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Effects of neonatal hyperbilirubinemia in cognitive performance in adulthood.

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Master's Thesis

Psychology

Faculty of Medicine

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ABSTRACT

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Tiivistelmä - Referat – Abstract

Objectives – Neonatal hyperbilirubinemia (HB), also referred to as neonatal jaundice, can alter child's neurodevelopment, and thus significantly increase infant's risk for severe neurological disability. Although the majority of neonatal HB cases benign, there are several cases where bilirubin levels grow alarmingly and remain elevated, eventually causing permanent physical harm and frequently altering the development of central nervous system. Research on the long-term effects of HB has been lacking: the follow-ups have been relative short, and there are not many studies focusing on how neonatal HB might influence neurocognition in later adulthood (> 30 year of age). The aim of this study is to further investigate the association between neonatal HB and later cognitive performance in adulthood by using data from over 40-year-long Finnish follow-up study.

Methods – In a longitudinal prospective study, data were collected from 125 subject who had experienced neonatal HB and from 77 controls. Cognitive performance was assessed at age of 40 by using various previously validated methods designed to assess executive function and attention, memory, verbal functions, and visuo-perceptual functions. Four factors were formed for neuropsychological variables: Cognitive flexibility, Visual memory and perception, Verbal memory, and Reading. In addition, all subjects had performed WAIS-IV assessments. Data from these assessments were used to create four new factors – Verbal comprehension, Working Memory, Perceptual Reasoning, and Processing Speed – reflecting different cognitive areas. Also, Full-Scale Intelligence Quotient (FSIQ) was included. Linear regression analyses were used to assess the relation between HB-classification and neuropsychological variables. Differences between the groups were further studied by pair-wise comparisons using t-test, after which Mann–Whitney-U test was used to take into account moderate to highly skewed distributions of the variables. Effects of different HB levels on later neurocognition was studied by using linear regression, where sex, mother's age at birth, and mother's education level were controlled.

Results – Neonatal HB was associated with slower performance in Cognitive Flexibility, and with lower performance in Perceptual Reasoning and in FSIQ. Highest measured neonatal bilirubin levels within HB group had a linear effect on Verbal Comprehension at age of 40; however, the effect was not found in other cognitive domains.

Conclusions – Neonatal HB has effect on performance in FSIQ at age of 40 years. In addition, it was associated with both poorer Perceptual Reasoning and slower Cognitive Flexibility. Results might be due to perceptual reasoning's high vulnerability to neuronal damage and to difficulty of compensating perceptual biological limitations with learning. Since the measured neonatal bilirubin levels within HB group was associated only with lower performance in Verbal Reasoning in this study, it could be concluded that after reaching the inclusion criteria the excess level of bilirubin was no longer significant influence on severity of the outcome.

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bilirubinemia, neonatal jaundice, longitudinal study, follow-up, neurocognition in adulthood

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Tiivistelmä - Referat – Abstract

Tutkimuksen tavoite – Syntymän aikaisen hyperbilirubinemian (HB), joka tunnetaan myös vastasyntyneen keltaisuutena, on osoitettu aikaisemmissa tutkimuksissa olevan yhteydessä muutoksiin lapsen hermostollisessa kehityksessä, ja siten merkittävästi lisäävän lapsen riskiä myöhemmin sairastua neurologisiin sairauksiin. Suurin osa vastasyntyneiden hyperbilirubinemia-tapauksista ovat harmittomia, mutta jossain tapauksissa bilirubiinin tasot nousevat nopeasti ja pysyvät korkeina pitkään, mikä saattaa lopulta aiheuttaa pysyviä fysiologisia vaurioita sekä muutoksia keskushermostossa. Tutkimukset HB:n pitkittäisvaikutuksista ovat olleet vähäisiä sekä puutteellisia. Seurantatutkimukset ovat jääneet suhteellisen lyhyiksi, eikä toistaiseksi ole tehty juurikaan tutkimuksia siitä, miten syntymän aikainen HB saattaa vaikuttaa neurokognitioon myöhemmällä aikuisiällä. Tämän tutkimuksen tavoitteena on tutkia syntymän aikaisen HB:n yhteyttä kognitiiviseen suoriutumiseen 40-vuoden iässä.

Metodit – Prospektiivisessä pitkittäistutkimuksessa aineisto kerättiin 125 henkilöltä, joilla oli todettu HB vastasyntyneenä, sekä 77 verrokilta. Kognitiivinen suoriutuminen arvioitiin 40-vuoden iässä käyttämällä useita aikaisemmin validoituja menetelmiä, jotka mittasivat toiminnan- ja tarkkaavaisuudenohjausta, muistia, verbaalista suoriutumista sekä visuaalista hahmottamista. Testitulosten perusteella (WAIS-IV-testisarjan tuloksia lukuun ottamatta) muodostettiin neljä neuropsykologista muuttujaa: kognitiivinen joustavuus, visuaalinen muisti ja hahmottaminen, verbaalinen muisti sekä lukeminen. Tämän lisäksi WAIS-IV-testisarjan tuloksista muodostettiin toiset neljä faktoria, jotka noudattivat testisarjan taustalla olevaa teoriaa: kielellinen ymmärtäminen, prosessointinopeus, visuaalinen päättely sekä työmuisti. Lisäksi analyyseihin otettiin mukaan WAIS-IV-testien perusteella laskettu kokonaisälykkyysosamäärä (FSIQ). HB-ryhmän ja kontrolliryhmän välisiä eroja kognitiivisessa suoriutumisessa tutkittiin lineaarisilla regressioanalyyseillä, joissa kontrolloitiin henkilön sukupuoli, äidin ikä syntymähetkellä sekä äidin koulutus. Tämän lisäksi eroja tarkasteltiin t-testin avulla, ja koska neljän muuttujan jakauma oli selkeästi vino (> 5 tai < -5) pyrittiin vinoudesta johtuvaa mahdollista harhaa vähentämään suorittamalla Mann-Whitney-U-testi. Lisäksi tutkittiin mitattujen bilirubinemia-tasojen korkeuden vaikutusta myöhempään kognitioon HB-ryhmän sisällä lineaarisen regression avulla, kontrolloiden äidin iän, äidin koulutuksen ja tutkittavan sukupuolen vaikutus.

