are related to both birth complications and epilepsy.

Introduction

Postterm delivery, defined as delivery at or after 42 completed weeks (294 days) after the first day of the last menstrual period[1] (LMP), occurs with a reported prevalence of 2% to 14% of deliveries.[2] (Other terms, such as "postdate," and "postmature" sometimes have been used interchangeably with "postterm," but "postterm" currently is preferred.[2]) Predictors of postterm delivery include anencephaly, hormonal disturbances, nulliparity, young maternal age, and history of prolonged pregnancy.[3,4] The biological mechanisms that lead to postterm delivery are poorly understood and remain "a challenge for epidemiologic research."[2]

Children who are born postterm have higher perinatal mortality than term children.[5–10] Population-based studies in Denmark[6] and Sweden[7] report a 25% increase in risks for stillbirth and neonatal death in infants who are born after 42 weeks of gestation, with mortality increase being even greater when postterm infants are growth restricted,[7,8,11] malformed,[7] or first-born.[10]

The risks for labor complications, including induction, instrument or cesarean delivery,[2,3,6,12] and macrosomia,[2,3,6] all are increased after a prolonged pregnancy. For the newborn, there is a greater risk for a low Apgar score,[6,13] distress,[5,14] deteriorating cardiac function,[15] meconium aspiration,[2,6,7] asphyxia,[6] infection,[3,6] and NICU admission.[2,3] Reported neurologic complications include peripheral nerve paralysis,[6] trauma of central nervous system (CNS),[6] and convulsions.[6,7] Previously, we[13] and others[16] found an association between depressed Apgar score and risk for childhood epilepsy; we noted that postterm delivery exacerbated the increase in risk.

Most studies of postterm delivery have focused on perinatal outcomes.[3,6–8] Few studies have addressed long-term neurologic morbidity,[17,18] and, to our knowledge, no formal epidemiologic study has examined the association between postterm delivery and risk for childhood epilepsy. Epilepsy is the most common serious neurologic disorder, with a heterogeneous and poorly understood etiology. The perinatal period is thought to play an important role in causing some cases of the disease.[19,20] We examined the association between postterm delivery and the risk for epilepsy during the first 12 years of life.

Methods

We used electronic medical databases to conduct a cohort study within the Danish counties of Aarhus, North Jutland, and Viborg. From the Danish National Birth Registry,[21,22] we retrieved records of all live singleton births that occurred between January 1, 1980, and December 31, 2001. In Denmark, nearly all children with epilepsy are hospitalized at initial diagnosis. To identify cases of epilepsy, we used computerized local hospital discharge registries, which record, for each hospital admission, up to 20 discharge diagnoses and, starting in 1994, also contain data on outpatient and emergency visits. The discharge diagnoses were coded according to the *International Classification of Diseases, Eighth Revision* (ICD-8) through the end of 1993 and according to the ICD-10 thereafter. The codes for epilepsy were 345.xx in ICD-8 and G40.0 to G41.9 in ICD-10. Clinically, epilepsy is diagnosed according to the International League Against Epilepsy guidelines, which define epilepsy as either ≥2 unprovoked seizure episodes, relevant electroencephalography findings, or both.[23] We defined the outcome of epilepsy as the first-time hospitalization or outpatient visit recorded in the hospital discharge registry with a diagnosis of epilepsy

within the first 12 years of life. The date of diagnosis was considered to be the date of epilepsy onset.

Data on emigration and death were retrieved from the Danish Civil Registration System, which after being created in 1968, covers the entire Danish population and is updated daily.[24,25] We linked records from the different registries by the civil registration number, which is a unique administrative identifier that is assigned at birth to Danish residents.

In the birth registry, gestational age was recorded in completed weeks through 1996 and in fractional weeks (based on days) thereafter. We defined postterm delivery, according to the World Health Organization guidelines, as delivery at ≥42 completed weeks of gestation.[1] We calculated incidence rates of epilepsy and 95% confidence intervals (CI) by gestational age. For the main analysis, we included nonpreterm (≥39 weeks) births and computed crude and birth weight standardized incidence rates of epilepsy (using the person-time distribution in 500-g birth weight categories of the study cohort as the standard). We then calculated incidence rates of epilepsy in categories of completed gestational weeks (39-41, 42, and ≥43) according to the recorded age of onset. Within each gestational age category, we used Poisson regression[26] to obtain fitted values of age-specific incidence rates, with age in completed years, age squared, and the square root of age as predictors. We created an indicator variable for each combination of mode of delivery (unassisted vaginal, forceps/vacuum-assisted, and cesarean) and gestational age category and used them in a Poisson model to examine variation of the gestational age-epilepsy incidence rate ratio (IRR) by mode of delivery.

Because idiopathic epilepsies tend to have genetic determinants and therefore may be unrelated to prolonged gestation,[19,20,27] we did a subanalysis restricting the case definition to epilepsy cases that were not listed as idiopathic (censored when ICD-10 codes were G40.0 or G40.3). We did this subanalysis in the cohort of children who were born in 1994-2001, because their diagnoses were recorded using the ICD-10, in which idiopathic epilepsies are listed specifically.

