Gravens by Design: Global Research on Transition to Adulthood after Preterm Birth: Proceedings of the Graven's Conference, Clearwater, FL, March 8-11, 2023

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There is now a considerable body of research that shows that very preterm (VPT) birth is associated with an increased risk of neurological impairments, cognitive deficits, and behavioral and social problems that last from childhood to adolescence. Until recently, it was unclear whether these problems improved over time or persisted into adult life. In the last two decades, there has been an increasing interest in the outcomes at adulthood, which show that, although some problems have improved over time, newer issues have emerged with a high prevalence of mental health, cardiometabolic, and chronic health problems. (1)

This paper focuses on a broad range of outcomes from the world literature on former VPT/ELBW (very preterm/extremely low birthweight) infants in adulthood compared with full-term (FT) controls. In addition, the personal perspectives of the former preemies in adulthood will be highlighted.

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1. Cognition, Educational Attainment, and Employment:

Several studies have shown that cognitive deficits (2-5) and problems with executive functioning (5,6) persist into adulthood, with an incremental association with lower gestational age. Very preterm adults have lower rates of high school graduation and postsecondary educational attainment than their FT peers in cohort studies (2,7) and population-linked registries (8-10.) However, despite the inclusion of participants with neurological impairments, the McMaster study of extremely low birthweight infants (ELBW<1000g) showed no differences in the total years of education (16.0 vs. 16.7 years) or in postsecondary education at middle-adulthood (30–36 years). (11) The Norwegian population-linked study at ages 19-35 years showed a statistically significant association between gestational age and educational achievement, even after individuals with impairments were excluded, with 67.7% of individuals between 23 and 27 weeks gestation completing high school compared with 75.4% of FT adults, and 25% vs. 35% completing a bachelor's degree. (9) The Bavarian study showed that VLBW (very low birthweight) adults do not outgrow their earlier intellectual deficits, and the IQ was 0.9-1.27 and Executive Function 0.59-1.15 SD below that of controls. High SES can modify the impact of prematurity with a significant positive impact of 1.13 SD. (5) Lately, Individual Participant Data (IPD) meta-analyses from several international consortia: the Adults born Preterm International Collaboration (APIC) and Research on European Children and Adults born Preterm (RECAP), have highlighted several aspects with lower intelligence equivalent to 12 IQ points,(12) and poorer mathematical performance in childhood and adulthood. (13)

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Regarding employment, although no significant differences were observed in the McMaster young adults at age 23 years (48% vs. 57%), at middle adulthood (age 30–36 years), a significant disparity emerged in employment and income in ELBW compared with FT adults. (11) A lower proportion of ELBW adults was employed (80.4% vs. 91.8%, and the net income was $20,000/year lower than FT adults. The association with household income remained after excluding ELBW adults with impairments, with more ELBW adults requiring social assistance (13.8% vs 3.7%). (11) Norwegian extremely preterm (EPT) young adults from the National Registry had lower job-related income (23% vs. 20%, $P < 0.001$), and 1 in 9 persons born <28 weeks' gestation received a disability pension compared with 1 in 59 for those born FT ($P < 0.001$). (9) Scandinavian studies have shown that preterm birth was associated with a stepwise increase in disability, decreased chance of

completing university, and lower net income. However, despite the higher prevalence of disabilities, a significant proportion of young adults born prematurely completed high school were employed and were functioning well in society. (8) It was also reassuring that, as a group, they contributed more to income tax than they received in benefits.

"Many reports have shown that a higher proportion of VLBW and VPT young adults continue to live with their parents compared to FT adults (7,14), which is more so in individuals with disabilities. (11) Compared with FT adults, those born EPT/VPT were less likely to have romantic relationships, cohabitation, and experience sexual intercourse and parenthood. (2,10,11,14) "

2. Social Outcomes, Relationships, and Reproduction:

Many reports have shown that a higher proportion of VLBW and VPT young adults continue to live with their parents compared to FT adults (7,14), which is more so in individuals with disabilities. (11) Compared with FT adults, those born EPT/VPT were less likely to have romantic relationships, cohabitation, and experience sexual intercourse and parenthood. (2,10,11,14) The McMaster study reported that 1 in 5 ELBW adults had never experienced sexual intercourse, and these differences remained even after excluding those with impairments. (11) Furthermore, the likelihood of experiencing romantic partnership, sexuality, and parenthood showed a significant dose-response with a lower probability with decreasing gestational age. (9,11,14,-16) Several studies have shown poorer social relations and fewer friends among prematurely born adults than controls. (7,9,14,17) They also engaged less often in risk-taking behaviors than FT. (2,7,8,11)

Both cohort (2,11) and population-linked registries (9,10,18,19) report reproductive problems among individuals born prematurely. The Norwegian National Birth Registry of 60,354 premature births between 1967–1988 found a dose-response association by degree of prematurity with lower rates of reproduction in both males and females, higher rate of stillbirths (20.8/1000 births in <28 weeks vs. 7.6 FT/1000 births); and recurrent premature offspring in prematurely born women (14% in 22-27 weeks vs. 6.4% in FT). (17) The Swedish population-based registry (1973-83 births) also reported a reduced probability of reproduction in both males and females. (19)