Tulokset – Syntymänaikainen HB oli yhteydessä hitaampaan suoriutumiseen kognitiivisessa joustavuudessa ja heikompaan suoriutumiseen visuaalisessa päättelyssä sekä alhaisempiin pisteisiin kokonaisälykkyysosamäärässä. HB-ryhmäläisten korkein mitattu bilirubiini-arvo ennusti alhaisempaa suoriutumista kielellisessä ymmärtämisessä 40-vuotiaana; vaikutusta ei kuitenkaan löytynyt muilla kognition osa-alueilla.

Pohdinta – Syntymänaikainen hyperbilirubinemia ennusti kognitiivista suoriutumista kokonaisuutena aikuisuudessa. HB oli kuitenkin yhteydessä spesifimpiin kognition osiin, kuten heikompaan visuaaliseen päättelyyn ja hitaampaan kognitiiviseen joustavuuteen. Visuaalisen kyvykkyyden uskotaan pohjautuvaan melko vahvasti synnynnäisiin, biologispohjaisiin kykyihin ja hermoverkon toimintaan. Tästä syystä visuaalinen kyvykkyys on mahdollisesti haavoittuvaisempi HB:n aiheuttamille hermoston vaurioille, eikä sitä voida kompensoida mm. myöhemmän elämänaikaisen opettelun avuin yhtä hyvin kuin esimerkiksi verbaalista kyvykkyyttä. Sisäänottokriteereistä johtuen kaikkien HB ryhmäläisten bilirubinemian tasot olivat melko korkeat. Voi olla, että tästä syystä suurin osa ryhmäläisistä kärsi hyperbilirubinemian aiheuttamista kognitiivisista seurauksista, eikä rajan ylittäneiden tasojen välisillä eroilla ollut enää suurta lineaarista vaikutusta kognitiivisten heikentymien vakavuuteen.

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1. Introduction

Neonatal hyperbilirubinemia (HB), the cause of neonatal jaundice, can significantly increase infants' risk for severe neurological disability and death when severe (Ip, Chung, Kulig et al., 2004). Although the majority of neonatal HB cases are mild and the infants recover fully, there are several cases where bilirubin levels grow alarmingly and remain elevated, eventually causing permanent physical harm and damaging the development of central nervous system (Ip, Chung, Kulig et al., 2004; Mitra & Rennie, 2017). This condition occurs not only in developing countries with emerging medical systems, but also in highly developed Westernized countries that have unequal or lacking healthcare systems in place (Sgro et al., 2006). Indeed, severe neonatal HB is being reported all around the world in otherwise healthy term infants (Kaplan et al., 2011), and different levels of HB – mild to moderate to severe – have been estimated to affect as many as 60% of neonates (Brits et al., 2018). Neonatal HB is currently the most common reason for readmission to hospital in otherwise healthy term infants, although, in some cases it has been argued, that the risk factors could have been identified before discharge (Mitra & Rennie, 2017; Sgro et al., 2006).

Neonatal HB is caused by infants' inability to process bilirubin fast enough. Neonates' immature liver cannot properly metabolize foetal haemoglobin, which leads to an accumulation of bilirubin in the body (Lauer & Spector, 2011). High levels of bilirubin might lead to lethargy, poor feeding, irreversible brain damage, and kernicterus of the infant (Brits et al., 2018; Kaplan et al., 2011). The pathogenesis of encephalopathy by unconjugated bilirubin has remained rather obscure, but there is some evidence indicating that it involves both oxidative stress and a passage of high levels of the pigment across the blood-brain barrier, which combined can lead to a damage of neuronal cells (Palmela et al., 2011). Long term effects include a range of subtle processing disorders with disturbances of visual-motor, auditory, speech, cognition, and language processes (Johnson & Bhutani, 2011). However, the manifestation of symptoms seems to depend on a number of aggerating factors, such as duration and severity of bilirubin exposure, perinatal-neonatal complications, altered bilirubin-albumin binding, prematurity, and individual vulnerability related to genetic, family, social and educational predilection, regardless of the cause of HB (Shapiro, 2003; Johnson & Bhutani, 2011).

1.1 Neonatal hyperbilirubinemia

Over half of the newborns seem to develop jaundice during the first few weeks after birth. Mild HB (85–270 μmol / l) peak from 3rd day 5th, after which in the majority of cases the bilirubin level return normal during a few weeks (Schwartz et al., 2011). Although jaundice is usually transient and harmless, severe jaundice (> 20mg/dl or > 340 μmol/l) is considered toxic for newborns and might lead into HB-related neurological damage (Lee et al., 2016; Porter & Dennis, 2002). Approximately 10% to 25% of infants will need to undergo phototherapy and exchange transfusion for HB in an attempt to prevent later adversities, such as acute bilirubin encephalopathy and kernicterus (Sarici et al., 2004). In addition, current treatment options for jaundice include chemotherapy, and vaccinations (Ullah, Rahman, & Hedayati, 2016). Increased vigilance to prevent these complications has led to HB becoming the most common cause of hospital readmission in westernized countries (Sgro et al., 2006; Kaplan et al., 2011).

