Does normal variation in birthweight confer susceptibility to health problems? A co-twin control study

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ABSTRACT

Population-based twin data were used to study whether normal variation in birthweight confers disadvantage for a variety of health outcomes from birth through young adulthood. The sample consists of 5,864 identical and fraternal twins and includes 2,570 intact pairs. Variation in birthweight may be associated with an increased risk for epilepsy in males and with refractive disorders, chronic ear infections and intestinal problems in women. Two variants of the co-twin control design, based on identical twins only, were used to control for genetic and shared environmental effects that influence both birthweight and the health outcome. Results indicated that the prevalence of health outcomes was not greater among the lighter twin from birthweight discordant pairs. Furthermore, intra-pair differences in birthweight between members of pairs who were health-discordant were significant only for nearsightedness among the MZ males. Due to lack of statistical power these results should be interpreted with caution.

INTRODUCTION

Impaired fetal growth, as indicated by very low birth weight, is known to have negative consequences for a number of health and developmental outcomes including the cerebral palsies, language, hearing and vision deficits and mental retardation (1,2). However, the influence of less extreme, or normal variation in fetal growth for health outcomes later in life is an issue of debate and speculation. Although it seems unlikely that small variation in birthweight could have a large impact on health, fetal development does consist of critical periods for the development of organ systems such that insult can lead to compromised growth that may irrecoverably affect the structure or function of physiological systems. Some evidence suggests an amplification effect such that small variations in birthweight are associated with large variation in cardiovascular mortality (3). Several studies propose that the inverse relationship between birthweight and health may be due to persistent effects from influences in utero. For instance, deficiencies in adult lung function may arise because factors that restrict fetal weight gain also hinder airway growth, either directly by affecting lung size, or indirectly through a greater risk of infant respiratory infection (4). A study of adult blood pressure revealed that men who had failed to achieve growth potential (defined as light at birth and tall as adults) in utero (5) were at greater risk for high blood pressure than those who had reached their full potential growth in utero. Here it is hypothesized that high blood pressure is associated with impairment in fetal growth which affects the structure and elasticity of the blood vessels. Finally, underdeveloped mastoid and immunological systems may explain why lower birthweight could be a risk factor for recurrent ear infections in children (6).

The purpose of this study is to use population-based twin data to explore whether normal variation in birthweight confers disadvantage for a variety of health outcomes from birth through young adulthood. First, the association between birthweight and the prevalence of illness or symptoms is tested without reference to the twin structure of the data. Next, co-twin control applications are used to explore the effects of birthweight on health while simultaneously controlling for genetic and shared environmental effects on birthweight and on the health outcome.

METHODS

Sample

The data are based on identical (MZ) and fraternal (DZ) twins who are part of the New Norwegian Twin Panel (7). All 10,156 twins who were born in Norway between 1967 and 1974 were identified using the Medical Birth Registry (8). In November 1992 a postal questionnaire was sent to the 7,992 twins who were at least 18 years old and for whom both twins in the pair

were alive and had current addresses in Norway. The response rate was 73 percent and included 5,864 individuals from 2,750 complete pairs and 724 single responders. The results here are based on data from the complete pairs only. Questionnaire methodology was used to classify zygosity: there were 416 male MZ (MZm) pairs, 387 male DZ (DZm) pairs, 528 female MZ (MZf) pairs, 443 female DZ (DZf) pairs, and 796 unlike-sexed DZ (DZu) pairs.

Measures

Birthweight and gestational age are routinely recorded as part of the Medical Birth Registry. A check-list for 23 self-report illnesses and symptoms for the period from birth through early adulthood was included as part of the questionnaire. For those items for which the respondent indicated a positive history they were also asked to report their ages at onset and at the last episode (if they no longer experienced that illness/symptom). Two additional measures were created from the illness checklist to represent a general vulnerability to illness and co-morbidity. The measure called ANYILL indexes a positive history of any of the health-related problems from the checklist, and ILL3 measures comorbidity, defined as a history of at least 3 health problems.

