

## Twin Births in Singapore: A Population-Based Study Using the National Birth Registry

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### Abstract

**Introduction:** Twin studies are a most effective method to analyse gene and environment interactions. Using data from the Singapore National Registry of Births and Deaths (SNRBD), this paper describes the number of twin and multiple births among different ethnic populations in Singapore. **Materials and Methods:** All births recorded in the SNRBD from 1 January 1986 to 31 December 2001 were analysed. Outcomes measured were twin and triple birth rates (per 1000 maternities) of the 3 main ethnic groups in Singapore (Chinese, Malays and Asian Indians). Further outcomes were calculated using Weinberg's differential rule to estimate the number of monozygotic and dizygotic twins. **Results:** Overall twin birth rates have steadily increased across all ethnic groups (7 to 9/1000). The largest increase in multiple births among the ethnic groups were twins born to Asian Indian fathers (6.9 to 9.9/1000) and Malay mothers (5.9 to 9.8/1000). A significant difference in birth rates between the ethnic groups was found during the years 1994 to 1997, where Chinese parents had the lowest multiple birth rates and Asian Indians the highest. Estimation and ratios of monozygotic and dizygotic twin births differed among the ethnic groups: Asian Indians had the highest ratios, followed by the Chinese and, lastly, the Malays. **Conclusion:** The SNRBD has provided an overview of multiple births in Singapore, although the establishment of a national twin register would enable more detailed analysis of genetic and environmental effects in multiple births.

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**Key words:** Birth rates, Epidemiology, Registry, Twins

### Introduction

Twin studies are regarded as one of the better ways to study the effects and significance of gene, environment and interactions of both.<sup>1,2</sup> The study of monozygotic (MZ) and dizygotic (DZ) twins allows for an estimation of the relative importance of genes and environment.<sup>1</sup> However, apart from this, new approaches in study design and statistical analyses have been formulated to study complex diseases.<sup>2</sup> One of the main limitations of previous twin studies are small numbers<sup>1</sup> and ascertainment bias.<sup>2</sup> Thus, population-based registers are valuable for epidemiologic research being usually of large numbers and lack ascertainment bias.<sup>2,3</sup>

Singapore is an island state of about 4 million people. Its population is composed of 3 main ethnic groups consisting

of Chinese (76.9%), Malays (14.6%) and Asian Indians (6.4%). Other ethnic groups make up a small percentage of the total population (2.1%). It is a unique location where these relatively homogeneous ethnic groups reside in similar environmental conditions. All births and deaths of Singaporean citizens are required by law to be registered in the Singapore National Registry of Births and Deaths (SNRBD). Thus, registration is virtually complete since a birth or death certificate is an important document for administrative purposes. Each individual also has a unique national registration identity card (NRIC) number.

Using data from the SNRBD, this paper describes twin and other multiple births in Singapore. Estimation of the number of MZ and DZ twins in this population was also undertaken.

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## Materials and Methods

All births recorded in the SNRBD from 1 January 1986 to 31 December 2001 were included in this study. Data used from the SNRBD for this study included gender and date of birth of the liveborn, parental NRIC number and ethnic group (Chinese, Malays, Asian Indians and others). Twin and other multiple birth status were determined by identifying liveborns that were born within 2 days of each other and with the same maternal NRIC number. Information is virtually complete for all livebirths during this period.

Numbers and birth rates (per 1000 maternities) were calculated for twin and multiple pregnancies, i.e., triplets or more liveborns. For this study, the term “triplets” was used for births of 3 or more liveborns. The birth rates and 95% confidence intervals (CI) over the whole time interval, 4-year periods and by the 3 main ethnic groups (Chinese, Malays and Asian Indians) of, first, fathers and then mothers, were calculated. Chi-square test was used to determine differences between ethnic groups within the same 4-year

period and changes in rates over the 4-year time periods. A *P* value of 0.05 was considered significant.

Weinberg's differential rule was used to estimate the number of MZ and DZ twins in this population.<sup>4</sup> It states that the number of DZ twin pairs is calculated as twice the number of opposite gender pairs and the number of MZ pairs is the total number of twin pairs minus the estimated number of DZ pairs. The DZ/MZ ratio was also calculated.