Hyperbilirubinemia is generated by the immature conjugating capacity of the newborn infant's liver, leading to high collection of unconjugated bilirubin in the body. Bilirubin is generated when red blood cells degrade and release heme, which is first metabolized into biliverdin and then to bilirubin. This unconjugated bilirubin binds to albumin in the blood and is transported to hepatocytes for conjugation, thus allowing it to pass through the gastrointestinal tract. In neonates, the majority of conjugated bilirubin gets unconjugated in the gut, resulting in recirculation. In addition, neonates have high volume of red blood cells, and combined with slow conjugation system it results in excess unconjugated bilirubin, which often manifests as physiologic, non-pathologic jaundice (Lee et al., 2016).

Since the unconjugated form of bilirubin is lipid-soluble and can be deposited in the central nervous system, bilirubin unbound to albumin becomes neurotoxic when the level exceeds age-specific thresholds for tolerance (Yueh et al., 2017). Mild levels of unbound bilirubin results in apoptosis, while moderate-to-high levels lead into neuronal necrosis and damage especially basal ganglia and thalamus (Cayabyab & Rangasamy, 2019; Tsao et al., 2020). Therefore, moderate to severe levels of unconjugated bilirubin may lead to neurological damage including kernicterus, cerebellar injury with a decreased number of Purkinje cells, and disruption of multisensory feedback loop between cerebellum and cortical neurons, and

thus become major cause of death and disability (Lee et al., 2016; Cayabyab & Rangasamy, 2019).

1.2 Effects of HB in childhood

Neonatal HB seems to have a number of effects in early childhood. As an immediate effect, the infant might suffer from lethargy, poor feeding, irreversible brain damage, and in severe cases kernicterus (Brits et al., 2018; Kaplan et al., 2011). Infants often have also visible changes in skin color making them look yellowish, which is often the symptom that alarms the parents to bring the child back to the hospital.

Later long-term effects have also been investigated in longitudinal study, follow-up ranging from few months to decades. In their study of neonates with moderate to severe HB, Johnson and Butani (2011) discovered that high bilirubin levels perinatally were associated with a range of subtle processing disorders with disturbances of visuo-motor, auditory, speech, cognition, and language at ages 4 and 7 years. In their article, Johnson and Butani called these disturbances as symptoms of "the syndrome of bilirubin-induced neurologic dysfunction (BIND)." They proposed that it was essential to create better tools for assessing BIND specific domains of multisensory processing disorders, identified by psychometric, audiologic, speech, language and visuo-motor, and motor examination, to establish effective surveillance of infants at risk for the syndrome.

The studies on the long-term effect of HB have been mostly relatively short follow-ups, ranging up to school age. According to these studies, mild to moderate HB appears to remain relatively, if not completely, benign (Culley et al., 1970; Newman & Klebanoff, 2002; Ip, Lau, Chung, et al., 2004; Gamaleldin et al., 2011). However, there is still controversy concerning whether or not infants with moderate HB are at risk for neurodevelopmental disorders in later childhood or adulthood (Johnson & Bhutani, 2011; Koziol et al., 2013).

1.3 Effects of HB in adulthood

There are currently only a few studies that follow neonates with HB until adulthood, the longest ranging up to 30 years (Ebbesen et al., 2010). According to this study, neonatal HB does not appear to cause significant problems for later cognitive performance, nor does it

correlate with disorders, such as ADHD and Autism, even though they have been associated with neonatal HB in previous studies (Jangaard et al., 2008; Maimburg et al., 2010). These studies have been based on retrospective analysis of birth data during military drafting of conscripts and have typically relied heavily on IQ data, thus offering very limited outcome information (Nilsen et al., 1984; Seidman et al., 1991; Ebbesen et al., 2010).

According to a Danish national cohort study, neonates that had been exposed to HB had 56–88% greater risk of psychological development disorders, compared with participants not exposed to HB (Maimburg et al., 2010). Therefore, conclusions of HB being benign based on IQ tests might be inaccurate. There is some evidence of a link between neonatal HB and autism (Jangaard et al., 2008; Maimburg et al., 2010). In addition, an association between neonatal HB and neurodevelopmental syndromes, e.g., ADHD has been suggested (Jangaard et al., 2008), although the studies have failed to provide conclusive evidence (Kuzniewicz, Escobar & Newman, 2009). Unfortunately, there is little to no information on vocational and social outcomes of neonatal HB in adulthood, and the research on more subtle cognitive problems remain scant. Therefore, there is a need for more long term follow up studies up to later adulthood on the effects of neonatal HB.

Overall, the research on cognitive effects of HB has been sparse. Majority of studies involve rather short follow-up periods and limited assessment methods. In a Norwegian 18-year-follow-up study of 39 males, the mean intelligence scores between HB group and control group did not differ significantly; however, seven HB subjects with more severe hyperbilirubinemia had significantly low scores compared to the national average (Nilsen et al., 1984). In an Israeli study on cognitive performance at age of 17 (n = 1948) no linear link between neonatal HB and intelligence scores was found, although low intelligence scores were more frequent among males (but not females) who had had neonatal HB with serum bilirubin levels above 342 μmol/l (Seidman et al., 1991).

