Birthweight and Adult Health in a Population-Based Sample of Norwegian Twins

Andrej M. Grjibovski,[1,2] Jennifer R. Harris,[1] and Per Magnus[1]

[1]*Division of Epidemiology, Norwegian Institute of Public Health, Oslo, Norway*

[2]*Unit for Preventive Nutrition, Department of Biosciences at NOVUM, Karolinska Institutet, Huddinge, Sweden*

Population-based twin data were used to test (a) whether lower birthweight confers a greater risk of adult health disorders, and (b) whether within-pair birthweight differences in twins explain discordance for health outcomes. The sample consisted of 1201 monozygotic (MZ) male twins, 1048 dizygotic (DZ) male twins, 1679 MZ female twins, 1489 DZ female twins, and 2423 opposite-sex DZ twins, born in Norway between 1967 and 1979. The relationship between birthweight and self-reported health outcomes were studied using multivariable logistic regression. In the full sample (n = 7840), birthweight was negatively associated with risk for nearsightedness (odds ratio OR = 0.76, 95% CI: 0.65 – 0.92) and minimal brain disorder (OR = 0.27, 95% CI: 0.16–0.44) when adjusted for gestational age, sex, zygosity, age, education and body mass index after correction for intraclass correlations and multiple comparisons. Within-pair analysis of 159 MZ and 224 DZ pairs revealed that myopic twins were on average 2 g (p = .966) and 64 g (p = .040) lighter than nonmyopic twins in MZ and DZ pairs respectively, suggesting that genetic factors may play an important role in the associations between birthweight and nearsightedness. Within-pair analysis of twins discordant for a minimal brain disorder indicated that affected twins were 80 g (p = .655) and 85 g (p = .655) lighter than their healthy co-twins in MZ and DZ pairs respectively, although there were only 2 MZ and 2 DZ discordant pairs.

There is a growing body of evidence that suggests that several adult health problems have their origins in antenatal life. Growth restriction in the fetal period, clinically expressed as reduced birthweight, has been consistently shown to be a risk factor for coronary heart disease, type 2 diabetes and hypertension (Barker, 1995; Godfrey & Barker, 2001; Holness, et al., 2000) later in life. These epidemiological findings, known as the *fetal origins* hypothesis, suggest that diseases that present later in life may originate through fetal adaptations to inadequate nutrient supply in certain periods of antenatal development (Barker, 1998). Moreover, increased risk of adult diseases is not only associated with low birth weight (< 2500 g) but is found throughout the entire birthweight distribution. For example, the prevalence of impaired glucose tolerance and death rates from coronary heart disease fall progressively with increases in birthweight (Barker, 1995; Hales et al., 1991). Similar associations have been found between being small at birth and neurological, psychological and articulatory impairment in children (Michelsson & Noronen, 1983). Birthweight was negatively related to asthma in some (Shaheen et al., 1999; Steffensen et al., 2000) but not all studies (Hagström et al., 1998; Katz et al., 2003). Positive associations between birthweight and hayfever (Katz et al., 2003), rheumatoid arthritis (Jacobsson et al., 2003), and lower back pain (Hestbaek et al., 2003) have been recently reported. These associations could reflect fetal programming, but could also be explained by genetic factors common to antenatal growth and susceptibility to the studied outcome.

Twin studies offer unique opportunities to test aspects of the fetal origins hypothesis by resolving whether associations between impaired fetal growth and later illnesses are attributed to common genetic factors or fetal programming (Leon, 2001). The twin applications are founded on expectations of genetic similarity derived from biometric models. Monozygotic (MZ) twins are genetically similar whereas dizygotic (DZ) twins share, on average, 50% of their segregating genes. Shared environments are assumed to be equal for both types of twinships in infancy and childhood. Studying differences in size at birth and later health in twins provides optimal control for maternal characteristics, duration of gestation, and shared effects of early environments. Moreover, MZ twin design controls for the influence of genes on the association between birthweight and later health. Thus, an association between birthweight and the disease of interest within both MZ and DZ pairs provides evidence of fetal programming. If such an

Received 24 March, 2004; accepted 24 December, 2004.

Address for correspondence: Andrej M. Grjibovski, Unit for Preventive Nutrition, Department of Biosciences at NOVUM, Karolinska Institutet, SE 141 57, Huddinge, Sweden. E-mail: andrej.grjibovski@prevnut.ki.se

https://doi.org/10.1375/twin.8.2.148 Published online by Cambridge University Press

association is present in DZ twins, but not in MZ twins, the role of genetic factors, which are responsible for both fetal growth and susceptibility to the disease, should be considered. No association between birthweight and the disease both in MZ and DZ pairs suggests a prominent role of environmental factors (Hubinette et al., 2003).

