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published in
Twin Research
2001

DOI (link to publisher)
10.1375/twin.4.5.332

document version
Publisher's PDF, also known as Version of record

Potential Bias Regarding Birth Weight in Historical and Contemporary Twin Data Bases

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In this study we examine the hypothesis that monozygotic (MZ) twins in historical databases are less discordant for birth weight due to negative selection of severely discordant MZ twins. Furthermore, we test the hypothesis that MZ twins are less discordant for birth weight when comparing a volunteer based twin registry with a population based twin registry, due to selective registration. Data were available on 3927 twin pairs from the volunteer Australian Twin Registry born before 1964, 3059 volunteer twin pairs from the Netherlands Twin Register born 1987–1989 and 454 Belgian twin pairs from The East Flanders Prospective Twin Survey born 1987–1989. Intrapair relative birth weight differences (RBWD) were computed for MZ and dizygotic (DZ) twins from each twin registry. Comparing birth weight differences between MZ and DZ twins provides support for the hypothesis that MZ twins are subject to a negative selection in historical databases. Furthermore, Australian MZ twins have a lower RBWD compared to Dutch MZ twins when corrected for the RBWD of Australian and Dutch DZ twins, indicating circumstances which only affect MZ twins. Our hypothesis that MZ twins are less discordant for birth weight in a volunteer based twin registry compared to a population based twin registry had to be rejected. We suggest that investigators using historical databases to test the fetal origins hypothesis should be aware of this increased likelihood of selective exclusion of individuals with extreme morphometric parameters at time of birth.

Over the last decade there has been increasing evidence that adverse intrauterine conditions are associated with adult onset disease such as high blood pressure and mortality rates (Barker, 1994). Low birth weight is often seen as an indicator for these adverse intrauterine conditions. Twin data have frequently been used to investigate these issues with inconsistent results. When using twin data, some authors fail to find an association between intrauterine growth retardation experienced by twins and increased blood pressure or increased mortality rates in adults (Christensen et al., 1995; Williams et al., 1999). Other investigators however find an association between low birth weight and increased blood pressure in adult life when testing the fetal origin hypothesis in twins (Dwyer et al., 1999; IJzerman et al., 2000). These inconsistent findings might be due to selection bias, whereby severely discordant monozygotic (MZ) twins are unknowingly excluded from some twin databases and not from others, thereby introducing a bias when comparing research results or data from different databases. MZ twins are known to be at a higher risk of perinatal mortality than dizygotic (DZ) twins (Glinianaia et al., 1998; Rydhstrom, 1990). This may be due to the effects of circumstances specific to MZ twin pregnancies, in particular monochorionic pregnancies, such as vascular anastomosis, unequal sharing of placenta perfusion zones or Twin-To-Twin Transfusion Syndrome (TTTS) (Machin et al., 1996; Victoria et al., 2001). TTTS is a condition with a high mortality rate up to 100% and accounts for large intrapair birth weight differences between MZ twins (Blickstein, 1990; Steinberg et al., 1990). The reported incidence of TTTS varies from 5% up to 20% of monochorionic twin pregnancies (Duncan et al., 1997; Hecher et al., 1999; Seng et al., 2000).

Birth weight is influenced by genetic factors; however, as demonstrated among extremely discordant twins, environmental factors such as TTTS or unequal sharing of placenta perfusion zones may have a more profound influence (Machin et al., 1996). Since 1980 improved diagnostic and therapeutic tools, combined with advanced neonatal care, have contributed to increased survival of twins, of MZ twins in particular (Forssas et al., 1998; Skupski, 1998). Accordingly, historical databases in which adult twins are recruited on a volunteer basis could be expected to have a lower rate of discordance among MZ twins, due to the lower survival of low birth weight twins before 1980.

With decreasing mortality rates the number of severely discordant twins surviving extreme intrauterine and neonatal conditions increases. Twins surviving extreme intrauterine conditions can encounter severe health problems (Cincotta et al., 2000). These health problems among the surviving twins might negatively influence the willingness of parents to register their children. Because of this, MZ twins in volunteer twin registers may be less discordant compared to population based twin registers. Data on biometrical birth parameters might therefore be influenced by birth year of the twins and recruitment methods.