## Results

A total of 742,547 births were recorded during this 15-year period. Of these, 5935 were twin births and 212 were triplets. The overall twin rate was 8 (95% CI, 7.8 to 8.2) per 1000 maternities and the triplet rate was 0.29 (95% CI, 0.23 to 0.32) per 1000 maternities. The birth rates for twins from 1989 to 2001 are shown in Figure 1. It shows a steady increase in rates of twin births from 7 per 1000 maternities to over 9 per 1000 maternities.

Table 1 shows 4-year time period-specific rates of twin

Table 1. Twin Deliveries by Parental Ethnic Group for all Years Combined and 4-year Groups

Year	Father's ethnic group			Mother's ethnic group		
	Chinese	Malay	Indian	Chinese	Malay	Indian
<b>1986 to 2001</b>						
Total maternities	506,710	97,117	50,460	508,104	102,375	47,644
Twins	3972	744	419	3991	784	402
Rate per 1000 maternities (95% CI)	7.8 (7.6 to 8.1)	7.7 (7.1 to 8.2)	8.3 (7.51 to 9.1)	7.9 (7.6 to 8.1)	7.7 (7.1 to 8.2)	8.4 (7.6 to 9.3)
<b>1986 to 1989</b>						
Total maternities	124,546	23,882	11,802	125,474	25,416	11,281
Twins	868	152	81	868	150	78
Rate per 1000 maternities (95% CI)	7 (6.5 to 7.4)	6.4 (5.4 to 7.4)	6.9 (5.4 to 8.4)	6.9 (6.5 to 7.4)	5.9 (4.9 to 6.8)	6.9 (5.4 to 8.4)
<b>1990 to 1993</b>						
Total maternities	135,213	26,701	13,260	135,777	28,094	12,627
Twins	1022	200	94	1027	199	96
Rate per 1000 maternities (95% CI)	7.6 (7.1 to 8)	7.5 (6.5 to 8.5)	7.1 (5.7 to 8.5)	7.6 (7.1 to 8)	7.1 (6.1 to 8.1)	7.6 (6.1 to 9.1)
<b>1994 to 1997</b>						
Total maternities	131,676	24,544	12,771	131,664	25,672	12,052
Twins	1003	201	119	1012	208	118
Rate per 1000 maternities (95% CI)	7.6 (7.2 to 8.1)	8.2 (7.1 to 9.3)	9.3 (7.7 to 11)	7.7 (7.2 to 8.2)	8.1 (7 to 9.2)	9.8 (7.2 to 8.2)
<b>1998 to 2001</b>						
Total maternities	115,275	21,990	12,627	115,189	23,193	11,684
Twins	1079	191	125	1084	227	110
Rate per 1000 maternities (95% CI)	9.4 (8.8 to 9.9)	8.7 (7.5 to 9.9)	9.9 (8.2 to 11.6)	9.4 (8.9 to 10)	9.8 (8.5 to 11.1)	9.4 (7.7 to 11.2)
<i>P</i> value for trend for year groups	<0.001	0.003	0.002	<0.001	<0.001	0.01

CI: confidence interval

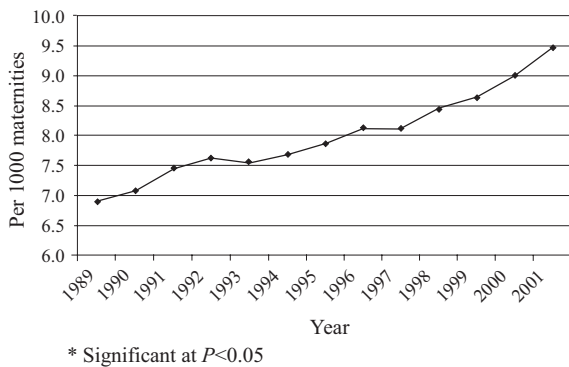


Fig. 1. Twin births per 1000 maternities in Singapore from 1989 to 2001.

births for the 3 ethnic groups. There was an increase in twin births for all the ethnic groups regardless of the ethnicity of either parent. However, the largest differences were for twins born to Asian Indian fathers (6.9 to 9.9 per 1000 maternities) and Malay mothers (5.9 to 9.8 per 1000 maternities) from 1986-1989 to 1998-2001. The test for trend over the 4 time periods was significant for all ethnic groups over the 4-year time periods. However, birth rate between ethnic groups within the 4-year period was found to be only significantly different from 1994 to 1997. Here, the difference was found for fathers ( $P = 0.03$ ) and mothers ( $P = 0.02$ ), with the rates being lowest for Chinese parents and highest for Asian Indian parents.

