Adult Outcome of Extremely Preterm Infants

This is the fourth article in our series "Transitions to Adult Care."

abstract

Survival rates for extremely preterm (<28 weeks' gestational age) infants have increased and are approaching 3 in 4 with the advent of modern perinatal and neonatal intensive care. In contrast with some children with chronic diseases such as cystic fibrosis, most survivors of extreme prematurity have no ongoing health issues. However, as a group, they do have higher rates of adverse health outcomes, and more of them will present to pediatricians over time and, ultimately, to adult physicians as they grow older. Pediatricians can aid the transition to adult health care by being aware of the nutritional, cardiovascular, respiratory, motor, cognitive, psychiatric, and functional outcomes into adulthood of survivors of extreme prematurity. *Pediatrics* 2010; 126:342–351

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KEY WORDS

extremely preterm infants, growth and nutrition, pulmonary function, cerebral palsy, cognitive function

ABBREVIATIONS

EP—extremely preterm
BPD—bronchopulmonary dysplasia
CP—cerebral palsy
ELBW—extremely low birth weight
VLBW—very low birth weight
NBW—normal birth weight
OR—odds ratio
CI—confidence interval
FEV_1—forced expiratory volume in 1 second

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Extremely preterm (EP) (<28 weeks' gestation) infants comprise <1% of all live births yet consume much of our neonatal intensive care resources. Before the advent of successful assisted-ventilation techniques derived specifically for newborn infants, very few EP infants survived long-term; thus, they had little impact on the burden of illness in either childhood or adulthood. However, because survival rates for EP infants have risen dramatically, their outcomes into adulthood cannot be ignored. Pediatricians in all specialties will deal with more survivors of extreme prematurity over time and must be aware of their unique health problems, particularly as they hand over care to their adult colleagues. The aim of this report is to review the adult outcomes of extreme prematurity.

METHODOLOGIC ISSUES

Knowledge of adult outcomes of extreme prematurity comes from 2 types of studies. The first type comprises cohort studies of survivors who have been followed longitudinally from birth into adulthood. These cohorts are predominantly from single hospitals but can be from geographically defined regions or from survivors of specific studies, such as randomized, controlled trials (eg, of antenatal betamethasone to accelerate fetal lung maturation),[1] or with specific diagnoses, such as bronchopulmonary dysplasia (BPD).[2] The disadvantages of long-term studies from birth into adulthood include the time taken to obtain the outcomes of interest and the high likelihood that follow-up rates will diminish over time; those who are not followed or are followed with difficulty have a different, usually worse, prognosis than those who are followed with ease.[3] The advantages of longitudinal studies are that diagnostic criteria can be specified and confirmed at all stages, and causal pathways are more readily established by knowing the chronology of events with more certainty. The second type of study is becoming more prevalent in the literature: population-linkage studies, in which data from early in life are linked to data later in life and relationships between exposures and outcomes are established. These linkage studies have the advantage of large sample sizes on whole populations. When there is little migration from the country of birth, as seems common in Scandinavian countries, it is possible to have virtually complete outcomes on the populations of interest. In a study from Norway of births in 1967–1983, 97.5% of 5-year survivors were still resident in the country at 20 to 36 years of age.[4] The outcome databases are either records obtained at times of enrollment in the armed services, which predominantly affects men,[5] or are from databases of various disease diagnoses recorded according to *International Classification of Diseases* (ICD) codes.[4,6] One disadvantage of these large, whole-population–linkage studies is uncertainty in the diagnoses recorded at both extremes of life; for example, in a study of cerebral palsy (CP), the sensitivity of a diagnosis of CP was 70% and the specificity was 99%.[7] In addition, the large sample sizes can lead to statistical differences that do not translate into important clinical differences. A problem common to both longitudinal studies and cross-sectional data-linkage studies is that the outcome for survivors of extreme prematurity cannot be interpreted completely without an appropriate comparison group of term survivors. Many cohorts have been selected according to birth weight rather than gestational age, largely because gestational age was more uncertain in the era before routine antenatal ultrasound testing; consequently, some studies in this review were of survivors of extremely low birth weight (ELBW) (<1000 g) or very low birth weight (VLBW) (<1500 g) rather than of those with EP gestational ages. Moreover, in some studies, outcomes from infants <28 weeks' gestation alone have not been reported but were included among outcomes for those <29, <32, or <33 weeks.

