Genetic Regulation of Growth in Height and Weight from 3 to 12 Years of Age: A Longitudinal Study of Dutch Twin Children

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Human growth is a complex and poorly understood process. We studied the effect of genetic and environmental factors on height and body mass index (BMI, kg/m^2) based on maternal reports at 3, 4, 5, 7, 10 and 12 years of age in a large longitudinal cohort of Dutch twins (7755 complete twin pairs at age 3). Several multivariate variance component models for twins were fitted to the data using the Mx statistical package. The first-born twin was taller until age 10 and heavier until age 12 than the second-born co-twin. Heritability estimates were high for height (a^2 = .58–.91) and BMI (a^2 = .31–.82), but common and unshared environmental factors were also important. The phenotypic correlations across the ages for height and BMI were mainly explained by correlated additive genetic factors (r_a = .77–.96 for height and .43–.92 for BMI), but common (r_c = .40–.84 and .09–.78, respectively) and specific environmental correlations (r_e = .50–.81 and .42–.80, respectively) were also significant. Additive genetic factors decreased with increasing age difference for both height and BMI. However, the full Cholesky model, which does not make any assumptions regarding the underlying genetic structure, had the best fit. High genetic correlations across the ages, especially for height, may help further molecular genetic studies of human growth. Environmental factors affecting height and BMI during growth period are also important, and further studies are needed to identify these factors and test whether they interact with genetic factors.

Recent studies have suggested that growth during childhood in height and weight is associated with several metabolic outcomes in adulthood such as obesity (Sachdev et al., 2005), impaired glucose tolerance (Bhargava et al., 2004), hypertension (Barker et al., 2002), and increased risk of coronary heart disease (Barker et al., 2005). Thus, finding factors affecting human growth may help to better understand the mechanisms behind these metabolic disorders and diseases. Information on the relative contributions of genetic and environmental influences affecting variation in growth, information on the stability of the genetic and nongenetic influences, and information on the extent to which genes affect variation in height and weight at specific ages is also important when trying to map genes affecting growth. Genetic regulation of height and weight throughout childhood was already revealed by early United States (Wilson, 1976) and Japanese (Ooki & Asaka, 1993) twin studies. During the first year, genetic effects were usually small, possibly because of discordance in birthweight in monozygotic (MZ) twins, which may reflect higher neonatal environmental variation in MZ than in dizygotic (DZ) twins (Cao & Monni, 2005). A Danish study reported that body mass index (BMI) of adoptive children from 7 to 13 years of age correlated more strongly with biological relatives than adoptive relatives suggesting that genetic factors are more important than common environmental factors (Sørensen et al., 2002). A Polish twin study found that variance in BMI from 7 to 18 years of age was mainly explained by additive genetic factors whereas dominance genetic effects were small (Huggins et al., 2000). Unfortunately, both of these studies failed to report the exact heritability estimates. Belgian (Beunen et al., 2000) and Polish (Hauspie et al., 1994) twin studies modeling parameters derived from the Preece-Baines growth model 1 (Preece & Baines, 1978) found that pubertal growth characteristics were strongly genetically regulated and heritability estimates for different parameters varied from .49 to .96.

The above studies examined height and weight separately for different ages and thus are not informative with respect to the genetic architecture of growth. The

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question about the role of genetic and environmental factors underlying the stability of height and weight at different ages is, however, not new. An early Swedish twin study found that both genetic and environmental factors contributed to the tracking of height and weight measured at age 10 and at semiannual measures up to 16 years in girls and 18 years in boys (Fischbein & Pedersen, 1987). The phenotypic correlations decreased when the time between the measures increased but remained high (the lowest correlation was .76 found in weight between 11 and 18 years of age in boys) showing that both height and weight are stable phenotypes during the growth period. This study relied on comparisons of MZ and DZ correlations, but more advanced modeling was applied in later studies. A Dutch study based on a large number of infant twins (more than 4500 pairs) found that additive genetic factors, environmental factors shared by a twin pair, and environmental factors unique to each twin individual affected different parameters of growth curve from birth to 2.5 years of age (van Dommelen et al., 2004). Genetic and shared environmental factors affecting different growth parameters were also correlated over time, indicating that some genes and shared environmental factors are expressed during early growth. In a United States adoption study, longitudinal genetic modeling was applied to BMI data from birth to 9 years of age (Cardon, 1995). After age 1, persistent genetic influences were found and genetic transmissions were high varying between .71 and 1.00.

