Nonresponse Bias in a Follow-up Study of 19-Year-Old Adolescents Born as Preterm Infants

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ABSTRACT. Objective. To assess the effect of demographic and neonatal risk factors and outcome at the last available assessment on the probability of full responders, postal responders (those who only responded to the mailed questionnaire), or nonresponders in a follow-up study of 19-year-old adolescents who were born as preterm infants.

Design. The 19-year follow-up program was part of a large ongoing collaborative study in the Netherlands on the long-term effect of prematurity and dysmaturity on various medical, psychological, and social parameters. In the original cohort, 1338 infants (94%) with a gestational age of <32 weeks and/or a birth weight of <1500 g were enrolled. Neonatal mortality was 23% (n = 312), and another 67 children had died between the ages of 28 days and 19 years, leaving 959 survivors (72% of the original cohort) for follow-up at the present assessment. To study the effect of nonresponse, we divided the 959 survivors into 3 groups: full responders (596 [62.1%]), postal responders (109 [11.4%]), and nonresponders (254 [26.5%]). In the 3 groups we compared demographic and neonatal data, as well as outcome at the last available assessment.

Results. The odds ratios (ORs) for male versus female for the probabilities of nonresponse and postal response were statistically significant: 2.7 (95% CI: 1.9–3.9) and 1.6 (95% CI: 1.0–2.5), respectively. The same holds for the ORs for nonresponse versus Dutch and low versus high maternal education for nonresponse: 2.0 (95% CI: 1.3–3.2) and 3.7 (95% CI: 2.0–6.7), respectively. Special education and severe handicap showed a statistically significant influence on nonresponse (OR: 1.6; 95% CI: 1.1–2.4 and OR: 2.6; 95% CI: 1.3–5.2) and postal response (OR: 2.0; 95% CI: 1.2–3.3 and OR: 4.4; 95% CI: 2.0–9.9), respectively. At the age of 19 years, primary school and special education were found significantly more frequent in the postal responders than in the full-response group (20% and 21% vs 6% and 12%), respectively. The full responders, on the other hand, were higher educated than were the postal responders.

Conclusions. In this follow-up study at the age of 19 years, boys, non-Dutch adolescents, and low maternal education were overrepresented in the nonresponse and postal-response groups. Nonresponse decreased the proportion of infants with adverse outcome in assessed children. To be able to present reliable results for the total group of survivors in long-term follow-up studies, the nonresponse bias needs to be quantified. Therefore, it is evident that more research using statistical methods such as imputation of missing data is needed.

Methods

The 19-year follow-up program was part of a large ongoing collaborative study in the Netherlands on the long-term effect of prematurity and dysmaturity on various medical, psychological, and social parameters. In the original cohort, 1338 infants (94%) with a gestational age of <32 weeks and/or a birth weight of <1500 g were enrolled (Project on Preterm and Small for Gestational Age Infants [POPS]).6,7 Neonatal mortality was 23% (n = 312), and another 67 children had died between the ages of 28 days and 19 years, leaving 959 survivors (72% of the original cohort) for follow-up at the present assessment.

Before the start of the multicenter, 19-year assessment, the medical ethical committees of the participating NICUs and coordinating center had approved the study protocol. Before the ini-
tation for the assessment, all adolescents were informed of the study and its methods with a brochure. Written informed consent was obtained from all participants.

Two months after their 19th birthday, the POPS adolescents willing to participate were approached to join the forthcoming study at either the hospital that had provided neonatal intensive care or the NICU nearest to their present address. A confirmation of the appointment was sent to the subject’s home, with an informed consent letter and a questionnaire including questions about acute and chronic illnesses, complaints, medical consumption, medication, perceived health, pain coping, and behavior. The assessment was performed at the outpatient clinic of the involved NICU and included blood pressure and carotid intima media thickness measurements, blood and urine testing, an intelligence test, a pain-tolerance test, anthropometry, audiometry, a neuro-motor examination, and a second questionnaire (regarding school, work, lifestyle, behavior, and coping). A few months after the appointment, every participant received an individual report of the assessment. If the results warranted additional clinical examination, the participant received a letter to inform the family doctor. In addition to the information from the participants themselves, parents also filled in a questionnaire about health of the child, family impact, and their coping strategies. In case of a handicapped young adult, these parents were also asked to assist in filling in the subject’s questionnaires. From April 1, 2002, until April 31, 2003, the young adults were scheduled for an appointment in 1 of 10 NICUs. In each NICU an investigator and a local coordinator had been appointed. Every other month the investigators discussed the progress of the project (quality control). All data (questionnaires and assessments) have been stored in a central database and were coded by the original patient identification number. Blood and urine were stored separately.