In this overview we focus on results from cohort studies of EP infants, whether from single hospitals, geographic regions, or whole countries, rather than cohorts selected according to particular treatments or diagnoses and those for which there was a term (>36 weeks) or normal birth weight (NBW) (>2499 g) group for comparison.

GROWTH AND NUTRITIONAL OUTCOMES

Given their very small size at birth and that it can take many weeks to tolerate milk feeds and to regain the weight lost in the first days after birth, it is little wonder that parents of EP children are concerned about the growth of their child and, ultimately, their adult size. There are 4 studies that have measured the growth of survivors of extreme prematurity in early adulthood and compared the results with NBW or term controls: 2 studies followed subjects born at <1001 g birth weight,[8,9] and the birth weight was <1500 g in the other 2 studies.[10,11] The adult stature of most survivors of extreme prematurity is within the expected range, although they are, on average, shorter than controls, and the men, but not always the women, are lighter than controls (Table 1). Consistent with the increasing rates of overweight and obesity in the developed world, survivors of extreme prematurity, too, are heavier relative to their height in early adulthood.[8–10] It seems that individuals born EP are likely to achieve a height in adulthood that is close to their genetic potential; in the only study that measured the height of

TABLE 1 Height and Weight in Survivors of Preterm Birth Measured in Early Adulthood Compared With Controls

Study	Subject Characteristics, Preterm (*n*)/ control (*n*)	Year of Birth	Age, Mean, y	Height, cm			Weight, kg		
				Preterm, Mean (SD)	Control, Mean (SD)	Mean Difference (95% CI)	Preterm, Mean (SD)	Control, Mean (SD)	Mean Difference (95% CI)
Saigal et al[9]	BW 501–1000 g, geographical, no exclusions, 147/131	1977–1982	23	M: 170.6 (9.5); F: 158.3 (6.8)	M: 177.8 (7.7); F: 164.5 (6.7)	M: −7.2 (−10.3 to −4.1)[a]; F: −6.2 (−8.3 to −4.0)[a]	M: 70.7 (14.9); F: 60.1 (13.6)	M: 77.2 (14.6); F: 67.2 (16.0)	M: −6.5 (−11.7 to −1.2)[a]; F: −7.1 (−11.8 to −2.4)[a]
Doyle et al[8]	BW 500–999 g, single hospital, CP excluded, 42/37	1977–1980	20	M: 172.3 (7.7); F: 161.0 (7.4)	M: 178.0 (3.9); F: 165.5 (7.5)	M: −5.7 (−9.8 to −1.5)[a]; F: −4.4 (−9.0 to 0.1)	M: 67.6 (11.9); F: 64.0 (16.5)	M: 75.5 (12.8); F: 62.9 (15.1)	M: −8.0 (−16.7 to 0.8); F: 1.1 (−8.6 to 10.9)
Hack et al[10]	BW < 1500 g, single hospital, NSI excluded, 195/208	1977–1979	20	M: 173.7 (7.9); F: 161.7 (7.3)	M: 177.0 (6.8); F: 163.0 (7.0)	M: −3.1 (−5.2 to −1.1)[a]; F: −1.2 (−3.2 to 0.9)	M: 69.2 (13.9); F:64.9 (16.8)	M: 79.9 (16.7); F: 67.6 (18.3)	M: −10.5 (−14.8 to −6.2)[a]; F: −2.0 (−6.9 to 2.8)
Hovi et al[11]	BW < 1500 g, single hospital, no exclusions, 163/169	1978–1985	22	M: 174.6 (7.8); F: 162.0 (7.7)	M: 180.5 (6.4); F: 167.2 (6.8)	M: −5.9 (−8.3 to −3.5)[a]; F: −5.3 (−7.3 to −3.2)[a]	M: 66.0 (13.7); F: 57.3[b] (12.0)	M: 75.1 (11.9); F: 62.6[b] (10.9)	M: −9.1[b] (−12.7 to −5.1)[a]; F: −5.3[b] (−8.1 to −2.4)[a]

BW indicates birth weight; M, male; F, female; NSI, neurosensory impairment.

