

# Twinning Rates According to Maternal Birthweight

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Dizygotic twinning rates have changed over time, which has been seen as a sign of a decline in fecundity. Since a woman's birthweight has been shown to be a marker of her fecundity, maternal birthweight may correlate with subsequent twinning rates. In the Danish National Birth Cohort (1996–2002), we examined if maternal birthweight, and whether she was born at term or preterm, correlated with her probability of multiple birth. For 20,719 live born infants, we had self-reported information about maternal birthweight, collected during the first wave of the 7-year follow-up, and information on multiple births from record linkage. The association between maternal birthweight and multiple births was investigated by use of logistic regression and presented as odds ratios (ORs) with 95% confidence intervals (CIs). Compared to women born at term with a birthweight of 3001–4000 g, women with a birthweight > 4500 g appeared to have higher chance of multiple birth while women with a birthweight of 4001–4500 had a lower chance, especially if the analysis was restricted to women with a BMI < 25 (Adjusted ORs 2.3 [1.0–5.4] and 0.4 [0.2–0.9] respectively). Odds ratios for dizygotic twinning were of the same magnitude. In women with a BMI ≥ 25, no obvious pattern was present. Our findings do not indicate that twinning is a fecundity indicator. Women with a birthweight that may indicate a pregnancy complicated with gestational diabetes had the highest rate of multiple birth. These findings are new and should be put to a critical test in other data sources.

**Keywords:** maternal birthweight, twinning, multiple birth, epidemiology

Changes in twinning rates over time have been among the best documented changes in reproduction but the underlying reasons for these changes are still unknown (Herskind et al., 2005; Rachootin and Olsen, 1980). Some have interpreted a decline in dizygotic (DZ) twinning rate as an indication of a decline in fecundity, the biological capacity to reproduce (Basso et al., 2004). Litter size is for example in animal studies an indicator of fecundity (Halloran and DeLuca, 1980),

and better semen quality and lower waiting times to pregnancy have been reported in couples who had dizygotic twins (Asklund et al., 2007; Basso et al., 2004). Others see twinning as a reproductive anomaly since one of its determinants is high maternal age.

Adult fecundity is partly determined during the time period of organogenesis and the further development of testes and ovaries in fetal life (Gluckman and Hanson, 2006; Main et al., 2006). The majority of Sertoli cells are produced before birth, and all oocytes are established in fetal life. Research have indicated that factors that determine or correlate with fetal growth correlate with disease susceptibility later in life, mainly for diabetes and cardiovascular diseases (Barker, 1995; Joseph and Kramer, 1996). Recently, some studies have also indicated that female birthweight correlates with her adult fecundity by analyzing different markers of fecundity (Ekholm et al., 2005; Hack et al., 2002; Ibanez et al., 2000; Swamy et al., 2008; Nohr et al., 2009), but none have used DZ twinning as one of these markers.

In this study we examined if female birthweights and birth at term or preterm correlated with multiple birth rates. We also examined if these associations were modified by maternal BMI, which is a known correlate of twinning rates. Our hypothesis was that if twinning is a marker of fecundity we would expect women with a normal birthweight and who were born at term to have the highest rates of multiple births, especially for dizygotic twins.

## Methods

### Subjects

The study is based on data from the Danish National Birth Cohort (DNBC), a nationwide study of 100,419 pregnancies recruited in 1996–2002. Detailed descriptions of study methods, data, and the recruitment have

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been published (Nohr et al., 2006; Olsen et al., 2001) and are available on the website [www.dnbc.dk](http://www.dnbc.dk). Briefly, data were collected during 2 telephone interviews during pregnancy at approximately 16 and 30 week of gestation, and two telephone interviews after birth when the child was approximately 6 months and 18 months old. For all children alive at 7 years of age, a follow-up questionnaire was initiated in July 2005, and is planned to be finalized in 2010. As part of the 7-year follow-up, we asked the mothers to report their own and the child's father's birthweight.

For this study, we initially considered the first wave of 30,355 pregnancies that resulted in live born children where mothers had participated in the 7 year follow-up before July 2007 (participation rate 65%) and also in the first pregnancy interview (96% of the women who took part in the 7 year follow-up). From this group, we excluded women with missing information about her own birthweight and whether she was born preterm or term ( $n = 8,311$ ). We also excluded women who reported that they had received infertility treatment in the present pregnancy ( $n = 1325$ ). This resulted in a final study population of 20,719 pregnancies including 266 multiple births.