To study the effect of nonresponse, we divided the 959 survivors into 3 groups: full responders (596 [62.1%]), postal responders (109 [11.4%]), and nonresponders (254 [26.5%]). The full responders were assessed at the outpatient clinic of the involved NICU and completed the questionnaires. The postal responders only completed the mailed questionnaires. The nonresponders did not respond to any of our mailed requests and several telephone calls and personal requests, and it was traced because their family had moved (within the Netherlands or abroad). In this group were included adolescents who had promised repeatedly to cooperate but nevertheless did not respond and those who specifically refused additional participation.

In the 3 groups we compared demographic and neonatal data, as well as outcome at the last available assessment. Demographic data included maternal age, educational level of the mother (number of years of completed education), socioeconomic level, origin of the parents (Dutch or non-Dutch), and gender of the child. Neonatal data included gestational age [SGA; <10th centile] according to the Amsterdam growth charts,5 birth weight (small for gestational age [AGA; ≥10th centile]), and birth weight and ventilatory support (intermittently positive pressure ventilation and/or continuous positive airway pressure, none; 1–7, 8–28, and >28 days). Handicap status (normal, impairment, mild handicap, severe handicap) and school type (special versus normal education) at the last available assessment were used as intermediate outcome measures. Intermediate outcome measures from earlier follow-ups were available for 89% of the survivors at age 14 (N = 854), 77% at age 10 (N = 712), 84% at age 9 (N = 813), 96% at age 5 (N = 927), and 97% at age 2 (N = 946).5 In the Netherlands, after completing primary school at the age of 12 years, pupils choose 1 of 3 levels of secondary school. The school-placement system aims to keep every adolescent in mainstream education. Special secondary education is limited and consists of education for adolescents with either cognitive, behavioral, motor, sensory, or multiple disabilities. At the age of 19 years, the highest level of completed or current education in relation to the response groups was assessed.

Statistical Analysis

Univariate analysis of the relation between demographic and neonatal data, as well as outcome at the last available assessment and the highest level of completed or current education results, and the response groups was performed by using the chi² test on the usual 2-way cross tabulations. Associations were considered to be significant if the P value was <.05. Data from the 3 response groups were compared by using a stepwise multinomial logistic-regression analysis assessing the effect of demographic and neonatal risk factors and outcome at the last available assessment on the probability of full response, postal response, or nonresponse simultaneously.

RESULTS

Of the 959 surviving adolescents, 705 (73.5%) participated in the follow-up study at 19 years of age. With 93.2% of the addresses and 88.9% of the telephone numbers of the 959 survivors contact could be established. In the postal-response group, 96.3% of the adolescents could be contacted by telephone. In the nonresponse group, 76% of the addresses and 59.4% of the telephone numbers were attainable. Of the 959 survivors, 596 (62.1%) adolescents participated in both the mailed questionnaire and the assessment in the NICU (full responders), 109 (11.4%) adolescents only completed the mailed questionnaires (postal responders), and 254 (26.5%) of the adolescents did not participate (nonresponders). Of the 254 nonparticipants, 132 (52%) refused to take part in the follow-up study. For 15% of the adolescents, the reason for not complying was “being physically or mentally unable to participate in the assessment,” and in 33% of the cases, no reason was given at all.

Table 1 shows a univariate analysis of demographic and neonatal outcome data for the 3 response groups. In Table 2 the educational status and handicap status at 14 years are shown in relation to the response groups. SGA status, maternal age, and artificial respiration did not show a significant difference between the full responders, the postal responders, and the nonresponders. Gender, educational level of the mother, origin of the parents, and socioeconomic status of the parents were different in the 3 response groups, showing significantly more boys and more of those with non-Dutch origin, lower educational background, and lower socioeconomic status in the nonresponse group.