A more recent study was conducted on 463 Danish men (median age 18.8) in military drafting (Ebbesen et al., 2010). This study was retrospective, and the data on neonatal levels of HB was ascertained from hospital records. According to this study there was no association between HB levels and IQ scores. However, it could be criticized that the test methods were not sensitive enough to detect milder deficits in cognitive performance. In addition, there was a larger proportion of men that were determined to be unfit for military

service in the HB group. Also, only 6% of all HB cases in this study were exposed to bilirubin levels above 340 μmol/l (the cut-off value regarded significant).
To date, there is preliminary evidence suggesting that neonatal HB might be linked to decline in cognitive performance in later adulthood, however, results are often not significant. There is also a lot of controversy concerning the effects of moderate HB cases, although, there is stronger consensus that severe neonatal HB will lead to impaired cognitive performance in future.

1.4 Rationale of the present study

The aim of this study is to investigate the relation between neonatal hyperbilirubinemia and cognitive performance in adulthood and to seek answers for the following research questions:

1. Is there a link between neonatal hyperbilirubinemia and cognitive performance in adulthood?
2. Does this association occur in global performance or in specific areas of cognitive performance?
3. Is there a linear association with the severity of HB levels and cognitive performance?

Hypotheses within this research question include:

H1: The group with a history of neonatal HB shows poorer cognitive performance in later adulthood compared to the group with no neonatal HB.

H2: HB will affect different areas of cognitive performance in different ways.

H3: Higher levels of HB are linearly associated with lower cognitive performance.

2. Material and Methods

2.1 Participants

Participants were recruited in 1971–74 from a single maternity hospital in Helsinki, Finland. During the recruitment period there were 22,359 births in the hospital, out of which 1196 (5,4%) of infants had one or more predefined risk: APGAR score lower than 7 at 5 or 15 min (n = 372), birth weight under 2000 grams (n = 317), jaundice with exchange transfusion or bilirubin > 340 μmol/l (n = 368), severe respiratory difficulties necessitating external ventilation (n = 161), neurological symptoms (n = 195), maternal diabetes (n = 95), infant hypoglycemia (n = 104), and severe infection (n = 36). Neonates who died during early childhood or suffered from severe disabilities (incl. kernicterus) were excluded from the longitudinal follow up.

At the age of 40, the cohort was invited to a follow-up including neurological, neuropsychological and neuroradiological evaluation. Participants with hyperbilirubinemia were included for the present study. For inclusion, neonates needed to have two or more serum bilirubin values of 340 μmol/l (20 mg/100 ml). Children who had received blood exchange transfusion because of rapidly increasing serum bilirubin values were also included. Those with gestational age below 37 weeks, or birth weight below 2500 g, were excluded. In addition, participants who were later diagnosed with acquired neurological injury, alcohol abuse, or schizophrenia (e.g. problems that are likely to influence cognitive performance) were excluded. Two participants were found to have an early aqueduct stenosis in the MRI, but they were not excluded. Thirteen participants were lacking MRI. A total of 125 HB cases, out of which 51 were women, fulfilled the inclusion and exclusion criteria and provided full assessment information at the follow-up. All of these subjects were Caucasian and spoke Finnish.

The control subjects were recruited from the same birth cohort, born in the same hospital. The controls attended the same schools and had no perinatal risk factors. For the present study, controls were required to have gestational age at or above 37 weeks, birth weight at or above 2500 g and full assessment information from 9 years of age (n = 77, out of which 41 were women). One control subject was found to have an early aqueduct stenosis in the MRI but was not excluded. Six control subjects were lacking MRI. Ethical review has been

conducted over the course of the longitudinal study, and all participants gave their written consent to the study. The latest approval was obtained from the Ethical Review Board of the Helsinki and Uusimaa hospital district in 2013.

This cohort was studied previously in childhood (Michelsson, Lindahl, Helenius & Parre, 1988) and at the age of 30 (Hokkanen et al., 2014) to find out the relationship between neonatal hyperbilirubinemia and academic achievement and later self-reported neurobehavioural problems.

2.2 Methods and procedures

Neurocognitive performance was assessed at age of 40 by using multiple neuropsychological assessment methods. The assessments were carried out during a single visit mostly in an office in Helsinki, and single subjects were assessed at the department facilities in Jyväskylä. The neuropsychological evaluation session lasted for approximately three hours, which included one 15-minute break. Only tests analyzed in the current study are described below.

General intelligence level was assessed using seven subtests from Wechsler Adult Intelligence Scale IV: *Similarities, Vocabulary* (every second item)*, Information, Block Design, Matrix Reasoning, Digit Span, and Digit Symbol / Coding* (Wechsler, 2008). Raw and scaled scores from these subtests were used for analysis.

Executive functions and attention were assessed by methods including Trail Making Test (A & B) (Reitan, 1955), Word Fluency: semantic (animals, CERAD) and phonemic (words beginning with letter K) (Hänninen et al., 2010), and the Stroop: color naming & color-word naming (Stroop, 1935).

Memory was assessed by using Wechsler Memory scale III *(Word List I and II, Logical Memory (story A) I and II)* (Wechsler, 1997), Rey complex figure test immediate & delayed recall (Rey & Osterrieth, in Corwin & Bylsma, 1993), and Figure memory (CERAD) (Hänninen et al., 2010). Verbal functioning was assessed with Word and pseudoword reading (Nevala, Kairaluoma, Ahonen, Aro, & Holopainen, 2006), and Rapid alternating stimulus naming (Wolf, M. 1986). For assessment of visuo-perceptual functions participants were required to perform the Figure copy (CERAD) (Hänninen et al., 2010), and Rey complex figure test (copy) (Rey & Osterrieth, in Corwin & Bylsma, 1993).