#### Exposure variables

The main risk factor was maternal birthweight self-reported at the 7-year follow-up. Half of the mothers chose to fill out a questionnaire electronically while the other half requested a self-administered mailed questionnaire. The mother was asked 'What was your own birthweight (in grams)?' and 'Were you born preterm?' To maximize the quality and completeness of the self-report, the mother was sent a letter and asked to retrieve important information including her own and the father's birthweight before she filled out the questionnaire.

Prior to data analysis, maternal birthweight was divided into two sets of categories depending on whether the woman was born term or preterm. Term births were divided into 5 categories using the cut points 2500 g, 3000 g, 4000 g, 4500 g, such that the interval contained the upper limit. Preterm births were categorized using the cut points 1500, 2000, 3000, and 3500.

Since little is known about the quality of self-reported birthweight in Denmark, we carried out a validation study where we compared self-reported birthweights with birthweights available in the National Birth Register as reported by the midwife who took part in the birth of the child. The electronic Birth Register was established in 1974, and it includes women born after this year (18.5% of the study population). We found that the mean self-reported birthweight was 3320 g, which was very similar to the corresponding mean birthweight based on the Birth Register of 3295 g. When we used register data on birthweight and term/preterm birth to generate the same 10 combined categories as we used in the study, the agreement rate was 82%. A more detailed descrip-

tion of the validation study is described elsewhere (Nohr, Vaeth et al., 2008).

From the first pregnancy interview, we used self-reported information on weight and height to calculate pre-pregnancy BMI, which was categorized as underweight (BMI < 18.5 kg/m<sup>2</sup>), normal weight (18.5 ≤ BMI < 25 kg/m<sup>2</sup>), overweight (25 ≤ BMI < 30 kg/m<sup>2</sup>), and obese (BMI ≥ 30 kg/m<sup>2</sup>) (World Health Organization, 2000). We also extracted data on mother's age at conception, smoking during pregnancy, social status defined by education and occupation, and infertility treatment. In the civil registration system, we identified if the woman was a twin herself based on a sister or brother born within one day of her own birthday.

#### Outcomes

Multiple births were defined as pregnancies that ended with the birth of twins or triplets as identified in the Medical Birth Registry. Information on zygosity was based on standardized questionnaires on likeness between the twins as reported to the Twin Register and allowed division of twin births into three categories (dizygotic twins, monozygotic twins, and unknown) (Christiansen et al., 2003). Based on the National Discharge Register, we identified pregnancies complicated with preeclampsia and diabetes/gestational diabetes. We suspected some underreporting of gestational diabetes in the register and therefore we supplemented with self-reported information about this disease from the pregnancy interviews.

The study was approved by the Scientific Ethics Committee for Copenhagen and Frederiksberg on behalf of all the committees in Denmark and by the Danish Data Protection Agency.

#### Statistical Methods

First, we described the distribution of birthweights in women born term or preterm across different types of multiple birth and potential confounders.

Next, we used logistic regression to examine the association between maternal birthweight and multiple birth. To examine the importance of whether the woman was born preterm or term, maternal birthweight was entered with 10 categories (5 categories for each term and preterm births) and with term birthweight of 3001–4000 grams as reference group. In an adjusted model, we controlled for age, pre-pregnancy BMI, height, twinning status of the mother, cigarette smoking in pregnancy, and social group. These variables were chosen a priori, because they have been associated with twinning rates and/or maternal birthweight in other studies.

Because we examined if a potential association between maternal birthweight and multiple birth was modified by pre-pregnancy BMI, we divided women into normal weight (BMI < 25) and overweight (BMI ≥ 25) for women born at term. Too few twins were born by women who were born preterm to allow for a separate analysis in this group. We generated a maternal

**Table 1**

Multiple Births across Categories of Maternal Birthweight

	Total	Maternal birthweight										
		Women born at term					Women born preterm					
		2500 g	25–3000 g	30–4000 g	40–4500 g	> 4500 g	Total	≤1500 g	15–2000 g	20–3000 g	30–3500 g	> 3500 g
<b>Multiple birth*</b>												
Total ( <i>n</i> )	18,644	692	3220	13007	1462	283	2,055	89	268	1350	277	71
		%	%	%	%	%		%	%	%	%	%
Singleton	18,426	98.8	98.8	98.7	99.1	97.5	2,027	98.9	98.5	98.8	97.8	98.6
Multiple	238	1.2	1.2	1.3	0.9	2.5	28	1.1	1.5	1.2	2.2	1.4
<b>Zygosity</b>												
Singleton	18,426	98.8	98.8	98.7	99.1	97.5	2,027	98.9	98.5	98.8	97.8	98.6
Dizygotic	146	0.7	0.7	0.8	0.6	1.8	17	1.1	0.4	0.9	1.1	0.0
Monozygotic	57	0.3	0.3	0.3	0.1	0.7	9	0.0	0.8	0.3	1.1	0.0
Unknown zygosity	35	0.1	0.2	0.2	0.2	0.0	2	0.0	0.4	0.0	0.0	1.4

Note: The study population consisted of 20,719 pregnancies including 266 multiple births.