3. Chronic Physical and Mental Health Conditions:

Individuals born prematurely have been reported to experience a high prevalence of adult-onset medical conditions such as hypertension, Type 2 diabetes, and metabolic syndrome in mid-to-late adulthood. (1) Higher blood pressure has been consistently reported in adults born VPT compared to FT controls. In IPD analyses, the mean difference in blood pressure in 1571 adults born VPT versus 777 FT controls was 3.4 mmHg systolic and 2.1 mmHg in diastolic blood pressure. (20) There is also an association between preterm birth and with risk of ischemic heart disease at adulthood. (21) Recent cohort studies have reported a higher prevalence of dysglycemia, insulin resistance, and hepatic fat content in adults born ELBW, which collectively increase cardiometabolic risk. (22-24) The McMaster cohort found differences in body composition, elevated body fat, and reduced lean mass at middle adulthood, which likely contributed to the differences in metabolic health. (23) IPD meta-analysis showed that individuals born preterm were at risk of not reaching their full airway growth potential at adulthood, which places them at higher risk for future chronic obstructive pulmonary disease. (25) There are also adverse effects on the developing kidneys that can retard nephrogenesis. (1)

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Preterm birth increases the risk for psychiatric disorders such as anxiety, inattention, depression, and autistic traits later in life. (26-31) The risk is also higher for psychosis, schizophrenia, and mood disorders. (26-31) There was a stepwise increase in psychiatric hospital admissions with decreasing gestational age. (30) Using clinical interviews, the ELBW survivors exhibited higher rates of anxiety and depression compared with FT controls. (27) This was confirmed in a larger sample by Individual Participant Data meta-analysis, which suggested that individuals born VP/VLBW have higher odds of meeting criteria for certain psychiatric disorders into adulthood than FT controls. (31) IPD analysis of self-reported mental health by VP young adults shows they have higher internalizing problems and more avoidant personality problems. (32) Several studies have also shown that young adults born preterm have a lower tendency for antisocial and risk-taking behaviors, such as smoking and drinking, than term controls. (33-35) Due to their timid personality and behaviors, they are at greater risk for increased bullying, peer victimization, and social exclusion. (36)

4. Health-related quality of life and Personal perspectives:

The Health Utility Index Mark 3 (HUI III) has been widely used in several studies to obtain the perspectives of health-related quality of life (HRQL) of ELBW/VPT. (37-40) When the HRQL was

obtained directly from the McMaster ELBW participants at YA (eliciting their own health status and own preferences using the Standard Gamble (SG) technique), the scores were equivalent to FT (0.85 vs. 0.88), where the scale of 0.00 is equivalent to dead, and 1.00 is perfect health. (41) No differences were observed between ELBW adults with and without impairments. However, in comparing the longitudinal trajectories of the same cohort using the SG perspectives of Ontario parents (*HUI3 community/societal preferences*), the HRQL of ELBW was clinically lower than FT at each of the three-time points. (40) Also, The HRQL of ELBW with impairments was statistically lower at all ages compared to those without neurosensory impairments. Compared with data from other countries that used *HUI3 community preferences*, the HRQL of the McMaster cohort at 30-36 years of age(40) was significantly lower than the Netherlands (37) and the German cohorts (39,) and there was no substantial improvement over time. This may be partly explained by the fact that the McMaster cohort included ELBW births, and the other two cohorts had VLBW participants. Again, using *HUI3 community preferences*, both the EPCURE participants (<26 weeks) and their parents rated their HRQL less favorably than the controls at both adolescence and adulthood, and there was a further decline at older age. (42) IPD meta-analysis of HRQL of over 2100 VLBW/VPT 18-29 years showed a significant difference in the HUI3 multi-attribute utility score of −0.06 (95% CI −0.08, −0.04) in comparison to FT controls, especially concerning physical and cognitive functioning. (43)

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In a newer methodology of 'Narrative Medicine,' (44) 41 ELBW participants in their mid-30s provided candid personal stories about their lives, struggles, and accomplishments and, against all odds, showed remarkable resilience in overcoming their challenges. (45) These letters express a much broader view of their lives than the restricted health-related quality of life studies: Preemie Voices, Press, 2014, accompanied by a video documentary, www.preemievoicesbook.com. (45)

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6. Comments and Limitations

Preterm birth is a chronic, life-long condition. Except for specific brain lesions, early biomedical risk factors play a smaller role, and environmental and social factors exert a greater influence on later outcomes. Subsequently, plasticity, resilience, and recovery come into play, and therefore, the future of premature children must be looked at from a lifespan perspective, as 'recovery' may not be evident until early adulthood.

The VPT/ELBW adult participant cited in the above studies were born in the early post-neonatal care era and did not receive the advanced technology and other 'gentle interventions' offered to the current survivors. Although these data may not be entirely applicable to today's survivors, the findings can guide and design effective strategies to improve the health, social well-being, and psychiatric and cardio-metabolic problems of future vulnerable premature infants. In addition, obtaining the personal perspectives of children and adults born prematurely cannot be over-emphasized. It is now clear that health professionals' perspectives on the outcome of premature infants are often discordant with that of the premature individuals themselves. (46) Finally, it should be reiterated that despite disabilities and significant health issues, a significant majority of EP/VPT showed amazing resilience, placed a high valuation on their quality of life, and enjoyed a fulfilling lifestyle in adulthood. (11,41)

" Based on our current knowledge of the high prevalence of cardiometabolic and mental health problems in adults born VPT, transition to adult physicians should include taking a birth history of prematurity so that preventative measures and anticipatory guidance can be undertaken. (47)"

Although the complex psychosocial needs of parents of extremely preterm infants in the NICU are now recognized, the long-term needs and advice for the future health and development of VPT at adulthood are sorely neglected. Based on our current knowledge of the high prevalence of cardiometabolic and mental health problems in adults born VPT, transition to adult physicians should include taking a birth history of prematurity so that preventative measures and anticipatory guidance can be undertaken. (47)

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Acknowledgments: I am grateful to the premature and term-born adults for participating in our studies, my colleagues, and the Research agencies, NIH and CIHR.

Disclosure: The author has no disclosures.

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