Previous twin and adoption studies have thus solidly shown the strong genetic regulation of height and weight from infancy to adulthood. They have also suggested that the genes affecting height and weight are largely the same during the growth period. These studies, however, have generally not formally tested different hypotheses about the underlying genetic architecture of growth. Secondly, most studies are based only on small datasets, that is, less than 200 twin pairs or adopted families. This hampers the separation of real biological differences in growth at different ages from random variation. In this study, we address these questions by analyzing a large longitudinal Dutch twin data set with information on height and weight from age 3 to 12 years. Several quantitative genetic models (e.g., independent pathway models and simplex models) are applied to obtain an understanding of the role of genetic and environmental factors on growth.

Materials and Methods

Subjects were recruited from the Netherlands Twin Registry (Boomsma et al., 2002). A survey was sent to parents when the children were 3, 4, 5, 7, 10 and 12 years of age. After 2 months a reminder was sent to nonrespondents, and after 4 months subsets of those who did not respond were telephoned. We used height, weight, birth order and zygosity reported by mothers. The reliability of maternal reported height and weight was analyzed in a subsample of 94 twins at 5 years of age, and the correlations between measures and maternal reports were .96 for height and .92 for weight (Estourgie-van Burk et al., 2006). This can be regarded as good reliability, especially since some time difference existed between the maternal reports and the laboratory measures (the maximum time difference was 3 months). Zygosity was determined by questions on physical similarity and frequency of confusions of the twins by family and strangers

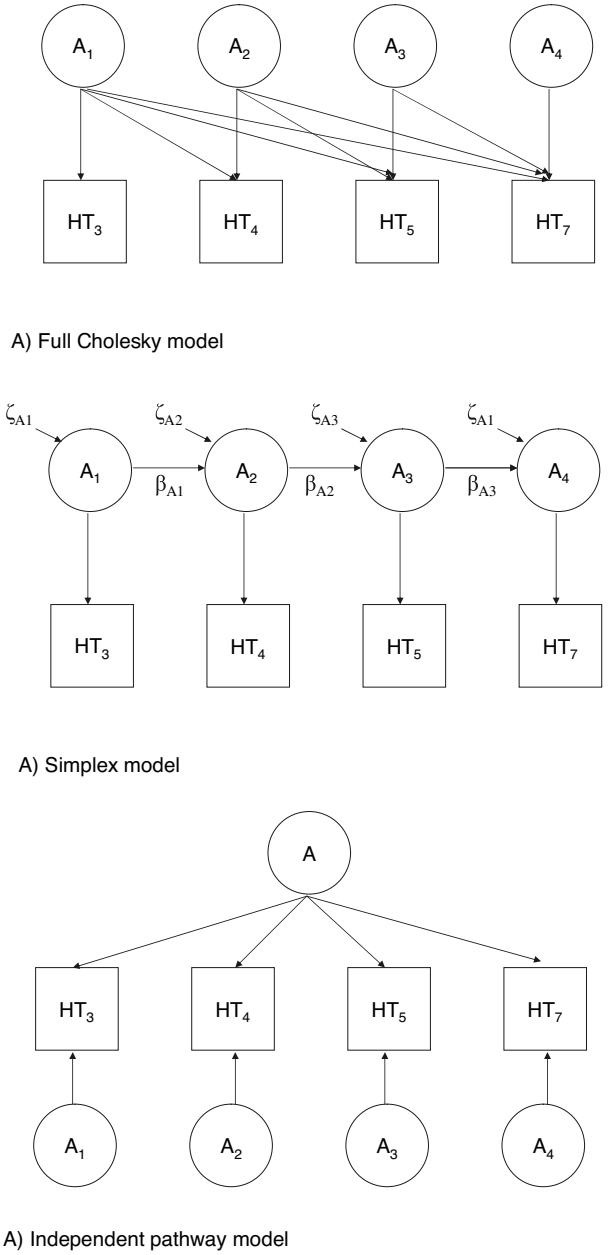

Figure1

Simplified schematic presentation of the multivariate models used to investigate genetic architecture of growth. Models are presented only for four ages and additive genetic factors.