Analyses

Simple cross tabulation frequency analyses and chi-square statistics were used to test for sex differences in the prevalence of the health outcomes. The relationship between birthweight and the health outcomes was analyzed next. Birthweight and gestational age are highly correlated and could confound results if health problems are associated with failure to reach full developmental status in utero and not simply due to variation in birth weight. Thus, adjustments for gestational age were conducted. To study the relationships between birthweight and the health outcomes, birthweight was categorized into two levels representing the lower (0-25th percentiles) or upper (26th through 100th percentiles) part of the birthweight distribution for each sex. Likewise, the distribution for gestational age was classified into two levels (0-25th and 26th-100th percentiles). Crude and adjusted (for gestational age) odds ratios were computed using a logistic regression model that regressed the illness outcomes on the dichotomous measures for birthweight and gestational age.

The effects of birthweight on health were examined more closely with a co-twin control design. In general, this approach uses data from exposure-discordant identical twins because they are perfectly matched on genetic and sociodemographic influences for the outcome. In the present application birthweight is considered the exposure variable and members of a pair were classified as discordant if the within-pair differences in birthweight were at least as large as 25 percent of the heavier twin's weight. Differences in prevalence rates for the health outcomes were then tested between the heavier and the lighter twin in these pairs.

Next, a variant of the co-twin control design was used to test whether differences in the prevalence of the health outcome among MZ pairs discordant for health were associated with birthweight differences within the pair. Again, genetic effects for the exposure and the outcome are controlled by using MZ pairs only, and intra-pair differences in the health outcome are ascribed to environmental influences. Data from illness discordant pairs were ordered such that the healthy twin was first and the intra-pair difference in birthweight was calculated. Differences in birthweight between the first and second twin were then tested using a t-test procedure to determine if the within-pair differences deviated significantly from zero.

RESULTS

Descriptive information for the birthweight distributions and gestational age are listed in Table 1 by sex. The correlations between birthweight and gestational age were 0.57 for both the males and the females. Analyses were performed separately by sex because the reported prevalence of the health outcomes differed significantly between men and women for all of the measures with the exception of asthma, psoriasis, diabetes, epilepsy and lumbar pain, and rates were higher among women than men for all of the measures except hay fever (Table 2). Seventy percent of the men and eighty-six percent of the women reported a positive history of at least one health problem, and co-morbidity rates were more than doubled among the women compared to the men.

Table 1. Descriptive values for birthweight and gestational age by sex.

	Birthweight (grams)		Gestational Age (days)	
	Males	Females	Males	Females
N	2762	3099	2683	3011
Mean (±SD)	2762.3 (± 535.7)	2620.8 (± 517.1)	266.9 (±17.7)	267.6 (±17.5)
Range	960–4440	1060–4460	193–309	186–309
25th percentile	2400	2280	257	257

Table 2. Lifetime prevalence rates and chi-square test of sex differences for the health outcomes.

	Prevalence (%)		
Problems with:	Males (n=2751)	Females (n=3097)	$\chi^2_{(df=1)}$
hay fever	11.6	8.8	13.32***
nettle rash	4.7	7.3	13.31***
asthma	6.0	5.4	1.00
nickel allergy	2.3	16.4	324.34***
childhood (atopic) eczema	4.0	6.6	19.81***
psoriasis	2.9	3.3	0.71
other skin disease/eczema	7.4	11.9	32.52***
migraine	3.5	6.0	19.46***
other headache	4.5	12.1	105.91***
intestinal	2.6	6.6	51.52***
stomach	2.2	3.8	12.90***
sleep disturbance	4.8	6.7	9.20**
diabetes	0.7	0.5	0.75
epilepsy	1.3	1.6	0.43
nearsightedness	23.8	33.9	72.85***
farsightedness	5.5	11.5	65.46***
astigmatism	15.8	25.5	83.39***
chronic ear infections	8.5	13.1	31.82***
tonsillitis	7.7	12.3	33.19***
sinusitis	3.1	4.7	9.42**
bladder infections	0.7	19.4	537.30***
neck/shoulder pain	7.8	19.2	158.56***
lumbar pain	16.7	18.4	3.08
ANYILL	70.0	86.0	235.49***
ILL3	21.0	44.0	364.03***

