ARTICLE

Functional Outcomes and Participation in Young Adulthood for Very Preterm and Very Low Birth Weight Infants: The Dutch Project on Preterm and Small for Gestational Age Infants at 19 Years of Age

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ABSTRACT

OBJECTIVE. Young adults who were born very preterm or with a very low birth weight remain at risk for physical and neurodevelopmental problems and lower academic achievement scores. Data, however, are scarce, hospital based, mostly done in small populations, and need additional confirmation.

METHODS. Infants who were born at <32 weeks of gestation and/or with a birth weight of <1500 g in the Netherlands in 1983 (Project on Preterm and Small for Gestational Age Infants) were reexamined at age 19. Outcomes were adjusted for nonrespondents using multiple imputation and categorized into none, mild, moderate, or severe problems.

RESULTS. Of 959 surviving young adults, 74% were assessed and/or completed the questionnaires. Moderate or severe problems were present in 4.3% for cognition, 1.8% for hearing, 1.9% for vision, and 8.1% for neuromotor functioning. Using the Health Utility Index and the London Handicap Scale, we found 2.0% and 4.5%, respectively, of the young adults to have ≥3 affected areas in activities and participation. Special education or lesser level was completed by 24%, and 7.6% neither had a paid job nor followed any education. Overall, 31.7% had ≥1 moderate or severe problems in the assessed areas.

CONCLUSIONS. A total of 12.6% of young adults who were born very preterm and/or with a very low birth weight had moderate or severe problems in cognitive or neurosensory functioning. Compared with the general Dutch population, twice as many young adults who were born very preterm and/or with a very low birth weight were poorly educated, and 3 times as many were neither employed nor in school at age 19.

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Key Words
very low birth weight infants, very preterm infants, young adulthood, long-term outcome, cognitive function, neurosensory function, quality of life, education, employment

Abbreviations
VLBW—very low birth weight
POPS—Project on Premature and Small for Gestational Age Infants
WHO—World Health Organization
HUI3—Health Utility Index Mark 3
LHS—London Handicap Scale
CI—confidence interval

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PRETERM BIRTH MAY have long-lasting effects. Although most preterm infants survive without major disabilities, follow-up studies at preschool age have revealed major disabilities such as cerebral palsy, mental retardation, blindness, and deafness.[1,2] Follow-up studies at school age have shown socioemotional, cognitive, and learning problems in addition.[3,4] The first studies in young adults who were born preterm in the 1970s reported risk for physical and neurodevelopmental problems, higher incidence of chronic illness, and lower IQ and academic achievement scores in comparison with term-born young adults.[5–9] Regrettably, virtually all information on outcomes in adulthood has been collected from small numbers of infants in individual hospitals. Multicenter studies in individuals from defined geographic regions are now being recommended.[10] Moreover, ranges of functional outcomes among successive cohorts of very low birth weight (VLBW) and very preterm infants have been lacking uniformity.[11]

The Dutch nationwide follow-up study, Project on Premature and Small for Gestational Age Infants (POPS), ongoing since 1983, gave us the opportunity to investigate cognitive and neurosensory functioning as well as activities and participation in society in relation to environmental and personal factors.[12–15] We examined the degree to which these survivors from the early era of neonatal intensive care have become fully independent and satisfied with their role in society.[12–15]

METHODS

Study Population

The original POPS cohort comprised 1338 individuals who were live-born very preterm (at <32 weeks of gestation) and/or had a VLBW (<1500 g) in the Netherlands in 1983.[13] As a total of 379 children did not survive to their 19th year; 959 young adults aged 19 years were eligible for this follow-up study that examined long-term effects of preterm birth on various medical, psychological, and social parameters (Fig 1).

Assessment

Shortly after their 19th birthday individuals were invited to participate in the study. Participation involved standard assessment at 1 of the 10 participating hospitals and completion of a set of questionnaires. Parents completed the questionnaires when individuals were incapable. Assessments were conducted by trained nurses; details, logistics, and response rate were reported previously.[16]

Ethical Approval and Informed Consent

The respective medical ethics review boards approved the study protocol. All participants provided written informed consent to participate in the study before assessment started.