In all birthweight categories, the upper limit is contained in the interval, e.g., 25–3000 is 2501–3000.

birthweight variable with 10 categories (5 birthweight categories for each thin/normal weight and overweight/obese women). We used logistic regression to examine the association between this BMI-specific birthweight variable and multiple birth. Normal weight women with a birthweight of 3001–4000 grams were used as reference. We adjusted for the same variables as in the model described above. Effect measure modification between maternal birthweight and BMI group was assessed by computing ratios of odds ratios and checked if these ratios differed significantly from 1.

Because dizygotic twinning requires fertilization of two eggs and therefore is believed to be more related to fecundity, we repeated all analyses in dizygotic twins.

Diabetes is a known risk factor for high birthweight and diabetes may confound results for example through its heritable component. We therefore repeated all analyses after excluding women with diabetes in the hope to exclude some women with a diabetic mother. We also repeated the analyses after excluding women who were twins themselves.

A two-tailed significance level of 0.05% was used in all statistical tests, and results were presented with 95% confidence intervals. All analyses were made using STATA 9.0 (Stata-Corp, College Station, TX).

## Results

Altogether, we had 20,719 pregnancies that resulted in live born children. Ten per cent of mothers reported that they were born preterm. The self-reported mean birthweight was 3340 g.

Multiple birth was seen in 1.3 % of the pregnancies, and 0.8 % were classified by the Twin Registry as dizygotic twins. The detailed distribution of multiple birth according to maternal birthweight is presented in Table 1. In women born at term with a birthweight > 4500 g, 2.5% had multiple birth compared to approximately

1.0% in all other women born term. According to Table 2, high birthweight was associated with being taller and having a high BMI later in life. Lower birthweight was seen in women who were a twin themselves, or who smoked while being pregnant.

Being born preterm was not associated with the frequency of giving multiple birth (adjusted OR: 1.1, 95% CI: 0.7–1.6). Only women born at term with a high birthweight > 4500 g had a higher chance of giving birth to twins, although this finding did not reach statistical significance (Table 3). Table 4 shows that this association was only seen in women with a pre-pregnancy BMI < 25. In this group, the odds for multiple birth were more than doubled if the mother was born large > 4500 g (adjusted OR 2.3 [95% CI 1.0–5.4]). Underweight and normal weight women with a birthweight of 4001–4500 g had a significantly decreased chance of giving birth to twins (adjusted OR 0.4 [95% CI 0.2–0.9]) compared to women with a birthweight in the normal range (3001–4000 g).

When the analysis was restricted to dizygotic twins, the magnitude of the association between a high maternal birthweight and twinning was unchanged, but the association was no more statistically significant (adjusted OR 2.3 [95% CI 0.8–6.5]). In women with a BMI ≥25, no obvious pattern between maternal birthweight and multiple birth was observed. We found no association between BMI ≥25 and multiple birth (adjusted OR 1.0 [95% CI 0.8–1.4]). Also, we found no effect measure modification between maternal birthweight and BMI group on multiple birth ( $p = .2$ ).

Women who were twins themselves ( $n = 668$ ) had more often multiple birth and dizygotic twinning (adjusted OR 1.9 [95% CI 1.1–3.3] and 2.1 [95% CI 1.1–4.1] respectively). Excluding these women from the study instead of adjusting for this characteristic