The raw scores of the tests for executive, memory, verbal and visuo-perceptual functions were standardized over the whole data for the later analyses. Group performance was used as a reference value and combined scores were calculated for verbal reasoning, non-verbal reasoning, learning, long term memory, attention and reading speed. The feedback involved evaluations on a percentile scale illustrated as below 25%, 25-75% and above 75% performance levels.

2.3 Statistical analyses

Statistical analyses and data manipulations were performed using IBM SPSS Statistics Version 25.

Principal components analysis was conducted on the neuropsychological variables. Analyses were performed separately on the WAIS-IV-variables and neuropsychological variables related to executive, memory, verbal and visuo-perceptual functions. On both analysis rotation was conducted using Varimax with Kaiser Normalization. Rotation converged in 7 iterations for neuropsychological variables and 7 iterations for WAIS-variables. Results of Principal component analysis are presented in Tables 1 and 2. In addition to these variables, WAIS-IV Full Scale Intelligence Quotient (FSIQ) was included in the analyses.

Table 1. Rotated Component Matrix for neuropsychological variables related to executive, memory, verbal and visuo-perceptual functions. The components were named Cognitive flexibility (CF), Visual memory and perception (VMP), Verbal memory (VM) and Reading.

	Component			
	1 CF	2 VMP	3 VM	4 Reading
RAS2 time	**.698**	.120	-.073	-.185
STROOP naming time	**.685**	.058	-.138	-.168
STROOP interference time	**.678**	-.112	-.132	-.183
TMB time	**.647**	-.179	-.010	-.061
Rey-picture: copy time	**.572**	-.064	.050	.294
TMA time	**.560**	-.298	.059	.080
Fluency: phonemic	**-.455**	-.006	.275	.145
Rey-picture: delayed	-.128	**.836**	.202	-.153
Rey-picture: immediate	-.179	**.823**	.164	-.146
C-picture: delayed	-.004	**.662**	0.45	.214
Rey-picture: copy	.130	**.648**	.032	.134
C-picture: copy	.026	**.601**	.045	.169
WMS3 LM delayed	-.049	0.33	**.882**	.013
WMS3 LM immediate	-.089	.043	**.825**	-.024
WMS3 SS Immediate	-.113	.271	**.713**	.232
WMS3 SS Delayed	.053	.329	**.628**	.126
Word Fluency: Semantic	-.403	-.087	**.494**	.068
Reading un-word: time	.567	.095	-.053	**-.665**
Reading word: correct	-.124	.115	.207	**.634**
Reading time	.487	-.027	-.057	**-.623**

Extraction method: Principal Component Analysis.

Rotation Method: Varimax with Kaiser Normalization. Rotation converged in 7 iterations.

Table 2. Rotated Component Matrix for WAIS-IV variables

	Component			
Variables	1 Working Memory	2 Verbal Comprehension	3 Perceptual Reasoning	4 Processing Speed
Digit Span	**.965**	.487	.174	.157
DS Forward raw score	**.812**	.089	.220	-.059
DS Backward raw score	**.828**	.116	.047	. 238
DS Order raw score	**.672**	.172	.231	-.235
Similarities	.087	**.797**	.118	.155
Vocabulary	.134	**.778**	.065	.220
Information	.223	**.803**	.117	-.064
Matrix Reasoning	.259	.447	.320	-.070
Block Design	.131	.162	**.951**	.121
Block Design No time bonus (BNT)	.141	.151	**.943**	.106
Coding	.120	.181	.178	**.894**

Extraction method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization. Rotation converged in 7 iterations.

Before further analyses, the distribution of these factors was observed using frequency tables and visual representations (histograms), which revealed that four out of eight variables had moderate to highly skewed distribution (> 0.5 or < -0.5) including Cognitive Flexibility, Visual Memory and Perception, Reading, and Verbal Comprehension. It was also confirmed that there was no data missing.

First, independent samples t-tests were conducted to compare HB- and control groups in all variables, after which the Mann–Whitney-U test was conducted due to high skewness of many of the variables. Linear regression analyses were then used to assess the relation between HB-classification and neuropsychological variables taking confounding variables into account. For these analyses, the effects of sex, maternal age at the time of birth and mother's education level were included in model 1 and HB-classification was added in model 2. Linear regression was also used to further study the effects of the confounding variables on later neurocognition in HB and control groups separately.

Lastly, linear regression was used to study whether or not neurocognitive outcome at age of 40 could be predicted from the highest measured levels of HB at birth. For these analyses the effects of sex, maternal age at the time of birth and mother's education level were controlled as well.

Table 3. Sample Characteristics

	HB group		Control group	
Characteristics at Infancy	Mean (SD) or n (%)	Range	Mean (SD) or n (%)	Range
Gestational age (weeks)	38.7 (.22)	33–43	39.9 (.27)	37–42
Sex (boys)	74 (58.7%)		35 (44.9%)	
Maternal age at birth	25.5 (.22)	18–42	26.9 (.27)	18–40
Highest bilirubin level, µmol/l	380.3 (47.7)	213–470		
Cognitive performance at 9 years				
Verbal IQ	114.1 (.26)	76–138	118.7 (.23)	90–152
Performance IQ	117.5 (.26)	90–146	123.2 (.33)	94–150
General IQ	117.3 (.26)	86–143	122.9 (.33)	101–147
Diagnoses				
ADHD				
None	86 (71.1%)		68 (87.2%)	
Possible/Probable	25 (20.7%)		10 (12.8%)	
Diagnosed	10 (8.3%)		0 (0.0%)	
Socio-economic factors				
Education				
Highschool or lower level	88 (69.8%)		40 (51.3%)	
Undergraduate Degree	11 (8.7%)		14 (17.9%)	
Graduate Degree	27 (21.4%)		24 (30.8%)	
Mother's education				
Highschool or lower level	90 (78.3%)		58 (81.7%)	
Undergraduate Degree	12 (10.4%)		6 (8.5%)	
Graduate Degree	13 (11.3%)		7 (9.9%)	
Father's education				
Highschool or lower level	88 (80.7%)		51 (71.8%)	
Undergraduate Degree	6 (5.5%)		5 (7.0%)	
Graduate Degree	15 (13.8%)		15 (21.1%)	