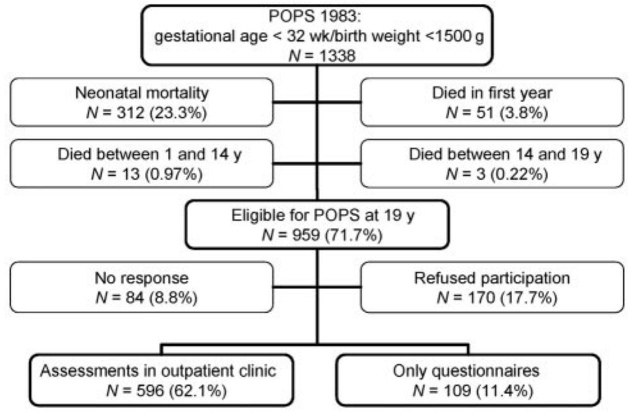

FIGURE 1
Flow chart inclusion of participants of the POPS study at 19 years of age.

Measures at 19 Years of Age

Cognitive and neurosensory functioning as well as activities and participation in society at 19 years of age were classified according to the World Health Organization's (WHO's) International Classification of Functioning, Disability and Health.[17] For each of these areas, we ascertained possible problems, and, when present, we rated them as mild, moderate, or severe.

With regard to cognitive and neurosensory functioning, the WHO defines impairments as a significant deviation or loss. Four areas were assessed: cognition, hearing, vision, and neuromotor function.

Cognition was assessed with the use of the computer version of the Multicultural Capacity Test–Intermediate Level developed by Bleichrodt and Berg.[18] This test provides an overview of a person's capacity and skills, covering a fairly broad spectrum of intelligence factors: verbal and numerical factors, appreciation of spatial dimensions, fluent speech, memory, reasoning, and speed of perception. Cognition was classified according to the SD scores of the general population (IQ ≥85, no problem; IQ ≥70 and <85, mild problem; IQ ≥55 and <70, moderate problem; IQ <55, severe problem).

Hearing was tested for each ear separately by pure-tone audiometry with a hand-held audiometer, fitted for air and bone conduction. We determined auditory sensitivity as the mean of the threshold levels at 500, 1000, 2000, and 4000 Hz. Classification was according to the definitions of the WHO's International Classification of Impairments, Disabilities and Handicaps (loss in the best ear ≤25 dB, no problem; >25 and ≤55 dB, moderate problem; >55 dB, severe problem).[19]

Vision status was ascertained from the participant's self-report. Being blind or having severe visually impairment was classified as a moderate problem.

Neuromotor function assessment was based on Touwen's examination of minor neurologic dysfunction,[20] as revised by Samsom et al.[21] This examination focuses on 5 subcategories of function—hand function, quality of walking, coordination, posture, and passive muscle tone—resulting in 5 scores on the subcategories and a total score of the summed subcategories of 68 points. Outcome was expressed on a 3-point scale: the items were classified in an ordinal scale as being optimal (2 points), slightly deviant (1 point), or poor (0 points). Classification was according to the percentile scores of the mean of the Dutch norm group (score: 96%–100% [total score: 59.50–68.00], no problem; score: 76%–95% [total score: 46.98–59.49], mild problem; score: 51%–75% [total score: 31.32–46.97], moderate problem; score: ≤50% [total score: ≤31.31], severe problem).[22]

Individuals may experience limitations in activities and participation in society. The WHO defines activity limitations as difficulties that an individual may have in executing activities; participation restrictions are problems that an individual may experience in involvement in life situation.[17] We assessed 4 areas that are relevant to this domain: health status, perceived health, education, and occupation.

Health status was determined with use of the Health Utilities Index Mark 3 (HUI3). Focusing on functional capacity, the HUI3 consists of 8 attributes of health status (vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain) with 5 or 6 levels per attribute.[23]

Perceived health was measured by the London Handicap Scale (LHS), a generic (utility) measure of disability. The LHS is based on the first version of the *International Classification of Impairments, Disabilities and Handicaps*. It incorporates a 6-point hierarchical scale of disadvantages for each of 6 dimensions of disability: mobility, physical independence (self-care), occupation (daily activities), social integration, orientation, and economic self-sufficiency.[24]

HUI3 attributes and LHS dimensions tend to be extremely skewed; as a result, relevant differences in distributions may go undetected. This is why we dichotomized HUI3 and LHS scores: scores 1 and 2 were considered to reflect no problem or a mild problem and scores ≥3 to reflect a moderate or severe problem. Total scores of 6 HUI attributes (we excluded emotion and pain as being subjective measures) and the 6 LHS dimensions were then classified as follows: 0 affected, no problem; 1 to 2 affected, mild problem; 3 to 4 affected, moderate problem; and 5 to 6 affected, severe problem.