[a] Statistically significant compared with controls.

[b] Geometric mean, SD and mean difference.

both parents, the EP subjects' height *z* scores were consistent with their mid–parental height *z* scores.[8]

In addition to these 4 studies in which subjects were measured, Cooke[12] obtained data by questionnaire from 79 of 138 (57%) neurodevelopmentally normal VLBW survivors at the age of 19 to 22 years born at Liverpool Maternity Hospital (Liverpool, United Kingdom) between 1980 and 1983. Similar to subjects in the previous studies, those in the VLBW cohort were significantly shorter than controls, with a mean difference of 4 cm for VLBW men and 8 cm for VLBW women, and only the men were found to be significantly lighter than the controls. Ericson and Källén[5] reported that 289 VLBW men at 19 years of age had odds ratios (ORs) of 4.8 (95% confidence interval [CI]: 3.6–6.5) for having a height of <170 cm and 3.6 (95% CI: 2.8–4.7) for having a weight of <65 kg compared with the remainder of 150 229 men who registered for national service in Sweden. They did not, however, report mean values for height or weight.

Other data on nutritional outcomes are available from the Helsinki Study of Very Low Birth Weight Adults. Bone density was measured at a mean age of 22.6 years by dual-energy radiograph absorptiometry in 144 VLBW subjects and compared with 139 term controls, excluding those with CP or who were pregnant[13]; the bone density *z* scores were lower by 0.51 (95% CI: 0.28–0.75) SD units in the lower lumbar spine and by 0.56 (95% CI: 0.34–0.78) SD units in the femoral neck. The odds of having a bone density *z* score of less than −1 SD were 2.3 (95% CI: 1.4–3.8) times higher in the VLBW group; results were not reported separately for men and women. The reduced bone density did not translate into more VLBW subjects with vertebral body compression deformities, but at such a young age compression

fractures of the vertebral bodies would be rare. Given the propensity for women, in particular, to develop osteoporosis and have excessive fractures in later life, the early loss of bone mineral density in VLBW subjects needs to be confirmed in other adult studies, and its long-term consequences for bone health need to be determined. In another study on the same cohort (163 VLBW subjects, 169 controls), a 75-g glucose-tolerance test revealed an increase in fasting insulin level, impaired glucose tolerance, and an increase in insulin resistance in the VLBW subjects, although none of them had diabetes.[11] Given the impending epidemic of type II diabetes in the developed world associated with obesity and other lifestyle factors, these findings in VLBW subjects are yet another area of concern for the survivors of extreme prematurity in the future.

CARDIOVASCULAR HEALTH

Diseases of the heart and cardiovascular disease remain the leading cause of death in the developed world and were responsible for 33% of deaths in the United States in 2004–2005.[14] High blood pressure is one of the major risks for cardiovascular disease; consequently, pediatricians need to be aware of the blood pressure of their patients not only in childhood but also into adulthood. There are now many studies that have revealed higher blood pressure in survivors of extreme prematurity in early adulthood. Some authors have reported results from standard clinical measurement of blood pressure, others have measured ambulatory blood pressure, and some have measured both (Table 2). The advantages of ambulatory blood pressure measurements over conventional sphygmomanometry include improved objectivity in measurement and, thus, limitation of expectation bias, as well as avoidance of "white-coat hypertension." There is increasing evidence

TABLE 2 Blood Pressure in Survivors of Preterm Birth Measured in Early Adulthood Compared With Controls

