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Neonatal treatment philosophy in Dutch and German NICUs: health-related quality of life in adulthood of VP/VLBW infants

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Abstract
Purpose Although survival after very preterm birth (VP)/very low birth weight (VLBW) has improved, a significant number of VP/VLBW individuals develop physical and cognitive problems during their life course that may affect their health-related quality of life (HRQoL). We compared HRQoL in VP/VLBW cohorts from two countries: The Netherlands ($n = 314$) versus Germany ($n = 260$) and examined whether different neonatal treatment and rates of disability affect HRQoL in adulthood.
Method To analyse whether cohorts differed in adult HRQoL, linear regression analyses were performed for three HRQoL outcomes assessed with the Health Utilities Index 3 (HUI3), the London Handicap Scale (LHS), and the WHO Quality of Life instrument (WHOQOL-BREF). Stepwise hierarchical linear regression was used to test whether neonatal physical health and treatment, social environment, and intelligence (IQ) were related to VP/VLBW adults' HRQoL and cohort differences.
Results Dutch VP/VLBW adults reported a significantly higher HRQoL on all three general HRQoL measures than German VP/VLBW adults (HUI3: .86 vs .83, $p = .036$; LHS: .93 vs. .90, $p = .018$; WHOQOL-BREF: 82.8 vs. 78.3, $p < .001$). Main predictor of cohort differences in all three HRQoL measures was adult IQ ($p < .001$).
Conclusions Lower HRQoL in German versus Dutch adults was related to more cognitive impairment in German adults. Due to different policies, German VP/VLBW infants received more intensive treatment that may have affected their cognitive development. Our findings stress the importance of examining effects of different neonatal treatment policies for VP/VLBW adults' life.

Keywords Prematurity · Low birth weight · Neonatal treatment · Health-related quality of life · Longitudinal study · Cross-cultural study

Over the last two decades, survival after very preterm birth (VP; gestational age at birth <32 weeks) and very low birth weight (VLBW; <1500 grams) has improved considerably [1]. Still, more VP/VLBW infants develop major cognitive impairments and physical disabilities such as cerebral palsy (CP), blindness, and deafness than full-term comparisons [2, 3]. However, objective health states of chronic illnesses may only show a weak relationship to health-related quality of life (HRQoL) [4] and may also depend on the informant of an individual's HRQoL. Parents of preterm adolescents, but not the adolescents themselves, generally report a lower HRQoL than those of term-born children, especially in areas of motor, social, and emotional functioning [5]. Currently, only a few studies have examined VP/VLBW infants' HRQoL longitudinally in adolescence [6] and in adulthood [4, 7, 8]. It is important to follow-up

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VP/VLBW infants' HRQoL from adolescence into adulthood as it relates to real-life implications such as job success, wealth, level of living independently, and social functioning such as dating a romantic partner and having friends [9–11]. To our knowledge, no study has yet compared HRQoL in VP/VLBW adults from different countries and has examined how different neonatal treatment and rates of disability affect HRQoL.

In the early 1980s, the neonatal treatment policy in the Netherlands could be described as "wait until certain" and intensive treatment for preterm children was initiated only when these infants showed a range of vital signs [6]. In contrast, neonatal treatment in Germany was given to infants of lower gestation than in the Netherlands and consisted of more intensive treatment such as initiating and maintaining mechanical ventilation for longer periods [6]. In recent years, there has been a move towards less intensive treatment including reduction in mechanical ventilation [12]. A comparison between countries with different neonatal treatment philosophy provides a natural experiment to study potential effects on HRQoL. Previously, we reported that in early adolescence, extremely preterm Dutch adolescents scored higher on HRQoL than German adolescents [6]. These results were independent of birth weight, gestational age, and cerebral palsy and were tentatively attributed to a better developing nervous system of Dutch VP/VLBW adolescents compared with German VP/VLBW adolescents, as a result of neonatal treatment differences. This study aimed to answer two research questions. First, do German and Dutch VP/VLBW still differ in HRQoL in adulthood? We expected Dutch VP/VLBW adults to score higher than German VP/VLBW adults on HRQoL, based on higher survival rates of German VP/VLBW infants with higher neonatal morbidity. Second, can differences between Dutch and German VP/VLBW adults' HRQoL be explained by neonatal health and treatment, social environment, and/or individual characteristics such as intelligence? We expected that neonatal health and treatment, social environment, and intelligence would explain differences in HRQoL between Dutch and German VP/VLBW adults.