**Table 2**  
Mean Maternal Birthweight According to Maternal Characteristics at Conception

	Women born term Maternal birthweight			Women born preterm Maternal birth weight		
	Total (n)	Mean (g)	SD	Total	Mean (g)	SD
Total	18,664	3,425	526	2,055	2,566	594
Age at conception						
Below 20 y	116	3,404	530	14	2,428	603
20–24 y	2,228	3,428	574	279	2,585	710
25–29 y	7,994	3,414	511	860	2,591	581
30–34 y	6,449	3,436	534	701	2,541	573
35–39 y	1,732	3,435	503	186	2,533	539
40 y+	145	3,412	476	15	2,439	611
Prepregnancy BMI						
< 18.5	820	3,287	543	91	2,493	610
18.5–24.9	13,133	3,422	518	1,410	2,561	588
25–29.9	3,245	3,455	546	389	2,577	597
30+	1,164	3,468	539	131	2,666	638
Missing	302	3,471	491	34	2,451	585
Height						
< 1.60 m	821	3,133	526	138	2,333	492
1.60–1.69 m	9,015	3,345	509	1,075	2,528	576
1.70 m +	8,815	3,535	518	841	2,654	614
Missing	13	3,405	420	1	750	
Cigarette smoking in pregnancy						
No smoking	15,961	3,430	522	1,696	2,581	585
0–10 cig./day	2,157	3,409	554	273	2,524	647
> 10 cig./day	527	3,356	518	83	2,385	554
Missing	19	3,541	669	3	2,850	934
Social group						
High	10,486	3,437	513	1,058	2,580	542
Middle	6,708	3,408	541	786	2,543	600
Low	1,415	3,423	544	204	2,582	795
Missing	55	3,394	505	7	2,561	762
Woman born as						
Singleton	18,215	3,432	521	1,836	2,603	582
Twin	449	3,164	647	219	2,252	607

**Table 3**  
Odds Ratios for Multiple Birth<sup>a</sup> and Dizygotic Twins According to Maternal Birth Weight

Maternal birthweight	Multiple birth			Dizygotic twins		
	Crude OR	Adj. OR <sup>b</sup>	95% CI	Crude OR	Adj. OR <sup>b</sup>	95% CI
Term, ≤ 2500 g	0.9	0.9	0.4 ; 1.8	0.9	0.9	0.4 ; 2.3
Term, 2501–3000 g	0.9	0.9	0.6 ; 1.3	0.9	0.9	0.6 ; 1.5
Term, 3001–4000 g <sup>c</sup>	1.0	1.0	reference	1.0	1.0	reference
Term, 4001–4500 g	0.7	0.6	0.4 ; 1.1	0.8	0.7	0.3 ; 1.4
Term, > 4500 g	1.9	1.8	0.8 ; 3.9	2.2	2.0	0.8 ; 5.0
Preterm, ≤ 1500 g	0.8	0.8	0.1 ; 5.8	1.4	1.3	0.2 ; 10.0
Preterm, 1501–2000 g	1.1	1.0	0.4 ; 2.8	0.5	0.4	0.1 ; 3.1
Preterm, 2001–3000 g	0.9	0.8	0.5 ; 1.4	1.1	1.0	0.5 ; 1.8
Preterm, 3001–3500 g	1.7	1.6	0.7 ; 3.7	1.4	1.3	0.4 ; 4.2
Preterm, > 3500 g	1.1	1.1	0.2 ; 8.2	—	—	not applicable

Note: <sup>a</sup>Crude analysis: n = 20,719; Adjusted analysis: n = 20,300.<sup>b</sup>Adjusted for maternal age, height, prepregnancy BMI, twin status, social group and smoking habits in pregnancy.<sup>c</sup>Maternal birthweight 3001–4000 g is reference group.

**Table 4**

Odds Ratios for Multiple Births According to Different Combinations of Maternal Birthweight and Prepregnancy BMI in Mothers Born at Term

Maternal birthweight	BMI < 25 ( <i>n</i> = 13,953)			BMI ≥ 25 ( <i>n</i> = 4,409)		
	Crude OR	Adj. OR <sup>b</sup>	95% CI	Crude OR	Adj. OR <sup>b</sup>	95% CI
Multiple birth						
≤ 2500 g	0.7	0.7	0.3 ; 1.8	1.4	1.4	0.4 ; 4.5
2501–3000 g	0.9	0.9	0.6 ; 1.4	1.0	1.0	0.5 ; 2.0
3001–4000 g <sup>c</sup>	1.0	1.0	reference	1.0	1.1	0.7 ; 1.5
4001–4500 g	0.4	0.4	0.2 ; 0.9	1.3	1.3	0.6 ; 2.9
> 4500 g	2.5	2.3	1.0 ; 5.4	0.8	0.8	0.1 ; 5.7
Dizygotic twins						
≤ 2500 g	1.0	1.1	0.4 ; 2.8	0.7	0.8	0.1 ; 5.4
2501–3000 g	0.9	0.9	0.5 ; 1.6	0.9	1.0	0.4 ; 2.4
3001–4000 g <sup>c</sup>	1.0	1.0	reference	1.0	1.0	0.6 ; 1.6
4001–4500 g	0.4	0.4	0.1 ; 1.1	1.5	1.5	0.6 ; 3.8
> 4500 g	2.4	2.3	0.9 ; 6.5	1.2	1.2	0.2 ; 8.8

Note: <sup>a</sup>Adjusted for maternal age, height, twin status, social group and smoking habits in pregnancy.<sup>c</sup> Maternal birthweight 3001–4000 g in women with BMI < 25 is reference group

had no impact on the main findings. However, after this exclusion, we found that being born at term with a low birthweight ≤ 2500 g may be related to a lower chance of having twins (adjusted ORs 0.4 [95% CI 0.1–1.2] for multiple birth and 0.2 (95% CI 0.0–1.6) for dizygotic twins).