***$p \leq .001$ **$p \leq .01$ *$p \leq .05$

The crude and adjusted (for gestational age) odds ratios for the relationship between the dichotomous measure of birthweight and health, and prevalence rates for the two parts of the birthweight distribution, are listed in Table 3 for males, and Table 4 for females. With few exceptions, the associations are in the expected direction with greater prevalence rates among those whose birthweight was in the lower part of the birthweight distribution. In particular, lower birthweight conferred a more than double risk of epilepsy among the males, and an increased risk of refractive problems, chronic ear infections, intestinal problems and comorbidity among the females. Adjustments for gestational age did not alter these risks appreciably except for comorbidity among the females. These findings suggest a small, independent influence of birthweight for some health outcomes.

The percent of birthweight discordance, defined as an intra-pair difference of at least 25 percent of the weight of the heavier twin, was 7.5 (31 pairs) among the MZm and 10.6 (56 pairs) among the MZf. The difference between the birthweights in these discordant pairs ranged from 640 to 1510 grams (M=924 ±240) for the males and from 400 to 1770 grams (M=892 ±257) for the females. Prevalences did not differ between the lighter and the heavier twin in these birthweight discordant pairs for any of the health measures.

The number of MZ pairs discordant for each health outcome and the mean within-pair difference in birthweight are listed in Table 5 by sex. In general, birthweights did not vary significantly for the health outcomes between MZ twins and their co-twins from the discordant pairs. However, lower birthweight may be a predisposing factor for nearsightedness among the males, the average within-pair birthweight difference between the discordant MZ male pairs was 138 grams.

DISCUSSION

Twin data were used to study whether normal variation in birthweight confers disadvantage for a wide range of health outcomes from birth through young adulthood. Sex differences in the prevalence of the health outcomes were significant for all but five of the measures. Comorbidity and prevalence rates were,

Table 3. Odds ratio and prevalences for the relationship between health outcomes and birthweight for males.

	Birthweight[a]		Adjusted[c]
problems with:	OR (95% CI)	prevalences[b]	OR (95% CI)
hay fever	0.74 (0.55-0.98)	9.4/12.4	0.76 (0.55-1.06)
nettle rash	0.92 (0.60-1.40)	4.4/4.7	0.81 (0.50-1.32)
asthma	1.24 (0.88-1.76)	7.0/5.7	1.18 (0.78-1.77)
nickel allergy	0.70 (0.37-1.31)	1.7/2.5	0.83 (0.40-1.72)
childhood (atopic) eczema	0.98 (0.63-1.53)	3.9/4.0	1.02 (0.61-1.71)
psoriasis	1.29 (0.79-2.10)	3.5/2.7	0.87 (0.48-1.58)
other skin disease/eczema	1.11 (0.80-1.53)	8.0/7.2	1.23 (0.85-1.78)
migraine	0.72 (0.43-1.20)	2.8/3.8	0.55 (0.30-1.00)
other headache	1.17 (0.78-1.74)	5.1/4.4	1.06 (0.66-1.69)
intestinal	0.87 (0.49-1.52)	2.3/2.7	0.85 (0.44-1.63)
stomach	1.16 (0.66-2.04)	2.5/2.1	1.20 (0.61-2.37)
sleep disturbance	1.22 (0.83-1.79)	5.5/4.6	1.38 (0.88-2.17)
diabetes	1.15 (0.41-3.23)	0.7/0.6	1.03 (0.31-3.43)
epilepsy	2.57 (1.34-4.94)	2.5/1.0	2.85 (1.33-6.09)
nearsightedness	1.14 (0.94-1.40)	25.7/23.2	1.11 (0.88-1.39)
farsightedness	0.96 (0.65-1.40)	5.4/5.6	0.80 (0.51-1.26)
astigmatism	1.12 (0.89-1.41)	17.0/15.4	1.01 (0.77-1.33)
chronic ear infections	1.23 (0.91-1.65)	9.7/8.1	1.36 (0.97-1.92)
tonsillitis	1.19 (0.87-1.63)	8.7/7.4	1.30 (0.90-1.88)
sinusitis	0.87 (0.52-1.45)	2.8/3.2	0.91 (0.50-1.64)
bladder infections	0.35 (0.08-1.51)	0.3/0.8	0.41 (0.08-1.99)
neck/shoulder pain	0.92 (0.67-1.28)	7.4/8.0	1.12 (0.77-1.62)
lumbar pain	1.04 (0.83-1.31)	17.1/16.6	1.06 (0.81-1.38)
ANYILL	1.03 (0.86-1.25)	70.4/69.8	0.97 (0.78-1.20)
ILL3	1.16 (0.94-1.42)	22.6/20.2	0.92 (0.72-1.17)