Study	Subject Characteristics, Preterm (*n*)/control (*n*)	Year of Birth	Age, Mean, y	Method	Systolic Blood Pressure			Diastolic Blood Pressure		
					Preterm, Mean (SD)	Control, Mean (SD)	Mean Difference (95% CI)	Preterm, Mean (SD)	Control, Mean (SD)	Mean Difference (95% CI)
Kistner et al[17]	Women <32 wk gestation, 15/17	NS	24.7	Clinical: oscillometric	123 (13)	110 (7)	13[a]	69 (8)	64 (7)	5[b]
				Ambulatory: 24 h	120 (7)	116 (7)	4[b]	72 (7)	69 (4)	2[b]
Doyle et al[18]	BW < 1501 g, single hospital, 156/38	1977–1982	18.6	Clinical: sphygmomanometer	124.8 (14.8)	116.1 (14.1)	8.6 (3.4 to 13.9)	72.4 (9.6)	68.2 (7.2)	4.3 (1.0 to 7.6)
				Ambulatory: 24 h	122.1 (9.6)	117.4 (7.4)	4.7 (1.4 to 8.0)	69.2 (7.0)	68.0 (4.8)	1.1 (−1.2 to 3.5)
Hack et al[19]	BW < 1501 g, single hospital, 195/208	1977–1979	20	Clinical: sphygmomanometer	114.2 (11.0)	111.9 (13.0)	2.3[a]	73.1 (9.0)	72.6 (9.0)	0.5[b]
Johansson et al[20]	Swedish male singletons, 24–28 wk gestation, 162/275 895	1973–1981	18.2	Clinical: sphygmomanometer	132 (13)	129 (11)	3[a]	67 (11)	67 (10)	0[b]
Hovi et al[11,21]	BW < 1500 g, single hospital, no exclusions 163/169	1978–1985	22	Clinical: automated sphygmomanometer	121.8 (13.6)	117.5 (13.0)	4.0 (1.5 to 6.5)[a]	78.8 (8.6)	75.2 (8.2)	3.6 (0.8 to 6.3)[a]
				Ambulatory: 24 h	M: 121.7 (6.8); F: 117.1 (10.7)	M: 122.1 (9.4); F: 114.0 (6.9)	2.4 (0.2 to 4.6)[c]	M: 68.9 (6.1); F: 71.6 (7.8)	M: 70.1 (6.4); F: 71.6 (7.8)	0.8 (−0.8 to 2.5)[c]

BW indicates birth weight; NS, not specified; M, male; F, female.
[a] Not calculated in the publication but statistically significant between groups.
[b] Not calculated in the publication but not statistically significant between groups.
[c] For both genders combined, adjusted for age and gender.

that an average of ambulatory blood pressure recordings may be a better predictor of cardiovascular morbidity than clinic blood pressure in hypertensive subjects.[15,16]

Studies in which clinical blood pressures were measured are summarized in Table 2; of the 5 studies, 3 measured blood pressure both clinically and with 24-hour ambulatory blood pressure monitoring. Kistner et al,[17] in a study of 15 female survivors of very preterm birth compared with 17 non–growth-restricted term controls found higher adult systolic blood pressure but not diastolic blood pressure when measured clinically but no statistically significant differences in ambulatory blood pressures. From a hospital cohort study, Doyle et al[18] reported that only ambulatory systolic blood pressure and both systolic and diastolic clinical blood pressures were significantly higher in VLBW subjects compared with term controls. Hack et al[19] reported higher systolic blood pressure in 195 adult subjects born at VLBW compared with 208 term controls, but the differences for diastolic blood pressure were not statistically significant. In a population-based study of men recruited for military service in Sweden at 18 years of age, Johansson et al[20] observed that systolic blood pressure increased progressively with decreasing gestational age at birth by 0.31 mm Hg (SE: 0.1) for each weeks' decrease in gestational age. Of the 162 subjects of 24 to 28 weeks' gestation, 31.5% had elevated systolic blood pressure (≥140 mm Hg) compared with 20.2% of 275 895 subjects born at 37 to 41 weeks' gestation (OR: 1.93 [95% CI: 1.34–2.78], adjusted for sociodemographic variables). Few had high diastolic blood pressure in any gestational age group. Hovi et al[11] reported significant elevations compared with controls in both systolic and diastolic clinical blood pressures in their cohort study of VLBW subjects from Helsinki but only in ambulatory systolic blood pressures.[21]

In the 3 studies in which blood pressure was measured both clinically and also with 24-hour ambulatory monitoring, there was less variation in the mean ambulatory values, the differences between preterm and term subjects were narrower with ambulatory monitoring than with clinical measurements, and the only statistically significant differences between groups were in systolic blood pressures (Table 2).