Table 3 describes the effect of demographic, neonatal, and outcome factors on the probability of nonresponse and postal response in a polytomous logistic-regression model adjusted for demographic and neonatal risk factors, with the full-response group as reference. The odds ratios (ORs) for male versus female for the probability of nonresponse and postal response were statistically significant: 2.7 (95% confidence interval [CI]: 1.9–3.9) and 1.6 (95% CI: 1.0–2.5), respectively. The ORs for non-Dutch versus Dutch and low versus high maternal education for nonresponse were 2.0 (95% CI: 1.3–3.2) and 3.7 (95% CI: 2.0–6.7), respectively, and therefore are also statistically significant. Special education and severe handicap showed a statistically significant influence on nonresponse (OR: 1.6; 95% CI: 1.1–2.4 and OR: 2.6; 95% CI: 1.3–5.2) and postal response (OR: 2.0; 95% CI: 1.2–3.3 and OR: 4.4; 95% CI: 2.0–9.9), respectively.

The highest level of completed or current education in 19-year-old adolescents in relation to full response and postal response is described in Table 4. Primary school and special education were found significantly more frequently in the postal responders than in the full-response group (20% and 21% vs...
DISCUSSION

At the age of 14 years, 89% of the survivors responded to the mailed questionnaires. At the age of 19 years, only 73.5% of the adolescents responded to these questionnaires. This can be explained by the fact that in this study the adolescents were approached to participate in a physical examination. The results show a remarkably high percentage of boys in the nonresponse and postal-response groups (66.1% and 55%, respectively), whereas 51.8% of all survivors are male. The multivariate analysis adjusted for origin, gestational age, SGA status, and maternal education showed 2.7 and 1.6 times more boys in the nonresponse and postal-response groups than in the full-response group. A possible explanation might be that girls at this age are generally more socially involved and therefore better motivated to participate in a follow-up. Another reason could be that the parental influence on adolescent girls is more pronounced than in boys of this age. This is supported by the findings in the follow-up study at age 14, in which no difference was found in participation between boys and girls. Ethnicity, maternal education, school type, and handicap status seem to have a pronounced influence on response as well. There were 2 times more non-Dutch and 3.7 times more lower educated mothers in the nonresponse group. These findings correspond with the results reported by Hack et al. The adolescents who received special education at age 14 were significantly more often present in the nonresponse and postal-response groups than in the full-response group (OR: 1.6; 95% CI: 1.1–2.4 and OR: 2.0; 95% CI: 1.2–3.3, respectively). Severe handicap at last assessment showed a significant influence on nonresponse and postal response (OR: 2.6; 95% CI: 1.3–5.2 and OR: 4.4; 95% CI: 2.0–9.9, respectively). This result is in accordance with the findings of Wolke et al and oth-
ers, who found that nonresponse decreases the proportion of infants with adverse outcomes in assessed children. Castro et al and McCormick et al, on the other hand, found that compared with children who were lost to follow-up, those who were compliant with follow-up had more adverse outcomes.

It seems that the adolescents with higher completed or current education are overrepresented in the full-response group at the age of 19 years. In the postal-response group, there were as many high- as low-educated 19-year-old adolescents.

The effect of selective nonresponse on parameter estimates in response studies is often underestimated. In an editorial comment in the *European Journal of Epidemiology*, Stang pointed out that nonresponse may introduce bias of the effect measures and emphasized that there is no logical connection between low response and nonresponse bias and that analysis of the nonresponse criteria, where possible, should be performed and published to allow comparison between follow-up studies. We realize that also in our study the decrease in response rate introduces a bias in the outcome results. It is for this reason that we have put emphasis on the analysis of the differences between the nonresponse and response groups. From a methodologic point of view, simulation studies (imputation of missing data) might provide a better understanding of the influence of nonresponse on the outcome of follow-up.

To be able to present reliable results for the total group of survivors in long-term follow-up studies, the nonresponse bias needs to be quantified. Therefore, it is evident that more research using statistical methods such as imputation of missing data is needed.