Evidence from twin studies suggests that genetic factors might account for the associations between birthweight and blood pressure (Ijzerman et al., 2000), low-density lipoprotein cholesterol (Ijzerman, et al., 2001), and plasma fibrinogen (Ijzerman et al., 2003a), whereas intrauterine environmental influences might contribute to the associations between birthweight and type 2 diabetes (Poulsen et al., 2002). Importantly, these studies were performed on relatively small samples (53 MZ and 61 DZ twin pairs in the former three studies, and 104 MZ and 88 DZ pairs in the latter study) and demonstrate the capability of this study design to detect the importance of genetic and/or intrauterine factors in the associations between birthweight and adult diseases (Ijzerman et al., 2003b).

Despite the great potential of twin studies to examine the possible influence of genetic factors and intrauterine environment on the associations between fetal growth indices and later health in a number of diseases, most of the research has concentrated on the common degenerative conditions, such as coronary heart disease and type 2 diabetes, and their risk factors.

This study uses data from a large population-based twin cohort to examine birthweight effects on 30 health outcomes, which are poorly studied with respect to birthweight. A further goal is to investigate how the relationship between birthweight and later health is influenced by genetic and intrauterine factors.

Materials and Methods

Sample and Data Collection

The data are from a population-based sample of Norwegian twins participating in a study on health and development at the Norwegian Institute of Public Health (NIPH) in Oslo (Harris et al., 2002). A total of 15,374 twins were born in Norway between 1967 and 1979. All twins were identified through the National Medical Birth Registry. A postal questionnaire was sent out in 1998 to 8229 twins born between 1967 and 1974 who had given consent in 1992 to take part in the research projects, and to 4472 twins born between 1975 and 1979 belonging to the pairs where both twins were alive and residing in Norway in 1998. Responses were received from 8045 twins (63.3%) and included 3334 complete pairs and 1377 single responders.

The questionnaire included a checklist for 30 illnesses and symptoms (listed in Table 1), which was prefaced with 'do you have or have you ever had, any of the following health problems'. Zygosity classification was based on responses to 7 items, which showed 97% accuracy (Magnus et al., 1983). Information on height, weight and education were also obtained from the questionnaire. Education was classified in three groups: secondary, upper secondary and higher levels of education. Body mass index (BMI) was calculated as weight(kg)/height(m^2). Data on birthweight and gestational age were obtained from the Medical Birth Registry.

After excluding pairs with missing data on birthweight or length of gestation, the final sample included 7840 twins: 1201 MZ and 1048 DZ male twins, 1679 MZ and 1489 DZ female twins, and 2423 opposite-sex DZ twins.

Table 1

Lifetime Prevalence Rates and Chi-Square Test of Sex Differences for the Health Outcomes

History of:	Prevalence: %		p^a
	Males $N = 3347$	Females $N = 4493$	
Hay fever	15.0	13.2	.031
Nettle rash	5.9	10.2	< .001
Asthma	7.7	8.7	.107
Nickel allergy	3.5	20.9	< .001
Childhood eczema	4.1	7.6	< .001
Psoriasis	3.7	4.5	.084
Other skin disease	10.2	13.6	< .001
Migraine	5.2	10.2	< .001
Other headache	5.8	15.3	< .001
Stomach pain	3.1	4.9	< .001
Inflammatory bowel disease	0.6	0.8	.256
Sleep disturbance	6.3	9.9	< .001
Diabetes	0.8	0.8	.967
Epilepsy	1.6	1.8	.422
Nearsightedness	29.0	37.7	< .001
Farsightedness	7.4	13.2	< .001
Astigmatism	21.2	29.3	< .001
Ear infections	9.9	13.4	< .001
Tonsillitis	7.1	12.5	< .001
Sinusitis	4.1	7.0	< .001
Bladder infections	1.3	21.3	< .001
Neck/shoulder pain	7.2	18.7	< .001
Lumbar pain	17.7	21.0	.001
Muscle pain	2.8	5.6	< .001
Fibromyalgia	0.1	0.7	.001
Bechterew's disease	0.5	0.2	.038
Rheumatoid arthritis	0.4	0.8	.050
Dizziness	1.8	5.1	< .001
Hyperactivity	1.0	0.5	.004
MBD[b]	0.2	0.1	.112

Note [a] Adjusted for clustering on pair number.
[b] Minimal brain disorder.

