Associations of Preterm Births with Child Health and Development: Japanese Population-Based Study

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Objective To examine associations between the duration of gestation and health and development outcomes at 2.5 years and 5.5 years using a Japanese population-based longitudinal survey (n = 47 015).

Study design Hospitalization was used as an indicator of physical health, and responses to questions about age-appropriate behaviors were used as an indicator of behavioral development. We conducted logistic regression analyses controlling for a set of neonatal and family factors. We also estimated population-attributable fractions.

Results We observed a steady increase toward shorter duration of gestation in the risk of hospitalizations at age 2.5 years and 5.5 years and developmental delays at 2.5 years ($P_{\text{linear trend}} < .001$ for all outcomes). We found associations only between extremely preterm birth and delayed behavioral development at age 5.5 years.

Conclusion There is a linear relationship between shorter duration of gestation and increased risk of later health and developmental problems. In line with Rose's "population paradox," the population-attributable risks for these problems are greater for moderately preterm infants compared with extremely preterm infants. *(J Pediatr 2013;163:1578-84)*.

The proportion of preterm births has been increasing in developed countries in recent years, although reasons for this trend are not fully understood.[1] Japan is no exception in following this worldwide trend. The incidence of preterm births has been increasing steadily over the last 2 decades, rising from 4.5% in 1990 to 5.7% in 2010.[2] In contrast, the proportion of postterm births has decreased from 1.7% to 0.3%. Preterm births can be separated into 3 subcategories: births at or before 27 weeks of gestation (extremely preterm), births between 28 and 31 weeks of gestation (very preterm), and births between 32 and 36 weeks of gestation (moderately preterm).[3] In Japan, the rate of moderately preterm births has increased from 3.9% in 1990 to 5.0% in 2010, whereas the rates of extremely preterm and very preterm births have remained stable during this period (increasing from 0.2% to 0.3% and from 0.4% to 0.5%, respectively). In sum, an increase in moderately preterm births is the main driving force behind the overall increase in preterm births.

Compared with extremely preterm and very preterm births, the adverse effects of moderately preterm births have been understudied.[4] Reviews and meta-analyses indicate that even moderately preterm births are often associated with unfavorable consequences in both the short term and the long term.[5-9] Some previous studies have shown that children born moderately preterm demonstrate deficits in schooling, such as placement in special education;[10-13] however, other studies failed to detect differences between moderately preterm births vs full-term births on behavioral and cognitive development at later ages.[14-16]

A study conducted in the United Kingdom highlighted a substantial impact of moderately preterm birth on young children's health in the study population (eg, hospital admissions and longstanding illness/disability at age 3 and 5 years).[17] Other studies have found an adverse impact on household financial burden associated with moderately preterm birth.[18,19] However, to date no studies have examined the population impact of moderately preterm birth on behavioral development. In the present study, we used a nationwide survey to estimate the impact of moderately preterm birth on Japanese children's behavioral development in addition to physical health at age 2.5 years and 5.5 years.

Methods

The Japanese Ministry of Health, Labour, and Welfare (MHLW) has conducted an annual survey on newborn infants and their parents since 2001. The purpose of this survey, known as the Longitudinal Survey of Babies in the 21st Century, is to help the MHLW develop strategies in response to Japan's rapidly declining fertility rate.[20] This study was approved by the Institutional Review Board of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences (no. 486).

MHLW	Ministry of Health, Labour, and Welfare
PAF	Population-attributable fraction

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Questionnaires were sent to all families in Japan with a birth (or births) between January 10 and 17, 2001, on July 10-17, 2001, when the newborns were 6 months old. Of the 53 575 questionnaires mailed, 47 015 were completed and returned, for a response rate of 88%. Follow-up questionnaires have been sent to these participants every year (at age 18 months, 30 months, 42 months, and so on). Data for 2001-2011 are currently available from the MHLW. For this study, we used data for the first 8 years (ie, 2001-2009). Birth records from Japanese vital statistics are also linked to each child in this survey. Birth records data include length and weight, gestational age, singleton or multiple birth, sex, and parental age. We excluded postterm births, to focus on subsequent development of preterm and full-term infants. The 47 015 births included 414 postterm births and 36 births missing data on gestational age, leaving a total of 46 565 births for analysis (99%).