Other cardiovascular markers that are related to later cardiovascular disease, including left ventricular hypertrophy assessed by ultrasound and measurements of carotid intima-media thickness, have yet to be fully reported for survivors of extreme prematurity compared with term controls in adulthood, although in an abstract from the Helsinki Study of Very Low Birth Weight Adults, increased carotid intima-media thickness in VLBW survivors compared with term controls was reported.[22]

RESPIRATORY HEALTH

Pulmonary Function

Survivors of extreme prematurity have more airway obstruction and air-trapping compared with term controls on pulmonary function testing in early adulthood, and this is even more marked in those who survived with BPD, as illustrated in Table 3, in which results from 3 cohort studies in which the forced expiratory volume in 1 second (FEV_1) at 18 to 19 years of age was measured are shown.[23–25] The reductions in FEV_1 are consistent with those in another study of a convenience sample of 25 survivors with BPD born between 1964 and 1973; FEV_1 was reduced at 18 years of age when compared with other preterm survivors without BPD and when compared

TABLE 3 FEV_1 (% predicted) in preterm survivors measured in early adulthood compared with controls

Study	Subject Characteristics	Year of Birth	Age, Mean, y	Preterm Groups		Controls; *n*	Mean Difference (95% CI)		
				BPD, Mean (SD); *n*	No BPD, Mean (SD); *n*		BPD vs no BPD	BPD vs Controls	No BPD vs Controls
Halvorsen et al[23]	<29 wk gestation or BW < 1001 g, regional cohort	1982–1985	17.7	87.8 (13.8); 12[a]	97.7 (12.9); 34	108.1 (13.8); 46	−9.9 (−18.8 to −1.0)	−20.3 (−29.3 to −11.3)	−9.9 (−18.8 to −1.0)
Doyle et al[24]	BW < 1501 g, single hospital	1977–1982	18.9	81.6 (18.7); 33[b]	92.9 (12.8); 114	99.4 (9.5); 37	−11.3 (−16.9 to −5.7)	−17.8 (−24.8 to −10.8)	−6.5 (−11.0 to −2.0)
Vrijlandt et al[25]	<32 wk gestation or BW < 1500 g, 2 hospitals	1983	19	90.1 (19.8); 8[c]	99.2 (17.9); 12	109.6 (13.4); 48	−9.1 (−27.0 to 8.8)	−19.5 (−30.5 to −8.5)	−10.4 (−19.7 to −1.1)

BW indicates birth weight.

[a] The BPD group had oxygen requirement at 36 weeks; the remainder in this table are considered to have no BPD, although 24 of those in the preterm group with no BPD were oxygen dependent at 28 days.

[b] BPD was determined by ventilator dependency, oxygen requirement for >28 days, and chest radiograph consistent with Northway stage 3 or 4 changes.[60]

[c] BPD was defined as need for oxygen at 28 days and chronic changes (not specified) on chest radiograph; data only for males in both preterm groups.

with term controls.[2] In contrast, in a study of 60 survivors of birth weight at <2500 g, FEV_1 was not significantly lower than in controls at 21 years of age.[26] In both of these studies, few subjects would have been EP. Although the EP group had more abnormalities, most had respiratory function values within the expected range.[23–25] In a study that assessed exercise tolerance in survivors of extreme prematurity in early adulthood, maximum workload was 15% lower than in controls, and there were other abnormalities compared with controls.[25]

Other Respiratory Health Issues

Asthma has been reported to be significantly more frequent in young adult survivors of extreme prematurity than in controls in some[26–29] but not all studies,[24] and rates of recurrent bronchitis were also higher in the EP group in 1 study.[29] Sleep-disordered breathing in the Helsinki Study of Very Low Birth Weight Adults was 2.2 (95% CI: 1.1–4.5) times more common in VLBW survivors compared with controls at a mean age of 22 years after adjustment for confounding variables.[30]

NEUROSENSORY IMPAIRMENTS

Neurodevelopmental, behavioral, and functional outcomes of preterm subjects in adulthood were recently reviewed extensively[31]; some aspects are covered here, with a focus on the most immature and smallest survivors where possible.