Of the 5935 twins, 4724 were of the same gender and 1211 were of different gender, irrespective of the ethnic group of either parent. Thus, there was an estimated 2422 DZ and 3513 MZ twins (DZ/MZ ratio of 0.69). The estimation of the number of DZ and MZ twin pairs and subsequent DZ/MZ ratio for ethnic groups are shown in Table II. It is important to note that the twin pairs for each parental ethnic group may not sum to the total number of twins in the population. This is because parents of the twin may be of similar or different ethnicity. The DZ/MZ ratio

ranged from 0.55 for twins born to Malay mothers and 0.99 for twins born to Asian Indian mothers. In general, the DZ/MZ ratio ranged from the lowest in Malays (0.63 and 0.55 for fathers and mothers, respectively) to the highest in Asian Indians (0.87 and 0.99 for fathers and mothers, respectively), with Chinese in between. Twins born to either Chinese fathers or mothers had similar DZ/MZ ratio.

## Discussion

The 5513 twin births between the years 1986 and 2001 gave an overall twin birth rate of 8 per 1000 maternities. Except for the time period 1994 to 1997, twin rates were not significantly different among the ethnic groups. However, they did vary significantly over time. Interestingly, the estimations of DZ and MZ twin births and subsequent DZ/MZ ratio appeared to be quite different for the ethnic groups, with Asian Indians having the highest ratios followed by the Chinese and, lastly, Malays.

Despite the steady increase in multiple births, Singapore still has one of the lowest twinning rates compared to elsewhere.<sup>5-7</sup> In general, Asian populations tend to have low twinning rates followed by the Caucasians; African blacks have the highest. Pollard et al<sup>6</sup> compared twin births in ethnic groups from a national registry. The age standardised rates ranged from 13.2 per 1000 maternities for Blacks to 5.87 per 1000 maternities for Thais.<sup>6</sup> The rate for Chinese in Pollard's study was 7.18 per 1000 and 7.5 per 1000 for Asian Indians. In Singapore, although the overall rates for these ethnic groups for all the years combined are similar to these, the twin rates for the most recent period, 1998 to 2001, appear to be higher at 9.4 and 9.9 per 1000 maternities for Chinese and Asian Indians, respectively. However, comparisons are limited because of variations in source of information of the populations studied, definition of twinning rate, differing maternal age structure, birth order and secular trends over time.<sup>6</sup>

Table 2. Gender Combination of Twins and Estimation of Zygosity by Ethnic Group for All Years Combined

Variable	Father's ethnic group			Mother's ethnic group		
	Chinese	Malay	Indian	Chinese	Malay	Indian
Same gender twins (individual)						
Male	1612	298	155	1624	323	147
Female	1573	302	166	1577	320	154
Total	3185	600	321	3201	643	301
Different gender twins	788	143	97	790	139	100
DZ twins estimated*	1576	286	194	1580	278	200
MZ twins estimated*	2397	457	224	2411	507	202
DZ/MZ ratio	0.66	0.63	0.87	0.65	0.55	0.99

\* Weinberg's differential: number of dizygotic twins = 2 X different-gender twin pairs. Number of monozygotic twins = total twins - estimated dizygotic twin pairs.

DZ: dizygotic; MZ: monozygotic.