There was little confounding by any of the variables that were available for analysis. For the adjusted analyses, we retained fetal presentation as a potential risk factor for neurologic morbidity, county of birth as a marker for coding practices, and an indicator for birth defects diagnosed at birth because having such a birth defect was a strong predictor of epilepsy in our data and affected the magnitude and the precision of IRR estimates for forceps-assisted deliveries. (In addition, a recent study found maternal use of antiepileptic medication to be a risk factor for birth defects, making the latter a correlate of maternal epilepsy.[28]) Birth weight may be a correlate of traits that causally link prolonged gestation and risk for epilepsy (e.g., malnutrition in overly small infants, trauma as a result of large size in overly heavy infants), which is an argument against using birth weight for adjustment in this analysis. Removing birth weight from any of the analyses had little effect on the results. We retained birth weight for the standardization and adjustment, because it may be a marker of antenatal hormonal or metabolic perturbations that may affect both the size and the susceptibility to disease.[29] Variables for infant's gender and birth order; confidence of the LMP; and mother's age, smoking, and cohabiting with the partner were not used in the final analytic models because in these data they were not associated with

epilepsy risk and their inclusion did not change the results. We analyzed the data with SAS 9.01 software (SAS Institute, Cary, NC) and used Episheet[30] to calculate standardized estimates.

Results

During the study period, 338633 single live births were recorded in the 3 counties. We excluded 336 (0.1%) records with missing gestational age. Among the remainder, 277435 (82%) births occurred at 39 completed weeks of gestation or later. Of these, 32557 (12%) infants were delivered postterm, including 3396 (1%) delivered at 43 weeks or later.

Compared with term newborns, postterm infants were less likely to weigh ≤2500 g and more likely weigh >4000 g, to undergo cesarean or instrument delivery, to be first born, or to have a 5-minute Apgar score <7. Compared with mothers who delivered at term, mothers who delivered postterm were somewhat more likely to cohabit with a partner and less likely to have smoked during pregnancy (Table 9).

Across the full range of gestational age, the crude incidence rate of epilepsy decreased with increasing gestational age through week 41, after which it increased again, although the precision of estimates was low at both extremes of gestational age distribution (Figure 4). Overall, 2805 epilepsy cases were recorded among the members of the cohort during the follow-up period. Regardless of gestational age, incidence rates of epilepsy were the greatest in the first year of life, with 657 (23%) of the cases recorded with the onset during this period (Table 10; Figure 5). In year 2 after birth, there were 357 (13%) cases; in year 3, there were 283 (10%); in year 4, there were 240 (8%); in year 5, there were 197 (7%); in year 6, there were 204 (7%); in year 7, there were 170 (6%); in year 8, there were 163 (6%); in

year 9, there were 157 (6%), in year 10, there were 158 (6%); in year 11, there were 117 (4%); and in year 12, there were 102 (4%). The first year of life was the period when the differences in the epilepsy rates according to gestational age were most pronounced (Figure 5). We therefore focused subsequent analysis on epilepsy that occurred before age 1.

Of the epilepsy cases with the recorded onset during the first year of life, the proportion of girls with the diagnosis was ~48% regardless of gestational age at birth. Table 11 shows crude and birth weight standardized incidence rates and rate ratios. The standardized IRR was 1.3 (95% CI: 1.0–1.7) for 42 completed weeks of gestation and 2.0 (95% CI: 1.2–3.5) for gestation of 43 weeks or longer.

The magnitude of the IRR varied according to delivery mode (Table 12). For children who were delivered vaginally without help of vacuum or forceps, postterm gestation of any length was associated with 1.3-fold increase in epilepsy risk in the first year of life. Among children who were born by cesarean section, delivery at 42 weeks was not related to an increase in risk beyond that associated with cesarean section itself, but delivery at 43 weeks or later was associated with a 3.5-fold increase in risk compared with term cesarean births and a nearly fivefold increase in risk compared with term unassisted vaginal births. For vacuum- or forceps-assisted deliveries, our point estimates showed a dose–response pattern, with longer postterm gestation conferring greater epilepsy risk. When mode of delivery was added as a covariate to the other variables that were used in the adjusted analysis, adjusted IRR was 1.3 (95% CI: 1.0–1.6) for birth at 42 weeks and 1.9 (95% CI: 1.1–3.1) for birth at 43 weeks onward. In this analysis, adjusted IRR were 1.4 (95% CI: 1.0–1.8) for cesarean delivery and 1.1 (95% CI: 0.8–1.4) for vacuum/forceps-assisted delivery,

compared with unassisted vaginal delivery.