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Table 1

Number of Twin Individuals and Means and Standard Deviations of Height and BMI at Ages of 3, 4, 5, 7, 10 and 12 by Sex and Zygosity

		Height (cm)		BMI (kg/m^2)	
	N of twin individuals	Mean	*SD*	Mean	*SD*
Age 3					
Male MZ	2404	97	4.13	15.7	1.20
Female MZ	2906	96	4.18	15.4	1.33
Male DZ	5351	97	4.15	15.7	1.22
Female DZ	5175	96	4.14	15.5	1.30
Age 4					
Male MZ	1640	104	4.32	15.3	1.21
Female MZ	1882	104	4.55	15.0	1.37
Male DZ	3401	105	4.35	15.3	1.22
Female DZ	3205	104	4.47	15.1	1.32
Age 5					
Male MZ	972	113	5.43	15.0	1.51
Female MZ	1107	112	5.65	14.8	1.56
Male DZ	2002	114	5.41	15.0	1.48
Female DZ	1878	113	5.44	14.9	1.55
Age 7					
Male MZ	1271	128	5.73	15.2	1.61
Female MZ	1487	127	6.06	15.3	1.86
Male DZ	2517	128	5.88	15.3	1.65
Female DZ	2382	128	5.93	15.4	1.92
Age 10					
Male MZ	979	143	6.57	16.3	2.18
Female MZ	1160	143	7.15	16.4	2.14
Male DZ	1744	144	6.72	16.3	2.08
Female DZ	1736	143	6.63	16.4	2.35
Age 12					
Male MZ	691	154	7.26	16.9	1.96
Female MZ	758	155	7.91	17.4	2.38
Male DZ	1144	155	7.67	17.1	2.28
Female DZ	1141	156	7.38	17.5	2.61

Note: *SD* = standard deviation

(Goldsmith, 1991; Rietveld et al., 2000). Maternally reported zygosity was validated in a subsample, and the agreement with DNA marker based zygosity was found to be around 93% (Rietveld et al., 2000). The number of complete twin pairs with information on height, weight and zygosity was 7818 at age 3, 4975 at age 4, 2899 at age 5, 3793 at age 7, 2786 at age 10, and 1835 at age 12. Body mass index (kg/m^2) was used as a measure of relative weight at each age since it is a commonly recommended obesity indicator after 2 years of age (Cole et al., 2000; Dietz & Robinson, 1998). We found that at all ages both height ($p < .0001$) and BMI ($p < .069$) correlated with the exact age of measurement, and we thus decided to adjust height and BMI for exact age of measurement separately in men and women across age groups. The distribution of BMI was normalized by using the natural logarithm of BMI.

Quantitative genetic modeling of the twin data is based on linear structural equation modeling (SEM). The modeling was carried out using the statistical package Mx (Neale, 2003). Classical twin analysis allows the decomposition of phenotypic variation in the data into variation caused by additive genetic factors (A), which is the sum of allelic effects affecting the phenotype over all loci, dominance genetic effect (D) including nonadditive effects between alleles in the same locus and interactions between alleles at different loci (epistasis), environmental factors shared by twins (C) and environmental factors unique to each individual (E) including measurement error. Our data include only twins reared together and therefore do not allow the simultaneous modeling of genetic dominance and shared environmental effects. We assume random mating and lack of gene-environment interaction and recognize that assortative mating by height or weight may increase DZ correlations and therefore possibly increases the estimated influence of the common environment. Possible gene-environment interaction will be included as part of the additive genetic variance or unique environmental variance regarding whether the environmental factors are shared or unshared by a twin pair, respectively.

We first tested the assumptions of twin analyses. This was done by fitting a series of saturated models to the data, which began with a model that does not make any assumptions about equality of means, variances or correlations. Next, we used univariate genetic modeling to find the best model for height and BMI at each age and used this information in further multivariate modeling. The fit of more constrained models was compared to models that permitted fewer constraints by likelihood-ratio tests. The difference in the log-likelihoods follows a χ^2-distribution given the degrees of freedom (*df*). If the difference in χ^2-values between two nested models compared to the difference in *df* (χ^2_{df}) is statistically significant, the more parsimonious model fits significantly worse and lacks important parameters.