Information concerning educational attainment and current enrollment in an educational program was ascertained from the participant's self-report. Graduation from or enrollment in university, higher vocational education, or senior or general secondary education was considered to reflect no problem; special education or junior secondary vocational education was a moderate problem; primary school and no certificate or current education on any level was a severe problem.

Occupational activities were ascertained from the participant's self-report and were classified as follows: full-time (≥32 hours/week) job or full-time education or part-time education with a job for 16 to 31 hours/week, no problem; part-time education with a job for <16 hours/week or only a job for <32 hours/week, mild problem; part-time job and/or education with a disability allowance, moderate problem; no paid job and no education (with or without disability allowance), severe problem. Both education and occupation were classified according to the level of education and expectations of the general population for a 19-year-old individual.

In addition, we established the following environmental and personal factors: gender (male versus female), gestational age (≥32, 31, 30, 29, 28, 27, or 26 to 25 completed weeks of gestation), birth weight (≥1500, 1000 to 1500, or <1000 g at birth), and highest level of parental education (low [primary school or junior secondary vocational education], middle [general or senior secondary education], or high [higher vocational education, or university]).

Multiple Imputation and Data and Statistical Analyses

Multiple imputation[25] was applied to adjust for missing values in some or all of the variables at age 19. This simulation-based approach creates a number of imputed (completed) data sets by "filling in" plausible values for the missing data. The imputations are based on a model that uses information from other variables to achieve optimal estimates. Only imputations for the missing values between the lowest and highest values of the measured outcome variable are valid. Uncertainty about the model estimates is reflected in differences between imputations in the different completed data sets. Realistic complete data estimates can be attained through pooling results from the completed data sets.

We used the MICE (Multivariate Imputation by Chained Equations) software program[26] to create 5 imputed data sets, based on the environmental and personal factors mentioned, as well as maternal age at delivery; disability status at 5 years of age; available outcome-specific data at ages 5, 10, and 14 years; and all other outcomes at 19 years of age. We applied predictive mean matching[27] to create multiple imputations. CIs for the outcomes were estimated through pooling of the multiple imputations in S-plus.

First, problem rates for areas separately were determined. Next, overall outcomes for cognitive and neurosensory functioning as well as activities and participation in society were calculated, followed by the total overall outcome. Problem severity in the overall outcome was based on the worst area of functioning, in agreement with recently published data.[28] For example, a combination of multiple mild problems was still considered to be a mild problem in the overall outcome. Relationships between these outcomes were analyzed. Finally, relationships between the different outcomes and environmental and personal factors were determined.

Role of the Funding Source

The organizations that sponsored the study, mentioned in the acknowledgments, had no involvement in study design, data collection, analysis, interpretation of the data, or writing of the report.

RESULTS

Of the 959 POPS cohort survivors, 705 (74%) completed the questionnaires, and 596 (62% of total) of these underwent full assessment at the hospital as well. The mean age of the 705 respondents was 19.3 years (SD: 0.2 years). The group of 254 (26% nonrespondents) was found to include significantly more men and more children of low-educated parents (Table 1). Individuals with disabilities were overrepresented among respondents who did not undergo assessment and among nonrespondents.[16] Multiple imputation indeed slightly increased the abnormal outcomes on all areas (Table 2). For IQ, the average from the naive analysis lies outside the 95% confidence interval (CI) that accounts for the nonresponse.