Of the 202 epilepsy cases recorded in the first year of life among children who were born in 1994–2001, 36 (18%) were recorded as idiopathic. Rates of epilepsy excluding these cases (per 10 000) were 15 (95% CI: 12–17) for children who were born during weeks 39 to 41 of gestation and 23 (95% CI: 15–33) for children who were born at 42 weeks or later; crude rate ratio was 1.6 (95% CI: 1.0–2.3). An analysis of a "low-risk" subgroup (restricted to children with optimal birth weight for gestational age [between 10th and 90th percentiles], no malformation at birth, Apgar score >6 at 5 minutes, and vaginal delivery in cephalic presentation without assistance of forceps or vacuum) yielded IRR of 1.4 (95% CI: 0.9–1.9) for delivery at 42 completed weeks and 1.7 (95% CI: 0.6–3.7) for delivery at 43 weeks or later.

We were able to access data on labor induction for the small subset of the most recent (1997–2001) births in our study cohort. Restricting this subcohort to vaginal deliveries, we calculated incidence rates of epilepsy in the first year of life, according to labor induction and postterm delivery (Table 13). Although all of the confidence intervals overlap and the data are sparse, the point estimates suggest that the effect of prolonged gestation on the risk for epilepsy may be more pronounced in the absence of labor induction.

Discussion

In this large, population-based cohort study, we found delivery at ≥42 weeks of gestation to be associated with an increased risk for epilepsy in the first year of life. The magnitude of the risk increase depended on the duration of prolonged gestation. Little

evidence for an association in subsequent years lends support to the conjecture that perinatal causes and postterm delivery in particular play a greater role in determining early-life neurologic susceptibility. During the first year of life 42 (6%) of 657 children with epilepsy also had a diagnosis of cerebral palsy: 36 among term infants (incidence: 1.5 in 10 000) and 6 among infants who were born at 42 completed weeks (incidence: 2.0 in 10 000). These findings suggest that prolonged gestation may be a risk factor for other neurologic disability.

The overall prevalence of postterm deliveries did not change substantially with the year of birth in our cohort, but the prevalence of deliveries at 43 weeks or more decreased from ~2% in the 1980s to <0.5% in 2000–2001. Thus, over time, very late deliveries have accounted for a decreasing proportion of postterm births. This could be caused either by a true decrease of prevalence resulting from more routine labor induction before 43 weeks or by better pregnancy dating. We calculated IRRs for epilepsy in the first year of life in 3 strata of birth year (with comparable prevalence of delivery at 43+ weeks): 1980–1990, 1991–1993, and 1994–2001. The respective periods' IRRs were 1.0 (95% CI: 0.7–1.5), 1.3 (95% CI: 0.8–2.0), and 1.5 (95% CI: 1.0–2.2) for delivery at 42 completed weeks and 1.8 (95% CI: 0.9–3.2), 1.9 (95% CI: 0.5–5.1), and 2.0 (0.3–6.4) for delivery at 43 completed weeks or later. The slight upward trend of the point estimates is consistent with the conjecture of better pregnancy dating, resulting in diminished misclassification of gestational age over time.

Postterm delivery may precipitate or accelerate epilepsy through increasing risk for infectious, hypoxic, or mechanical injury to the developing brain. A potential causal mechanism for the observed association could involve intrauterine exposure to meconium,

occurring in up to 30% of postterm births.[31] Meconium passage is associated with impaired fetal oxygenation and may increase risk for fetal bacterial invasion, leading to inflammatory brain damage.[31,32] Prolonged pregnancy also is associated with up to a 33% decrease in amniotic fluid volume,[33,34] which can lead to fetal distress[15,34,35] and cause early CNS damage.

Increased likelihood of labor induction and instrument deliveries after prolonged pregnancy,[3] coupled with greater fetal size, set the stage for mechanical injuries during labor and delivery. Approximately 24% of deliveries that occur after the 42nd week of gestation in Denmark are induced.[6] Induced contractions may be forceful and prolonged, causing extended occlusion of the umbilical cord, reduced oxygenation, and fetal acidosis, all of which may contribute to neurologic damage.[36] Labor induction could be a confounder in this study if contraindications for labor induction, such as breech presentation or maternal severe hypertension, also were markers of a fetus's neurologic susceptibility.[37] At the same time, the analysis of the recent births with available induction data suggests that, at least for vaginal deliveries, the effect of prolonged gestation on the risk for epilepsy may be more pronounced when the labor is not induced.

In a study of singleton infants who weighed 2500 to 4000 g and were born in cephalic presentation to nulliparous mothers, Towner et al[38] found that birth that was assisted by vacuum or forceps, compared with unassisted vaginal birth, was associated with up to a threefold increased risk for cerebral hemorrhage and CNS depression and nearly a twofold increased risk for convulsions; the increase in risk was doubled or tripled when a failed vacuum extraction necessitated the use of forceps (which occurs in 9% to 14% of vacuum-assisted deliveries[39]). In our cohort, instrument delivery at term alone was

associated with only a slight increase in epilepsy risk, as was postterm delivery alone (Table 12). The 2 conditions together, however, were more likely to produce a more substantial increase in risk. This observation also is consistent with the current view that some cases of epilepsy are a result of accumulated CNS insults.[19,20] A limitation of our study is the inability to distinguish between emergency and elective cesarean sections and between forceps deliveries with and without attempted vacuum extraction.

