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Genetic and environmental influences on chest circumference during infancy: a longitudinal study of Japanese twins

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Abstract

Background: Chest circumference (CC) is suggested to be a good indicator of early life nutrition, but little is known on the heritability of CC. Thus we analyzed the effects of genetic and environmental factors on the development of CC in Japanese infants.

Methods: CC was measured longitudinally from birth until one year of age in a cohort of 211 monozygotic and 160 dizygotic complete Japanese twin pairs born in 1989-2002. The data were analyzed using applications of structural linear equation modelling for twin data.

Results: No sex-specific differences in the variance components were found. Environmental factors unique to each twin explained the major part of the variation of CC at birth whereas environmental factors shared by co-twins were more important at 1-3 months of age. From three months of age, the effect of genetic factors become steadily stronger and they explained the majority of the variation at one year of age. Strong genetic continuity in the development of CC was found, but also new sets of genes were activated during the first year of life. The origin of the environmental part of the variation could be tracked before three months of age. A substantial part of common and specific environmental factors affecting CC affected also birthweight.

Conclusions: CC is sensitive to intrauterine environmental factors, but these effects diminish during the first year of life, at least if post-natal environment is good. CC can be a useful indicator when identifying newborns who have suffered suboptimal pre-natal conditions.

Anthropometrical measures, especially height and weight but also head circumference, are routinely measured in paediatric health care because they offer important information on factors affecting the physical development of the child.[1] However, chest circumference (CC) has received much less scientific and public health interest. A recent meta-analysis showed that CC was a more precise predictor of low birthweight than other basic anthropometric measures, and thus it may be a useful indicator of the nutritional status of newborn in developing countries.[2] The use of CC in developed countries is less common, but it can well offer advantages when identifying thinness at birth and in infancy.

Twin and other family studies offer a useful tool to disentangle the effects of genetic and environmental factors on the variation of the trait, which is important when developing screening tools to identify normal and abnormal growth patterns. Heritability estimates for height, relative weight and head circumference are available in many populations,[3] but little is known on the heritability of CC. Heritability of body mass index (BMI) is high already in early childhood when from 60% to 75% of the variation of BMI is attributed to genetic variation and it increased more than 80% after 7 years of age.[4] For height and head circumference measured in childhood the heritability estimates were over 90%,[5,6] but for birthweight the heritability was estimated to be only from 11% to 17%.[7] This large variation in the heritability estimates indicates different susceptibilities of these anthropometric traits to environmental factors and suggests their different values as indicators of suboptimal environment. We are aware of only one study on the heritability of CC, but this study was small and the age of the participants ranged from 10 to 27 years.[8] Therefore, we decided to analyze the genetics of growth in CC during the first year of life in Japanese twins. Further we analyzed the common genetic and environmental factors behind the association between birthweight and CC.

Participants and methods

The participants of this study were recruited from the Osaka City University Twin and Higher Order Multiple Births Registry.[9] Questionnaires were sent to 803 mothers of twins yielding the response rate of 52%. All participating mothers gave written consent to participate in this study. We removed nine twin pairs who were born before 1989 or after 2002, four twin pairs without information on sex and 27 pairs for whom we could not determine zygosity accurately which left us with 369 complete twin pairs (53% girls) including 211 monozygotic (MZ), 77 same-sex dizygotic (DZ) and 81 opposite-sex DZ complete twin pairs. CC at birth was measured at hospitals and until one year of age in health check-ups covering virtually all Japanese children. CC was measured by placing the tape under the arm in the axillae. The measurement was taken when the child was inhaling normally and rounded to the nearest 0.1 cm. These measures were recorded in the Maternal and Child Health Handbooks, and the mothers were advised to refer to these records when filling in the questionnaire. Information on zygosity was based on validated questions on physical similarity and confusion of identity by others.[10]

We removed 11 measurements we found as outliers, i.e., that were more than 3 standard deviations (SD) from the mean. There was only one CC measurement for 41 children whereas for 14 children we had all seven measurements. The median number of measurements was four. Because the mothers reported CC measures retrospectively, there was no attrition in these data. However, the number of valid measures decreased from 686 at birth to 138 at 11-13 months of age because the measurement of CC during the health examination become rarer at one year of age and ceased after that. We tested whether the cessation of CC measures was affected by the neonatal status of the child and may thus bias the results. However we did not find any evidence for this because there was no statistically significant difference in CC at birth between those having information on CC at 11-13 months of age and those without this information (p=0.86) when adjusted for Caesarean section, gestational age and sex.