Moderate or severe problems for cognition were established in 4.3% of the survivors, for hearing in 1.8%, for vision in 1.9%, and for neuromotor function in 8.1%. Thus, for the overall domain of cognitive and neurosensory functioning, 12.6% were found to show moderate or severe problems (Table 3). Three or more affected areas of health status (as measured by the HUI3) or of perceived health (as measured by the LHS) were noted in 2.0% and 4.5% of survivors, respectively. Moderate or severe problems in education were found in 24%. Nearly 8% of survivors stated that they neither to had a paid job nor followed any educational program. Overall, 31.7% of survivors had moderate or severe problems in functioning, activities, and participation (Table 3). Furthermore, 40% had problems in ≥ areas (data not shown). Half of the individuals with moderate or severe problems in education had full-time jobs, and 62% of those who neither had a paid job nor were enrolled in an educational program reported no or only mild problems with respect to health status and perceived health (data not shown).

We found clear associations between cognitive or neurosensory functioning problem severity and mean numbers of affected HUI3 attributes or LHS dimensions (Table 4). Furthermore, proportions of survivors with special or primary education and those without a paid job or education increased with increasing cognitive and neurosensory functioning problem severity (Table 4). Most of the survivors who were neither employed nor in school at age 19 and had severe problems in cognitive or neurosensory functioning had cerebral palsy. All survivors with problems in cognitive and neurosensory functioning (from mild to severe) experienced more activity limitations and participation restrictions than did survivors with no problems in this domain (Table 4).

As shown in Table 5, most of the impairments in cognitive and neurosensory functioning, activity limitations, and participation restrictions were related to environmental and personal factors. Most striking is the impact of parental education level: the lower the level, the higher the proportion of problems in any domain or overall. Figure 2 shows the relations between overall problem severity with mortality included and gestational age. It seems that only 13.2% of infants who were live born at 25 to 26 weeks of gestation had no or just mild problems at 19 years of age (78% mortality), compared with 61.5% of those who were live born at 31 weeks of

TABLE 1 **Environmental and Personal Factors in Eligible and Assessed 19-Year-Olds and Nonrespondents**

Factor	POPS Survivors Until Age 19 ($N = 959$), n (%)	Assessed at Age 19 ($N = 705$), n (%)	Nonrespondents ($N = 254$), n (%)	P (Assessed vs Nonrespondents)
Gender				
Male	497 (51.8)	328 (46.5)	169 (66.5)	<0.0001
Female	462 (48.2)	377 (53.5)	85 (33.5)	
Gestational age, wk				
≥32	283 (29.5)	207 (29.4)	76 (29.9)	NS
31	211 (22.0)	150 (21.3)	61 (24.0)	
30	158 (16.5)	112 (15.9)	46 (18.1)	
29	129 (13.5)	102 (14.5)	27 (10.6)	
28	88 (9.2)	70 (9.9)	18 (7.1)	
27	56 (5.8)	40 (5.7)	16 (6.3)	
25–26	34 (3.5)	24 (3.4)	10 (3.9)	
Birth weight, g				
≥1500	198 (20.6)	144 (20.4)	54 (21.3)	NS
1000–1500	632 (65.9)	460 (65.2)	172 (67.7)	
<1000	129 (13.5)	101 (14.3)	28 (11.0)	
Parental education				
High	218 (24.9)	198 (29.2)	20 (10.1)	<0.0001
Middle	317 (36.2)	255 (37.6)	62 (31.3)	
Low	341 (38.9)	225 (33.2)	116 (58.6)	

NS indicates not significant.

TABLE 2 Outcome in Assessed 19-Year-Olds Compared With Outcome in Survivors at Age 19 After Multiple Imputation