Methods

Participants

HRQoL was assessed in VP/VLBW infants from two large prospective cohort studies in the Netherlands and Germany. Data from the Netherlands encompassed the national cohort of the Project On Preterm and Small-for-gestational-age infants (POPS). This cohort consists of 1338 Dutch infants born premature in 133 obstetric departments between January 1983 and December 1983 in the Netherlands, 94 % of all children born in 1983 in the Netherlands [13]. Of this cohort, 928 surviving VP/VLBW adults were eligible to participate in the follow-up data collection in adulthood between July and August 2011 at 28 years of age and 314 (33.8 %) participated. German data came from the Bavarian Longitudinal Study (BLS) of 682 VP/VLBW infants born in a geographically defined area of southern Bavaria between January 1985 and March 1986 who required admission to one of 16 children's hospitals within the first 10 days after birth [14]. Of this cohort, 411 surviving adults were eligible for inclusion and 260 (63 %) participated in the adulthood data collection between September 2010 and February 2014 (mean age 26.5 years (SD: .81), age range: 25.3–29.1 years). Figure 1 presents the flow diagram of participants of both cohorts through the study. More information on these two cohorts can be found elsewhere [7, 15, 16].

Ethical approval for these studies was obtained from the medical ethics committee of the Leiden University Medical Centre, the University of Munich Children's Hospital, the Landesärztekammer Bayern, and the Ethical Board of the University Hospital Bonn. All participants gave fully informed written consent to participate in the study prior to the assessments in adulthood. In case of severe impairment of the adult participant, consent was provided by an assigned guardian (usually the parents).

Measures

Self-ratings were used to assess adults' HRQoL. Assessments in adulthood were conducted at comparable ages; at age 28 years for the Dutch and at age 26 for the German cohort. Methods of data collection varied between cohorts. In the Netherlands, most VP/VLBW adults completed the HRQoL questionnaire online ($n = 305$, 97.1 %), yet a small group completed the questionnaire on paper send by mail on request ($n = 9$, 2.9 %). All questionnaires were completed by the VP/VLBW adults themselves. In Germany, most participants completed the questionnaires (paper version) during the follow-up visit in a quiet room ($n = 202$, 77.7 %). Some respondents preferred a telephone interview ($n = 21$, 8.1 %), while others preferred to complete questionnaires on paper send by mail ($n = 13$, 5.0 %). For 14 (5.4 %) German VP/VLBW adults, parents were used as proxy informants to rate their child's HRQoL, due to severe impairments of these VP/VLBW adults (i.e. having a major handicap, such as severe CP, mental retardation, blindness, or deafness).

The Health Utilities Index 3 (HUI3) is a widely used, comprehensive, multiplicative, multi-attribute approach to assess health status and HRQoL, encompassing eight attributes—vision, hearing, speech, ambulation, dexterity,