The data were analyzed using classic twin modelling based on comparisons of MZ twins, who share the same gene sequence, to DZ twins who share, on average, 50% of their segregating genes.[11] In the genetic twin modelling based on linear structural equations, the trait variation is expected to be because of four sources of variation: additive genetic variation (A), dominance genetic variation (D), environmental factors common to co-twins (C) and environmental factors unique to each twin individual (E). However, we were not able to estimate D and C simultaneously, since we had information available only on twins reared together. The technical assumptions of twin modelling, i.e. equal means and variances for MZ and DZ twins, were tested by comparing univariate genetic models to saturated models. We also tested the equality of variance components between boys and girls and whether there was evidence on sex-specific genetic effect affecting CC. These comparisons between nested models were done by studying the change of χ^2-goodness-of-fit statistics and degrees of freedom ($\Delta\chi^2_{\text{degrees of freedom}}$).

In longitudinal analyses we used Simplex model (Figure 1).[12] In this model at each age new genetic and environmental variation starts to affect the trait; this new part of variation is denoted as innovation parameters (ζ_{A1}- ζ_{A3} for genetic and ζ_{E1}- ζ_{E3} for specific environmental innovations). Simultaneously some, or all, of the variance affecting at the previous age can be transmitted to the subsequent age explaining the correlations of the trait over ages; this genetic or environmental persistence is denoted as transmission parameters in the model (β_{A1}- β_{A2} and β_{E1}- β_{E2}, respectively). Further, error variance terms are estimated for all measures (ε_1-ε_3). To test the fit of this model to the data, we compared it to Cholesky decomposition, which does not make any assumptions on the underlying genetic architecture.[11] This method was also used to estimate genetic and environmental variance components because it uses all information available and thus increases the statistical power. Using Cholesky decomposition, we also analyzed the genetic and environmental factors behind the association between birthweight and CC. The genetic models were carried out using the maximum likelihood method by the Mx statistical package, version 1.7.03, using raw data option.[13]

CC at birth and birthweight were adjusted for gestational age and CC after that for exact age at the time of the measurement. We also found minor differences in CC between normal deliveries and deliveries by Caesarean section and thus adjusted CC and birthweight also for this variable. These adjustments were performed by computing regression residuals of CC and birthweight with age and Caesarean section as independent variables in a regression model separately for boys and girls.

Results

Table 1 presents descriptive statistics for CC during the first year of life. No systematic differences in means or variances were seen between boys and girls or between MZ and DZ twins. In the pooled data, CC increased rapidly from birth (29.1 cm) until 3-5 months of age (40.4 cm) and then more slowly until one year of age (45.2 cm).

First we tested the assumptions of twin modelling and selected the best fitting model. DZ correlations were more than half of the size of MZ correlations suggesting the presence of common environmental factors (Appendix table 1), and thus we selected the additive genetic/ common environmental/ specific environmental (ACE) model as the starting point of the genetic modelling. Common environmental component was statistically significant at 1-3 months of age ($\Delta\chi^2_2$=30.9, p<0.0001) but not at other ages ($\Delta\chi^2_2$=0.1-3.8, p=0.97-0.15).

However, because common environmental component was systematically found at all ages, we decided to include these effects into the further multivariate modelling. We did not find any evidence on differences between boys and girls in the size of the variance components or the presence of sex-specific genetic factors ($\Delta\chi^2_4$=2.5-8.5, p=0.64-0.07) and thus treated boys and girls together. Our final models, i.e. the ACE model with same parameter estimates for boys and girls and without sex-specific genetic effect, offered good fit at most of the ages when compared to the saturated models ($\Delta\chi^2_{16}$=15.9-26.3, p=0.46-0.05); only at birth the difference was statistically significant ($\Delta\chi^2_{16}$=28.1, p=0.03) when using the conventional alpha level ($p<0.05$) but not if the Bonferroni correction of seven tests was used ($p<0.007$).