Area	Total Assessed, *n* (%)	Assessed Outcome, Mean (SD) or %	MI Outcome, Mean (SD) or %	95% CI of Imputed Data
Cognitive and neurosensory functioning				
Cognition, IQ	562 (59)	100.2 (15.0)	97.8 (15.6)	96.5–99.1
Hearing loss, best ear, dB	587 (61)	6.2 (7.4)	6.7 (8.9)	6.0–7.3
Vision problems	690 (72)	1.4	1.9	0.9–2.8
Neuromotor, total score	592 (62)	58.1 (9.5)	57.6 (10.1)	56.8–58.4
Activities and participation				
HUI				
Cognition	690 (72)	21.9	22.9	19.4–26.4
Hearing		1.7	2.0	0.9–3.0
Vision		1.0	1.4	0.5–2.3
Ambulation		2.3	2.5	1.4–3.6
Dexterity		3.2	3.2	2.0–4.4
Speech/language		6.5	6.8	5.1–8.6
Emotion		4.4	4.3	2.8–5.8
Pain		8.8	8.7	7–11
No. of affected attributes[a]		0.37 (0.69)	0.39 (0.72)	
LHS				
Mobility	690 (72)	2.3	2.5	1.5–3.5
Physical independence		4.2	4.6	3.3–6.0
Occupation		5.2	5.6	4.0–7.2
Social integration		6.1	6.3	4.6–8.1
Orientation		2.6	3.1	1.9–4.3
Economic self-sufficiency		8.2	9.3	7.4–11.2
No. of affected dimensions		0.29 (0.86)	0.32 (0.90)	
Special or primary education	688 (72)	21.2	24.0	20.9–27.1
No paid job and no education	688 (72)	7.0	7.6	5.8–9.4

MI indicates multiple imputation.
[a] Emotion and pain excluded.

TABLE 3 Outcomes in Cognitive and Neurosensory Functioning, Activities, and Participation in Survivors at Age 19 After Multiple Imputation

Area	No Problem, %	Mild Problem, %	Moderate Problem, %	Severe Problem, %
Cognitive and neurosensory functioning				
Cognition	80.8	14.8	4.3	
Hearing	98.2		0.9	0.9
Vision	98.1		1.9	
Neuromotor	53.5	38.4	4.9	3.2
Overall cognitive and neurosensory functioning	47.1	40.4	8.6	4.0
Activities and participation				
HUI affected attributes	71.4	26.6	1.9	0.1
LHS affected dimensions	83.8	11.7	3.3	1.2
Education	76.0		15.0	9.0
Profession/occupation	78.1	10.5	3.8	7.6
Overall activities and participation	47.4	24.8	14.6	13.2
Total overall outcome in functioning, activities, and participation	27.2	41.1	16.5	15.2

gestation (14% mortality). Excluding mortality, the overall percentage of adverse outcome (moderate and severe problems) decreased for 39.9% of survivors who were born at 25 to 26 weeks of gestation to 28.6% of survivors who were born at 31 weeks of gestation (Table 5).

DISCUSSION

Earlier studies already had established that very preterm and VLBW infants are at risk for neurodevelopmental problems in young adulthood.[6,7,29] This study in a geographically defined population of such infants at 19 years of age showed 1 in 8 survivors to experience moderate or severe problems in any cognitive or neurosensory function. One in 4 survivors was poorly educated. These outcomes compare well to the outcomes in the POPS cohort at younger age.[12,14] Most frequent in this study population were problems in neuromotor functioning, including minor neurologic dysfunction

TABLE 4 Activity Limitations and Participation Restrictions in Relation to Impairments in Cognitive and Neurosensory Functioning in Survivors at Age 19 Years After Multiple Imputation

Area	Cognitive and Neurosensory Functioning, Mean (95% CI)			
	No Problem	Mild Problem	Moderate Problem	Severe Problem
No. of affected HUI attributes	0.25 (0.20–0.31)	0.35 (0.28–0.43)	0.69 (0.41–0.98)	1.70 (0.97–2.43)
No. of affected LHS dimensions	0.11 (0.06–0.17)	0.24 (0.16–0.31)	1.00 (0.58–1.42)	2.06 (1.23–2.88)
Special or primary education, %	12.1 (8.7–15.6)	27.4 (20.6–34.1)	56.9 (43.4–70.5)	60.7 (44.0–77.4)
No paid job and no education, %	2.8 (0.9–4.6)	7.3 (4.1–10.6)	18.5 (7.9–29.1)	44.0 (25.4–62.7)

TABLE 5 Proportions of Moderate or Severe Problems in Cognitive and Neurosensory Functioning, Activities, and Participation at Age 19 in Relation to Environmental and Personal Factors in Survivors After Multiple Imputation