One of the major neurologic complications of EP birth is CP; survivors of extreme prematurity have rates of CP in childhood 70 to 80 times higher than those in term infants in CP registers.[32] Reported rates of CP in adulthood are consistent with these observations and are a little higher in cohorts of those who were either of <1001 g birth weight or <28 or <29 weeks' gestation (13.4%[33] or 7.2%[34] in ELBW cohorts, 9.1% at 23–27 weeks' gestation,[4] or 8.7% at either <29 weeks' gestation or <1001 g birth weight[23]) compared with rates in VLBW cohorts (6.9%,[5] 6.6%,[35] 4.7%,[36] or 8.5%[37] on self-report), or 4.1% in those born at <33 weeks' gestation in a population-linkage study.[6] Rates of CP in controls are typically low and mostly zero in cohort studies with concurrent controls,[23,34,35,37] because the sample sizes are relatively small compared with the expected frequency of <1 in 500.[32] There was, however, 1 case of CP in 133 (0.8%) controls in 1 study.[33] The population-linkage studies have reported rates of CP in term adults of 0.19% in Denmark[6] and 0.13% in Norway.[4]

Rates of other sensory impairments are higher in EP subjects than in controls and are generally higher in ELBW cohorts than in VLBW cohorts; bilateral blindness ranged from 7.4% in an ELBW cohort[33] to 1.9%[37] and 0.4%[35] in 2 VLBW cohorts, and deafness ranged from 8.7%[34] and 0%[33] in 2 ELBW studies compared with 0.4%[5] and 1.2%[35] in 2 VLBW studies. Blindness has not been reported for term controls in any cohort study, and rates of deafness in control cohorts are mostly zero,[33,34] although in 1 study there was 1 case of deafness of 233 controls (0.4%).[35] In addition to blindness, more survivors of extreme prematurity require prescription glasses than do controls (64% vs 37% in 1 study[29]). In the same study late retinal detachment was reported in 4% of 149 ELBW subjects during the late teen years, and another 3 of 45 ELBW subjects as adults had retinal tears on examination that required surgery.[29]

Intellectual impairment has not been defined identically in all studies, but survivors of extreme prematurity have higher rates of intellectual impairment compared with term controls.[4,5,35]

The overall rates of 1 or more neurosensory impairments in survivors of extreme prematurity compared with controls vary from 26.8% vs 2.3%[33] and 14.5% vs 0% (not including intellectual impairment)[34] in ELBW studies to 14.5% vs 1.7% in 1 VLBW study[35] and 11.6% vs 0% by self-report in the Helsinki Study of Very Low Birth Weight Adults.[37] In another large study of young adults who were either <32 weeks' gestation or <1500 g at birth, but without concurrent controls, the rate of moderate or severe cognitive or neurosensory dysfunction was 10.9% (7 of 64) in survivors of <28 weeks' gestation.[38]

EDUCATIONAL ACHIEVEMENT

Rates of completing high school have been generally lower in both population-linkage and cohort studies of survivors of extreme prematurity. In Sweden, 71.0% of those born at 24 to 28 weeks' gestation vs 78.6% born at term completed 12 or more years of school[39]; and in Denmark, 23.9% born at <33 weeks' gestation vs 16.3% born at term had only basic schooling (<10 years formal schooling).[6] In 2 studies from Norway that clearly overlapped, 67.7% of those born at 23 to 27 weeks' gestation vs 75.4% born at term completed high school in 1 study,[4] and in the other study of singleton births the rate of completing high school was 65.5% in those born at 22 to 27 weeks' gestation compared with 75.0% in controls.[40] For the cohort studies, 56.1% of ELBW subjects aged 18 or more years vs 84.6% of controls completed high school in 1 study,[34] and 83.2% vs 88.0% in another study completed high school.[41] In VLBW cohorts, 74.0% vs 82.8% of controls completed high school in 1 study,[35] and in another, 35.4% of VLBW boys completed high school compared with an expected rate of 47.8%.[5] In addition to schooling, adults who were born extremely prematurely score worse on tests of academic achievement such as word decoding and mathematical