Analyses

Sex and zygosity differences in the overall prevalences of the health outcomes were tested with chi-square statistics. Differences in birthweight, gestational age,

https://doi.org/10.1375/twin.8.2.148 Published online by Cambridge University Press

Table 2

Mean (*SD*) Birthweight, Gestational Age, Age and BMI by Sex and Zygosity

	MZ male pairs *N* = 1201	DZ male pairs *N* = 1048	MZ female pairs *N* = 1679	DZ female pairs *N* = 1489	DZ males from opposite-sex pairs *N* = 1098	DZ females from opposite-sex pairs *N* = 1325	*p* ANOVA *df* = 5
Birthweight: g	2684 (519)[b,c,e]	2816 (516)[a,c,d,f]	2559 (529)[a,b,d,e,f]	2680 (500)[b,c,e]	2825 (518)[a,c,d,f]	2697 (499)[b,c,e]	< .001
Gestational age: days	265 (18)[b,d,e,f]	269 (18)[a]	267 (19)	269 (18)[a]	268 (18)[a]	268 (18)[a]	< .001
Age: years	25.5 (3.6)	25.7 (3.7)	25.3 (3.7)[e,f]	25.5 (3.7)	25.8 (3.8)[c]	25.7 (3.7)[c]	.001
BMI: kg/m^2	21.4 (2.6)[c,d,e,f]	21.6 (2.7)[c,d,f]	18.6 (2.8)[a,b,d,e]	19.0 (3.0)[a,b,c,e]	22.0 (2.9)[a,c,d,f]	18.9 (2.8)[a,b,e]	< .001
Education: %[g]							< .001[h]
Secondary	5.1	3.5	4.9	6.9	5.7	4.8	
Upper secondary	58.5	61.3	53.4	55.5	56.5	54.7	
Higher	34.0	33.6	39.0	35.4	35.6	37.1	
Unknown	2.4	1.6	2.8	2.1	2.2	3.3	

Note [a] Significantly different from MZ males at $p < .05$ after Bonferroni correction.
[b] Significantly different from same-sex DZ males at $p < .05$ after Bonferroni correction.
[c] Significantly different from MZ females at $p < .05$ after Bonferroni correction.
[d] Significantly different from same-sex DZ females at $p < .05$ after Bonferroni correction.
[e] Significantly different from opposite-sex DZ males at $p < .05$ after Bonferroni correction.
[f] Significantly different from opposite-sex DZ females at $p < .05$ after Bonferroni correction.
[g] The sum is not always 100% due to rounding.
[h] *p*-value for the chi-square test.

age and BMI across zygosity categories were tested using one-way ANOVA with Bonferroni post-hoc tests. The relationships between birthweight and the health outcomes were studied by multivariable logistic regression. Crude and adjusted odds ratios (OR) with 95% CI were calculated for each disease or symptom. Birthweight, gestational age, BMI and age were introduced into the models as continuous variables. Zygosity and education were entered as categorical dummy variables. Adjustments for intraclass correlations were performed. Given that 30 outcomes were studied and a large number of tests were performed, a conventional *p*-value of .05 was divided by 30 and a *p*-value < .0016 was chosen as the significance level to adjust for multiple comparisons.

Within-pair analyses were performed only for those outcomes which were significantly associated with birthweight in the regression models after Bonferroni correction. Opposite-sex pairs were excluded as the effects of gender difference within a pair may influence both birthweight and the outcome. For the within-pair analyses, 510 male MZ, 763 female MZ, 390 male DZ, and 643 female DZ pairs, of which both twins responded to the questionnaire, were available. The birthweight distribution of the pairs in the study sample was assessed by Shapiro-Wilk and Kolmogorov-Smirnov tests. Paired *t* tests (for normally distributed data) and Wilcoxon signed ranks tests were used to test within-pair differences in birthweight in health discordant twins in MZ and DZ twins separately. Stata version 7.0 (StataCorp., 2001) and SPSS version 12.0 (SPSS Inc., 2003) software packages were used for all calculations.

Results

Self-reported rates of the illnesses and symptoms were greater in women with the exceptions of hay fever, asthma, psoriasis, inflammatory bowel disease (IBD), diabetes, epilepsy, Bechterew's disease, rheumatoid arthritis, hyperactivity and minimal brain disorder (MBD), where sex differences were not significant (Table 1). No differences in lifetime prevalences of the studied outcomes were found across zygosity categories.

The distribution of birthweight, gestational age and sociodemographic characteristics of the participants by sex and zygosity is presented in Table 2. In same-sex pairs, MZ twins were lighter than DZ twins for both sexes, MZ males were heavier than MZ females, and DZ males were heavier than DZ females. Boys in opposite-sex DZ pairs were on average 128 g heavier than girls. There were no differences in birthweight between males or females from same-sex DZ pairs compared to twins from opposite-sex pairs. Gestational length was similar in MZ male and MZ female twins. There were no differences in gestational length between all groups of DZ twins. Gestational age differed significantly between MZ and DZ males, but not females. There were no age differences among participants in same-sex pairs. BMI was significantly greater in males than in females across all zygosity categories.

Crude and adjusted odds ratios for the relationships between birthweight and health outcomes are summarized in Table 3. In the unadjusted analysis, birthweight was negatively associated with risks of developing nickel allergy, headache, nearsightedness, astigmatism, ear infections and neck/shoulder pain. Adjustment for gestational age, sex, age, zygosity, BMI and education

https://doi.org/10.1375/twin.8.2.148 Published online by Cambridge University Press

Table 3

Crude and Adjusted Odds Ratios (OR) for the Associations Between Birthweight and Health Outcomes Determined by Logistic Regression Analysis in a Full Sample ($N = 7840$).