The increase in rates, over the years, could possibly be related to 2 main effects that have been previously well-documented in analyses of multiple births in other countries: increasing age of mothers and use of assisted reproductive techniques.<sup>8,9</sup> It is possible that both have had an effect on the rising trend of multiple births in Singapore. The mean ( $\pm$ SD) age of mothers of all babies born in the period 1986–2001 has increased linearly from 28.02 ( $\pm$ 11.06) years in 1986 to 30.26 ( $\pm$ 10.88) years in 2001. The proportion of women equal to or older than 35 years has also increased from 11.1%, 14.3% and 17.6% for the 4-year periods of 1986–1990, 1991–1995 and 1996–2001, respectively. Assisted reproduction (AR) is also known to have commenced successfully since 1988. Although the proportion of AR during this period is relatively low (0.02% to 0.06% of maternities from 1990–2000), the proportion for AR leading to twin births is significant and increasing (7%, 11.3% and 16.1% of twin births from 1990–1993, 1994–1997 and 1998–2000, respectively) (Personal communication—Ministry of Health, Singapore). Furthermore, improved antenatal care and delivery process would improve outcome of multiple pregnancies to achieve liveborn status for registration in the SNRBD. These and, possibly, other aspects leading to an increase in multiple births merit further study.

The overall DZ/MZ ratio of 0.69 in this population indicates that these ethnic groups have a higher proportion of MZ twinning than DZ twinning. This is consistent with findings from other studies.<sup>10</sup> Caucasian populations generally have twice as many DZ twins than MZ twins, while the reverse is true in Asian populations.<sup>4</sup> However, this appears to be changing with an increase in MZ twins in Caucasian populations.<sup>11</sup> The MZ/DZ ratio has also been regarded as an index of fertility. Twin (DZ) ovulations are believed to be highly heritable, but are also strongly influenced by maternal age, race and nutrition. MZ twinning, however, is believed to be a random embryological event not subject to environmental influences.<sup>4</sup> The variation of the DZ/MZ ratio among the ethnic groups is also interesting and warrants further study, such as over different time periods.

Although the strength of this study lies in the availability of a national population-based database, there are many limitations with regard to the study of twins. The information available is derived only from data collected from birth certificates. Weinberg's differential has been shown to be essentially correct in humans by assessment with blood grouping.<sup>12</sup> However this formula has been questioned,<sup>13</sup> and indeed may not be valid or broadly applicable to different human populations. Bulmer<sup>12</sup> also cautions that these estimates are subject to random sampling error and may differ considerably from the true twinning rates when

the number of observations is small. Thus, these results are at best only crude estimates. It is also not possible to determine which twin birth is "natural" or due to AR. Methods that could be implemented to determine this include the use of questionnaires.<sup>14,15</sup> This method has been shown to be very reliable, with agreement between questionnaires and blood typing to be approximately 93%.<sup>14</sup> Nevertheless, the best method is still collecting blood and genotyping each individual.<sup>16</sup> However, such an exercise requires the establishment of a twin register with active contact of individuals.

Although twin registries have been established successfully elsewhere around the world, fewer are based in Asian populations.<sup>2</sup> Compared to studies based upon usual populations, the response rates for participation by twins appear to be reasonably good. For example in Denmark, response rates of 92.5% have been reported for answering of questionnaires.<sup>17</sup> Furthermore, 96% of the respondents expressed willingness to participate in additional studies. Despite this, it is important to determine response rates and measures for obtaining the best response in the local population. Once established, it is also possible to extend twin studies to families and offspring of twins themselves, thus making this cohort even more powerful.<sup>18</sup>

Twin studies allow for the examination of the contribution of genes, environment and their interactions among individuals of differing genetic relatedness.<sup>2</sup> Boomsma et al<sup>2</sup> provides an excellent review on the applications of types of twin studies. Examples of such studies include disentangling the genetic contribution of subtypes of attention deficit hyperactivity disorder,<sup>19</sup> searching for cholesterol-lowering genes,<sup>20</sup> to providing evidence that genetic factors account for the association of low birthweight with an atherogenic lipid profile.<sup>21</sup> However, it is recognised that large, unbiased study samples are required to provide the best results.

The use of the SNRBD has provided an overview of multiple births in this country. Though having lower rates of twin births compared to Caucasian or Black populations, the greater preponderance of MZ twins makes twin studies in this population even more efficient for an analysis of genetic and environmental effects. However, this study has only examined twins born between 1986 and 2001. It is currently not possible to identify older twins by using population-based registries. Furthermore, information available within this registry is limited to predominantly demographic factors. The establishment of a national twin register would enable more detailed and useful collection of social and biomedical data of all twins who wish to participate and would, thus, create a valuable resource for the study of complex diseases in this post-genomic era.