We continued modeling by fitting several parallel multivariate models shown in Figure 1 (Neale & Cardon, 1992); for the matter of simplicity the models in this figure are presented only for additive genetic factors and for four age groups instead of six age groups used in this study. A Cholesky decomposition (Figure 1a) provides a saturated description of the multivariate data, and will be used as the base model in multivariate analyses. A Cholesky decomposition does not make any assumptions on the underlying genetic architecture but simply decomposes the variation and covariation in the data into a series of uncorrelated genetic and environmental factors. The first factor influences all measurements, the second factor only influences the second and possibly subsequent measurements, the third factor only influences

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Table 2

Number of Complete Twin Pairs and Intraclass Correlations of Height and BMI at Ages 3, 4, 5, 7, 10 and 12 by Sex and Zygosity

	Age 3	Age 4	Age 5	Age 7	Age 10	Age 12
Male MZ	1186	808	474	630	488	341
Height[a]	.91	.90	.95	.92	.94	.92
BMI[a,b]	.84	.81	.79	.88	.86	.86
Male DZ	1292	859	497	645	425	288
Height[a]	.57	.56	.58	.58	.55	.55
BMI[a,b]	.49	.46	.64	.58	.46	.55
Female MZ	1429	925	544	738	577	373
Height[a]	.90	.92	.93	.92	.93	.93
BMI[a,b]	.84	.80	.88	.88	.85	.90
Female DZ	1204	750	437	580	422	279
Height[a]	.59	.61	.63	.58	.57	.50
BMI[a,b]	.50	.50	.57	.54	.51	.49
Opposite sex DZ	2644	1633	947	1200	874	554
Height[a]	.54	.55	.60	.53	.54	.46
BMI[a,b]	.48	.45	.48	.55	.47	.51

Note: [a]Adjusted for sex and the exact age at the time of measurement.

[b]Logarithmic transformation was used.

the third and possibly subsequent measurements, and so forth. Using a Cholesky decomposition, it is possible to estimate the genetic and environmental correlations of height and BMI between different ages.

The independent pathway model (Figure 1b) specifies a common genetic factor affecting height or BMI at different ages. Thus, the height and BMI correlations over the growth period are due to genetic (or environmental) influences common to all ages. Additionally, there are independent factors that can affect the measurement at each age. Simplex models (Figure 1c) represent growth as a more dynamic process in which new genes can start to affect the phenotype at each age. Simultaneously part, or all, of the genes affecting the phenotype at the previous ages can also be of importance. Further, it is possible to create models having, for example, a simplex structure for genetic factors and a Cholesky structure for environmental factors.

Simplex and independent pathway models both imply a certain degree of continuity. However in a longitudinal study, these mechanisms result in a different pattern of correlations between successive assessments. The simplex model therefore predicts higher correlations among adjoining assessments than those occurring more distantly in time. In contrast, the independent pathway model assumes that the same stable factors exert their effects at each assessment and does not imply that correlations between assessments vary as a function of the length of the time lag. Thus, simplex and independent pathway models predict different patterns of longitudinal correlations, and tests can be performed to derive the underlying mechanism by comparing observed and predicted correlations. The models are compared by computing Akaike's information criterion (AIC) for each model. AIC allows the comparison of the goodness-of-fit between parallel, that is, nonnested, models; the model with the smallest AIC-value is regarded as having the best fit.

Results

Table 1 presents the means and standard deviations (*SD*) of height and BMI at different ages. No systematic differences were found between MZ and DZ twins and also boys and girls had largely the same height and BMI over the study period; only at age 12 were girls were slightly taller. From 3 to 12 years of age, height increased from 97 cm to 155 cm in boys and from 96 cm to 156 cm in girls (data from MZ and DZ twins together). A slight decrease in BMI was found from age 3 to 4. BMI started to increase after age 7 and was highest (17.0 kg/m^2 in boys and 17.5 kg/m^2 in girls) at age 12.

Intraclass correlations for height and BMI are presented in Table 2. MZ correlations were higher than DZ correlations suggesting genetic effects. Since DZ correlations were greater than half the size of MZ correlations, we employed models including additive genetic, common environment, and specific environment variance components (ACE models) as the starting point of genetic modeling.