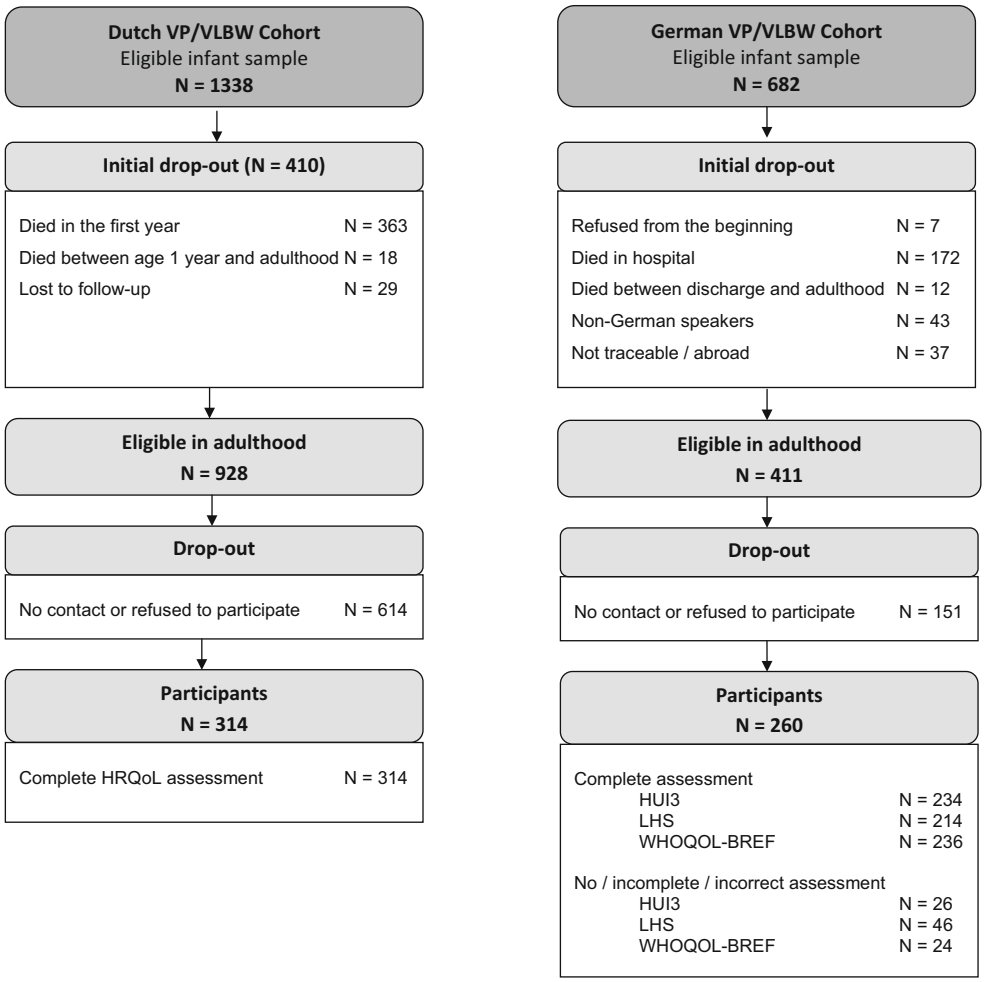

Fig. 1 Flow diagram of participants of both cohorts through the study

emotion, cognition, and pain—with five to six levels of functioning per attribute. A utility score is determined based on population preferences derived from a Canadian normative sample that allows to convert the health state description into a continuous multiple-attribute utility (MAU) score, ranging from 0 (dead) to 1 (perfect health), although it is possible to have a score <0, indicating health states worse than death [17]. The HUI3 is a holistic approach which provides a comprehensive yet compact way to describe the health status of an individual, which has been shown both reliable and valid [17, 18], and has been used in a variety of clinical studies [4, 6, 7].

The London Handicap Scale (LHS) also assesses HRQoL, focusing on six dimensions of disability: mobility, physical independence (self-care), occupation (daily activities), social integration, orientation, and economic self-sufficiency. Every dimension consists of a six-point hierarchical scale of disadvantages. To provide a generic measure of disability (scale 0–1, where 1 is perfect health), each dimension of disability was recoded into a weighted score and the resulting six scores were summed into one generic measure of HRQoL [19].

The WHO Quality of Life instrument, short edition (WHOQOL-BREF) was developed to provide a cross-culturally validated measure of HRQoL. It provides a quality of life profile focusing on four domains: physical health, psychological health, social relationships, and environment. Domain scores from the WHOQOL-BREF were transformed into weighted scores on a scale between 0 and 100, where 100 is perfect health [20].