Table 2 presents the estimates of genetic and environmental variance components of CC from birth until one year of age. The effect of genetic factors until 1-3 months of age was small and statistically non-significant. At birth the major part of the variation of CC was explained by specific (e^2=0.63) and at 1-3 months of age by common environmental factors (c^2=0.69). The effect of genetic factors emerged at 3-5 months of age and after that increased until 1 year of age when they explained 68% of the variation of CC; however the CIs of the parameter estimates were overlapping. Simultaneously the relative effect of common environmental effects decreased and finally disappeared at 11-13 months of age. The effect of specific environmental factors remained stable from 1-3 to 11-13 months of age, and they explained 18-32% of the variation of CC.

Next we conducted the Simplex modelling. When compared to the full Cholesky model, the fit was good ($\Delta\chi^2_{39}$=44.6, p=0.25) suggesting that this model captures sufficiently the complexity of the development of CC. We dropped all statistically non-significant parameters from the model to find the best fitting Simplex model ($\Delta\chi^2_{11}$=11.1, p=0.68). New common environmental variation (innovation parameters ζ in Figure 1) emerged at birth and 1-3 months of age (Table 3). This variation was transmitted until 9-11 months of age (transmission parameters β in Figure 1), but it then disappeared and was not present anymore at 11-13 months of age. New specific environmental variation emerged at birth and was then transmitted until 11-13 months of age. Genetic variation emerged first time at 3-5 months of age, and new genetic variation emerged at all subsequent ages except at 7-9 months of age showing that new genes affecting CC are activated during the first year of life. However also genetic transmission terms were strong, which indicates strong genetic persistence of the development of CC. Error variance term was strongest at birth reflecting difficulties when measuring the CC of newborn, but at later ages no systematic differences were seen (parameters ε in Figure 1).

Finally we analyzed the association between birthweight and CC from birth until 11-13 months of age (Table 4). The correlation declined from 0.83 at birth to 0.29 at 11-13 months of age. When we analyzed this trait correlation using Cholesky decomposition, we found that we were able to drop additive genetic correlation from birth until 5-7 months of age ($\Delta\chi^2_1$=0.57-1.64, p=0.45-0.20) and both additive genetic and common environmental correlations from 7-9 to 11-13 months of age ($\Delta\chi^2_2$=1.69-2.82, p=0.43-0.24). In this best fitting model common environmental correlation was highest at birth (r_C=0.97) but remained substantial until 5-7 months of age (r_C=0.37-0.85) and explained from 27% to 51% of the total trait correlation between birthweight and CC at these ages. Specific environmental correlation was also highest at birth (r_E=0.97) and it remained substantial until 11-13 months of age (r_E=0.66-0.42).

Discussion

The role of environmental factors on CC in early life is somewhat different when compared to previous studies on the genetic architecture of BMI or ponderal index,[14-16] birth length/height,[5,17] and head circumference in this and other twin cohorts.[6,18] Common environmental effect at birth diminishing during the first year of life has also been found for these traits in these previous twin studies, but still the effect of genetic factors was also present already in early life. In contrast in our study the effect of genetic variation on CC was totally masked until three months of age and emerged only after that. Interestingly similar results have been found for birthweight in several twin cohorts.[7] We found that the correlation between birthweight and CC was very high at birth and still substantial at 11-13 months of age. This association was because of common and specific environmental factors until 5-7 months of age and after that only because of specific environmental factors. These results are in concordance with the results that CC is the best predictor of birthweight and suggest that the same prenatal environmental factors affect both of these indicators.[2] New environmental variation affecting CC was not emerged after three months of age suggesting that environmental factors affecting CC have origin in intrauterine life and early infancy. These results suggest that CC and birthweight are good indicators of prenatal environmental stress.

There was clear fluctuation in the effects of common and specific environmental factors over the first year of life, and common environmental variation was strongest at 1-3 months of age. Both MZ and DZ correlations of CC were low at birth, and thus it is possible that the large specific environmental variation masked not only genetic but also common environmental effects on CC at birth. However it is interesting that also the total variance of CC was largest at 1-3 months of age, which may suggest that there are some environmental factors shared by co-twins affecting CC soon after the birth. The common environmental variation disappeared in the latter half of the first year of life. This suggests that it reflects rather prenatal environment, such as intrauterine nutrition, than postnatal environmental factors such as maternal care. However also the intrauterine environment can differ between co-twins, and thus these factors may also lay behind the specific environmental variation. The most extreme case is the twin-to-twin transfusion syndrome of monochorionic MZ twins.[19] This may be even likely because also specific environmental variation traced down to early age and substantial part of both common and specific environmental variation was common with birthweight.