Problems with:	Crude OR (95% CI)	*p*	Adjusted OR (95% CI)[a]	*p*
Hay fever	0.97 (0.85–1.10)	.615	0.97 (0.82–1.14)	.670
Nettle rash	0.80 (0.69–0.94)	.005	0.95 (0.78–1.45)	.565
Asthma	0.94 (0.79–1.12)	.498	0.95 (0.76–1.18)	.628
Nickel allergy	0.80 (0.70–0.91)	.001	0.94 (0.79–1.11)	.430
Childhood eczema	1.05 (0.87–1.28)	.596	1.21 (0.96–1.54)	.110
Psoriasis	1.02 (0.81–1.29)	.871	1.19 (0.90–1.57)	.216
Other skin disease	0.92 (0.80–1.05)	.220	0.97 (0.82–1.15)	.728
Migraine	0.95 (0.80–1.12)	.503	1.01 (0.82–1.23)	.949
Other headache	0.69 (0.60–0.79)	< .001	0.78 (0.65–0.92)	.004
Stomach pain	0.89 (0.72–1.10)	.279	0.85 (0.65–1.11)	.230
IBD[b]	0.87 (0.56–1.34)	.517	0.80 (0.45–1.43)	.449
Sleep disturbance	0.81 (0.69–0.96)	.013	0.92 (0.75–1.12)	.388
Diabetes	0.82 (0.54–1.25)	.352	0.59 (0.33–1.05)	.073
Epilepsy	0.71 (0.50–1.01)	.054	0.75 (0.46–1.20)	.227
Nearsightedness	0.84 (0.76–0.92)	< .001	0.76 (0.67–0.86)	< .001
Farsightedness	0.86 (0.74–1.00)	.045	0.98 (0.81–1.18)	.837
Astigmatism	0.83 (0.75–0.92)	.001	0.82 (0.72–0.94)	.003
Ear infections	0.79 (0.68–0.91)	.001	0.81 (0.68–0.97)	.022
Tonsillitis	0.81 (0.70–0.93)	.003	0.81 (0.68– 0.97)	.022
Sinusitis	0.91 (0.76–1.09)	.288	0.98 (0.78–1.25)	.874
Bladder infections	0.85 (0.75–0.97)	.014	1.12 (0.95–1.33)	.176
Neck/shoulder pain	0.77 (0.78–0.88)	< .001	0.81 (0.68–0.96)	.017
Lumbar pain	0.91 (0.81–1.01)	.087	0.88 (0.77–1.01)	.078
Muscle pain	0.80 (0.64–0.99)	.038	0.85 (0.64–1.13)	.258
Fibromyalgia	0.82 (0.43–1.58)	.562	0.69 (0.33–1.48)	.340
Bechterew's disease	0.97 (0.41–2.33)	.948	1.98 (0.77–5.16)	.164
Rheumatoid arthritis	0.72 (0.45–1.15)	.165	0.82 (0.45 –1.47)	.500
Dizziness	0.86 (0.67–1.09)	.211	1.07 (0.80– 1.45)	.640
Hyperactivity	0.53 (0.31–0.92)	.024	0.61 (0.30–1.23)	.168
MBD[c]	0.38 (0.16–0.90)	.028	0.27 (0.16–0.44)	< .001[d]

Note: [a] Adjusted for sex, age, gestational length, BMI, zygosity and education.

[b] Inflammatory bowel disease.

[c] Minimal brain disorder.

[d] Not adjusted for education, because all cases had the same educational level.

reduced the observed risks to nonsignificant levels except for the risk of nearsightedness, while the risk for developing MBD became significant. The results suggest that a 1 kg increase in birthweight is associated with a 1.3 times decreased risk of developing nearsightedness, and a 3.7 times decreased risk of minimal brain disorder later in life. Besides birthweight, education was also an important factor associated with nearsightedness: individuals with upper secondary and higher education had 1.6 and 3.0 higher risks respectively (both at $p < .001$) of developing myopia than the twins with secondary education.

Given that the length of education is an important confounder, birthweight differences were calculated only in those myopia-discordant pairs who were concordant for education (159 MZ and 224 DZ pairs). Significant differences in birthweight between myopic and nonmyopic twins were found in DZ twins (2686 g vs. 2750 g, $p = .040$), but not in MZ twins (2610 g vs. 2612 g, $p = .966$), indicating that genetic factors are important in the association between birthweight and nearsightedness later in life.

The low number of MBD discordant (2 MZ and 2 DZ) pairs did not allow conclusions to be drawn about the origins of the associations between birthweight and MBD, though affected twins were lighter than unaffected twins, 80 g ($p = .655$) and 85 g ($p = .655$) in MZ and DZ pairs respectively.