computations compared with controls.[35] Compared with NBW controls, VLBW adults have also been reported to have higher rates of grade repetition at school (40% vs 27%), and fewer VLBW men continued on to postsecondary education (30% vs 53%).[35]

COGNITIVE FUNCTION

The cognitive functioning of adults born EP has not been well studied, and the measures used in reports to date that have examined general intellectual ability were not comprehensive and less than ideal. Using a 2-subtest form of the Wechsler Adult Intelligence Scale-Revised (WAIS-R), Hack et al[35] found that their cohort of VLBW adults at 20 years scored nearly one-third SD lower than NBW controls, and the difference was higher in the men than in the women. In a more recent study that contrasted 94 very preterm (<33 weeks' gestational age) and 44 term-born adults, a difference of approximately two-thirds SD (8.7 points) in favor of controls was found using the Wechsler Abbreviated Scale of Intelligence (WASI) at a mean age of 19.5 years.[42]

Deficits have also been reported in processing speed and executive functioning. VLBW adults free of neurosensory impairment have been shown to have slower processing speed on a battery of computerized neuropsychological tests than have term controls.[43] The VLBW adults were slower to respond in a simple reaction-time task and in more complex processing tasks that required selective decision-making, working memory, and divided attention. Although slower to process and respond to visual stimuli, the VLBW cohort performed as accurately as controls except for a visual associative learning task, which is suggestive of a memory deficit. Another study of adults <33 weeks' gestation assessed at 22 to 23 years of age revealed higher rates of problems in executive functioning, which refers to skills that are important in goal-directed behavior such as attentional control, cognitive flexibility, and planning and organization.[44] The very preterm group performed below term controls in areas of response inhibition and cognitive flexibility, even after controlling for IQ, gender, and age at assessment. In the latter study, however, only 4 of 61 subjects had gestational ages of <27 weeks. These results of executive dysfunction in adulthood of cohorts born before 1990 are consistent with those of other studies of executive dysfunction in more recent cohorts of EP subjects assessed in childhood.[45]

PSYCHIATRIC DISORDERS

Low birth weight (birth weight < 2500 g)[46] and birth at <33 weeks' gestation[47] have been linked with higher rates of schizophrenia in adulthood. Given the low prevalence of the condition, none of the recent cohort studies of survivors of VLBW or extreme prematurity, with sample sizes in the low hundreds at best, has revealed excessive rates of schizophrenia. In a population-linkage study of over 900 000 subjects in Norway, rates of diagnosis of schizophrenia as a reason for receiving disability benefits ranged from 0.6% for those born at 23 to 27 weeks' gestation to 0.1% for those born at term but were not significantly higher with lower gestational ages ($P = .12$).[4] In the same study, on the other hand, a diagnosis of autism spectrum disorder ranged between similar values of 0.6% at 23 to 27 weeks' gestation to 0.05% at term, but this time the trend was statistically significantly higher with lower gestational ages ($P = .002$).[4] In the cohort study of Saigal et al,[41] 1.3% of ELBW subjects had a diagnosis of autism compared with none of the controls.