Covariates: Very preterm birth (gestational age at birth <32 weeks) was determined from the date of the last menstrual period and serial ultrasounds during pregnancy in both cohorts. Birth weight and sex were recorded at the time of birth. Duration of ventilator support (continuous positive airway pressure (CPAP) and/or mechanical ventilation) and duration of hospitalisation were recorded in both cohorts. Education of the parents was assessed at birth for the German sample and at age 5 years for the Dutch sample. For the Dutch cohort, when information about

parent education at 5 years was unknown (8.7 % missing data), parent education data at 10 years were used when available (26.4 % of missing education data were replaced, resulting in 6.4 % missing parent education data). The highest educational level of the parents in both cohorts was grouped as low (up to ten years of basic education), middle (vocational education), or high (professional education or university education). Adult intelligence (IQ) was assessed at different ages in both cohorts, yet IQ is highly stable in preterms from childhood onwards [21]. In the Dutch sample, adult IQ was assessed at 19 years with the use of the computer version of the Multicultural Capacity Test–Intermediate Level, which provided full-scale IQ scores based on a broad spectrum of intelligence domains such as verbal and numerical factors, appreciation of spatial dimensions, fluent speech, memory, reasoning, and speed of perception [22]. IQ was assessed in the German sample at 26 years with the short version of the Wechsler Adult Intelligence Scale (WAIS III), which provided a full-scale IQ score based on six subtests: Vocabulary, similarities, letter–number sequence, block design, matrix reasoning, and digit symbol coding [23, 24].

Data analysis

Statistical significance was set at $p < .05$, and all tests were two-tailed. Selective attrition into adulthood was related to lower socio-economic environment and/or more severe disabilities [7, 25]. Therefore, all analyses were run on both the adulthood samples (Dutch: $n = 314$; German: $n = 260$) and the full eligible samples with missing data imputed (Dutch: $n = 928$; German: $n = 411$), to help interpret findings. Missing data were imputed in SPSS using predictive mean matching. Ten datasets were generated using ten iteration procedures. Imputed values were based on all variables in the model (HRQoL self-reports in adulthood and covariates). Additional predictors in the imputation model consisted of the HUI3 self-reports in childhood (at 13 years for the German cohort, at 14 years for the Dutch cohort), HUI3 self-reports in adolescence (at 19 years, only available for the Dutch cohort), HUI3 parent reports in adulthood (at 26 years for the German cohort, at 28 years for the Dutch cohort), LHS self-reports in adolescence (at 19 years, only available for Dutch cohort), and latest available childhood IQ score.

To analyse whether cohorts differed in HRQoL in adulthood, linear regression analyses were performed for all three general HRQoL measures (HUI3, LHS, WHOQOL-BREF) with cohort as a dummy variable. Cohort differences in HRQoL were interpreted using norms for clinical relevance (i.e. >.03) [18] as well as using Cohen's *d* effect size [26]. To test whether cohorts differed in objective health states, logistic regression analyses were performed for the dichotomized health states representing optimal and suboptimal functioning (i.e. HUI3 attributes level 2 or above were recorded as suboptimal function) [6, 25]. These cohort differences were interpreted using odds ratios.

To test whether neonatal physical health and treatment, social environment, and intelligence are related to VP/VLBW adults' HRQoL and cohort differences, we used hierarchical linear regression on the eligible sample with missing data imputed. To predict each of the three HRQoL scores (HUI3, LHS, WHOQOL-BREF) we included the following predictors in a stepwise fashion: First the neonatal predictors (cohort, gestational age, birth weight, gender, duration of continuous positive airway pressure (CPAP)/mechanical ventilation, duration of neonatal hospitalisation), and second, social environment assessed in childhood (parents' education), and cognitive function assessed in adulthood (IQ scores). In a third step, interactions of these predictors with cohort were also examined. Finally, we performed two additional checks on our data analyses. First, we also run the same analyses on the adulthood sample, without missing data imputed. Second, because the HRQoL measures were highly skewed as most individuals report a good to optimal quality of life (ceiling effect) and as the assumption of homoscedasticity was not met, we rerun the analyses on the three outcome variables using logistic regression with (nearly) perfect health (HUI3 cut-off: .95; LHS cut-off: .95; WHOQOL-BREF cut-off: 87) versus no perfect health.