We started the genetic modeling by testing the assumptions of twin analyses. The presence of birth order effects was first tested. Statistically significant birth order effects were found for height and BMI at all ages ($\Delta\chi^2_3$ = 11–155, p = .014–.0001) except for

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Table 3

Standardized Variance Components in Univariate Models with 95% Confidence Intervals for Height and BMI at 3, 4, 5, 7, 10 and 12 Years of Age in Men and Women

	Additive genetic		Common environment		Unique environment	
	a^2	95% CI	c^2	95% CI	e^2	95% CI
Height[a]						
Men						
Age 3	.71	.64–.77	.20	.14–.27	.09	.09-.10
Age 4	.71	.64–.77	.19	.13–.26	.10	.09-.11
Age 5	.71	.63–.78	.24	.17–.32	.05	.05-.06
Age 7	.71	.60–.84	.21	.09–.33	.07	.06-.08
Age 10	.79	.68-.87	.15	.07–.26	.06	.05–.07
Age 12	.76	.63-.93	.16	.00–.30	.07	.06–.09
Women						
Age 3	.61	.53–.70	.28	.19–.35	.11	.10-.12
Age 4	.64	.56–.73	.28	.19–.36	.08	.07-.09
Age 5	.58	.49–.67	.35	.25–.44	.08	.07-.09
Age 7	.76	.61–.84	.17	.08–.32	.08	.07-.09
Age 10	.71	.60–.82	.21	.10–.32	.08	.07–.09
Age 12	.91	.67–.94	.02	.00–.26	.07	.06–.08
BMI[a,b]						
Men						
Age 3	.70	.62–.77	.14	.08–.22	.16	.14–.17
Age 4	.73	.66–.78	.09	.04–.15	.18	.17–.21
Age 5	.31	.21–.42	.47	.37–.56	.22	.19–.25
Age 7	.60	.51–.70	.28	.19–.37	.12	.11–.13
Age 10	.78	.67–.84	.08	.02–.19	.14	.13–.16
Age 12	.75	.60–.87	.14	.02–.28	.11	.10–.14
Women						
Age 3	.68	.60–.76	.16	.08–.24	.16	.15–.18
Age 4	.57	.47–.68	.23	.23–.32	.21	.19–.23
Age 5	.71	.64–.77	.17	.11–.24	.12	.10–.13
Age 7	.69	.61–.76	.20	.13–.28	.11	.11–.12
Age 10	.70	.57–.82	.17	.05–.29	.14	.12–.16
Age 12	.82	.67–.90	.09	.01–.24	.09	.08–.11

Note: CI = confidence intervals

[a]Adjusted for the exact age at the time of measurement.

[b]Logarithmic transformation was used.

height at age 12. When we studied this more carefully, we found that the first-born twin was, on average, taller and heavier than the second-born co-twin. The height differences varied from 0.20 cm at ages 3 and 4 to 0.34 cm at age 5 and BMI differences from 0.12 kg/m^2 at ages 4 and 7 to 0.22 kg/m^2 at age 12; the age differences were not significant.

Next, we selected the best univariate model for height and BMI at each age (data not shown but are available from the authors). When we compared an ACE model with birth order effect to the fully saturated model, the poorest fit was found for height at age 3 ($\Delta\chi^2_{15}$ = 48, p < .0001). However as seen in Table 1, no large differences in means or *SD*s between MZ and DZ twins were observed even at this age, and the poorer fit was probably due to a larger number of observations at this age compared to the other ages. Otherwise model fit was reasonably good for height and BMI ($\Delta\chi^2_{15}$ ranged from 12, p = .655 in BMI at age 7 to 32, p = .040 in BMI at age 5). A model including only additive genetic and specific environment fitted the data poorly ($\Delta\chi^2_3$ ranged from 6, p = .051 in height at age 12 to 144, p = .0001 in height at age 3) showing the importance of common environment for height and BMI at all ages. Sex-specific genetic effects were statistically significant only for height at two ages ($\Delta\chi^2_1$ = 8, p = .004 at age 3 and $\Delta\chi^2_1$= 6, p = .018 at age 7), and thus we decided not to include them into the models. Fixing the parameter estimates to be equal in men and women decreased the

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Table 4

Trait Correlations of Height and BMI Between 3, 4, 5, 7, 10 and 12 Years of Age and Decomposition of These Trait Correlations into Additive Genetic (r_A), Shared Environmental (r_C) and Unique Environmental (r_E) Correlations in Men and Women