When considering how to generalize our results to the general population, it is important to consider the special features of twin pregnancies. Twins have lower birthweight and lower gestational age than singletons, which is because of intra-uterine growth constraints on the twins especially during the last trimester of pregnancy.[20] This creates additional environmental variation related to twin pregnancies and hence much higher heritability estimates of birthweight found in studies on offspring of twins or twin families[21,22] when compared to studies comparing MZ and DZ twins.[7] Thus CC and birthweight may be especially sensitive to the environmental factors during late pregnancy whereas birth length and head circumference may be more affected by environmental factors in early pregnancy. However the effect of prenatal environmental factors on CC seems to largely disappear already during the first year of life.

Expectedly genetic factors had also important effect on CC, and at one year of age genetic differences explained 63% of the variation in CC. This estimate is at the same size than found for BMI,[14-16] length[5,17] and head circumference at this age. [6,18] We also found that new genetic variation emerged during the first year of life suggesting the activation of new sets of genes. However the development of CC also showed strong genetic continuity, which indicates that largely the same genes affect CC during the first year of life.

We are aware of only one previous study on the genetics of CC.[8] This Indian study included a small number of twin pairs (30 MZ and 24 DZ pairs) at 10 to 27 years of age from middle class families. In this study additive genetic factors explained 34% [95% CI 12%, 78%], common environmental factors 59% [95% CI 15%, 81%] and specific environmental factors 7% [95% CI 4%, 13%] of the variation of CC based on our recalculation of these estimates. Thus common environmental factors explained a larger proportion of the variation of CC in this study when compared to our study at one year of age. A likely reason for this discrepancy is that in this Indian study twin correlations were not adjusted for age and thus any age effect would have been modelled as part of common environmental variation; also these twins were much older than in our study.

Strength of our data is that it is the only genetically informative data set we are aware of having longitudinal measures of CC. Also the reliability of the measures is probably good because the information on CC is based on measures done by trained nurses. A limitation is that the response rate is only satisfactory (52%). However this problem was partly compensated because we did not have incomplete twin pairs or drop-out in our data. Further the MZ/DZ ratio in our data is very close to what is found in the general Japanese population suggesting that our data are representative.[23] It is also noteworthy that our data are not very large especially at 11-13 months of age.

In conclusion the environmental influences on the variation of CC was strong at birth and until three months of age but then decreased until one year of age. A substantial part of this environmental variation was common with birthweight. This suggests that CC is sensitive to prenatal environmental influences. It appeared that genetic effects on the development of CC increased in importance during the first year of life, probably indicating diminishing role of intrauterine environmental variation related to twin pregnancies. Given the sensitivity of CC to the intra-uterine environmental factors in twins, it should be evaluated whether it could be used to provide additional information to identify children who have disturbances in prenatal development.

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Table 1. Number of participants and means and standard deviations (SD) of chest circumference (cm) by sex and zygosity.

	MZ boys			DZ boys			MZ girls			DZ girls		
Age	N	mean	SD	N	mean	SD	N	mean	SD	N	mean	SD
Birth	181	28.9	2.43	138	29.4	2.40	212	29.1	2.27	155	28.9	2.21
1-3 months	140	34.1	3.27	116	34.9	2.55	173	33.9	2.53	134	34.0	2.33
3-5 months	132	40.7	2.39	89	41.7	1.88	131	39.7	1.82	102	39.9	2.22
5-7 months	77	42.9	2.80	62	43.9	1.87	81	41.9	1.98	60	42.0	2.11
7-9 months	38	43.1	1.62	35	44.1	1.96	51	42.4	1.99	48	43.3	1.89
9-11 months	87	44.7	2.43	73	45.2	2.08	108	43.9	1.79	84	43.7	1.98
11-13 months	40	45.7	1.99	31	46.4	1.62	32	44.5	1.79	35	44.3	1.83

Table 2. Standardized variance components of additive genetic (a^2), common environmental (c^2) and specific environmental (e^2) factors with 95% confidence intervals affecting chest circumference.[a]