Discussion

Population-based twin data were used to study the associations between birthweight and 30 health outcomes

https://doi.org/10.1375/twin.8.2.148 Published online by Cambridge University Press

in young adulthood. The findings indicate that lower weight at birth may confer a higher risk of developing nearsightedness and MBD later in life.

In general, large-scale epidemiological studies rely on self-reported measures of symptoms and diseases. Several studies report an acceptable quality of questionnaire-based self-reported rates of hay fever (Duffy et al., 1990), asthma (Duffy et al., 1990), ear infections (Stephenson, 1995) and diabetes (Martin et al., 2000). Moreover, studies from Nordic countries report the acceptable validity of questionnaires in detecting migraine, headache (Hagen et al., 2000) and skin diseases (Susitaival et al., 1995). The estimates of refractive disorders in this survey are close to those found in other studies from Norway (Kinge et al., 1998) and thereby indirectly support the reliability of our data. Haugland and Wold (2001) found that survey methods provide adequate quality of data on headache, sleeping problems, dizziness, neck ache and other subjective health complaints in Norwegian adolescents. Although recall bias may result in either overestimation or underestimation of prevalence rates for some outcomes in our sample, we do not think that this bias is differentially related to birthweight.

The response rate was 71.0% for women and 55.1% for men ($p < 0.001$). Those who did not return the questionnaires were 44g ($p = .001$ [males]) and 41g ($p = .004$ [females]) lighter at birth than those who responded. This could lead to a slight underestimation of the odds ratios for those illnesses/symptoms for which lower birthweight confers increased risks, and overestimations of the odds ratios for the outcomes where the association occurs in the opposite direction. At the same time, analyses in pairs where only one twin responded did not reveal birthweight differences between those who responded and those who did not in either male or female twin pairs, which suggests little effect of recall bias in our co-twin control analyses. Only pairs for which both twins were alive at the age of 18 years were included in the study. Twins who did not survive were 1412 g (males) and 1154 g (females) lighter than those who survived. Therefore we must restrict our conclusions to the variations in birthweight within the relatively normal range of birthweight.

Several studies have reported higher prevalence of childhood myopia in children who were born preterm or with low birthweight (Holmström et al., 1998; Larsson et al., 2003). Children born preterm have altered growth of the eye that contributes to the higher risk of developing myopia in these children (O'Connor et al., 2002). While the eye of a small infant is smaller in length, the reduced radius of curvature of the cornea and/or lens may promote development of myopia (Saunders et al., 2002). Fledelius (1976) reported that 10-year-old children who were born preterm had shorter axial length, more curved corneas, and thicker lenses. Contrary to myopia in children born at term, which is characterized by increased axial length, myopia in prematurely born children has been shown to be attributed to an increase in corneal curvature and/or lens thickness, and a decrease in the anterior chamber depth (Choi et al., 2000; Gallo & Fagerholm, 1993; O'Connor et al., 2002), although there is still no consensus on the mechanisms of myopia development in preterm infants.

It remains unclear whether most of the reported associations between size at birth and subsequent nearsightedness are primarily attributed to prematurity or to fetal growth restriction. We focused on the effects of fetal growth restriction on later health; therefore adjustment for gestational age was performed in the regression analysis. Saw et al. (2004) showed that 7- to 9-year-old Singaporean Chinese children who were lighter or less mature at birth had shorter axial length, shallower vitreous chambers, and more curved corneas in dose-response fashion across the normal range of birthweight and gestational age that corresponds with the previous studies, although no differences in refraction data were found. Failure to detect refractive errors despite significant changes in ocular biometric parameters at a young school age in the Singaporean study, followed by a significant relationship between birthweight and myopia across the whole birthweight spectrum in individuals aged between 18 and 31 years in this study, may raise speculations that some compensatory mechanisms that may still be present at a young school age are exhausted with increased years of schooling. However, since these studies were performed in two different populations and this study does not include biometric data, these speculations should be considered with due caution.

Twin studies have shown that myopia is mainly genetically determined (Hammond et al., 2001; Lyhne et al., 2001), while studies in selected population groups indicate that environmental factors are important (Mutti et al., 2002; Saw et al., 2002). Therefore, the multifactorial aetiology of nearsightedness in which both genetic and environmental factors contribute to the susceptibility to myopia has to be considered (Goldschmidt, 2003). Little is known as to whether the associations between birth parameters and myopia are due to genes that may be associated with both impaired fetal growth and myopia, or due to growth restriction per se. No difference in birthweight in discordant MZ twins suggests that intrauterine growth restriction per se cannot explain the revealed association between birthweight and nearsightedness. Given that the birthweight difference between affected and nonaffected twins in DZ pairs was significant, we hypothesize that there may be some genetic factors that are associated with both reduced fetal growth and susceptibility to myopia later in life.