		Height				BMI			
	N	r_{trait}	r_A	r_C	r_E	r_{trait}	r_A	r_C	r_E
Men									
Age 3 and 4	3657	.89	.94	.84	.66	.76	.83	.65	.59
Age 3 and 5	2037	.82	.93	.56	.68	.62	.86	.27	.53
Age 3 and 7	2494	.78	.87	.57	.56	.49	.60	.21	.48
Age 3 and 10	1841	.78	.83	.66	.61	.42	.44	.37	.48
Age 3 and 12	1253	.73	.78	.82	.53	.39	.43	.20	.45
Age 4 and 5	1986	.88	.94	.67	.73	.71	.91	.46	.58
Age 4 and 7	2013	.81	.90	.59	.59	.55	.69	.24	.52
Age 4 and 10	1465	.80	.85	.65	.58	.48	.52	.45	.42
Age 4 and 12	907	.77	.82	.74	.50	.47	.53	.26	.46
Age 5 and 7	1173	.83	.90	.59	.74	.58	.80	.35	.48
Age 5 and 10	838	.83	.88	.57	.79	.51	.64	.39	.42
Age 5 and 12	390	.78	.87	.44	.65	.41	.55	.32	.51
Age 7 and 10	1149	.86	.94	.60	.73	.66	.68	.78	.53
Age 7 and 12	622	.81	.91	.40	.73	.59	.79	.23	.60
Age 10 and 12	917	.88	.93	.71	.81	.76	.86	.42	.80
Women									
Age 3 and 4	3806	.89	.96	.79	.65	.77	.87	.62	.59
Age 3 and 5	2056	.85	.93	.62	.65	.65	.79	.22	.53
Age 3 and 7	2600	.78	.86	.63	.69	.57	.61	.36	.48
Age 3 and 10	2002	.75	.85	.56	.61	.46	.52	.28	.48
Age 3 and 12	1335	.68	.79	.46	.55	.41	.52	.09	.45
Age 4 and 5	1930	.89	.95	.70	.73	.73	.92	.21	.58
Age 4 and 7	2051	.84	.90	.66	.66	.61	.70	.37	.52
Age 4 and 10	1563	.79	.87	.58	.60	.54	.62	.30	.42
Age 4 and 12	961	.72	.77	.55	.51	.41	.59	.12	.46
Age 5 and 7	1219	.85	.91	.68	.67	.69	.74	.49	.48
Age 5 and 10	936	.80	.94	.38	.57	.54	.71	.22	.42
Age 7 and 10	1229	.85	.92	.63	.77	.75	.84	.65	.53

fit at all ages ($\Delta\chi^2_3$ = 8–78, p = .004 - .0001) except for height at ages 7 and 12 indicating that separate variance components were needed for men and women. Thus, we decided to use an ACE model with birth order effects and different parameter estimates for men and women but without a sex-specific genetic effect in the further modeling.

The estimates obtained by univariate modeling are presented in Table 3. The heritability estimates for height increased from age 3 and were highest at age 10 in men (a^2 = .79) and 12 in women (a^2 = .91). This increase was due to a decreasing effect of the common environment whereas the effect of the specific environment remained largely the same over the study period (e^2 = .05–.11). The differences in the heritability estimates between the ages were, however, relatively small and not statistically significant. For BMI the heritability estimates were lower (a^2 = .57–.82, except for .31 in men at age 5) and the relative effect of specific environment was higher (e^2 = .09–.22) than for height.

Table 4 presents the phenotypic correlations between the different ages for both height and BMI as well as the decomposition of these correlations into genetic and environmental correlations. The across-age correlations were systematically higher for height than for BMI, but no clear differences were seen between men and women. The additive genetic correlations were generally higher for height (r_a = .77–.96) and BMI (r_a = .43–.92) than common (r_c = .38–.84 and .09 - .78, respectively) or specific environmental correlations (r_e = .50–.81 and .42–.80, respectively). Additive genetic factors explained the major part of the phenotypic correlations of height (63–90%) and BMI (57–88%) reflecting the high heritability of these phenotypes (data not shown). In the across-age correlations, a clear decreasing pattern was found both in height and BMI; when the time between the

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Table 5

Fit Statistics of Additive Genetic/Common Environment/Specific Environment Multivariate Models for Height and BMI at 3, 4, 5, 7, 10 and 12 Years of Age[a]