Age	a^2	95% CI	c^2	95% CI	e^2	95% CI
Birth	0.15	[0.00, 0.38]	0.22	[0.03, 0.38]	0.63	[0.52, 0.73]
1-3 months	0.03	[0.00, 0.15]	0.69	[0.57, 0.76]	0.28	[0.23, 0.34]
3-5 months	0.36	[0.14, 0.60]	0.32	[0.10, 0.52]	0.32	[0.25, 0.41]
5-7 months	0.55	[0.16, 0.75]	0.20	[0.02, 0.46]	0.25	[0.19, 0.42]
7-9 months	0.69	[0.42, 0.89]	0.13	[0.00, 0.39]	0.18	[0.10, 0.28]
9-11 months	0.61	[0.40, 0.75]	0.12	[0.01, 0.31]	0.27	[0.20, 0.37]
11-13 months	0.68	[0.31, 0.86]	0.03	[0.00, 0.35]	0.29	[0.13, 0.47]

[a] Variance components were computed using full Cholesky decomposition with the same variance components for boys and girls.

Table 3. Parameter estimates with 95% confidence intervals for the best fitting Simplex model for the growth of chest circumference from birth to 11-13 months of age.

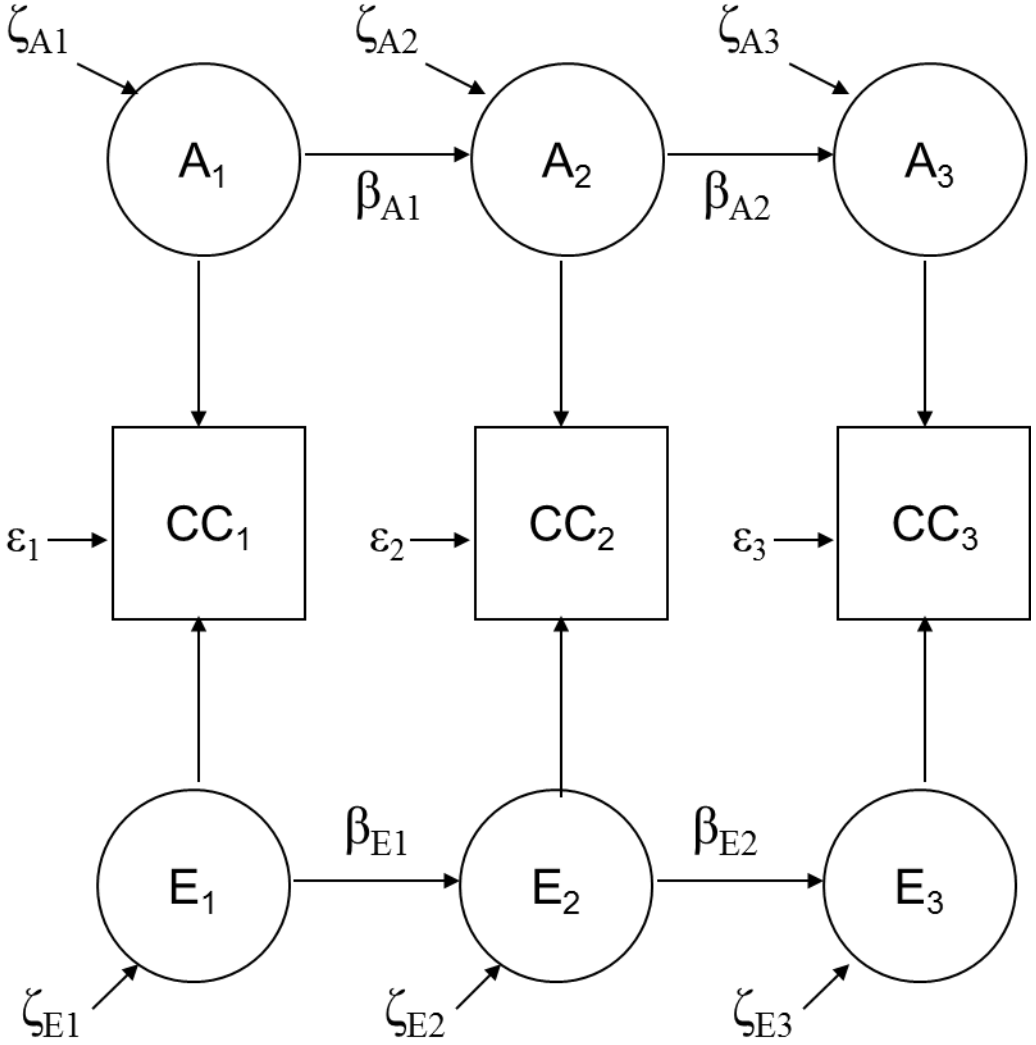
	Additive genetic factors				Common environmental factors				Specific environmental factors				Error terms	
	innovations		transmissions		innovations		transmissions[a]		innovations		transmissions			
Age	ζ_A	95 % CI	β_A	95% CI	ζ_C	95% CI	β_C	95% CI	ζ_E	95% CI	β_E	95% CI	ε	95% CI
Birth	-		-		10.5	[8.5, 12.4]	-		12.1	[10.3, 13.9]	-		10.2	[8.7, 11.6]
1-3 months	-		-		19.7	[17.8, 21.9]	0.89	[0.52, 1.29]	-		0.89	[0.73, 1.08]	8.8	[7.5, 10.1]
3-5 months	13.8	[12.4, 15.3]	-		-		0.37	[0.27, 0.46]	-		0.85	[0.69, 1.04]	6.9	[5.7, 8.2]
5-7 months	11.2	[9.3, 13.1]	0.82	[0.67, 0.99]	-		0.85	[0.56, 1.20]	-		0.76	[0.56, 1.00]	8.6	[7.3, 10.2]
7-9 months	-		1.01	[0.86, 1.20]	-		0.39	[0.13, 0.83]	-		0.57	[0.30, 0.91]	6.6	[5.3, 8.2]
9-11 months	9.7	[7.5, 11.8]	0.77	[0.63, 0.92]	-		2.32	[1.04, 5.00]	-		1.44	[0.87, 2.74]	9.4	[8.0, 11.0]
11-13 months	8.3	[3.9, 11.7]	0.75	[0.51, 1.01]	-		-		-		1.12	[0.63, 1.85]	7.5	[5.9, 9.7]