Although until now, no study specifically assessed the association of prolonged gestation with epilepsy risk, large population-based studies in Nordic countries report an association between birth after week 42 and increased incidence of convulsions, which are symptoms of epilepsy.[19] A Danish study of ~110000 nonpreterm births found an adjusted relative risk for convulsions to be 1.4 (95% CI: 0.90- 2.1),[6] and in a Swedish study of >500000 nonpreterm births, the relative risk estimate for convulsions was 1.5 (95% CI: 1.2–2.0).[7] These estimates are similar to the birth weight standardized IRRs for epilepsy in our study.

Lack of detailed clinical data is a limitation of our study. For example, because ICD-8, which was used to code diagnoses through 1993, does not have a special code for infantile spasms, it is possible that this common early-life epilepsy type was underascertained for children who were born before 1994. (ICD-10, used from 1994 onward, lists infantile spasms under the heading G40.4, which was included in our case definition.) We noted that more than half of the epilepsy cases in the first year of life received a code of "unspecified" or "other," precluding valid inferences about distribution of epilepsy types on the basis of routine registration data. At the same time, the abbreviated nature of computerized records

may be only partially to blame for this drawback. As Korff and Nordli[40] noted in their 2006 review, many infants with epilepsy "do not fit in any of the currently used subcategories."

The validity of our results depends on accurate classification of gestational age. Postterm deliveries accounted for 9.1% of all births in our cohort. As reviewed by Shea et al,[2] studies that used combined early ultrasonography/LMP dating method place the prevalence of postterm delivery between 4% and 7%. From published tables of a Danish nationwide study, we back-calculated the prevalence of postterm deliveries in 1978–1993 to be ≈7.6% of all births.[6] Reported prevalence depends to a large extent on the definition of postterm (as many as 8 different definitions are cited in studies[2]). In our data, excluding children who were born with gestational age recorded at exactly 42 weeks reduced the prevalence to 2.3% of all births. We included week 42 in our definition of postterm in accordance with current guidelines. Increased risk for some outcomes has been reported for births as early as week 41 of gestation. The present definition, although undoubtedly subject to misclassification, is a compromise between over- and underascertainment of true postterm deliveries.

Prevalence of postterm delivery also depends on the method of gestational age determination and on variations in menstrual cycle length (the LMP-based gestational age dating assumes a 28-day menstrual cycle[1]). Midwives in Denmark record gestational age in completed weeks after LMP and, whenever necessary, make corrections after ultrasound examination.[41] The use of ultrasound in Denmark increased during our study period.[41] Nevertheless, the prevalence of postterm births in our cohort decreased only slightly over time, suggesting that increased use of ultrasound did not affect pregnancy dating

profoundly, at least at the upper extreme of gestational age distribution. Although a good general agreement has been reported between LMP- and ultrasound-based gestation estimation,[42] misclassification tends to occur at the extremes of the distribution. According to some studies, LMP-based dating tends to overestimate the prevalence of postterm delivery by ~9%,[43] whereas ultrasound dating, in some cases, may underestimate the relative risk for postterm delivery by >10%.[44]

Nondifferential misclassification of gestational age would be expected to cause attenuation of relative effects.[45] Also, the incidence rate of epilepsy in this study is slightly higher than other reports from developed countries,[19] which may reflect overascertainment of epilepsy in electronic discharge records.[13] Any errors regarding the ascertainment of epilepsy are likely to be independent of the child's gestational age and therefore also would result in underestimation of the effect. The relative effect could be overestimated if misclassification of febrile seizures as epilepsy were more likely to occur among children who are born postterm. At the same time, children with febrile seizures are more likely to develop some types of epilepsy later in life.[46]

Conclusion

We offer evidence that prolonged gestation is a risk factor for epilepsy in the first year of life.

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Table 9. Newborn and maternal characteristics and postterm delivery

Characteristic	Gestational age		
	39-41 weeks N=244 878	42 weeks N=29 161	≥ 43 weeks N=3 396
Birth weight			
≤ 2500 g	2450 (1%)	96 (0.3%)	17 (0.5%)
2501-3000 g	23532 (10%)	1464 (5%)	175 (5%)
3001-3500 g	84416 (34%)	6861 (23%)	778 (23%)
3501-4000 g	91318 (37%)	11559 (40%)	1318 (39%)
4001-4500 g	35433 (14%)	6978 (24%)	783 (23%)
4501-5000 g	6359 (3%)	1859 (6%)	279 (8%)
> 5000 g	807 (0.3%)	280 (1%)	40 (1%)
Missing	563 (0.2%)	57 (0.2%)	2 (0.2%)
Mode of delivery			
Unassisted vaginal	206947 (84%)	22527 (77%)	2432 (72%)
Vacuum-assisted	18448 (7%)	3353 (11%)	462 (13%)
Forceps-assisted	1338 (0.5%)	191 (0.6%)	15 (0.4%)
Caesarean	18145 (7%)	3090 (10%)	487 (14%)
Fetal presentation			
Cephalic	230291 (94%)	27643 (95%)	3251 (96%)
Breech	6658 (3%)	387 (1%)	36 (1%)
Other	3324 (1%)	582 (2%)	63 (2%)