It has been reported that females from opposite-sex pairs have lower visual acuity (Miller, 1995) and an increased rate of fetal growth than females from same-sex twin pairs (Corey et al., 1979), suggesting influences of the male sex hormones on the female fetus development in opposite-sex twin pairs. However, in

https://doi.org/10.1375/twin.8.2.148 Published online by Cambridge University Press

this large study, female twins from opposite-sex DZ pairs were only 17 g heavier than female twins from same-sex DZ pairs, no difference in gestational duration was found, and the prevalences of the studied outcomes including myopia were similar across zygosity categories.

Several studies have identified low birthweight as a risk factor for hyperactivity disorders, behavioral problems and anxiety disorders in childhood and adolescence (Breslau, 1995; Elgen et al., 2002), which may support our findings in relation to MBD. We were unable to examine how the relationship between birthweight and MBD was explained by genes or intrauterine environment, due to a low number of discordant pairs.

Several other outcomes may deserve attention in future studies given that the Bonferroni adjustment for multiple comparisons is rather conservative; our data suggest that there may also be relationships between birthweight and increased risks of developing astigmatism, ear infections, tonsillitis, neck/shoulder pain, and headaches.

The results may not necessarily be generalizable to singletons given the different biology of twin pregnancies. The average birthweight among twins is lower than that of singletons and twins are more likely to be born preterm. However, the growth retardation experienced by twins compared to singletons does not result in increased risk of mortality in adulthood (Christensen et al., 1995). Nevertheless, in total groups of twins, negative associations between birthweight and blood pressure (Ijzerman et al., 2000), cholesterol levels (Ijzerman et al., 2001) and other outcomes were found to be similar to the findings in singletons, suggesting that differences in birthweight in twins can be used as a model for differences in birthweight in singletons. The prevalence of refractive errors was comparable in preterm twins and triplets with preterm singletons, and in within-pair analyses, the twins with lower birthweight were more likely to have ametropia than their heavier co-twins, though these results were not significant (Tomazzoli et al., 2003). Twins are at higher risk of neurological and behavioral problems than singletons, but these differences are mainly related to the shorter twin gestation, rather than to being a twin (Shinwell, 2002). While the findings in dichorionic twins regarding birthweight and later health can be valid for singletons, caution is needed regarding data from monochorionic twins (Morley et al., 2003). About two thirds of MZ twins are monochorionic, and the intrauterine environment may also be different for MZ and DZ twins, which in turn may influence the associations between intrapair differences in birthweight and adult health.

In summary, lower birthweight conferred increased risks of nearsightedness and MBD in the full sample. In relation to myopia, the findings are unlikely to be attributed to intrauterine growth restriction per se and suggest that genetic factors may account for the associations between birthweight and nearsightedness.

Acknowledgments

The Norwegian Institute of Public Health program of twin research is supported by grants from The Norwegian Research Council, The Norwegian Foundation for Health and Rehabilitation, and the European Commission under the program 'Quality of Life and Management of the Living Resources' of 5th Framework Programme (no. QLG2-CT-2002-01254). We thank the twins for their participation.

References

Barker, D. J. P. (1995). Fetal origins of coronary heart disease. *British Medical Journal, 311,* 171–174.

Barker, D. J. P. (1998). *Mothers, babies and health in later life*. Edinburgh, UK: Churchill Livingstone.

Breslau, N. (1995). Psychiatric sequelae of low birthweight. *Epidemiologic Reviews, 17*, 96–106.

Choi, M. Y., Park, I. K., & Yu, Y. S. (2000). Long term refractive outcome in eyes of preterm infants with and without retinopathy of prematurity: Comparison of keratometric value, axial length, anterior chamber depth, and lens thickness. *British Journal of Ophthalmology, 84,* 138–143.

Christensen, K., Vaupel, J. W., Holm, N. V., & Yashin, A. I. (1995). Mortality among twins after age 6: Fetal origins hypothesis versus twin method. *British Medical Journal, 310*, 432–436.

Corey, L. A., Nance, W. E., Kang, K. W., & Christian, J. C. (1979). Effects of type of placentation on birthweight and its variability in monozygotic and dizygotic twins. *Acta Geneticae Medicae and Gemellologiae, 28,* 41–50.

Duffy, D. L., Martin, N. G., Battistutta, D., Hopper, J. L., & Mathews, J. D. (1990). Genetics of asthma and hay fever in Australian twins. *The American Review of Respiratory Disease*, *142*, 1351–1358.

Elgen, I., Sommerfelt, K., & Markestad, T. (2002). Population based, controlled study of behavioural problems and psychiatric disorders in low birthweight children at 11 years of age. *Archives of Disease in Childhood. Fetal and Neonatal Edition, 87*, F128–F132.

