Born extremely low birth weight and Health Related quality of life into adulthood

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Short title: ELBW Quality of Life

Abbreviations: HRQL – Health Related Quality of Life; HUI 3 - Health Utility Index Mark 3; NBW: normal birth weight (> 2500g); NSI: neuro-sensory impairment; VP/VLBW – Very Preterm (<32 weeks gestation) /Very Low Birth Weight (birth weight <1,500g); ELBW – Extremely low birth weight (< 1000g)

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Health-related quality of life (HRQL) refers to the impact of health on an individual's overall psychological, social, and physical well-being (1). Rather than having different measures for specific conditions, having one measure of HRQL allows for the comparison of consequences or effects of treatment across all starting conditions. This is of practical importance when difficult decisions have to be reached by budget holders how to best employ limited health resources.

In this volume of *The Journal*, Saigal et al (…) report on the evaluation of long term HRQL outcomes associated with health after being born extremely low birth weight (ELBW). While several studies have evaluated HRQL after being born ELBW or very preterm (VP) or very low birth weight (VLBW) in adolescence or adulthood across two time points (2) (3-5) (6), this is the first study that evaluated HRQL from adolescence through early adulthood into the mid-thirties across 3 time points. This allowed the study team to analyze trajectories, i.e. does HRQL after ELBW tend to remain the same, increase or decrease significantly over time?

They employed the Health Utility Index Mark 3 (HUI-3) questionnaire that is widely used to obtain subject or patient-reported outcomes (PRO) and enquires about 8 attributes of functioning: Vision, Hearing, Speech, Ambulation, Dexterity, Emotion, Cognition and Pain – each with 5 or 6 levels of ability/disability (1). The health states are converted into multi-attribute utility scores (MAU) that represent mean community preferences. The utility (preference) scores range on a generic scale where dead = 0.00 and perfect health = 1.00.

Saigal et al. (…) defined two subgroups within the ELBW a priori; ELBW with and without neurosensory impairment (NSI), and a control group of normal birth weight (NBW). Their HRQL was assessed at three time points (ages 12-16; 22-26; and 29-36 years). Long-term studies are difficult to do and not easy to fund but their value increases with every

assessment wave. The major findings were, firstly, that there was both a statistically and clinically significant HRQL difference between ELBW without NSI and, in particular, of ELBW with NSI compared to NBW at each assessment point from adolescence. HRQL differences already emerged in adolescence and did not significantly widen as the ELBW progressed into early and mid-adulthood. This means, that long-term HRQL for ELBW can usually be determined in adolescence without an indication of improvement over time. This is consistent with recent findings from other cohorts who also analyzed the stability of HRQL scores over time (3, 5). The stability in HRQL is higher in VP/VLBW compared to NBW controls and the high stability is mainly carried by those with significant NSI, i.e. high health burden (2).

How do the mean HRQL levels reported by Saigal et al. compare with those of two other longitudinal studies of HRQL that assessed VP/VLBW with the same instrument from adolescence into adulthood (table 1)? Noticeable is that the weighted mean for all ELBW (with and without NSI) was significantly lower at 0.79 in adolescence and early adulthood in the Canadian compared to the German study (0.82 and 0.82, respectively) and notably lower compared to the Dutch findings in adolescence (0.87), early adulthood (0.83) and later adulthood (0.73 vs 0.85). This cannot be easily explained by cultural differences as the NBW means were exactly the same in Canada and Germany in adolescence (0.88) and early adulthood (0.89) (the Dutch study had no NBW controls). The difference is most likely due to the Canadian study investigating ELBW while the other two studies reported on more mature and larger VP/VLBW. A previous comparison of the three cohorts, focusing on ELBW indicated that at least the German and Canadian ELBW had similarly low HRQL in adolescence (8). This study provides further evidence that, firstly, HRQL of ELBW individuals is, on average, significantly lower than that of VP/VLBW who in turn report lower HRQL than NBW adolescents and adults. Secondly, consistently HRQL has been

found to not improve with age in ELBW or VP/VLBW. Thirdly, NSI reduces HRQL well into adulthood. The stability of these differences compared to NBW indicates that whatever services ELBW or VP/VLBW individuals received from early adolescence have made no difference to their HRQL well into adulthood.