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## REFERENCES

1. Martin N, Boomsma D, Machin G. A twin-pronged attack on complex traits. *Nat Genet* 1997;17:387-92.
2. Boomsma D, Busjahn A, Peltonen L. Classical twin studies and beyond. *Nat Genet Rev* 2002;3:872-82.
3. Lichtenstein P, De Faire U, Floderus B, Svartengren M, Svedberg P, Pederson NL. The Swedish Twin Registry: a unique resource for clinical, epidemiological and genetic studies. *J Intern Med* 2002; 252:184-205.
4. Bulmer MG. *The Biology of Twinning in Man*. Chap 4. Oxford: Clarendon Press, 1970:69-70.
5. Blondel B, Kogan MD, Alexander G, Dattani N, Kramer MS, Macfarlane A, et al. The impact of the increasing number of multiple births on the rates of preterm birth and low birthweight: an international study. *Am J Public Health* 2002;92:1323-30.
6. Pollard 1995, Pollard R. Ethnic comparison of twinning rates in California. *Hum Biol* 1995;67:921-31
7. Shek Y, Huang A, Shek Y, Keith L. Secular rates of twinning in Asia: recent observations and review of literature. *J Obstet Gynaecol Res* 1997;23:407-13.
8. Westergaard T, Wohlfahrt J, Aaby P, Melbye M. Population-based study of multiple pregnancies in Denmark, 1980-1994. *BMJ* 1997;314:775-9.
9. Reynolds MA, Schieve LA, Jeng G, Peterson HB, Wilcox LS. Risk of multiple birth associated with in vitro fertilization using donor eggs. *Am J Epidemiol* 2001;154:1043-50.
10. Tong S, Caddy D, Short RV. Use of dizygotic to monozygotic twinning ratio as a measure of fertility. *Lancet* 1997;349:843-5.
11. Murphy M, Hey K. Twinning rates. *Lancet* 1997;349:1398-9.
12. Bulmer MG. *The Biology of Twinning in Man*. Chap 4. Oxford: Clarendon Press, 1970:72.
13. James WH. The current status of Weinberg's differential rule. *Acta Genet Med Gemellol* 1992;41:33-42.
14. Rietveld MJ, van Der Valk JC, Bongers IL, Stroet TM, Slagboom PE, Boomsma DI. Zygosity diagnosis in young twins by parental report. *Twin Res* 2000;3:134-41.
15. Peeters H, Van Gestel S, Vlietinck R, Derom C, Derom R. Validation of a telephone zygosity questionnaire in twins of known zygosity. *Behav Genet* 1998;28:159-63.
16. Jackson RW, Snieder H, Davis H, Treiber FA. Determination of twin zygosity: a comparison of DNA with various questionnaire indices. *Twin Res* 2001;4:12-8.
17. Kyvik KO, Green A, Beck-Nielsen H. The new Danish Twin Register: establishment and analysis of twinning rates. *Int J Epidemiol* 1995;24:589-96.
18. Clausson B, Lichtenstein P, Cnattingius S. Genetic influence on birthweight and gestational length determined by studies in offspring of twins. *Br J Obstet Gynaecol* 2000;107:375-81
19. Todd RD, Rasumussen ER, Neuman RJ, Reich W, Hudziak JJ, Bucho KK, et al. Familiarity and heritability of subtypes of attention deficit hyperactivity disorder in a population sample of adolescent female twins. *Am J Psychiatry* 2001;158:1981-98.
20. Knoblauch H, Muller-Myhsok B, Busjahn A, Ben Avi L, Bahring S, Baron H, et al. A cholesterol-lowering gene maps to chromosome 13q. *Am J Hum Genet* 2000;66:157-66.
21. Ijzerman RG, Stehouwer CD, Van Weissenbruch MM, De Geus EJ, Boomsma DI. Evidence for genetic factors explaining the association between birthweight and low density lipoprotein cholesterol and possible intrauterine factors influencing the association between birthweight and high density lipoprotein cholesterol analysis in twins. *J Clin Endocrinol Metab* 2001;86:5479-84.