

Association of Birthweight and Head Circumference at Birth to Cognitive Performance in 9- to 10-Year-Old Children in South India: Prospective Birth Cohort Study

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ABSTRACT: To examine whether birthweight and head circumference at birth are associated with childhood cognitive ability in South India, cognitive function was assessed using three core tests from the Kaufman Assessment Battery for children and additional tests measuring long-term retrieval/storage, attention and concentration, and visuospatial and verbal abilities among 505 full-term born children (mean age 9.7 y). In multiple linear regression adjusted for age, sex, gestation, socioeconomic status, parent's education, maternal age, parity, body mass index, height, rural/urban residence, and time of testing, Atlantis score (learning ability/long-term storage and retrieval) rose by 0.1 SD per SD increase in newborn weight and head circumference, respectively ($p < 0.05$ for all), and Kohs' block design score (visuospatial ability) increased by 0.1 SD per SD increase in birthweight ($p < 0.05$). The associations were reduced after further adjustment for current head circumference. There were no associations of birthweight and/or head circumference with measures of short-term memory, fluid reasoning, verbal abilities, and attention and concentration. In conclusion, higher birthweight and larger head circumference at birth are associated with better childhood cognitive ability. The effect may be specific to learning, long-term storage and retrieval, and visuospatial abilities, but this requires confirmation by further research. (*Pediatr Res* 67: 424–429, 2010)

Recent evidence links poor fetal growth to lower “human capital” outcomes such as school achievement and adult income or assets (1). One mechanism could be suboptimal fetal brain development, leading to decreased cognitive ability in individuals with reduced intrauterine growth. A variety of adverse factors during pregnancy associated with lower birthweight could impair neurogenesis, which begins in early gestation and the processes of gliogenesis, cell migration, and dendrite formation, which occur throughout gestation (2,3). Head circumference at birth has been shown to correlate with brain size (4).

Studies reporting associations between lower birthweight or head circumference at birth and poorer cognitive function in later life (childhood or adulthood) have mainly focused on

“high-risk” individuals [born low birthweight, premature, or intrauterine growth restriction (IUGR)] (5,6). However, several recent studies, including one systematic review (7), have reported associations between birthweight and cognitive functions even in children who were born at full-term and across the normal range of birthweight and/or head circumference (8–14). Data from developing countries is scarce. Although it has been shown that, as in high-income countries, low birthweight and/or IUGR babies have poorer childhood cognitive ability compared with normal weight babies (15–17), no studies have assessed cognitive function across the full range of birth size. Mean birthweight in India is around 2.7 kg, almost 800 g lower than among white babies in high-income countries (18,19). This is thought to be mainly because of modifiable factors such as maternal stunting, dietary inadequacy, and infections (20). Evidence that small size at birth is associated with impaired cognitive development would strengthen advocacy for policies to invest in maternal health.

Studies have shown that childhood cognitive function is strongly influenced by the family's socioeconomic status (SES) (5,7,10,12,21). These factors are also related to birth size and, partly, may act through fetal development but could equally influence cognitive function through genetic mechanisms or through postnatal nutrition, stimulation, growth, and development. It is important to be able to adjust for these and other confounding variables to assess the potential importance of prenatal development on cognitive ability in children.

The Mysore Parthenon Study (19,22) provides an opportunity to examine associations between birth measurements and cognitive function in healthy 9- to 10-y-old children in an Indian population and control for potentially important confounders, including parental educational achievement and SES. Our objectives were to test the hypothesis that lower birthweight and smaller head circumference at birth are associated with poorer scores in tests of cognitive function, independent of socioeconomic factors.

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Abbreviations: GDM, Gestational diabetes mellitus; HMH, Holdsworth Memorial Hospital; KABC, Kaufman Assessment Battery for children; SES, Socioeconomic status

METHODS

Study design and participants. The Mysore Parthenon study (19,22) is a prospective birth cohort study, designed to examine the incidence and determinants of gestational diabetes (GDM) and its short and long-term effects in the offspring in India. Between June 1997 and August 1998, women booking consecutively into the antenatal clinic of the Holdsworth Memorial Hospital (HMH), Mysore, were recruited for the study. HMH is a general hospital and not a specialist referral unit. It is one of three large maternity units in Mysore and is situated in a relatively poor area of the city. Women who deliver at HMH are from all socioeconomic groups, with the majority from the middle and lower middle class. Although patients pay for treatment, HMH offers concessions for the poorest and provides a niche between the free government hospitals and private nursing homes. Of 1233 recruited women satisfying the eligibility criteria (singleton pregnancy; <32-wk gestation determined by last menstrual period date or a first trimester ultrasound scan; and no prior history of diabetes), 830 participated (67%) and 674 delivered at HMH (Fig. 1). Neonatal anthropometry was performed on 663 live born babies without major congenital anomalies. All the children (excluding 25 deaths and eight with major medical problem) were followed up, with repeat anthropometry, annually on the child's birthday (± 4 wk) till the age of 5 y and, thereafter, every 6 mo after the birthday (± 4 wk). These children were invited for assessment of their cognitive function at the age of 9–10 y (September 2007–May 2008). Of the 630 children, 542 (86%) underwent cognitive assessment, and the remaining 88 (14%) were lost to follow-up (Fig. 1). Excluding 37 preterm children, the current analysis is restricted to 505 (239 boys and 266 girls) full-term children. The study was approved by the HMH research ethics committee, and informed verbal consent was obtained from parents and children.