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In this study we examine the hypothesis that, in historical databases, MZ twins are less discordant in birth weight than MZ twins in contemporary databases, due to negative selection. Furthermore, we test the hypothesis that MZ twins are more discordant in population based twin registries than those enrolled in volunteer twin registries, due to selective registration. We chose to examine these hypotheses using data from three different twin registries, having access to data already available for other research purposes. Discordance in birth weight was tested among MZ twins and corrected for birth weight discordance between DZ twins.

Methods and Materials

Subjects

Australian Twin Registry (ATR). Data were available from 3927 twin pairs, all born before 1965, enrolled with the volunteer ATR. This volunteer register has more than 30,000 twin pairs enrolled, about 10–20% of the estimated number of pairs in the population (Treloar et al., 2000). Information was available on zygosity and birth weight. Zygosity was assigned on the basis of responses to standard items, followed up with further queries in the case of inconsistent responses, resulting in < 2% error when checked against genetic marker concordance. Data on 3909 twins were analysed after excluding twins with missing data on zygosity and with unlikely birth weights. The sample included 512 monozygotic male (MZM), 295 dizygotic male (DZM), 1340 monozygotic female (MZF), 822 dizygotic female (DZF) and 940 dizygotic opposite sex (DZOS) twin pairs. Self-reported birth weight was obtained by mailed questionnaire from an original twin cohort of 3,808 twin pairs aged 17 to 88 years in 1980–82 and an additional smaller cohort of twins aged over 50 to 95 years in 1993–1995 (Do et al., 1998). Birth weight was reported in pounds (lb) and ounces (oz) and converted to grams before analysis.

Netherlands Twin Register (NTR) (Boomsma, 1998). Twins born in 1987, 1988 or 1989 and registered on a volunteer basis at the NTR were included if birth weight of both twins was known (van Baal et al., 1998). Twins are recruited via commercial organisations and population registers. This volunteer registry consists of more than 20,000 twin pairs. About 45% of the estimated number of pairs born each year are enrolled. Information on birth weight, gestational age and zygosity was extracted from the register. Birth weight and gestational age were reported by the parents in a questionnaire that they received within 6 months after delivery. Birth weight was measured by a nurse or doctor shortly after birth in the hospital and passed on to the parents. Zygosity was determined by similarity questions in other questionnaires which were completed when the twins were 5 years old (van der Valk et al., 1998). Data on 3059 twin pairs were analysed after excluding twins with missing birth weights (30 pairs). The selection included 498 MZM, 518 DZM, 537 MZF, 483 DZF and 1023 DZOS twin pairs.

The East Flanders Prospective Twin Survey (EFPTS) (Loos et al., 1998; Boomsma, 1998). All twins born in 1987, 1988 or 1989 in the province of East Flanders in Belgium were selected. After excluding twins with unknown zygosities (15 pairs), data on 454 twin pairs were analysed. Birth weight was obtained from the obstetric records. Zygosity was determined through sequential analysis based on sex, fetal membranes, umbilical cord blood groups, placental alkaline phosphatase genotype and DNA fingerprints (Loos et al., 1998). The selection included 71 MZM, 80 DZM, 91 MZF, 71 DZF, 141 DZOS live born twins.

Statistical Analysis

For each twin pair we calculated the Relative Birth Weight Difference (RBWD). RBWD is commonly defined as the intrapair birth weight difference expressed as a percentage of the larger twin's birth weight [(heavier–lighter/heavier) x 100]. The mean RBWD of MZ and DZSS twins within each register was tested with a student t test.

An alternative method to test the same hypothesis is to compare the mean RBWD of MZ twins between registers. This was also tested with a student t test. To control for overall differences in RBWD of twins between registers, RBWD of DZ twins was included in the analysis. We expected no change in RBWD of DZ twins, but a decrease in RBWD in MZ twins when comparing historical with contemporary data or volunteer based with population based data. Analysis of variance (ANOVA) was conducted, with RBWD as dependent and zygosity and country as independent variables, to test for interaction between zygosity and country.

Data were analysed using SPSS.9 for Windows and SAS 6.12 computer package (SPSS INC, 1997; SAS Institute Inc, 1997). A difference was considered significant if $p < .05$.

Results

MZ monochorionic and MZ dichorionic Belgian twins were pooled as the Dutch and Australian selection did not contain information on chorionicity. MZM and MZF twins as well as DZM and DZF twins were also pooled for analysis, as there were no significant differences in mean RBWD between different sex groups within zygosities (see Table1).