Results

Dutch and German VP/VLBW cohorts

Background characteristics of both Dutch and German VP/VLBW samples are presented in Table 1. German VP/VLBW survivors had a lower mean gestational age than Dutch VP/VLBW survivors. In addition, 7.1 % (Dutch cohort, total $n = 928$) and 8.5 % (German cohort, total $n = 411$) of the infants were born before 28 weeks of gestation. Both groups had approximately the same birth weight. German VP/VLBW survivors more often received ventilator support, spent more days on ventilator support, and spent more days in hospital than Dutch VP/VLBW survivors. In both cohorts, participants in adulthood did not differ from dropouts in terms of gestational age, birth weight, days of ventilation and days of neonatal hospitalisation. Only in the Dutch cohort, more males dropped out, resulting in significantly more females in the Dutch compared with the German sample in adulthood. More Dutch VP/VLBW had parents with either lower or higher education than German VP/VLBW individuals, who more

Table 1 Descriptives of the German and Dutch VP/VLBW cohorts and test of differences between participants and dropouts

	Adulthood sample					Total sample					Dropout test	
	Dutch		German		p value[a]	Dutch		German		p value[b]	Dutch	German
	N	Mean	N	Mean		N	Mean	N	Mean		p value[c]	p value[d]
Gestational age (weeks)	312	31.0	260	30.6	**.039**	926	31.1	411	30.5	**<.001**	.601	.491
Birth weight (grams)	314	1310.1	260	1323.5	.607	928	1313.2	411	1302.1	.522	.815	.064
Sex (males)	314	37.9 %	260	53.1 %	**<.001**	928	51.7 %	411	51.6 %	.962	**<.001**	.426
Ventilator support (yes)	314	47.8 %	260	76.5 %	**<.001**	927	49.0 %	411	76.4 %	**<.001**	.596	.930
Ventilator support (days)	314	4.7	260	17.0	**<.001**	927	4.7	411	17.8	**<.001**	.995	.352
Hospitalisation (days)	314	66.1	260	75.5	**<.001**	928	66.8	411	77.6	**<.001**	.583	.138
Parent education (high)	304	33.2 %	254	22.4 %	**.005**	968	23.7 %	403	18.9 %	.052	**<.001**	**.018**
Parent education (middle)	304	30.6 %	254	49.2 %	**<.001**	968	30.2 %	403	45.4 %	**<.001**	.848	**.046**
Parent education (low)	304	36.2%	254	28.3 %	**.049**	968	46.1 %	403	35.7 %	**.001**	**<.001**	**<.001**

p values $\leq$.050 are indicated in bold

[a] Comparison between Dutch and German VP/VLBW using the adulthood sample with available data; [b] Comparison between Dutch and German VP/VLBW using the full eligible sample; [c] Comparison between Dutch participants and dropouts; [d] Comparison between German participants and dropouts

often came from families with educational backgrounds classified as "middle". In both cohorts, VP/VLBW adults from lower educated families more often dropped out.

Next to neonatal predictors, intelligence of Dutch and German VP/VLBW individuals was assessed in adulthood. IQ scores were significantly higher for Dutch (mean IQ = 103.8; $n = 251$) than German (mean IQ = 89.2; $n = 202$; $p < .001$) VP/VLBW adults. To impute missing adulthood IQ values for the full eligible sample, the latest available childhood IQ score was included as a predictor in the imputation model. Yet, even in the full eligible sample with missing data imputed, Dutch (mean IQ = 98.0; $n = 928$) had higher mean IQ scores than German (mean IQ = 88.4; $n = 411$; $p < .001$) VP/VLBW adults.

Differences across VP/VLBW cohorts in HRQoL and health states

Test of differences in HRQoL scores across German and Dutch VP/VLBW adults are presented in Table 2. Analyses on both the adult samples and full eligible samples (with missing data imputed) showed that the Dutch VP/VLBW adults reported a significantly higher HRQoL for all three general HRQoL measures (HUI3, LHS, WHOQOL-BREF) than German VP/VLBW adults. These differences were, however, small according to Cohen, yet clinically relevant according to the HUI3 scale developers (>.03 points) [18, 26]. Specifically, more optimal health states were reported for Dutch than for German VP/VLBW adults in areas of vision and cognitive ability. Also, more Dutch than German VP/VLBW adults reported high emotional health; however, this difference disappeared when missing data were imputed.