Missing	4605 (2%)	549 (2%)	46 (1%)
Boy	124036 (51%)	14941 (51%)	1777 (52%)
Apgar score <7 at 5 minutes	1588 (0.6%)	290 (1%)	49 (1%)
Birth defect at birth	12992 (5%)	1666 (6%)	227 (7%)
Firstborn	105418 (43%)	14269 (49%)	1685 (50%)
Mother's age at delivery			
< 20 years	8198 (3%)	1078 (4%)	168 (5%)
21-25 years	57095 (23%)	7060 (24%)	1010 (30%)
26-30 years	99801 (41%)	11787 (40%)	1297 (38%)
31-35 years	60333 (25%)	7071 (24%)	716 (21%)
36-40 years	17252 (7%)	1927 (7%)	188 (5%)
> 40 years	2063 (0.8%)	215 (0.7%)	13 (0.4%)
Mother is unsure of LMP*	30567 (12%)	3866 (13%)	628 (18%)
Mother smoked in pregnancy†	33057 (25%)	3561 (23%)	244 (24%)
Mother not living with a partner†	10438 (8%)	1202 (8%)	72 (7%)

* LMP=last menstrual period

† Data available on children born after 1990 (N=147 656)

Table 10. Crude incidence rates, rate ratios and rate differences for epilepsy according to gestational age

	Gestational age, completed weeks			
	39-41 N=244 848	42 N=29 161	≥ 43 N=3 396	Total N=277 435
Epilepsy diagnosed during the first 12 years of life				
Cases	2429	325	51	2805
Person-years	2 311 920	273 316	36 826	2 622 059
Crude incidence rate, per 10 000 PY	10	12	14	11
Crude IRR (95% CI)	1.0	1.1 (1.0 – 1.3)	1.3 (1.0 – 1.7)	
Epilepsy diagnosed during the first year of life				
Cases	560	82	15	657
Person-years	243 329	28 959	3 368	275 656
Crude incidence rate, per 10 000 PY	23	28	44	24
Crude IRR (95% CI)	1.0	1.2 (1.0 – 1.5)	1.9 (1.1 – 3.2)	

*IRR incidence rate ratio; CI confidence interval; PY person-years

Table 11. Occurrence of epilepsy in the first year of life by birth weight and gestational age

	Gestational age, completed weeks		
	39-41	42	≥ 43
Birth weight	Cases/person-years (incidence rate per 10 000)		
≤ 2500 g	17/2381* (71)	0/92 (0)	1/15 (667)
2501-3000 g	65/23351 (28)	9/1443 (62)	1/173 (58)
3001-3500 g	186/83914 (22)	21/6807 (31)	2/771 (26)
3501-4000 g	195/90836 (21)	28/11499 (24)	6/1312 (46)
4001-4500 g	73/32563 (21)	21/6935 (30)	4/777 (51)
4501-5000 g	16/6325 (25)	2/1848 (11)	1/278 (36)
>5000 g	2/804 (25)	1/279 (36)	0/40 (0)
Standardized incidence rate (per 10 000)	22	30	46
Standardized IRR (95% CI)	1.0	1.3 (1.0 – 1.7)	2.0 (1.2 –3.5)

* IRR incidence rate ratio; CI confidence interval

Table 12. Postterm delivery and epilepsy during the first year of life: adjusted* incidence rate ratios (95% confidence intervals), stratified by mode of delivery

	Gestational age					
	39-41 weeks		42 weeks		≥ 43 weeks	
Mode of delivery	Cases	IRR (95% CI)	Cases	IRR (95% CI)	Cases	IRR (95% CI)
Unassisted vaginal	452	1.0	63	1.3 (1.0 – 1.7)	7	1.3 (0.6 – 2.6)
Vacuum/forceps-assisted	50	1.1 (0.8 – 1.5)	10	1.3 (0.7 – 2.4)	3	2.9 (0.7 – 7.7)
Caesarean	58	1.3 (1.0 – 1.8)	9	1.4 (0.7 – 2.6)	5	4.9 (1.7 – 10.7)

* Adjusted for birth weight, county of birth, fetal presentation, and presence of birth defects detected at birth

Table 13. Incidence rates of epilepsy in the first year of life, according to induction and length of gestation, among children born vaginally in 1997-2003

Vaginal delivery	Births	Cases	Incidence rate (95% CI), per 10 000
Non-induced			
Term	45,696	66	14 (11 – 18)
Postterm	3,776	8	21 (10 – 42)
Induced			
Term	2,747	6	22 (10 – 48)
Postterm	1,763	3	17 (<1 – 50)

Figure 4. Crude incidence rate of epilepsy (cases per 10 000 person-years), according to completed gestation