First we tested the hypothesis that the mean RBWD between MZ and DZSS twins differed within a time period. The RBWD of Australian MZ twins was 1.49 % lower than in DZSS twins ($p < .0001$) while RBWD in younger Dutch MZ and DZSS twins did not differ (0.39%; $p = .36$).

Furthermore, we tested whether MZ twins have a higher RBWD in the young Dutch database compared to the historical Australian database. Between the MZ twins RBWD was higher in the Dutch than in the historical Australian database (0.76%; $p = .060$). ANOVA was conducted, whereby RBWD was set as dependent and zygosity and country as independent variables, the interaction between zygosity and country was significant, $p = .005$ (see Figure 1).

To determine the difference between volunteer based and population based twin registries, we used data from the Dutch and the Belgian register. We tested if the mean RBWD between MZ and DZSS twins within a country differed. The RBWD of Belgian MZ twins was 1.39 % lower than in DZSS twins ($p = .19$). To test if MZ twins have

Table 1

Mean Relative Birth Weight Difference (RBWD) in Percentage, According to Zygosity and Sex of Three Registers, Australia, Netherlands and Belgium. Monozygotic Males (MZM), Dizygotic Males (DZM), Monozygotic Females (MZF), Dizygotic Females (DZF), Dizygotic Opposite Sex (DZOS)

	Australia			Netherlands			Belgium*		
	n	RBWD	*SD*	*n*	RBWD	*SD*	*n*	RBWD	*SD*
MZM	512	10.19	9.72	498	11.46	9.58	71	9.74	7.49
MZF	1340	10.95	11.08	537	11.54	9.94	91	10.92	9.28
DZM	295	12.36	11.15	518	11.95	9.14	80	11.38	9.15
DZF	822	12.19	10.78	483	11.83	9.75	71	12.26	11.52
DZOS	940	13.78	12.17	1023	12.57	9.61	141	13.41	10.02

Note: * Live born twins

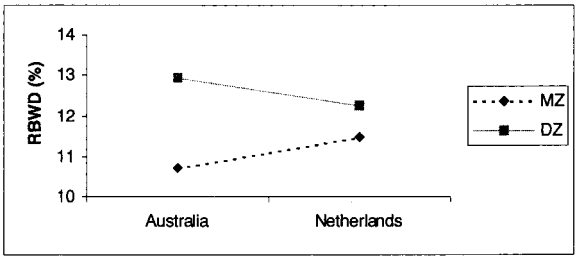

Figure 1

Relative birth weight difference (RBWD) pattern of monozygotic (MZ) versus dizygotic (DZ) Australian (1852 MZ, 2057 DZ) and Dutch (1035 MZ, 2024 DZ).

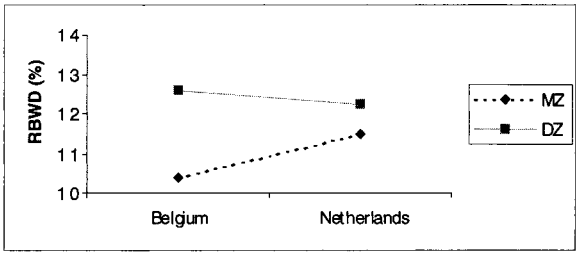

Figure 2

Relative birth weight difference (RBWD) pattern of monozygotic (MZ) versus dizygotic (DZ) Belgian (165 MZ, 294 DZ) and Dutch (1035 MZ, 2024 DZ).

a higher RBWD in the volunteer based Dutch database compared to the population based Belgian database a student *t* test as well as ANOVA was conducted. Within MZ twins the RBWD of Belgian twins was 1.10% lower than of Dutch twins ($p = .30$), and interaction between zygosity and country was not significant, $p = .15$. Both tests did not yield support for differences between volunteer and population based registers (see Figure 2).

Discussion

Our hypothesis was confirmed that MZ twins are less discordant in a historical twin database. When comparing Dutch twins in the late eighties with Australian twins early in the century, intrapair birthweight differences are influenced by many variables. Not only do health care and development of health care systems differ in both countries, genetic predisposition might also differ considerably. Most of these variables, however, are equal for MZ and DZ twins in the same country. Therefore a significant difference in RBWD between MZ and DZ twins in one database and not in another would indicate a higher survival rate of MZ twins in the latter.