[a] The estimates of common environmental transmission parameters are artificially limited between 0 and 5.

Table 4. Trait correlations between birth weight and chest circumference from birth to 11-13 month of age and correlations between common environmental and unique environmental variance components in the best fitting model explaining these trait correlations with 95% confidence intervals.

	Trait correlation		Common environmental correlation			Unique environmental correlation		
	r	95% CI	r_C	95% CI	% explained of trait correlation	r_E	95% CI	% explained of trait correlation
Birth	0.82	[0.80, 0.84]	0.97	[0.82, 1.00]	37	0.80	[0.76, 0.84]	63
1-3 months	0.51	[0.44, 0.57]	0.53	[0.35, 1.00]	48	0.64	[0.56, 0.71]	52
3-5 months	0.41	[0.33, 0.48]	0.37	[0.05, 1.00]	27	0.66	[0.57, 0.74]	73
5-7 months	0.50	[0.40, 0.58]	0.85	[0.42, 1.00]	51	0.55	[0.40, 0.67]	49
7-9 months	0.25	[0.10, 0.39]	-		0	0.42	[0.21, 0.59]	100
9-11 months	0.29	[0.19, 0.39]	-		0	0.58	[0.45, 0.69]	100
11-13 months	0.29	[0.12, 0.43]	-		0	0.45	[0.21, 0.62]	100

Figure 1. Schematic representation of the Simplex model (presented for three ages only) including additive genetic and unique environmental innovations (ζ_{A1}- ζ_{A3} and ζ_{E1}- ζ_{E3}, respectively) and transmissions (β_{A1}- β_{A2} and β_{E1}- β_{E2}, respectively) and random errors (ε_1-ε_3).



Appendix table 1. Number of complete twin pairs and within pair intra-class correlations of chest circumference by zygosity.[1]

	MZ twins			DZ twins		
	N	r	95% CI	N	r	95% CI
birth	187	0.35	[0.22, 0.47]	140	0.27	[0.11, 0.42]
1-3 months	150	0.73	[0.65, 0.80]	121	0.64	[0.52, 0.74]
3-5 months	129	0.68	[0.58, 0.76]	93	0.48	[0.31, 0.62]
5-7 months	78	0.76	[0.65, 0.84]	60	0.41	[0.18, 0.60]
7-9 months	44	0.79	[0.65, 0.88]	40	0.52	[0.26, 0.71]
9-11 months	95	0.73	[0.62, 0.81]	77	0.32	[0.11, 0.51]
11-13 months	35	0.74	[0.55, 0.86]	32	0.37	[0.04, 0.63]

[1] Sex differences in the correlations were not statistically significant and thus boys and girls were pooled together after taking account the sex difference in the means.