[a] Crude odds ratio based on two parts of the birthweight distribution: 0-25th percentiles/ 26th-100th percentiles.
[b] prevalences listed as: percent in lower/percent in upper part of birthweight curve.
[c] OR is adjusted for effects of gestational age which was classified into lower 0-25th percentiles or upper 26-100th percentiles.

generally, greater for the females. The predominance of female morbidity may, in part, be due to reporting bias. Responses to the questionnaire were received from a larger percentage of the females (78%) than from the males (69%). Also, gender-specific response sets may explain part of the sex differences in the prevalences of the health outcomes. In comparison to women, men may be less sensitive to their own health status or less willing to endorse health problems unless they are seriously ill.

In this study, a large number of tests were conducted, some based on the entire sample and some based on co-twin control designs using only the discordant MZ pairs. The associations with birthweight were, primarily, in the expected direction with larger prevalences of health problems among those in the lower part of the birthweight distribution. There is little a priori basis for interpretation of the reversed results for hay fever among males, but statistical probability would predict that five percent of the tests are significant merely due to chance. While caution should be exercised in interpreting the results of any single analysis, the results suggest effects of birthweight for epilepsy among the males and refractive vision, intestinal problems, chronic ear infections, and general comorbidity among the females. Clearly, it is important to distinguish between health impairments that may result from variation in birthweight *per se* from those confounded with birthweight and associated with incomplete fetal development. Addressing this issue fully is beyond the scope of this study, however gestational age was analyzed as a covariate. Due to inaccuracies in assessing gestational age, it can introduce a certain degree of error into our results.

Table 4. Odds ratio and prevalences for the relationship between health outcomes and birthweight for females.