Neonatal anthropometry. Neonatal birthweight and occipitofrontal head circumference were measured according to a standard protocol, within 72 h of birth (19). Birthweight was measured to the nearest 5 g using a digital weighing scale (Seca, Hamburg, Germany). Head circumference was measured in triplicate to the nearest 1 mm, using a blank fiber-glass tape, which was marked and measured against a fixed ruler. The average of three readings was used.

Cognitive tests. The cognitive measures consisted of a series of neuropsychological tests applicable for use in school-aged children related to specific cognitive domains (memory, attention, and fluid reasoning) consistent with the Carroll model (23). The cognitive battery included three core tests from

the Kaufman Assessment Battery for children—second edition, 2004 (KABC-II) (24) and additional tests (25–28) that underwent an extensive adaptation process to ensure their applicability in the local cultural context. The adaptation initially included judgemental (qualitative) procedure consisting of iterations of translating, piloting, and modifying the instrument (instructions, examples, and items) based on the construct, language, culture, theory, and familiarity applicable to the local cultural context (29). This was followed by a statistical (quantitative) procedure evaluating the adequacy of the adapted version using structural equation modeling, split-half technique measuring internal consistency of cognitive domains with substests, correlation tests for those domains without substests, and multivariate ANOVA to test the performance of the adapted version against gender and age. Subtests showed relatively high loadings on the general cognitive factor, reliabilities, largely replicating the Cattell-Horn-Carroll model underlying the original KABC-II, and external relations with demographic characteristics such as children's age, gender, and scholastic achievement were as expected (30). The description of these cognitive tests are summarized in Table 1 and covered the domains of short-term memory, long-term memory and retrieval ability, visuospatial ability, and language production. All tests were administered to each child in a single session of 60 to 90 min at the epidemiology research unit, HMH, in separate rooms free from distraction by one of the two trained masters' level child psychologists (unaware of children's birth measurements) in the local Kannada language.

Covariates. At the time of recruitment, details of maternal age, parity, and area of residence (urban or rural) were recorded. None of the mothers had ever smoked or consumed alcohol. At 30 ± 2 -wk gestation, the women had a 100-g oral glucose tolerance test (OGTT), and detailed anthropometric measurements were measured by one of two trained observers using standardized methods as described previously (22). Season of birth [summer: March–June (average temperature maximum: 33°C and minimum: 21°C); rainy: July–October (29°C and 19°C); and winter: November–February (29°C and 18°C)] were recorded at the time of birth. We also collected details of the parent's educational level in completed years and current SES using the Standard of Living Index (SLI), a standardized questionnaire designed by National Family Health Survey-2 (31). For the children's current anthropometry, data collected at the 9.5-y follow-up for 479 children and at the 9-y follow-up for the remaining 24 children were used.

Statistical methods. Variables not satisfying normality assumptions were either log transformed [maternal body mass index (BMI) and Kohs block design score] or square root transformed (pattern reasoning score). Sex-specific SD scores for birth measurements were calculated using internally generated growth charts, which were constructed using the LMS (L = skewness; M = median; S = coefficient of variation) method (32). Scores for cognitive tests were z -standardized to facilitate interpretation. Comparisons of birth size, current size, and cognitive scores between boys and girls were made using t test. Associations of covariates with birth measurements (exposures) and cognitive ability (outcomes) were initially assessed using multiple linear regression, adjusting for sex and current age. For categorical covariates, (parity and season at birth), the largest category was used as the reference, and tests of general association (Wald) were performed. Associations between birth measurements and cognitive function were then analyzed using multiple linear regression, adjusting for variables that were associated with either birth measurements or cognitive outcomes. A series of models were used: model 1: gestational age at birth, the children's sex, and current age; model 2: model 1 parameters plus the family's SES and parental education; model 3: model 2 parameters plus urban or rural residence, maternal age, BMI, height, parity, and time of the day when cognitive tests were administered; model 4: model 3 parameters plus child's current head circumference. Differences between the various cognitive tests in their associations with birth size were assessed by testing whether the difference in the Z -score for each test from the mean Z -score of the other tests was associated with birth size, using linear regression. Stata version 10 (Stata corporation, TX) was used for all analyses.