This is the case comparing MZ twins with DZ twins within the Australian and the Dutch database. Australian MZ twins differed significantly in RBWD from DZSS twins whereas Dutch MZ twins did not. For this particular analysis DZOS twins were excluded to eliminate sex-dependent birth weight differences when comparing MZ twins with DZ twins. We also tested if Australian MZ twins have lower RBWD compared to Dutch MZ twins when the difference in RBWD of DZ twins is taken into account. To eliminate intercontinental differences we set the difference in RBWD among Dutch and Australian DZ twins as standard, and examined if birth weight differences between Dutch and Australian MZ twins follow the same pattern as those of DZ twins. When MZ twins are set against DZ twins any additional difference in RBWD is due to specific circumstances only affecting MZ twins. Our data indicate that the birth weight differences between Dutch and Australian MZ twins indeed have been influenced differently compared to DZ twins. Australian MZ twins are less discordant than Dutch MZ twins and this effect is even more prominent if set against the difference between Australian and Dutch DZ twins.

MZ twins are more often born very prematurely and have less favourable neonatal outcomes than DZ twins (Glinianaia et al., 1998; Rydhstrom, 1990; Victoria et al., 2001). This perinatal mortality in MZ twins is only elevated in monochorionic pairs and not in dichorionic pairs (Derom et al., 1991). Unfortunately few twin registries have information on chorionicity. Due to the better survival chances of MZ twins over the years, this negative selection of severely discordant MZ twins would be less prominent in a contemporary database. The contribution of improved neonatal care is most probably the main reason for the

increased survival of MZ twins (Forssas et al., 1998; Skupski, 1998).

Data extracted from the Australian historical twin registry consists of more female MZ twins (72% of the MZ twins). Female MZ twins are know to have a higher intrapair birth weight difference compared to male MZ twins (Nores et al., 1997; O'Brien et al., 1987). Considering this, the Australian MZ Twins should be expected to have an even higher discordance rate than the Dutch twins, which consist of 52% females.

However we are aware that studying twin survival within one register throughout the years would be the most appropriate study design to confirm our hypothesis. A study addressing intrapair birth weight differences within one register throughout the years is underway.

We did not find significant intrapair birth weight differences between volunteer based twin registries and population based ones. Belgian MZ and DZSS twins did not differ significantly. RBWD between Dutch and Belgian MZ twins, when corrected for the difference between Dutch and Belgian DZ twins, did not differ significantly either. We therefore had to reject our hypothesis that in volunteer databases selection bias in relation to adverse birth outcomes is not prominent. Dutch MZ twins seem to differ even more than Belgian MZ twins regarding birth weight difference. Nevertheless, we have to take into account that sample size may have limited the power of this particular comparison.

We suggest that investigators using data from historical twin registries should bear in mind the likelihood of selective exclusion of severely discordant MZ twins. Although we tested our hypothesis in a twin setting, our findings are in accordance with findings in the literature, where an increased survival of small for gestational age singletons from the 1980s onward has been reported (Emsley et al., 1998; Forssas et al., 1998; Lefebvre et al., 1996; Skupski, 1998). This has important implications for studies regarding the fetal origins hypothesis. Only the strongest and fittest babies survived low birth weight in the early 20th century. Surviving infants had to adapt to the extreme circumstances in which they were born, developing mechanisms that made the difference between life and death. These adaptive mechanisms are the result of intrauterine and neonatal programming, reprogramming or genetic predisposition, but most probably an interaction between all these factors. With the number of surviving small for gestational age babies increasing, the number of adults encountering specific health problems related to intrauterine adverse conditions may consequently increase. On the other hand these adaptive mechanisms which enabled the fittest babies to overcome life-threatening conditions in their infant years, decades ago, might well be the same mechanisms which cause the diseases they encounter in later life such as diabetes. Due to modern intervention methods this selection of the fittest has partly lost its importance. Some low birth weight babies surviving today would not have survived 30 years ago. These babies do not require the adaptive mechanisms to survive today as they did decades ago. If these adaptive mechanisms are the causal connection between adult onset disease and adverse intrauterine and neonatal circumstances, infants surviving low birth weight due to modern technology today are possibly not programmed to develop the diseases of the generations before them.

Acknowledgements

We thank Professor Robert Derom, Professor Robert Vlietinck and Dr Catherine Derom for granting us access to data from The East Flanders Prospective Twin Survey (EFPTS). We also would like to thank Ruth JF Loos for helping us with the analysis of the EFPTS data.

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