			Fit statistics compared to full Cholesky model			
	χ^2	*df*	$\Delta\chi^2$	Δdf	*p* value	ΔAIC
Height[b]						
Full Cholesky model	237,758	48,789	—	—	—	—
Cholesky submodels						
Common genetic factor	238,715	48,819	957	30	< .001	897
Common and specific genetic factors	237,938	48,807	180	18		144
One common environmental factor	238,230	48,819	472	30	< .001	412
No specific environmental correlations	237,929	48,819	171	30	< .001	111
Independent pathway model	238,558	48,843	800	54	< .001	692
Full simplex model	238,036	48,848	278	59	< .001	160
Cholesky models with simplex genetic structure	237,817	48,809	59	20	< .001	20
Common environmental structure	237,841	48,809	83	20	< .001	43
Specific environmental structure	137,860	48,808	104	19	< .001	64
BMI[b,c]						
Full Cholesky model	327,294	48,789	—	—	—	—
Cholesky submodels						
Common genetic factor	328,270	48,819	976	30	< .001	916
Common and specific genetic factors	327,511	48,807	360	18	< .001	180
One common environmental factor	327,518	48,819	224	30	< .001	164
No specific environmental correlations	327,385	48,819	91	30	< .001	31
Independent pathway model	328,021	48,843	727	54	< .001	619
Full simplex model	327,491	48,848	197	59	< 001	79
Cholesky models with simplex genetic structure	327,375	48,809	81	20	< .001	42
Common environmental structure	327,349	48,809	55	20	< .001	16
Specific environmental structure	327,398	48,808	104	19	< .001	66

Note: [a]Different variance components for men and women in the model.
[b]Adjusted for the exact age at the time of measurement.
[c]Logarithmic transformation was used.

measures increases, the correlations simultaneously decrease. When we studied additive genetic correlations, a decreasing trend was found in men and women both in height and BMI. Some decrease was also found in common environmental and specific environmental correlations, but the pattern was less systematic compared to the additive genetic correlations. The decreasing pattern of correlations especially in additive genetic factors supports the Simplex model, which predicts decreasing size of correlations as a function of age.

Finally we examined several multivariate models to gain insight into the genetic architecture of growth (Table 5). First we tested different Cholesky submodels and compared them to the full Cholesky model using AIC-values. The fit indices of the models including only one additive genetic, common or specific additive genetic factors or one common environmental factor were all inferior compared to the full Cholesky model and could be rejected for height and BMI. The fit of the Cholesky model without specific environmental correlations was also poorer than the full Cholesky model but still better than the other Cholesky submodels. Next we tested the independent pathway model and the simplex model. Both models had a poorer fit than the full Cholesky model although the simplex model fitted the data better than independent pathway model for height and BMI. Thus we finally decided to test different combinations of Cholesky and simplex models. The model with a simplex structure for the specific environmental factors had poor fit for height and BMI. The models with a simplex structure for additive genetic (ΔAIC = 20 for height and 42 for BMI) or common environmental factors (ΔAIC = 43 and 16, respectively) had still poorer fit than the full Cholesky model, though the model fit was better than for the independent and full simplex models.

Discussion

Our study showed that the genetic architecture of growth from age 3 to 12 is a complex phenomenon both in height and BMI. Only a Cholesky decomposition, which does not make any assumption of the underlying genetic structure, fitted well to the longitudinal data on height and BMI whereas theoretically

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more parsimonious models, that is, the independent pathway and simplex models, showed poorer fit. This may partly reflect the real complexity of the genetic regulation of growth. It is possible, for example, that there are genes whose effects are temporarily inhibited during the growth process. However it is also noteworthy that our data are large and thus even relatively minor differences in the correlation structure easily leads to rejection of parsimonious models. A decreasing pattern of additive genetic correlations with increasing age supports that at least part of the genes affecting height and BMI during the growth period follows the simplex structure, that is, new genes exert their influence at specific ages.

The additive genetic correlations for height varied from .82 to .96 in our data showing that more than 67% of the genes responsible for variation in height in our study population are common from age 3 to 12; the genetic correlations of height between subsequent years were as high as .90 to .96 showing that 81 to 92% of the genes are shared. These results are in concordance with a previous United States adoption study, which also found high genetic transmission from age 1 to 9 (Cardon, 1995). These high genetic correlations are encouraging for further linkage and association studies, since it may be easier to find specific genes affecting growth when multivariate modeling including measures at different ages can be used. Also slight differences in maturation between children at the same chronological age may not be a major problem in these studies. For BMI the genetic correlations were lower than for height; the additive genetic correlation of BMI between 3 and 12 years of age was .39 in boys and .41 in girls showing that part of the genes affecting variation in BMI at these ages is the same. This is an expected result because human body composition changes during growth (Norgan, 1998), and it is quite possible that different genes regulate the growth of different tissues. More detailed measures of lean and adipose body mass would be useful in further genetic studies.