Explaining cohort differences in HRQoL

Table 3 shows that cohort differences in HRQoL scores were either partially (WHOQOL-BREF) or fully (HUI3, LHS) explained when taking into account other important predictors of HRQoL. For all three HRQoL measures (HUI3, LHS, WHOQOL-BREF), adult IQ was the main predictor. Duration of neonatal ventilation also predicted differences in LHS, but this effect disappeared when taking into account adult IQ. Hospitalisation length also tended to be related to HUI3 ($p = .061$), but this small effect also disappeared when adult IQ was included. These results suggest an overlap in explained variance by the functional measure of IQ. Interaction effects of cohort with other predictors including intelligence (eight interactions for three outcome variables) did not significantly add to the prediction of HRQoL scores and are therefore not included in Table 3.

The results of the linear regression analyses for the eligible sample with missing data imputed presented in Table 3 are relatively similar to both the results for the adulthood sample (no imputation of missing data) and the logistic regression analyses. Therefore, we only present the results of these additional data checks online in Supplement Table S1 and S2.

Discussion

This study examined HRQoL in adults born VP/VLBW, by comparing VP/VLBW cohorts from two European countries: the Netherlands and Germany. These countries differed in neonatal treatment policies in the 1980s with the

Table 2 Test of differences in optimal health states and HRQoL scores across Dutch and German VP/VLBW adults

	Adulthood sample						Eligible sample (missings imputed)					
	Dutch		German		*p* value	ES	Dutch		German		*p* value	ES
	N	Mean	*N*	Mean			*N*	Mean	*N*	Mean		
HRQoL												
HUI3	314	.89	232	.85	**.012**	−.22	928	.86	411	.83	**.037**	−.18
LHS	314	.94	214	.90	**.001**	−.31	928	.93	411	.90	**.018**	−.17
WHOQOL-BREF	314	85.7	236	77.4	**<.001**	−.48	928	82.8	411	78.3	**<.001**	−.33
Health states												
HUI3 vision	314	52.2 %	235	40.9 %	**.008**	1.58	928	52.3 %	411	42.3 %	**.005**	1.50
HUI3 hearing	314	97.1 %	236	98.3 %	.376	.58	928	97.4 %	411	96.4 %	.427	1.39
HUI3 speech	314	89.5 %	235	88.5 %	.716	1.11	928	86.7 %	411	83.6 %	.217	1.29
HUI3 ambulation	314	96.2 %	236	95.8 %	.806	1.11	928	94.5 %	411	92.8 %	.285	1.34
HUI3 dexterity	314	96.5 %	236	94.5 %	.258	1.61	928	94.3 %	411	92.5 %	.269	1.34
HUI3 emotion	314	71.3 %	235	60.4 %	**.007**	1.63	928	69.8 %	411	64.6 %	.128	1.27
HUI3 cognition	314	79.3 %	236	65.3 %	**<.001**	2.04	928	72.7 %	411	63.1 %	**.005**	1.56
HUI3 pain	314	73.9 %	236	68.2 %	.146	1.32	928	70.9 %	411	67.3 %	.390	1.18

Health states represent participants with optimal health states

p values ≤.050 are indicated in bold

ES effect size (HRQoL: Cohen's *d*; health states: odds ratio with Dutch VP/VLBW adults as reference category)

Dutch policy initiating intensive treatment only if VP/VLBW infants' survival was highly likely. We found differences in German and Dutch VP/VLBW adults' HRQoL scores across all three different measures of HRQL. These differences reduced—but remained significant—once accounted for selective attrition in the imputed samples. Our findings on HRQoL in VP/VLBW adults concur with previous findings for extremely low birth weight (<1000 g) adolescents [6] and imply that country differences in treatment policy relate to VP/VLBW cohort differences in HRQoL. This study adds to previous work by including neonatal factors, SES, and cognitive function as predictors of adults' HRQoL to help explain differences in HRQoL between VP/VLBW adults from different countries.