Parameter	Moderate or Severe Problems in Cognitive and Neurosensory Functioning, %	Moderate or Severe Problems in Activities and Participation, %	Moderate or Severe Problems in Overall Outcome, %
Gender			
Male	14.8	32.5	36.0
Female	10.1	22.7	27.1
Gestational age, wk			
≥32	11.5	26.8	31.1
31	10.7	25.9	28.6
30	12.8	28.1	32.0
29	16.8	29.2	34.1
28	15.5	30.7	35.2
27	7.4	26.3	29.1
25–26	16.7	35.7	39.9
Birth weight, g			
≥1500	11.2	29.2	31.5
1000–1500	12.3	26.9	30.8
<1000	15.5	30.2	36.0
Parental education			
High	7.4	12.2	16.2
Middle	11.8	24.5	27.9
Low	16.2	39.9	44.1

and abnormalities in the coordination of movement (46.5%). Almost 8% of survivors were neither employed nor in school, which suggests difficulties in becoming fully independent adults, yet 50% of the poorly educated individuals held full-time jobs. The vast majority (>95%) of the total study population reported to be satisfied with their activities and participation in society (as measured by HUI3 and LHS). However, when restricted to those who were neither employed nor in school, this proportion was 62%.

Because comparison with a formal control group was impossible (because of financial restrictions), we used validated assessments and questionnaires for which norm scores have been established. The mean IQ of 97.8 (95% CI: 96.5–99.1) in our study population did differ significantly from the standard of the adult general population (IQ 100).[18] The proportion of participants with hearing loss (1.8%) exceeded the norm (0.1%).[30] Neuromotor scores in a norm group ranged from 60 to 66, versus a mean of 57.6 (95% CI: 56.8–58.4) in our study population.[22] Data on vision, education, and occupation of 19-year-olds in the Dutch general population were derived from the Continuous Health Interview Survey 2001 and 2002 conducted by Statistics Netherlands. Frequency of self-reported vision problems in our study did not differ significantly from that in 19-year-olds in the general population. Twice as many 19-year-olds in our study population were poorly educated as compared with their age-peers in the general population (24.0% [95% CI: 20.9%– 27.1%] vs 12.8% [95% CI: 10.5%–15.6%]). Furthermore, thrice as many were neither employed nor in school (7.6% [95% CI: 5.8%–9.4%] vs 2.6% [95% CI: 1.6%–4.2%]). Scores on the HUI3 and LHS compared well with those in the general population.[31]

Earlier studies on very preterm and VLBW children consistently reported lower cognitive scores and lower academic skills in young adulthood as compared with control subjects (or the general population).[6–9,32] However, although the findings from our study are consistent with the educational disadvantage observed previously, the mean IQ in our cohort was only 2.2 IQ points lower