In addition to a genetic component, a strong common environmental effect was found in this study influencing height and BMI from age 3 to 12. These results are interesting since in adulthood common environmental effects have rarely been observed for height (Silventoinen, 2003; Silventoinen, Sammalisto, et al., 2003) or BMI (Maes et al., 1997; Schousboe et al., 2003). Previous studies on height and BMI in childhood, however, offer some evidence on the importance of common environmental effects. A twin study in the United Kingdom (Koeppen-Schomerus et al., 2001) found common environmental effects affecting BMI at 4 years of age, and the heritability of BMI at this study (.64 in boys and .61 in girls) was close to the estimates we found in our study (.73 and .57, respectively). Common environmental effects were also found to affect height and weight in infancy in a previous Dutch twin study (van Dommelen et al., 2004). It is noteworthy that both of these studies, as well as our study, relied on maternal reports, and thus possible systematic rater bias (e.g., under- or over-reporting of height and weight) introduced by mothers is estimated as part of common environmental factors. However, the maternal reports of height and weight at age 5 in our data were found to be reliable (Estourgie-van Burk et al., 2006). A close look at the twin correlations of previous twin studies using measured height and weight also revealed common environmental effect, that is, DZ correlations were more than half the MZ correlations (Ooki et al., 1993; Wilson, 1976). A previous Danish adoption study showed correlations in BMI between adoptive siblings during childhood, providing clear evidence for an effect of the common environment (Sørensen et al., 2002). There are twin (Bodurtha et al., 1990; Faith et al., 1999) and adoption studies (Cardon, 1995) that have not found common environmental effects on BMI during childhood. However, the quantitative genetic models that were used are insensitive to the distinction between additive genetic and common environmental effects (Hopper, 2000). Thus these negative results may be due to the lack of power to detect common environmental effect in these studies.

Specific environmental factors accounted from 5% to 11% of the variation on height and 9% to 22% of the variation of BMI. Part of this component may be explained by random reporting bias by mothers. Specific environmental factors showed correlations of .50 to .81 for height and .42 to .80 for BMI between different ages. These results may partly be due to epigenetic heritability (Wong et al., 2005), which is modeled as part of specific environmental factors. However, it is likely that these correlations also reflect real environmental factors, for example differences in nutrition within twin pairs. An unshared environmental component from .10 to .17 was found in food consumption already at age 4 to 5 in a study of twins in England and Wales (Breen et al., 2006).

We found a small but persistent birth order effect; the first-born twin was taller and heavier than the second-born co-twin. Previous studies have reported similar results at birth (Buckler & Green, 1994; Glinianaia et al., 2000) and 16 years of age (Pietiläinen et al., 2002). The background of this effect needs more detailed analyses, but a likely reason is that this reflects the position of fetuses in the uterus at the end of the pregnancy so that the heavier fetus is located at the bottom of the lighter fetus. The persistence of this birth order effect, however, suggests that prenatal factors can have long-lasting effects on body size.

The used quantitative genetic models have specific methodological limitations, and the results need to be interpreted in the light of them. First, possible gene-shared environment interactions are modeled as part of additive genetic component. Thus, additive genetic effects found in this study do not need to be solely because of the direct effect of genes on height or BMI

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but may also reflect genetic-based differences in the susceptibility to environmental factors. Second, a previous twin study found a clear tendency for assortative mating for height and BMI, and this was partly because of phenotypic assortment, which can increase the DZ correlation and may thus inflate the estimates of common environmental effect (Silventoinen, Kaprio, et al., 2003). Assortative mating should, however, inflate common environmental effects in adulthood as well, which is rarely seen in height (Silventoinen, 2003; Silventoinen, Sammalisto, et al., 2003) or in BMI (Maes et al., 1997; Schousboe et al., 2003). Thus in the light of previous twin studies, it is not likely that assortative mating could explain a large part of the common environmental effect found in this study.

In conclusion, the genetic architecture of growth is a complex process. Part of the genetic effect of growth in height and BMI may follow a dynamic simplex structure, but even this model did not capture the full complexity of growth. Especially when studying subsequent ages, the genetic correlations for height are high, which may help further molecular genetic studies. Environmental factors affecting height and BMI during the growth period are also important. A challenge in further studies is to identify these environmental factors and test whether they interact with genetic factors.

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