In both cohorts, functional cognitive ability (IQ) was found to be the main independent predictor of HRQoL in VP/VLBW adults, independent of the specific measure used. In general, our results indicate that lower HRQoL in German VP/VLBW survivors in adulthood is mainly related to their lower IQ after VP/VLBW birth compared to Dutch VP/VLBW. In addition, the effect of treatment factors such as ventilation or hospitalisation length reduced once the functional outcome IQ was considered as predictor of HRQoL. These results implicate that IQ may mediate the pathway from early VP/VLBW treatment to HRQoL in adulthood, consistent with previous research showing that both ventilation and length of hospitalisation are strong predictors of childhood IQ in VP/VLBW children [12] and that objective functioning is related to HRQoL in VP/VLBW adolescents [25].

Our findings stress the impact of cognitive function in VP/VLBW adults' life. IQ is an important marker of VP/VLBW brain health [27]. First, VP/VLBW birth is related to brain injuries that affect brain organisation [28, 29], and second, neonatal complications and mechanical ventilation in particular have been shown to lead to alterations in brain structure with adverse effects on cognitive functioning [30]. Even small IQ differences are important as they are not only related—as shown here—to HRQoL, but also to socio-economic status and even reduced survival and health into old age [31, 32].

Although IQ explained most differences in HRQoL between Dutch and German VP/VLBW adults, the differences were nevertheless real and clinically relevant. Dutch and German HRQoL as measured with HUI3 MAU scores differed by approximately .03 points, a difference previously considered to be clinically important [18]. Analyses on the health states showed that in addition to differences in cognition, more German than Dutch VP/VLBW adults had problems with vision and lower emotional health (although this effect disappeared when missing data were imputed). In addition, Dutch VP/VLBW adults still indicated higher HRQoL than German VP/VLBW adults on the physical WHOQOL-BREF HRQoL measure when corrected for neonatal treatment, SES, and IQ. Cohort differences in WHOQOL-BREF may thus be related to country

Table 3 Impact of predictors on HRQoL across VP/VLBW cohorts, eligible sample

	Eligible sample (missings imputed)							
	Step 1				Step 2			
	β	95 % CI		p value	β	95 % CI		p value
HUI3								
Cohort	.05	−.03	.13	.184	−.01	−.09	.07	.761
GA	−.01	−.09	.07	.766	.01	−.07	.09	.816
Weight	−.03	−.11	.05	.450	−.05	−.13	.02	.180
Sex	.00	−.06	.07	.971	.02	−.04	.09	.514
Ventilation	−.03	−.12	.06	.493	.03	−.05	.11	.477
Hospital	−.12	−.25	.01	.061	−.07	−.19	.06	.276
Edu_high					−.03	−.11	.04	.383
Edu_low					.07	.00	.14	.059
IQ					.37	.25	.48	**<.001**
R^2	2.3 %				12.9 %			
ΔR^2	2.3 %			**.003**	10.6 %			**<.001**
LHS								
Cohort	.02	−.04	.09	.502	−.05	−.11	.02	.162
GA	−.01	−.10	.08	.841	.02	−.07	.10	.713
Weight	−.02	−.10	.05	.538	−.05	−.11	.02	.165
Sex	.01	−.04	.07	.686	.03	−.02	.09	.219
Ventilation	−.12	−.20	−.04	**.003**	−.06	−.14	.03	.176
Hospital	−.08	−.18	.02	.100	−.02	−.11	.07	.667
Edu_high					−.05	−.13	.02	.163
Edu_low					.05	−.03	.12	.198
IQ					.40	.29	.50	**<.001**
R^2	3.3 %				15.7 %			
ΔR^2	3.3 %			**<.001**	12.4 %			**<.001**
WHOQOL-BREF								
Cohort	.13	.06	.20	**.001**	.09	.02	.16	**.009**
GA	−.03	−.13	.07	.520	−.02	−.12	.08	.686
Weight	−.04	−.13	.05	.334	−.06	−.16	.04	.207
Sex	.01	−.06	.09	.709	.03	−.05	.11	.494
Ventilation	−.02	−.14	.10	.725	.02	−.11	.15	.749
Hospital	−.10	−.22	.01	.077	−.07	−.19	.05	.232
Edu_high					−.07	−.15	.02	.148
Edu_low					.04	−.05	.12	.387
IQ					.23	.14	.31	**<.001**
R^2	3.4 %				7.6 %			
ΔR^2	3.4 %			**<.001**	4.2 %			**<.001**