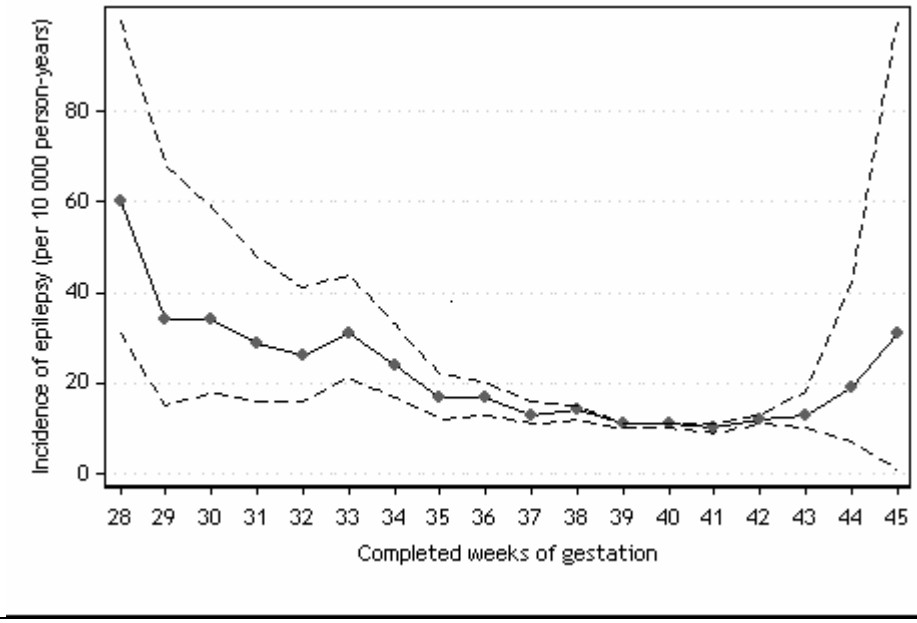
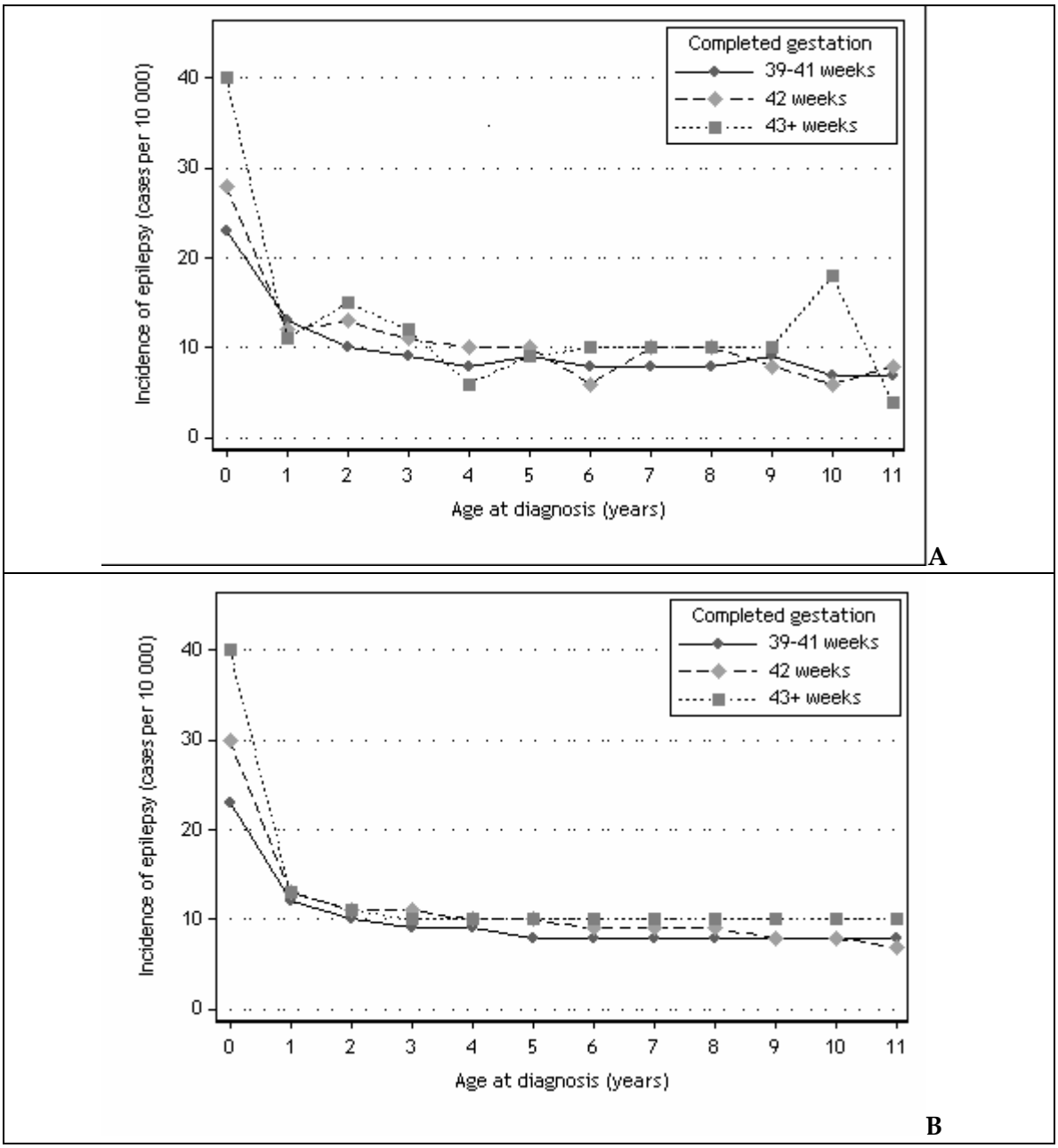