Table 4. Descriptive of study variables and comparison between the groups using parametric (t-test) and non-parametric (Mann-Whitney) tests. Significant differences (p <.05) bolded.

	HB group				Controls				t-test		Mann-Whitney	
Study Variables	N	Mean	SD	Range	N	Mean	SD	Range	t	p	U	p
Neuropsychological Variables												
Cognitive Flexibility	123	.12	.01	-2.25– 3.95	74	-.26	.01	-1.78–1.79	-2.592	.077	3531	**.008**
Visual memory and perception	123	-.02	.95	-3.02–1.78	74	.14	1.04	-3.02–1.74	1.068	.577	4034	.182
Verbal Memory	123	-.08	.99	-2.72–2.20	74	.14	1.02	-1.90– 2.45	1.487	.508	4040	.187
Reading	123	.04	.93	-3.39–2.39	74	.08	.80	-3.20– 1.64	.357	.383	4305	.526
WAIS-IV Variables												
Verbal Comprehension	125	-.01	.92	-1.88–2.65	77	.07	1.14	-2.07–3.22	1.639	.383	4202	.130
Perceptual Reasoning	125	-.08	1.10	-3.39–1.64	77	.13	.94	-2.65–1.81	1.436	.215	4277	.184
Processing Speed	125	-.15	1.01	-2.28–2.19	77	.24	.93	-1.83–2.58	2.739	.425	3751	**.009**
Working Memory	125	-.08	1.05	-3.46–1.88	77	.15	.91	-1.83–1.65	.533	**.040**	4734	.846
FSIQ	125	106.48	17.04	45–140	77	113.42	15.64	79–146	-2.916	**.004**	3757	**.005**

WAIS-IV = Wechsler Adult Intelligence Scale IV, FSIQ = Full Scale Intelligence Quotient

3. Results

Demographic information on the study groups is given in Table 3. Group distributions of the factor scores of the neuropsychological variables and of the WAIS-IV variables are given in Table 4. T-tests indicated difference between groups only in Working Memory (p=.040) and in FSIQ (p=.004). However, results from Mann-Whitney test showed that there was a statistically significant difference between groups also in Cognitive flexibility (p=.008) and Perceptual Reasoning Index (p=.009. These results are presented in Table 4.

The results of all the linear regression models are shown in Table 5. HB classification was added in model 2 and Table 6 shows the coefficients and their significance in the regression. According to linear regression analyses on neuropsychological variables, HB classification was associated with Cognitive Flexibility (p=.027). In addition, the linear regression analyses result on WAIS-IV variables indicated an association between HB classification and Perceptual Reasoning (p = .048) as well as FSIQ (p=.016).

The confounding variables were studied further, and the full results are in given in the Appendix. Sex had an effect on performance in both HB group (p<.001) and control group (p=.028) with women performing better at tasks requiring Verbal Memory, but men scoring higher in Processing Speed in both HB group (p=001) and control group (p=.006). In addition, women were found to perform better in Visual Memory (p=.006) and Verbal Comprehension (p=.031) in control group (p=.004), but not in HB group. Also, women performed better in Perceptual Reasoning in HB group (p=.010) but not in control group, whereas men were found to perform better in Visual memory and perception in control group (p=.009), but not in HB group (see Appendix Table 1). Mother's age at the time of birth seemed to have a positive effect on performance in Reading (p=.011), Verbal Comprehension (p=.015), Processing Speed (p=.008) and Full-Scale Intelligence Quotient (p=.028) in HB group but not in control group (see Appendix Table 2). Maternal education seemed to have effect on Verbal Comprehension in HB group (p=.041) but not in control group (see Appendix table 3).

In a separate linear regression, the highest measured HB levels at birth were found to have negative relation to Verbal Comprehension (p =.032) but not on other variables (see Table 7).

Table 5. The results of the linear regression analyses. Model 1 included sex, maternal age at the time of birth and maternal education level. In Model 2, HB classification was added. Significant models (p <.05) are bolded.

	Model 1			Model 2		
	R^2	F	p	R^2	F	p
Neuropsychological Variables						
Cognitive flexibility	.017	.879	.453	.047	1.924	.109
Verbal memory	.128	7.632	**<.001**	.129	5.746	**<.001**
Visual memory and perception	.027	2.478	.063	.040	2.661	**.035**
Reading	.050	2.711	**.047**	.029	2.187	.073
WAIS-IV Variables						
Perceptual Reasoning	.048	**2.662**	**.050**	**.071**	**3.026**	**.019**
Verbal Comprehension	.083	4.822	**.003**	.095	3.438	**.003**
Processing Speed	.174	11.247	**<.001**	.179	8.639	**<.001**
Working Memory	.000	.006	.999	.003	.111	.978
FSIQ	.073	4.238	**.006**	.106	4.763	**.001**

Table 6. Association between neonatal hyperbilirubinemia and cognitive performance in adulthood. Linear regression analyses and unstandardized coefficients (B) of the HB-classification for the component scores when sex, maternal age at the time of birth and maternal education level were also included in the model.