Cohort: 0 = German, 1 = Dutch; GA = gestational age; weight = birth weight; sex: 0 = male, 1 = female; hospital = duration hospitalisation; edu_high = high education; edu_low = low education; IQ = intelligence; β = beta; CI = confidence interval

p values $\leq$.050 are indicated in bold

differences such as social-economic differences and/or cultural differences in attitudes regarding disabilities and handicaps not measured in this study or to general differences in experienced well-being between countries, not related to preterm birth. For example, UNICEF reported that from the 29 countries with most advanced economies, the Netherlands were the leader for child well-being, measured both objectively and with self-reports. In

comparison, Germany occupied sixth place according to objective measures of well-being, but dropped to 22nd place when children themselves were asked to evaluate their life satisfaction.

Because of the found country differences in neonatal treatment and HRQoL, findings on VP/VLBW adult HRQoL may be quite country specific and thus not generalizable to other VP/VLBW populations. In contrast, our results indicate that the impact of cognitive function on adult HRQoL may be robust. Regarding the current population of VP/VLBW infants, future research must demonstrate whether the improvement in neonatal treatments and especially the development of less invasive treatments may lead to better cognitive development and therefore improved HRQoL or whether any gains through improved neonatal treatment will be nullified by more infants of smaller gestation surviving. Prospective cohort studies are essential in providing this information.

This study has a range of strengths. Most important among these are the long-term follow-up into adulthood of two large whole population samples of VP/VLBW individuals from two different European countries that had different neonatal treatment policies in the 1980s and the assessment of HRQoL in adulthood with multiple identical instruments. There are also limitations. First, adulthood response rates between the two countries differed largely and the dropout was not random. VP/VLBW with lower educated parents were less likely to continue participation, which is in line with previous reports that participants at social disadvantage are more likely to drop out of longitudinal studies than those more socio-economically advantaged [33]. In addition, for the Dutch VP/VLBW, gender also impacted dropout with females more likely to participate in adulthood. This finding again stresses the need to report on findings that are corrected for selective attrition. Thus, we report on the adult sample with available data and on the full eligible sample with imputed missing data to control for possible bias. Yet, the findings were generally consistent, independent of the chosen sample. Second, because studies were performed in two countries under the guidance of two research teams, not all predictor variables were measured identically or could be measured identically. For example, adulthood IQ was assessed with different measures in both cohorts, and different measures show different secular trends (i.e. Flynn effect) [34]. Nevertheless, additional analyses done separately for each country showed similar effects of IQ on HRQoL, indicating a true effect independent of how and when IQ was measured. Also, Dutch and German educational systems differ and are thus not exactly comparable, which was why parent education was categorised in three general, more comparable, classes (i.e. low, middle, high).

Conclusions

The present study showed that German VP/VLBW adults had lower quality of life compared with Dutch VP/VLBW adults. These differences were related to German VP/VLBW adults having higher levels of cognitive impairment than Dutch VP/VLBW adults, which was in turn related to German VP/VLBW infants receiving more intensive neonatal treatment while the Dutch policy initiated intensive treatment only if VP/VLBW infants' survival was highly likely. Thus, intensive neonatal treatment may reduce cognitive abilities which in turn increases VP/VLBW adults' vulnerability to a lower HRQoL with long-lasting consequences into adulthood. Our findings stress the importance of examining effects of cross-cultural differences in neonatal treatment policies and their consequences for VP/VLBW adults' life.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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