Figure 5. Age-specific incidence rates of epilepsy: observed (A) and fitted (B) by Poisson model



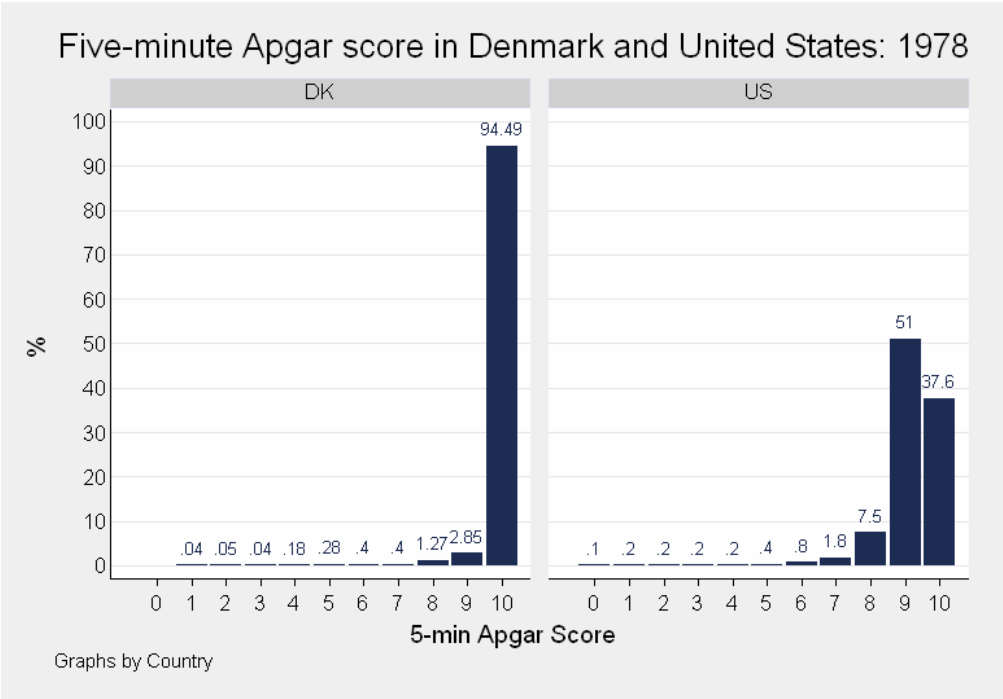
THESIS DISCUSSION

The three studies have examined associations between events and conditions at birth and long-term risk of neurologic morbidity. The first two studies, examined the association of a five-minute Apgar score<7 with severe (epilepsy, Study 1) and mild (mild cognitive impairment, Study 2) neurologic disability. Both studies provided evidence for an association. A low Apgar score alone is a poor predictor of long- or short-term neurologic disability. This finding is not surprising, because, for example, signs resulting in *higher* Apgar score (such as high heart rate and strong muscle tone) may also be symptoms of hypoxic-ischemic encephalopathy.[1] Still, the described associations point to potential occult biologic causes of the examined outcomes.*

There is evidence that practice of Apgar score assignment varies among centers and among countries. As shown in Panel 5, most infants receive the score of 9 in the United States and the score of 10 in Denmark at 5 minutes. The prevalence of depressed (<7) scores is lower in Denmark than in the United States. These data indicate systematic differences in the way medical staff is trained to assign Apgar scores, which may affect the apparent magnitude of any association between neurologic morbidity and 5-minute Apgar score, if infants' neurologic prospects depend on these particular differences in categorization.

* A recent study originating from the renewed interest in Apgar score has shown that an association between a low score and advanced paternal age[2]

Panel 5. Five-minute Apgar scores in Denmark and in the United States[3,4]



Within three months of publication of Study 1, Sun and colleagues published, in Epidemiology, a paper that was remarkably similar, including identical topic, same years of birth cohort, and same analysis (eg, Poisson regression).[5] Whereas we only had data on a single county, Sun and colleagues gained access to the Danish nationwide data (>1.5 million births) and used up to 22 years of follow-up (Study 1 of this thesis used 12 years). The large study size enabled Sun and colleagues to obtain more stable estimates of age-specific effects; to analyze finer categories of the Apgar score; and to evaluate the effect of the difference between the scores at 1 and 5 minutes. On the other hand, unlike Sun and colleagues, we estimated absolute effects (risk differences) associated with low Apgar scores. The average incidence of epilepsy reported by Sun et al. was higher than we reported in Study 1 (92 vs. 70 per 100 000 person-years), and somewhat higher than rates reported elsewhere,[6] probably because they included outpatient cases, while we focused on

hospitalizations. Their study and study 1 of this thesis reached similar conclusions and can be seen as complementary.