	N	B	95% confidence interval for B	p
Neuropsychological Variables				
Cognitive flexibility	160	.367	.042–.691	**.027**
Verbal memory	160	-.070	-.374- .234	.650
Visual memory and perception	160	-.281	-.596 - .034	.080
Reading	160	.119	-.177 - .416	.428
WAIS-IV Variables				
Perceptual Reasoning	164	-.337	-.670– -.003	**.048**
Verbal Comprehension	164	-.220	-.517–.078	.147
Processing Speed	164	-.141	-.444–.162	.358
Working Memory	164	-.109	-.439–.221	.515
FSIQ	166	-6.240	-11.292 – -1.188	**.016**

Table 7. Association between bilirubin levels and later cognitive performance at 40 years. Linear regression analyses and unstandardized coefficients (B) of the bilirubin level and for the component scores when sex, maternal age at the time of birth and maternal education level were also included in the model.

	N	B	95% confidence interval for B	p
Neuropsychological Variables				
Cognitive flexibility	103	.002	-.003–.007	.352
Verbal memory	103	.000	-.005–.004	.830
Visual memory and perception	103	.002	-.002–.006	.387
Reading	103	-.002	-.007–.003	.476
WAIS-IV Variables				
Perceptual Reasoning	105	.002	-.003–.007	.383
Verbal Comprehension	105	-.005	-.009–.000	**.032**
Processing Speed	105	-.002	-.006–.003	.448
Working Memory	105	.001	-.003–.005	.741
FSIQ	106	-.056	-.125–.014	.116

4. Discussion

Neonatal hyperbilirubinemia has been associated with a number of later problems in health and development. However, studies on more subtle effect on neurocognition have been scant and not many follow-up studies investigating cognitive performance that extent into further adulthood exist. The aim of this study was to investigate if neonatal HB could be associated with cognitive performance in later adulthood (>40 years of age). The results demonstrate that although neonatal HB does not seem to have direct effect in all cognitive domains, it does seem to be associated with overall cognitive performance in adults even when several childhood variables are controlled for.

The adults with a history of neonatal hyperbilirubinemia had a lower FSIQ compared to the control group. This seems to be in controversy with previous studies, where the linear link has not been found in research focusing on performance in IQ tests (Maimburg et al., 2010; Nilsen et al., 1984; Seidman et al., 1991). The mean performance was on the average level but individuals with poor performance were observed in the HB group even when cases with severe disabilities had been excluded from follow-up in childhood. The difference between the cognitive performance in the HB group and the controls was reported already previously when the children with HB had been found to manage less well in neurological and psychological tests and had poorer school achievement than controls at the ages of 5 and 9 (Michelsson et al, 1988). Based on the current study, the association between HB group and FSIQ was not explained by sex, maternal age at birth or maternal education.

Based on the results of the study, HB seems to have an effect on some specific aspects of cognitive performance, including Cognitive Flexibility and Perceptual Reasoning. Link between neonatal hyperbilirubinemia and lower performance in Perceptual Reasoning could perhaps be expected since perceptual reasoning seems to be rather inherited ability with emphasis on depending on a number of biological factors and high neuronal functioning (Swagerman et al., 2016; Good, Hou, & Norcia, 2010). Therefore, compared to other cognitive domains, Perceptual Reasoning might be more vulnerable to the effects of neuronal loss which cannot be compensated with learning as efficiently as verbal skills. Neonatal hyperbilirubinemia was also associated with slower performance in Cognitive Flexibility. This difference is linked with lower Perceptual Reasoning since, although the effect of speed

was decreased by adding the scores without time bonuses, the Block Design task is still a timed task.

In terms of the confounding variables, differences between men and women were observed in Visual memory and perception and Verbal Comprehension in control groups, however, these differences did not appear in HB group, indicating that perhaps the impairments caused by hyperbilirubinemia level out previously existing differences in men's and women's cognitive performance. However, this theory could be contradicted by our founding that there did not seem to be difference between sexes in Perceptual Reasoning in control group, yet men appeared to perform better than women in HB group. Since all these variables measured different cognitive abilities, it would be interesting to further study the effect of hyperbilirubinemia on each of these individual domains. Higher maternal age at birth combined with HB seemed to lead to better performance in multiple cognitive domains in adulthood. Therefore, our results were congruent with previous studies, where higher maternal age at birth has been associated with higher cognitive performance in future (Tearne, 2015). This is an interesting finding, since higher maternal age has overall been associated with more frequent complications during pregnancy and adverse long-term effects (Luke & Brown, 2007). However, it should be noted that maternal age of the present cohort was mostly in mid-twenties. Thus, biological complications due to mother's age were not very likely, and higher age could be correlated with higher education, creating more supportive learning environment for the child. Also, higher maternal education showed this effect in the HB group, which could be expected since higher educated mothers could be more likely to value education and support their child's academic learning.