Fledelius, H. (1976). Prematurity and the eye: Ophthalmic 10-year follow-up of children of low and normal birth weight. *Acta Ophthalmologica, 128,* S3–S245.

Gallo, J. E., & Fagerholm, P. (1993). Low-grade myopia in children with regressed retinopathy of prematurity. *Acta Ophthalmologica, 71,* 519–523.

Godfrey, K. M., & Barker, D. J. P. (2001). Fetal programming and adult health. *Public Health Nutrition*, *4*, 611–624.

Goldschmidt, E. (2003). The mystery of myopia. *Acta Ophthalmologica Scandinavica, 81,* 431–436.

https://doi.org/10.1375/twin.8.2.148 Published online by Cambridge University Press

Hagen, K., Zwart, J. A., Vatten, L., Stovner, L. J., & Bovim, G. (2000). Head-HUNT: Validity and reliability of a headache questionnaire in a large population-based study in Norway. *Cephalalgia, 20*, 244–251.

Hagström, B., Nyberg, P., & Nilsson, P. M. (1998). Asthma in adult life: Is there an association with birth weight? *Scandinavian Journal of Primary Health Care, 16,* 117–120.

Hales, C. N., Barker, D. J., Clark, P. M., Cox, L. J., Fall, C., Osmond, C., & Winter, P. D. (1991). Fetal and infant growth and impaired glucose tolerance at age 64. *British Medical Journal, 303*, 1019–1022.

Hammond, C. J., Snieder, H., Gilbert, C. E., & Spector, T. D. (2001). Genes and environment in refractive error: The twin eye study. *Investigative Ophthalmology and Visual Science, 42,* 1232–1236.

Harris, J. R, Magnus, P., & Tambs, K. (2002). The Norwegian Institute of Public Health Twin Panel: A description of the sample and program of research. *Twin Research, 5*, 415–423.

Haugland, S., & Wold, B. (2001). Subjective health complaints in adolescence: Reliability and validity of survey methods. *Journal of Adolescence, 24*, 611–624.

Hestbaek, L., Leboeuf-Yde, C., Kyvik, K. O., & Manniche, C. (2003). Is low back pain in youth associated with weight at birth? A cohort study of 8000 Danish adolescents. *Danish Medical Bulletin, 50,* 181–185.

Holmström, M., el Azazi, M., & Kugelberg, U. (1998). Ophthalmological long-term follow up of preterm infants: A population based, prospective study of the refraction and its development. *British Journal of Ophthalmology, 82,* 1265–1271.

Holness, M. J., Langdown, M. L., & Sugden, M. C. (2000). Early-life programming of susceptibility to dysregulation of glucose metabolism and the development of Type 2 diabetes mellitus. *The Biochemical Journal, 349*, 657–665.

Hubinette, A., Cnattingius, S., Johansson, A. L., Henriksson, C., & Lichtenstein, P. (2003). Birth weight and risk of angina pectoris: Analysis in Swedish twins. *European Journal of Epidemiology, 18,* 539–544.

Ijzerman, R. G., Stehouwer, C. D., & Boomsma, D. I. (2000). Evidence for genetic factors explaining the birth weight-blood pressure relation: Analysis in twins. *Hypertension, 36,* 1008–1012.

Ijzerman, R. G., Stehouwer, C. D., de Geus, E. J., Kluft, C., & Boomsma, D. I. (2003a). The association between birth weight and plasma fibrinogen is abolished after the elimination of genetic influences. *Journal of Thrombosis and Haemostasis, 1,* 239–242.

Ijzerman, R. G., Stehouwer, C. D., de Geus, E. J., van Weissenbruch, M. M., Delemarre-van de Waal, H. A., & Boomsma, D. I. (2003b). Low birth weight is associated with increased sympathetic activity: Dependence on genetic factors. *Circulation, 108,* 566–571.

Ijzerman, R. G., Stehouwer, C. D., Van Weissenbruch, M. M., De Geus, E. J., & Boomsma, D. I. (2001). Evidence for genetic factors explaining the association between birth weight and low-density lipoprotein cholesterol and possible intrauterine factors influencing the association between birth weight and high-density lipoprotein cholesterol: Analysis in twins. *Journal of Clinical Endocrinology and Metabolism, 86,* 5479–5484.

Jacobsson, L. T., Jacobsson, M. E., Askling, J., & Knowler, W. C. (2003). Perinatal characteristics and risk of rheumatoid arthritis. *British Medical Journal, 326,* 1068–1069.

Katz, K. A., Pocock, S. J., & Strachan, D. P. (2003). Neonatal head circumference, neonatal weight, and risk of hay fever, asthma and eczema in a large cohort of adolescents from Sheffield, England. *Clinical and Experimental Allergy, 33*, 737–745.

Kinge, B., Midelfart, A., & Jacobsen, G. (1998). Refractive errors among young adults and university students in Norway. *Acta Ophthalmologica Scandinavica, 76*, 692–695.