The last study showed that postterm delivery conferred an increased risk of epilepsy, which was limited to the epilepsies diagnosed before the first birthday. Unlike Apgar score, which is an artificial screening instrument, based on rating of largely non-specific clinical signs, postterm delivery is a biologic condition. Susceptibility to neurologic damage conferred by postterm delivery could derive, first, from fetus's exposure to hazards of prolonged intrauterine stay, and second, from increased risk of birth injury due to large size. Furthermore, protracted gestation in some women may indicate risk factors conferred by inadequate prenatal care, although it is not clear whether cases of postterm delivery can be at always detected in women whose pregnancy has not been regularly evaluated (since the woman may not remember her last menstrual period date). Studies validating LMP-against ultrasound-based dating suggest that the most important 'risk factor' for postterm delivery may be incorrect dating. Mothers incorrectly deemed postterm may become subjected to unnecessary measures to hasten delivery (cesarean section, labor induction), which themselves may increase a risk factor for adverse birth outcome and neurologic disability. Thus, via different pathways, both 'true' and 'perceived' postterm deliveries may be associated with adverse health outcomes.

One observation common to all three studies in this thesis is that the increases in the risks of long-term neurologic outcomes (epilepsy in studies 1 and 3 and impaired cognitive function in study 2) associated with the main exposure under study (Apgar score or postterm delivery) are greater when these exposures co-occur with delivery by forceps or

vacuum. Although instrument-assisted delivery is considered generally safe, in a small group of infants, it may result in mechanical or hypoxic injury (by becoming entangled with the umbilical cord[7]). Unfortunately, in all studies the estimates for this subgroup are based on few cases and are therefore imprecise. Because this obstetric characteristic is potentially modifiable, a larger study addressing risk factors in instrument-delivered babies would be important.

The strengths and limitations of each study in this dissertation are discussed in the individual manuscripts. Here I would like to briefly mention the overall experience of working with registry data and the associated peculiarities and caveats. Routine registry data offer unique opportunities to assemble large unselected cohorts and to conduct rapid retrospective cohort studies that include decades of follow-up. Rare conditions, such as epilepsy and postterm delivery, can be examined in a single study, in a cohort setting – an impossible task for a 'traditional' cohort study involving prospective enrollment and follow-up of subjects. Very important, high quality of Danish registry data in many areas has been demonstrated.

Yet, using registry data for research is not without caveats. First, both quality and substance of available data are time-varying characteristics. For example, partner status and maternal smoking became reportable to the Medical Birth Registry only in 1991, which precluded full evaluation of these potentially pertinent variables in this thesis's studies. Outpatient visits are only included from 1995, which, for epilepsy, could mean loss of milder cases. The Hospital Discharge Registry switched disease coding, in 1994, from the ICD-8 to the ICD-10. ICD-8 lists merely seven general diagnostic types of epilepsy, while

ICD-10 offers seven slightly different categories (some of which were absent in ICD-8), with 3 to 5 sub-diagnoses within each. This reflects the both the dynamics of data availability and development of knowledge about this condition.

Second, although dealing with vast unselected population-based datasets buffers the (inexperienced) investigator from making gross errors, the amount of 'informative data' – in particular, the exposed cases (eg, those with low Apgar score and epilepsy) can be small, making inferences more precarious. While in a 'traditional' study it may be possible to validate the entire case series or to re-contact a subject to resolve discrepancies, with nationwide registry data, it is hard to do so, because special approval would be required to contact subjects.

Finally, no analysis in this thesis or in the published literature takes into account within-family correlations, and therefore study results underestimate the variance of the findings to an unknown extent. In the future, it would be interesting to repeat some of the analyses in this thesis while taking into account correlations between children born to the same parents.

THESIS CONCLUSION AND PERSPECTIVES

The findings of the three studies of this thesis are consistent with the notion that some pathways of neurologic disability originate in antenatal and perinatal periods. Though all studies indicated increased risks associated with the examined exposures, the absolute increases in risk were small. The findings are also reassuring to the extent that they

suggest some developmental plasticity: if some environmentally modifiable factors can cause neurologic impairment, modification of these factors and others should be able to prevent it.

The studies in this thesis suggest the importance of perinatal and potentially prenatal period in determining long-term neurologic disability. Many involved mechanisms remain unexplored; though some studies indicate that silent infections or metabolic perturbations in utero may affect developing brain, large conclusive studies are lacking, and Danish administrative sources, with their data on blood samples and prescriptions, offer unique opportunities for further exploration.

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