The key question to answer is thus: How can we increase HRQL of ELBW and VP/VLBW children and adults? Despite efforts to prevent preterm birth, there will be the same or even a greater number of ELBW and VP/VLBW survivors in the community, at least, in the foreseeable future (9). Thus we have to understand and find ways to increase HRQL of ELBW/VLBW beyond considering NSI as those ELBW or VP/VLBW without NSI also have lower HRQL than NBW (table 1). An alternative to the approach chosen by Saigal et al (…) of defining a priori risk groups and plot their HRQL over time, would be to make full use of repeated HRQL measurements to identify adolescents whose HRQL grows in similar ways over time (trajectories). This approach is called latent class growth analysis (LCGA) (10). Having found specific trajectories (e.g., consistently low, consistently high, or changing over time), it can then be investigated what factors in infancy or childhood separate those individuals who are members of different trajectory groups (10, 11) (12). This would allow to identify both, early risk and protective factors beyond ELBW and NSI that may predict constantly low or improving scores in HRQL over time, for example. Some recent longitudinal research indicates that emotional problems such as worries, depression and anxiety in childhood (5, 13) are related to Quality of Life and adaptation into adulthood (14) beyond NSI. Furthermore, having friends, dating a romantic partner, receiving emotional support and generating an independent income are crucial factors in adulthood that increase HRQL in both VP/VLBW and term born adults (2). To overcome the problems of limited statistical power in individual samples and to detect universal factors related to HRQL, future

research may want to combine samples of ELBW or VP/VLBW across countries as successfully demonstrated for other outcomes (15) (16, 17).

Now that we know that HRQL is reduced in VP/VLBW and ELBW and remains lower than in NBW individuals well into adulthood, research should focus on identifying factors that can be modified from birth to adulthood in order to increase HRQL of ELBW and VP/VLBW. Factors providing protection against poor HRQL may lie in the universal application of evidence based peri- and neonatal treatment (18) (19) and in support to improve social skills, social relationships and emotional health from childhood into adulthood. The emerging evidence suggests that we have to look beyond excellent medical care and focus more on the social-emotional care of those born very or extremely preterm.

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Table 1. Health Related Quality of Life in longitudinal Studies of ELBW or VP/VLBW with 2 or more assessments from Adolescence into Adulthood

Study Country		**Adolescence (12-16 years)**	**Early Adulthood (19-26 years)**	**Adulthood (>26 years)**
	Maximum N	*M 95% CI*	*M 95% CI*	*M 95% CI*
Canada (in this Journal)				
ELBW without NSI	116	0.83 (0.79; 0.87)	0.83 (0.78; 0.87)	0.77 (0.70; 083)
ELBW with NSI	37			
ALL ELBW[a]	153	0.68 (0.58; 0.78)	0.65 (0.56; 0.75	0.60 (0.50; 0.70)
NBW	137	0.79	0.79	0.73
		0.88 (0.86; 0.91)	0.89 (0.86; 0.92)	0.85 (0.81; 0.90)
Germany [2]				
VP/VLBW (self-reported)	190	0.86 (0.83; 0.88)	0.86 (0.83; 0.88)	
ALL VP/VLBW[b]	203			
NBW controls	201	0.82 (0.79; 0.86)	0.82 (0.79; 0.86)	
		0.88 (0.86; 0.90)	0.89 (0.87; 0.91)	
Netherlands [3]				
VP/VLBW assessed	314		0.89[c] (SD 0.16)	0.88[c] (SD 0.22)
ALL VP/VLBW (imputed)	957			
Adolescents VP/VLBW assessed [5]	630	0.87[c] (SD 0.18)	0.83[c] (SD 0.22)	0.85[c] (SD 0.20)

ELBW: Extremely low birth weight (< 1000g); VP/VLBW very preterm (< 32 weeks gestation) or very low birth weight (< 1500g)

[a] *weighted mean computed from ELBW with and without NSI. 95% CI could not be computed.*

[b] Includes all VP/VLBW who self-reported and 13 proxy reports by parents as participant was too disabled to complete HUI 3. Differs from numbers in original publication[2] where these were added to parents' ratings of HRQL.

[c] only standard deviation reported in original report (SD)