Depression is associated with low birth weight.[48,49] In the Helsinki study, VLBW survivors as a group were not significantly more depressed clinically than controls and had lower, rather than higher, scores on a depression scale; however, VLBW subjects who were growth restricted at birth had more depression.[50] In the Saigal et al study, 14.1% of 149 ELBW subjects at 23 years of age were on prescription drugs for depression compared with only 6.0% of 133 NBW controls.[29] In another cohort study, 12.4% (21 of 169) of survivors born at <33 weeks' gestation in 1979–1984 had a psychiatric disorder at 18 years of age on the basis of the Clinical Interview Schedule-Revised compared with 4.9% (5 of 102) in nonrandomly selected controls, including 13 with depressive disorders compared with only 2 controls.[51]

EP children are at increased risk for hyperactivity and inattention.[52,53] In the 1 adult study that tested for attention-deficit/hyperactivity disorder, there were no important differences between 162 VLBW and 172 controls on overall scores on the Adult Problem Questionnaire, which includes items that assess behavioral symptoms of attention-deficit/hyperactivity disorder, apart from less alcohol use in the VLBW subjects.[54]

As a reflection of overall psychiatric morbidity, in a large population-based study there was a stepwise increase in psychiatric hospital admissions from ages 8 to 29 years with an increasing degree of preterm birth; 5.2% of adults born at 24 to 28 weeks' gestation were admitted at least once (OR: 2.3 [95% CI: 1.5–3.7] relative to those born at 39 to 41 weeks' gestation).[55]

QUALITY OF LIFE

Studies of both ELBW[33] and VLBW[36,56] adults have revealed either no differences or small reductions in self-reported quality of life compared with

controls, although those with neurologic or other health impairments do have lower scores than those without impairments. Information reported by the subjects themselves is important, particularly because it complements data obtained by other observers such as health professionals.

FUNCTIONAL OUTCOMES

Several authors have reported functional limitations in adulthood in survivors of extreme prematurity. In a study of ELBW subjects, Saigal et al[29] reported higher rates of functional limitations compared with controls in many areas, including vision, hearing, dexterity, clumsiness, learning disabilities, and reduced self-care abilities. Hack et al[57] reported differences in several domains of the Child Health and Illness Profile-Adolescent Edition between 20-year-old VLBW subjects and controls; specifically, the VLBW group reported better achievement than the controls, particularly in work performance, but less resilience and more risk avoidance, including individual risks of drug and alcohol abuse and sexual activity. Similarly, in the Helsinki study of 162 VLBW adults and 188 controls free of major disability, those in the VLBW cohort were less likely to leave the parental home and to start cohabiting with an intimate partner and were also less likely to experience sexual intercourse.[58] Given the lower reported rates of sexual activity, it is not surprising that fertility rates are relatively lower in survivors of extreme prematurity. In a population-linkage study from Norway of 1 167 506 singleton births, for those born at 22 to 27 weeks' gestation, the absolute reproduction rates were 25.0% for women and 13.9% for men compared with rates in term subjects of 68.4% for women and 50.4% for men.[40]

For several of the large population-linkage studies, higher rates of EP subjects receiving financial assistance because of disability have been reported compared with controls. In a Swedish study, 13.2% of 317 adults born at 24 to 28 weeks' gestation received a disability pension (for sickness or disability) compared with 1.3% of 500 197 term controls.[39] Similar rates of receiving a disability pension were observed for young adults in Norway: 10.6% in those born at 23 to 27 weeks' gestation and 1.7% in those born at term.[4]

CONCLUSIONS

As a group, survivors of extreme prematurity have higher rates of many adverse health outcomes in early adulthood compared with term controls; however, the majority of them lead productive and healthy lives. Survival rates for EP cohorts described in this review were all low compared with today's survival rates; survival rates for ELBW infants in Victoria, Australia, increased from 1 in 4 in the late 1970s to 3 in 4 in the late 1990s.[59] More very immature and tiny infants survive today, and they are at even higher risk of adverse long-term outcomes.[53] Thus, the adult outcomes for EP infants born today can only be determined with certainty by following them into adulthood. In the meantime, although they reflect clinical care from more than 2 decades ago, the adult outcomes described in this overview provide the best estimates of what to expect for today's survivors, until superseded by more contemporary data. It is vital that some of the cohorts described in this overview be followed until even later in adulthood to determine the rates of serious health outcomes such as stroke and myocardial infarction, but this will require new teams of researchers to take over the challenge from today's investigators.

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