**ACKNOWLEDGMENTS**

POPS-19 was supported by grants from the Netherlands Organization for Health Research and Development, Edgar Doncker Foundation, Foundation for Public Health Fundraising Campaigns, Phelps Foundation, Swart-van Essen Foundation, Foundation for Children’s Welfare Stamps, TNO Quality of Life, Netherlands Organization for Scientific Research, Dutch Kidney Foundation, Sophia Foundation for Medical Research, Stichting Astrabestrijding, and Royal Etha Guyot group.


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**TABLE 3.** Effects of Various Variables on the Probability of Nonresponse and Postal Response

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonresponders OR (95% CI)</th>
<th>P</th>
<th>Postal Responders OR (95% CI)</th>
<th>P</th>
<th>Overall P for the Effect of Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender Male</td>
<td>2.7 (1.9–3.9)</td>
<td>0.001</td>
<td>1.6 (1.0–2.5)</td>
<td>0.030</td>
<td>.001</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Origin Dutch</td>
<td>1</td>
<td></td>
<td>2.0 (1.3–3.2)</td>
<td>0.003</td>
<td>.012</td>
</tr>
<tr>
<td>Non-Dutch</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGA status AGA</td>
<td>0.77 (0.5–1.2)</td>
<td>NS</td>
<td>0.55 (0.3–1.0)</td>
<td>0.044</td>
<td>.091</td>
</tr>
<tr>
<td>SGA status SGA</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal education Low</td>
<td>3.7 (2.0–6.7)</td>
<td>0.001</td>
<td>1.3 (0.7–2.3)</td>
<td>NS</td>
<td>.001</td>
</tr>
<tr>
<td>Middle</td>
<td>1.3 (0.7–2.5)</td>
<td>NS</td>
<td>0.79 (0.4–1.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation Yes</td>
<td>1.1 (0.9–1.4)</td>
<td>NS</td>
<td>1.2 (0.9–1.5)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>School type Normal</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Special</td>
<td>1.6 (1.1–2.4)</td>
<td>0.019</td>
<td>2.0 (1.2–3.3)</td>
<td>0.005</td>
<td>.005</td>
</tr>
<tr>
<td>Handicap status Normal</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impairment</td>
<td>0.67 (0.4–1.0)</td>
<td>0.076</td>
<td>1.6 (1.0–2.6)</td>
<td>0.066</td>
<td>.001</td>
</tr>
<tr>
<td>Mild handicap</td>
<td>0.87 (0.5–1.4)</td>
<td>NS</td>
<td>1.2 (0.6–2.3)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Severe handicap</td>
<td>2.6 (1.3–5.2)</td>
<td>0.006</td>
<td>4.4 (2.0–9.9)</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

Variables were adjusted for gender, origin, gestational age, SGA status, maternal education, and mechanical ventilation. The reference category for each risk factor is indicated by 1. NS indicates not significant.

**TABLE 4.** Highest Level of Completed or Current Education in 19-Year-Old Adolescents

<table>
<thead>
<tr>
<th>Education Level</th>
<th>Total (N = 688), n (%)</th>
<th>Full Responders (N = 588), n (%)</th>
<th>Postal Responders (N = 100), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary school</td>
<td>56 (8.1)</td>
<td>36 (6.1)</td>
<td>20 (20.0)</td>
</tr>
<tr>
<td>Special education and junior secondary vocational education</td>
<td>90 (13.1)</td>
<td>69 (11.7)</td>
<td>21 (21.0)</td>
</tr>
<tr>
<td>General secondary education</td>
<td>71 (10.3)</td>
<td>68 (11.6)</td>
<td>3 (3.0)</td>
</tr>
<tr>
<td>Senior secondary education</td>
<td>305 (44.3)</td>
<td>269 (45.7)</td>
<td>36 (36.0)</td>
</tr>
<tr>
<td>Higher vocational education and university</td>
<td>166 (24.1)</td>
<td>146 (24.8)</td>
<td>20 (20.0)</td>
</tr>
</tbody>
</table>

*P = .001.
REFERENCES


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Pediatrics 2005;116:e662

DOI: 10.1542/peds.2005-0682

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