Larsson, E. K., Rydberg, A. C., & Holmström, G. E. (2003). A population-based study of the refractive outcome in 10-year-old preterm and full-term children. *Archives of Ophthalmology, 121,* 1430–1436.

Leon, D. A. (2001). The foetal origins of adult disease: Interpreting the evidence from twin studies. *Twin Research, 4*, 321–326.

Lyhne, N., Sjolie, A. K., Kyvik, K. O., & Green, A. (2001). The importance of genes and environment for ocular refraction and its determiners: A population based study among 20–45 year old twins. *British Journal of Ophthalmology, 85*, 1470–1476.

Magnus, P., Berg, K., & Nance, W. E. (1983). Predicting zygosity in Norwegian twin pairs born 1915–1960. *Clinical Genetics, 24,* 103–112.

Martin, L. M., Leff, M., Calonge, N., Garrett, C., & Nelson, D. E. (2000). Validation of self-reported chronic conditions and health services in a managed care population. *American Journal of Preventive Medicine, 18*, 215–218.

Michelsson, K., & Noronen, M. (1983). Neurological, psychological and articulatory impairment in five-year-old children with a birthweight of 2000 g or less. *European Journal of Pediatrics, 14*, 96–100.

Miller, E. M. (1995). Reported myopia in opposite-sex twins: A hormonal hypothesis. *Optometry and Visual Science, 72,* 34–36.

Morley, R., Dwyer, T., & Carlin, J. B. (2003). Studies of twins: Can they shed light on the fetal origins of adult disease hypothesis? *Twin Research, 6,* 520–525.

Mutti, D. O., Mitchell, G. L., Moeschberger, M. L., Jones, L. A., & Zadnik, K. (2002). Parental myopia, near work, school achievement, and children's refractive error. *Investigative Ophthalmology and Visual Science, 43,* 3633–3640.

O'Connor, A. R., Stephenson, T., Johnson, A., Tobin, M. J., Moseley, M. J., Ratib S., Ng, Y., & Fielder, A. R. (2002). Long-term ophthalmic outcome of low birth

https://doi.org/10.1375/twin.8.2.148 Published online by Cambridge University Press

weight children with and without retinopathy of prematurity. *Pediatrics, 109,* 12–18.

Poulsen, P., Levin, K., Beck-Nielsen, H., & Vaag, A. (2002). Age-dependent impact of zygosity and birth weight on insulin secretion and insulin action in twins. *Diabetologia, 45,* 1649–1657.

Saunders, K. J., McCulloch, D. L., Shepherd, A. J., & Wilkinson, A. G. (2002). Emmetropisation following preterm birth. *British Journal of Ophthalmology, 86,* 1035–1040.

Saw, S. M., Tong, L., Chia, K. S., Koh, D., Lee, Y. S., Katz, J., & Tan, D. T. (2004). The relation between birth size and the results of refractive error and biometry measurements in children. *British Journal of Ophthalmology, 88,* 538–542.

Saw, S. M., Zhang, M. Z., Hong, R. Z., Fu, Z. F., Pang, M. H., & Tan, D. T. (2002) Near-work activity, nightlights, and myopia in the Singapore–China study. *Archives of Ophthalmology, 120,* 620–627.

Shaheen, S. O., Sterne, J. A., Montgomery, S. M., & Azima, H. (1999). Birth weight, body mass index and asthma in young adults. *Thorax, 54,* 396–402.

Shinwell, E. S. (2002). Neonatal and long-term outcomes of very low birth weight infants from single and multiple pregnancies. *Seminars in Neonatology, 7,* 203–209.

SPSS, Inc. (2003). SPSS for Windows (Release 12.0.1) [Computer software]. Chicago, IL: Author

StataCorp. (2001). Stata statistical software (Release 7.0) [Computer software]. College Station, TX: Author.

Steffensen, F. H., Sorensen, H. T., Gillman, M. W., Rothman, K. J., Sabroe, S., Fischer, P., & Olsen, J. (2000). Low birth weight and preterm delivery as risk factors for asthma and atopic dermatitis in young adult males. *Epidemiology, 11,* 185–188.

Stephenson, H. (1995). Evaluation of self-report by adults of childhood otitis media histories. *Audiology, 34,* 124–134.

Susitaival, P., Husman, L., Hollmen, A., & Horsmanheimo, M. (1995). Dermatoses determined in a population of farmers in a questionnaire-based clinical study including methodology validation. *Scandinavian Journal of Work, Environment and Health, 21,* 30–35.

Tomazzoli, L., Renzi, G., & Mansoldo, C. (2003). Ophthalmologic follow-up of premature twins and triplets. *European Journal of Ophthalmology, 13,* 439–444.

https://doi.org/10.1375/twin.8.2.148 Published online by Cambridge University Press