Exposure Variable

We ascertained each newborn's gestational age from birth records. Gestational age ranged from 23 weeks to 41 weeks. We created 4 groups based on duration of gestation: 23-31 weeks, extremely preterm (including very preterm births); 32-36 weeks, moderately preterm; 37-38 weeks, early full term; and 39-41 weeks, full term. Although separating the 32-36 weeks group into moderately preterm (32-33 weeks) and late preterm (34-36 weeks) would have been preferable, we chose to combine the 2 groups because of the small number of births (and subsequent hospitalizations) of infants born at 32-33 gestational weeks.

Health and Behavioral Development Outcomes

To examine the long-term effects of preterm births, we used the children's history of overnight hospitalization at age 0.5-2.5 years and at age 2.5-5.5 years as an indicator of health status during these years. The survey elicited information on whether or not the child had been hospitalized during the previous 12 months for any reason. The same question was asked in each survey from the second wave (at age 1.5 years) to the sixth wave (at age 5.5 years). We dichotomized the history of hospitalization at age 0.5-2.5 years by comparing 2 hospitalizations against 1 hospitalization or no hospitalizations over the 2-year period. At age 2.5-5.5 years, we dichotomized by 2 or 3 hospitalizations against 1 hospitalization or no hospitalizations over the 3-year period. We considered children who had been hospitalized multiple times to be physically more vulnerable. We chose to examine the history of hospitalization over multiple years rather than prevalence at age 2.5 years and 5.5 years to take full advantage of our data, as well as to compare our results with those of the British study cited earlier.[17] Unfortunately, we could not ascertain the duration or frequency of hospitalization within 12 months.

For behavioral development outcomes, we used the survey questions that elicited information on age-appropriate behaviors. At age 2.5 years, the following questions were asked: (1) "Can your child run?"; (2) "Can your child climb stairs?"; (3) "Can your child say things that make sense?"; (4) "Can your child compose 2-phrase sentences?"; (5) "Can your child say his or her own name?"; and (6) "Can your child use a spoon to eat?" We did not include several questions—"Can your child brush his or teeth by himself or herself?"; "Does your child wear a diaper during the day?"; and "Can your child put on clothes by himself or herself?"—because these behaviors seemed to be heavily dependent on parenting practices. We also did not include the question "Can your child walk?" in our analyses, because almost all responses were affirmative (>99%).

According to the MHLW, these behavioral questions were derived from the Maternal and Child Health Handbook ("*Boshi Kenkou Techyou*"). The Handbook is a record of health and child development given to every pregnant mother in Japan, with all information from postnatal visits recorded prospectively until the child is 6 years old. The dissemination and use of the Handbook is mandated under Japanese law and has been implemented for decades. The MHLW extracted the behavioral observations used in our analyses from the Handbook.

At age 5.5 years, the following questions were asked: (1) "Can your child listen without fidgeting?"; (2) "Can your child focus on one task?"; (3) "Is your child patient?"; (4) "Can your child express emotions appropriately?"; (5) "Can your child get along with others in a group setting?"; and (6) "Can your child keep promises?" According to the MHLW, these questions were developed for this survey to capture early signs of behavioral and developmental problems. Over the past decade, the MHLW has been attempting to track the prevalence of behavioral and developmental problems; however, we could not confirm whether these questions have been externally validated.

Statistical Analyses

We conducted logistic regression analyses to evaluate the relationships between duration of gestation and physical health as well as behavioral development at age 2.5 years and 5.5 years. We first estimated the crude OR and 95% CI for each outcome, then examined the OR and 95% CI for each outcome after controlling for neonatal and family factors. The full-term group (ie, 39-41 weeks gestation) served as our reference group for all analyses.

In our analyses, we controlled for a set of neonatal and family factors. Neonatal factors included sex (dichotomous) and singleton birth or not (dichotomous). Family factors included maternal age at delivery (continuous), maternal smoking habit (dichotomous), and father's and mother's educational attainment (categorical). We recorded maternal age and singleton birth or not from the birth record, maternal smoking habit from the first survey (ie, when the infants were aged 6 months), and educational attainment from the second survey. The question on smoking habit ascertained whether or not the mother was a regular smoker, followed by a question about the number of cigarettes smoked per day if the response was "yes." We categorized educational attainment into 3 levels: completed high school or less, completed a 2-year college or vocational school, and completed a 4-year