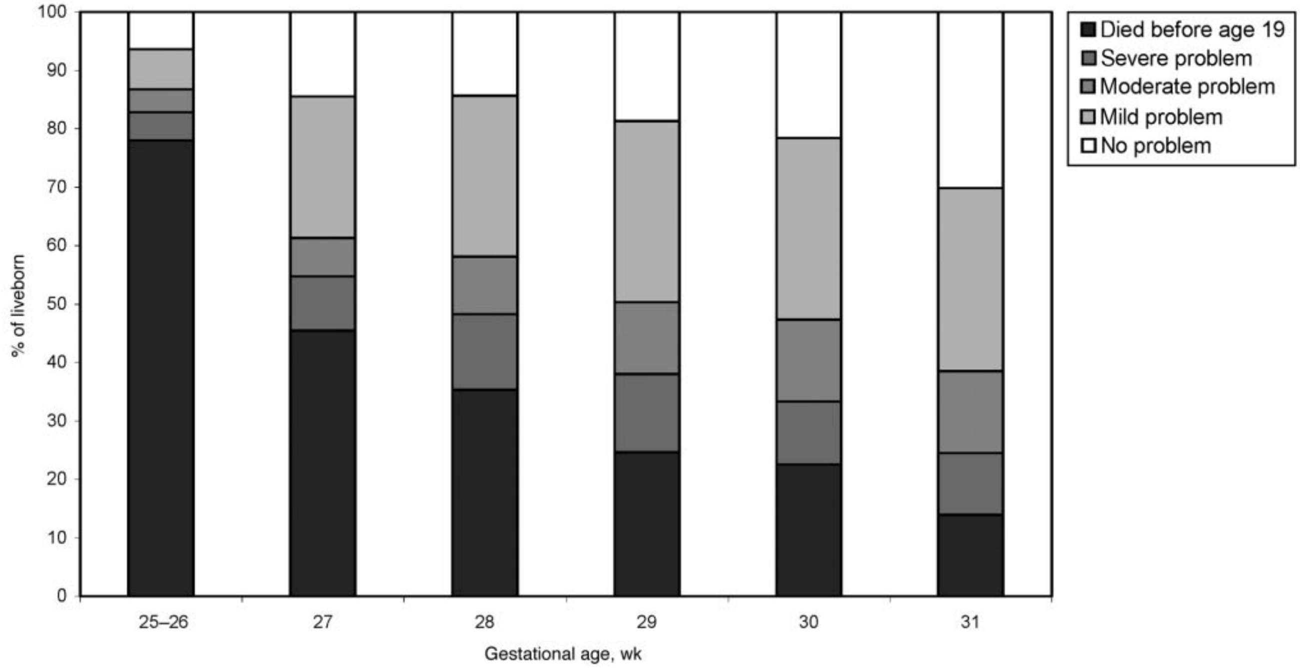

FIGURE 2
Relation between total overall outcome (including mortality) at age 19 and gestational age (<32 weeks) in live-born individuals after multiple imputation.

than that in the Dutch adult general population. One possible explanation for this surprisingly good result is that individuals with severely disabilities were unable to do the computer test. Furthermore, our result indicates that apart from IQ, several factors, such as socioeconomic circumstances, behavior, and neurosensory impairments, explain the educational attainment.[33]

Most earlier studies found a normal perceived quality of life in early adulthood.[9,29,34,35] Similarly, in our study, health status and perceived health (measured by HUI3 and LHS) were better than expected from the impairments in cognitive and neurosensory functioning. Dinesen and Greisen[34] reported several reasons for the discrepancy between objective and subjective quality of life: people often neglect needs that they consider unattainable; needs that are satisfied with no effort are not considered to be needs; actual needs may differ from person to person.

For reasons of comparability, we based problem severity in the overall outcome on the worst area of functioning.[28] Thus, overall 31.7% of survivors were found to have ≥1 moderate or severe problems. Another 41.1% had ≥1 mild problems. Seeing that this classification is arbitrary, we recalculated overall outcome defining ≥2 mild problems (eg, IQ of 75, mild neurologic dysfunction) as a moderate problem. Doing so, 44.1% of survivors would show a moderate or severe problem and 28.7% only 1 mild problem.

A limitation of our study might be that we focused on the traditional areas of functioning, leaving out physiologic parameters (eg, several chronic diseases[36–42]). Therefore, the overall proportion of young adults with a moderate or severe problem of any kind is likely to be underestimated in this study.

A problem that is inherent to long-term follow-up of preterm infants is that outcomes might not be relevant to survivors of current neonatal intensive care. Major changes have occurred since the early days of the development of intensive care treatment for preterm neonates. Since the 1980s, the survival rate has increased significantly. One might speculate that advances in medical technology and increased understanding of how to prevent neonatal damage may have led to a reduction in rates of disabilities.[43] However, because of these advances, ever-increasing numbers of extremely immature and sick infants now have a chance to survive and may add to the total number of children with problems in functioning in the community.[28] Recent Dutch cohort studies confirmed that improvements in perinatal and neonatal care have led to an increased survival of especially extremely preterm infants. However, increased survival has resulted in more morbidity.[44–46] We therefore suggest that our results have relevance to current survivors of current neonatal intensive care.

CONCLUSIONS

Our study documents that 12.6% of very preterm and/or VLBW infants experience moderate or severe problems in cognitive or neurosensory functioning at 19 years of age. Overall, 31.7% were found to experience ≥ moderate or severe problems in the assessed areas. The vast majority (>95%) of the total study population reported to be satisfied with their activities and participation in society. Compared with the general Dutch population, twice as many very preterm and/or VLBW infants are poorly educated and thrice as many are neither employed nor in school at 19 years of age.

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