

# The Effect of Birth Weight Discordance on Infant Mortality Rates Among Zygotic Twins in Japan, 1995-2008

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## Abstract

Infant mortality rates (IMRs) of monozygotic (MZ) and dizygotic (DZ) twins were estimated using vital statistics from Japan between 1995 to 2008. Using the same data, Imaizumi [1] reported that mortality risk factors were maternal ages of <20 years and gestational ages of up to 35 weeks. In the present study, 128,236 MZ and 180,920 DZ twins were used as denominators to compute IMRs in zygotic twins. Numbers of infant deaths were 1,858 MZ and 1,620 DZ twins. Birth weight discordance (BWD) levels were classified into seven groups from <5% to 30% $\geq$ . Fig. 1 shows the relationship between IMRs and BWD levels. The lowest IMR was 7.5 per 1000 live births at 5–9% in MZ and 6.7 at <5% in DZ twins. IMRs were significantly higher in MZ than DZ twins except two BWD levels from 5%–9% to 10–14%. The lowest IMR in MZ twins was significantly increased after 10–14%. The lowest IMR in DZ twins was 6.7 at <5% and significantly increased at 10–14% and after 25–29%. As for gestational age (GA) <28 weeks, the ratios of the highest vs. the lowest IMRs were 2.2(376.2/173.6) for MZ and 1.3 (275.2/207.2) for DZ twins. As for 28 weeks GA, the corresponding ratios were 13.8 (53.7/3.9) vs. 9.1 (29.1/3.2), respectively. Namely, under GA 28 weeks, a risk factor of BWD was not a main factor.

An alternative way to assess the etiological role of retarded fetal growth is to study twins.<sup>6</sup> Twins are smaller, on average, than singletons of the same gestational age, and even within pairs of twins of the same sex there are commonly substantial differences in birthweight and other anthropometric measures. The risks of mortality from coronary heart disease<sup>7</sup> and overall mortality among twins are similar to those of the general population.<sup>8</sup> Through investigation of the association between birthweight and coronary heart disease within same-sexed twin pairs, confounding by genetic and early environmental factors can be substantially decreased. In the population-based Swedish Twin Registry, linked with the registries of cause of death and hospital discharge, we investigated the association between birth characteristics and acute myocardial infarction (AMI) among same-sexed twins in Sweden. So that we could assess the impact of confounding by genetic factors and by early environmental influences other than fetal growth, we carried out a case-control study with two control groups. The first control group was unaffected external (unrelated) control twins, and the second was unaffected co-twins. This design enabled us to test two different hypotheses explaining the association between birth characteristics and AMI. First, the finding of an association between birth characteristics and AMI both among external control twins and among within-pair co-twin controls would strongly suggest a causal effect of birth characteristics on risk of AMI. Second, if the association were observed among external controls but not among co-twin controls, the

likely explanation for the discrepant results is confounding by genetic or early environmental influences.

In Japan, the fetal death rate (FDR; defined as death after GA of  $\geq 22$  weeks) decreased significantly between 1980/81 and 1998. During this period, FDRs for monozygotic (MZ) and dizygotic (twins decreased from 73 to 32 per 1000 twin deliveries and from 33 to 10 per 1000 twin deliveries, respectively [3]. However, there is no information on early neonatal deaths (ENDs) and PMRs for zygotic twins and singletons in Japan. This study aimed to estimate PMRs for MZ twins, DZ twins, and singletons between 1995 and 2008 and to identify risk factors associated with perinatal mortality.

Data on live births (LBs), fetal deaths (FDs), and ENDs for twins were obtained from statistical records between 1995 and 2008. We used the records maintained by the Statistics and Information Department, Ministry of Health, Labour and Welfare (Tokyo, Japan) that covered the entire Japanese population. LB certificates included details about the nationality, sex, date of birth, BW, and GA, as well as the ages and dates of birth of parents and dates of birth, whether the birth was single or multiple, and the birth order in multiple births. FD certificates were provided for deaths occurring at  $\geq 12$  completed gestational weeks and mostly contained the same information, including the date, but excluding the dates of parents' births. ENDs refer to deaths of live-born babies before the first week of life. Infant death certificates contained the same information as the LB and FD certificates; however, they excluded paternal age. PMR included all FDRs from 22 completed weeks of gestation and over (i.e., FDR for GA of  $\geq 22$  weeks) and all ENDs. Data for singleton births (males and females) were obtained using the vital statistics records.

Twin pairs at delivery were described as LB–LB (2LB), FD–FD (2FD), and LB–FD. The 2LB and 2FD cases were obtained from the LB and FD records, respectively, while the LB–FD cases were obtained from the LB and FD records that excluded 2LB and 2FD twin pairs. We identified 99.99% of the 166,690 twin pairs (including unknown sexes) during the study period. Data for ENDs were obtained from twin pairs of 2LBs (2LB–2END or 2LB–END) and LB–FD (LB–END). The number of MZ and DZ twins was estimated using the Weinberg method [15]. MA and GA were not always the same between twin pairs because each twin could be born on different dates.