According to the results of this study, the level of measured hyperbilirubinemia among the HB group had negative influence only for Verbal Comprehension. These results would seem to be in opposition to previous studies where higher HB levels have been found to be in linked with more severe symptoms/lower cognitive performance (Lunsing, Pardoen, & Hadders-Algra, 2013; Seidman et al., 1991). However, it should be noted that in previous studies only severe hyperbilirubinemia cases have been associated with relatively grave impairments (Lunsing, Pardoen, & Hadders-Algra, 2013; Seidman et al., 1991), whereas research on whether moderate HB has more significant outcomes than mild HB has remained controversial (Johnson & Bhutani, 2011; Koziol et al., 2013; Soorani-Lunsing, Woltil, & Hadders-Algra, 2001). Due to the inclusion criteria, data collected for the present study

included mainly moderate to severe cases (bilirubin levels above 340 μmol/l or blood exchange transfusion) but the most severe consequences had been excluded in childhood. Also, the highest measured bilirubin level did not fully describe the graveness of the situation because in some cases the exchange transfusion had been started before waiting for the critical level to be exceeded. Thus, it could be concluded that in this study after the bilirubin levels had reached or exceeded the inclusion criteria differences in their severity did not further influence later cognitive performance in other domains. In addition, since Verbal Comprehension is perhaps the most "trainable skill" (it also correlated strongly with education and can be enhanced significantly with practice, and thus is not as vulnerable to neuronal loss as some other aspects of cognition), it could be speculated that only very high bilirubin levels will cause significant enough damage that cannot be compensated with enhanced training anymore, whereas this threshold would be reached earlier for other domains.

There are some limitations worth noting in this study. We did not have the data on the length of the bilirubin exposure. MRI had not been performed on all cases. There was, however, a long and detailed follow-up on the cohort, and other birth risks, such as prematurity, had been excluded.

5. Conclusions

To the best of our knowledge, this is the longest available prospective follow-up study of adults with a history of neonatal hyperbilirubinemia. Based on the results, neonatal hyperbilirubinemia may manifest as impaired cognitive performance in adulthood. HB appears to influence performance in specific cognitive functions including cognitive flexibility and perceptual reasoning. In contrast with previous studies, highest measured levels of HB did not seem to be associated with significantly lower performance in majority of assessed cognitive domains. Therefore, to further study the linear effect of different bilirubin levels, a data with more variety in values is needed.

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APPENDIX

Table 1. Association between sex and later cognitive performance at 40 years when maternal age at birth and maternal education are controlled.

	HB group				Controls			
Neuropsychological Variables	N	B	Range	p	N	B	Range	p
Cognitive flexibility	99	.035	-.293–.462	.872	61	-.289	-.722–.144	.186
Verbal memory	99	-.674	-1.042 – -.306	**<.001**	61	-.557	-1.053–-.062	**.028**
Visual memory and perception	99	.153	-.212–.517	.408	61	.745	.218 – 1.273	**.006**
Reading	99	-.332	-.697–.033	.074	61	-.142	-.592–.307	.529
WAIS-IV Variables	N	B	Range	p	N	B	Range	p
Perceptual Reasoning	101	.551	.132–970	**.010**	63	.427	-.079–.933	.096
Verbal Comprehension	101	.202	-.169–.573	.282	63	.490	.045–.934	**.031**
Processing Speed	101	-.648	-1,032– -.264	**.001**	63	-.659	-1.115– -.203	**.005**
Working Memory	101	-.002	-.369–.364	.990	63	.098	-.494–.690	.742
FSIQ	102	3.332	-2.884–9.509	.287	64	6.626	-1.398–14.649	.104

Table 2. Association between maternal age at birth and later cognitive performance at 40 years when sex and maternal education are controlled.

	HB group				Controls			
Neuropsychological Variables	N	B	Range	p	N	B	Range	p
Cognitive flexibility	99	-.020	-.063–.023	.361	61	-.014	-.067–.039	.600
Verbal memory	99	.016	-.021–.053	.396	61	.022	-.038–.083	.467
Visual memory and perception	99	.001	-.036–.038	.972	61	.005	-.059–.069	.875
Reading	99	.048	.011–.085	**.011**	61	-.008	-.063–.047	.773
WAIS-IV Variables	N	B	Range	p	N	B	Range	p
Perceptual Reasoning	101	-.028	-.071–.015	.201	63	.010	-.050–.070	.750
Verbal Comprehension	101	.048	.009–.086	**.015**	63	-.003	-.056–.049	.899
Processing Speed	101	.054	.014–.093	**.008**	63	.045	-.009–.099	.103
Working Memory	101	-.008	-.046–.029	.657	63	.010	-.060–.080	.776
FSIQ	102	.709	.078–1.341	**.028**	64	.275	-.686–1.235	.569

Table 3. Association between maternal education and later cognitive performance at 40 years when sex and maternal age at birth are controlled.

	HB group				Controls			
Neuropsychological Variables	N	B	Range	p	N	B	Range	p
Cognitive flexibility	99	-.204	-.527–.118	.212	61	.163	-.202–.529	.375
Verbal memory	99	.165	-.113–.443	.242	61	.167	-.251–.581	.427
Visual memory and perception	99	-.110	-.386–.165	.428	61	-.347	-.792–.098	.124
Reading	99	.244	-.032–.520	.082	61	-.020	-.399–.360	.918
WAIS-IV Variables	N	B	Range	p	N	B	Range	p
Perceptual Reasoning	101	.029	-.290–.349	.856	63	.091	-.341–.524	.674
Verbal Comprehension	101	.296	.013–.579	**.041**	63	.094	-.286–.474	.622
Processing Speed	101	.134	-.159–.426	.366	63	.048	-.342–.438	.807
Working Memory	101	.024	-.256–.304	.865	63	-.076	-.583–.430	.765
FSIQ	102	3.998	-.721–8.716	.096	64	1.325	-5.601–8.252	.703