	Birthweight[a]		Adjusted[c]
Problems with:	OR (95% CI)	prevalences[b]	OR (95% CI)
hay fever	1.27 (0.96-1.67)	10.2/8.3	1.10 (0.79-1.52)
nettle rash	1.26 (0.94-1.70)	8.6/6.9	1.25 (0.88-1.77)
asthma	1.36 (0.97-1.91)	6.7/5.0	1.31 (0.88-1.95)
nickel allergy	1.05 (0.84-1.30)	16.9/16.2	1.12 (0.87-1.44)
childhood (atopic) eczema	0.85 (0.61-1.20)	5.9/6.8	0.92 (0.62-1.35)
psoriasis	1.31 (0.85-2.00)	4.0/3.1	1.26 (0.76-2.08)
other skin disease/eczema	1.22 (0.95-1.55)	13.4/11.3	1.21 (0.92-1.61)
migraine	1.19 (0.86-1.66)	6.8/5.8	1.34 (0.92-1.99)
other headache	1.06 (0.83-1.35)	12.5/11.9	1.07 (0.80-1.43)
intestinal	1.58 (1.16-2.13)	8.8/5.8	1.80 (1.26-2.58)
stomach	1.05 (0.69-1.59)	4.0/3.8	1.16 (0.71-1.90)
sleep disturbance	1.24 (0.90-1.69)	7.7/6.3	1.44 (1.00-2.07)
diabetes	1.98 (0.70-5.58)	0.8/0.4	1.99 (0.54-7.27)
epilepsy	0.78 (0.39-1.57)	1.3/1.6	0.82 (0.36-1.85)
nearsightedness	1.26 (1.06-1.49)	37.9/32.6	1.24 (1.02-1.52)
farsightedness	1.05 (0.82-1.36)	11.9/11.4	1.05 (0.78-1.41)
astigmatism	1.27 (1.06-1.53)	29.0/24.3	1.36 (1.10-1.68)
chronic ear infections	1.56 (1.25-1.95)	17.1/11.7	1.60 (1.23-2.08)
tonsillitis	0.98 (0.77-1.26)	12.2/12.4	0.83 (0.62-1.11)
sinusitis	0.77 (0.51-1.16)	3.8/4.9	0.84 (0.53-1.35)
bladder infections	1.05 (0.86-1.29)	20.0/19.2	1.04 (0.82-1.32)
neck/shoulder pain	1.08 (0.88-1.32)	20.1/18.9	1.14 (0.90-1.45)
lumbar pain	1.08 (0.88-1.33)	19.3/18.1	1.02 (0.80-1.30)
ANYILL	1.16 (0.91-1.48)	87.5/85.8	0.93 (0.70-1.23)
ILL3	1.29 (1.09-1.51)	49.0/42.7	0.74 (0.61-0.90)

[a] Crude odds ratio based on two parts of the birthweight distribution: 0-25th percentiles/ 26th-100th percentiles.
[b] prvalences listed as: percent in lower /percent in upper part of birthweight curve.
[c] OR is adjusted for effects of gestational age which was classified into lower 0-25th percentiles or upper 26-100th percentiles.

Although gestational age is not exact, the crude classification that we have used here (categorizing individuals into the lower 25 versus upper 75 percent of the gestational age distribution) is probably sufficient for detecting whether gestational ages within the range of these data are influencing the birthweight results. After correcting for gestational age, the influence of birthweight persisted for the above named outcomes with the exception of co-morbidity. Our findings are similar to those from another Norwegian study which conducted an 18 year follow-up of medical and psychological status in low-birthweight (<2500 grams) males compared to their birth cohort (9). In that study, health related to ten organ systems was analyzed and differences between those with low versus normal birthweight were present for minor impairments of vision.

Twin data offer several advantages to explore the question of birthweight and health outcomes. Specifically, comparison of the prevalences in twins versus singletons provides a natural design for testing the fetal origins hypothesis (10) because the average birthweight of twins is considerably lower than that of singletons. As seen from Table 1, the birthweights for more than 25% of our sample are lower than 2500 grams, which is commonly used to define low birthweight. Although tests of differences between twins and singletons have not been conducted for the health measures used here, studies of mortality after age six in Danish twins compared to the general population (11) and ischaemic heart disease based on Swedish twins and singletons (12) indicate that the type of intrauterine growth retardation experienced by twins is not a risk factor for mortality or ischaemic

Table 5. Number of discordant MZ pairs and intra-pair mean birthweight difference in grams for each health outcome by sex.