We excluded all women with diabetes to examine if the association between very high birthweight and multiple birth would be attenuated and thus indicate confounding by genetic factors related to diabetes. We found no support for this concern. The same conclusion was reached after excluding 242 pregnancies where the women had already provided one pregnancy to the study.

## Discussion

We found no support for our hypothesis that women who were born with a high birthweight indicating that they had reached their full growth potential had increased multiple birth rates. On the contrary, they had significantly lower rates than women with a birthweight in the normal range. Underweight and normal-weight women born with a birthweight over 4500 gram that may indicate maternal disease had however a higher multiple birth rate.

We have previously shown that women with a birthweight over 4500 g had a higher risk of subfertility measured as a waiting time to pregnancy of more than a year (adjusted OR 1.5 [95% CI 1.0–2.0]) while women with birthweights between 4000–4500 g had the shortest waiting times to pregnancy (Nohr et al., 2009). In the present study, we actually found that the latter group (4000–4500 g) had the lowest multiple birth rates. Twinning rates have declined over time for many decades and in many countries which may reflect that many more infants are now actually born with a weight that reflect their full growth potential. Why this should decrease twinning rates is left to spec-

ulation, but our findings do not indicate that twinning is a fecundity indicator.

While fecundity decreases with age (Menken et al., 1986), the chance of twinning increases (Bortolus et al., 1999). It has been suggested that the increasing risk of multifollicular development seen with increasing age reflects a decline in ovarian feedback capacity leading to elevated FSH levels above the normal threshold for monofollicular growth (Beemsterboer et al., 2006). Because of the low levels of available oocytes, the overall chance of producing an oocyte of sufficient quality is less likely. However, if it happens, it is more likely that more than one good-quality oocyte is available. The Polycystic Ovarian Syndrome (PCOS), a disease which has insulin resistance as a strong etiologic component, also presents with extreme development of immature multiple follicles, leading to infertility (Franks et al., 2008; Galluzzo et al., 2008). However, contrary to what is seen in ageing women, the underlying mechanism has shown to be a suppression of FSH below the threshold that is needed for normal follicle development (Franks et al., 2008). Women born with a very high birthweight may have been exposed to an intrauterine environment making them more prone to insulin resistance. Maybe insulin resistance in a milder form than the one seen in women with PCOS is associated with a disturbance of ovarian function leading to the same paradox as seen in ageing women. It may be that a mildly suppressed level of FSH increases both the risk of cycles with no good-quality oocytes available and cycles with more than one oocyte of high quality. Such disturbance of ovarian function could also explain why the same paradox of impaired fertility and increased DZ twinning rates is seen in obese women (Basso et al., 2004; Ramlau-Hansen et al., 2007). In the present study, we did not find obesity to be associated with DZ twinning, maybe due to sparse data on twins. Our results indicate that

the association between obesity and twinning may be confounded or modified by birthweight.

Maternal birthweight was recalled but part of the cohort gave birth after the National Birth Registry was established. For the majority of women, the self-reported birthweight was close to the one reported at birth, and we had an acceptable agreement rate for the combined categorization of term/preterm birth and birthweight. Also, the definition of high (4000–4500 g) and very high birthweight (> 4500 g) were so extreme that these categories should truly reflect being born large, regardless of gestational age.

We find it unlikely that differential recall can explain the associations we see and most of the recall covered shorter time spans. The hypotheses we examine were furthermore not presented to the women in the study. Selection bias is also an unlikely explanation as participation in the cohort was decided by the women without revealing the hypotheses we address.

Confounding should be considered. The association between a very high birthweight and increased multiple birth rates most probably does not reflect a direct effect of abnormal growth, but rather the underlying determinants of fetal growth. We have limited data to study genetics or environmental determinants of fetal growth, but dietary factors may for example play a role.

Women who were born very large had the highest rate of DZ twinning. Most of these findings are novel, and some of the associations could be due to chance. Replication of study findings in a different data source is needed.

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