	MZ males (416 pairs)		MZ females (528 pairs)	
History of:	discordant pairs	mean birthweight difference (± SEM)	discordant pairs	mean birthweight difference (± SEM)
hay fever	39	–82 (± 75)	49	6 (± 53)
nettle rash	27	–72 (± 70)	51	8 (± 71)
asthma	24	49 (± 93)	33	–90 (± 73)
nickel allergy	18	89 (± 91)	93	–72 (± 50)
childhood eczema	19	16 (± 59)	40	1 (± 56)
psoriasis	15	10 (± 66)	21	–86 (± 98)
eczema	42	90 (± 89)	74	–33 (± 57)
migraine	18	–130 (± 91)	39	48 (± 82)
headache	25	–36 (± 84)	104	37 (± 36)
intestinal problems	15	–47 (± 77)	63	63 (± 61)
stomach problems	17	64 (±137)	25	19 (± 98)
sleep disturbance	26	–47 (± 78)	46	72 (± 61)
diabetes	1	40 (–)	2	95 (± 25)
epilepsy	7	30 (±300)	11	–74 (±157)
nearsightedness	48	138* (± 62)	91	40 (± 50)
farsightedness	22	62 (± 61)	58	–14 (± 51)
astigmatism	67	35 (± 47)	120	42 (± 42)
chronic ear infections	37	–5 (± 64)	75	67 (± 53)
tonsillitis	27	22 (± 81)	56	–92 (± 62)
sinusitis	17	–101 (±133)	27	–35 (± 96)
bladder infections	3	–100 (± 90)	116	45 (± 36)
neck problems	42	2 (± 57)	129	34 (± 40)
lumbar pain	91	33 (± 42)	122	34 (± 40)
ANYILL	92	37 (± 39)	93	33 (± 46)
ILL3	77	–16 (± 42)	167	–18 (± 36)

Note: birthweight difference calculated as birthweight $_{(\text{non-affected twin})}$ − birthweight $_{(\text{affected twin})}$.

*$p < .056$-100 percentile.

heart disease. Rather, different mechanisms probably underlie low-birthweight deviations in twin compared to singleton populations, but this does not imply that birthweight variation within each population is differentially related to health outcomes.

Two variants of the co-twin control design were employed here, both of which provide the unique possibility to control fully for genetic and shared environmental effects that influence both birthweight and the health outcome. First, differential prevalence in health outcomes for members of MZ pairs who were birthweight discordant was investigated. Intra-pair differences in birthweight among MZ twins are only due to non-shared, intrauterine environmental influences. To maximize putative influences of birthweight, data from MZ pairs who were birthweight discrepant by more than 25% of the heavier twin's birthweight were analyzed. Results based on the small sample of discordant MZ twins indicated that, after controlling for genetic effects and shared environmental effects, there was no evidence that lower birthweight is a predisposing factor for later health problems, or for a general susceptibility to illness. Next, analyses of birthweight differences in MZ twins who were discordant for the health outcomes were significant only for MZ males from pairs discordant for nearsightedness. The seeming discrepancy between the results based on the two co-twin control applications most likely reflects a lack of statistical power, only 31 male pairs (7.5%) were birthweight discordant, whereas 48 pairs (12%) were discordant for nearsightedness. However, in addition to the larger sample, analyzing health-discordant pairs exploits within-pair birthweight variation more fully because all variation, and not only that which exceeds 25% of the heavier twin's weight, is included.

In summary, normal variation in birthweight may predispose to some health problems including epilepsy

in males, and refractive disorders, chronic ear infections, intestinal problems and comorbidity in females. However, the small effect of birthweight on these health outcomes disappear after controlling for genetic and shared environmental influences, with perhaps the exception of refractive vision, but the number of cases is too small to permit interpretation. More thorough research is needed to determine whether the critical periods for development of vision are particularly sensitive to disturbances of growth in utero. We can only speculate whether the negative findings for the relationship between birthweight and the other health outcomes are merely due to low statistical power or indicative that small variation affecting intra-uterine growth has little consequence for health. The results differed between the individual and co-twin control methods. This is expected if the relationship between birthweight and health is, primarily, mediated by genetic and shared environmental effects, and also implies that differences experienced in utero are relatively unimportant for these health outcomes in this sample. However, once again, conclusions are tentative due to low statistical power.

Although twins have lower birthweights than singletons, this sample is selected because data on pairs where both did not survive to age 18 are excluded. The average birthweights were significantly less among the non-surviving compared to the surviving pairs, the average difference being about 1050 grams for the males and 901 grams for the females. Thus, it is important to emphasize that these results are relevant for normal, and not extreme, variation in birthweight. For deviations within the normal range, a nurturing post-natal environment may lead to recovery of any minor disadvantages that may be conferred by lower birthweight.

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