RESULTS

Characteristics of the study cohort are summarized in Table 2. At birth, boys were heavier and had larger head circumference than girls. Birth measurements [mean (SD)] were similar in those who took part in the study to those who did not [birthweight 2.905 (0.428) kg versus 2.892 (0.432); $p = 0.8$ and head circumference 33.9 (1.3) cm versus 33.7 (1.5); $p = 0.3$]. At the time of the study, boys were taller and had larger

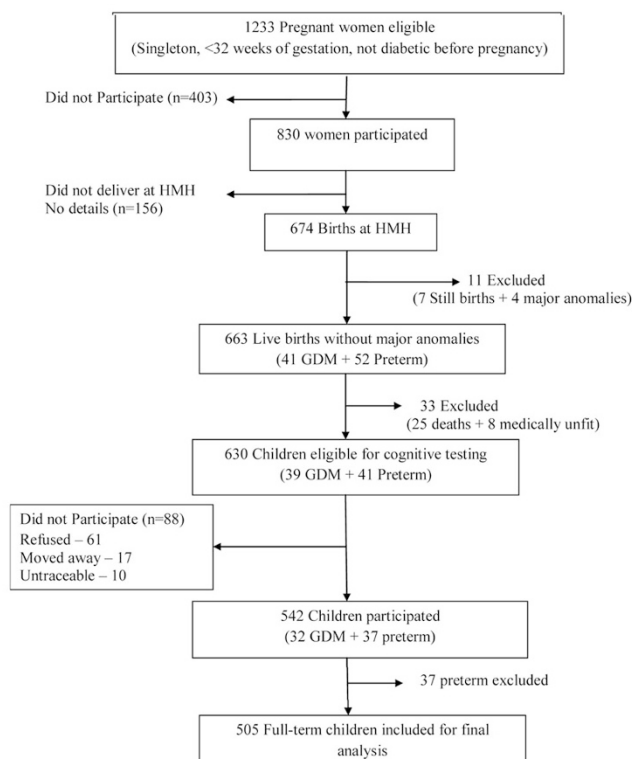


Figure 1. Flow diagram depicting the study participants.

Table 1. Description of the cognitive tests used in the study

Name of the test	Description	Cognitive abilities
Tests from KABC-II (24)		
Atlantis	The child is taught nonsense names for fish, plants, and shells and is asked to point to the named object among an array of pictures	Learning ability/long-term storage and retrieval, associative memory
Word order	The child points to a series of silhouettes of common objects in the same order as mentioned by the examiner; an interference task (color naming) is added between the stimulus and the response for the more difficult items	Memory span, short-term memory, and working memory
Pattern reasoning	The child completes a pattern by selecting the correct image from a set of four to six options shown; most stimuli are abstract, geometric shapes and the difficulty of the task increases as the test progresses	Reasoning abilities such as induction and deduction and fluid reasoning
Additional tests		
Verbal fluency (25); a) animals and b) first names	The child is asked to name as many animals as possible in 1 min and then asked to name as many first names as possible in 1 min	Broad retrieval ability; speed and flexibility of verbal thought process; and neuropsychologic test of language production
Kohs block design (26, 27)	A psychometric test in which the child arranges groups of 4, 9, or 16 multicolored blocks to copy picture designs presented on test cards	Visuospatial problem solving, visual perception, and organization
Coding-WISC-III (28)	The child has to substitute specific symbols for numbers presented in boxes and complete as many items as possible in 2 min	Visual-motor processing speed and coordination, short-term memory, visual perception, visual scanning, cognitive flexibility, and attention

WISC-III-Wechsler intelligence scale for children-third edition.

head circumference than girls. Girls scored better than boys in tests of word order, pattern reasoning, and verbal fluency-names and coding. Correlations between the various cognitive test scores ranged from 0.2 to 0.3.

One percent of mothers were illiterate; ~34% had received only primary school education; 51% had completed secondary school education; and 14% were graduates/postgraduates/professionals. Corresponding figures for fathers were 3%, 34%, 40%, and 23%, respectively. Approximately 33% of children were born during winter, 35% during summer, and 32% during the rainy season.

Associations between confounding variables and birth measurements. Birthweight and head circumference increased with increasing gestational age, SES, parental education, maternal age, height and BMI, and parity and were higher in those whose mothers had GDM ($p < 0.05$ for all; data not shown). There was no association of rural/urban residence or season of birth with birthweight and head circumference.

Associations between confounding variables and cognitive outcomes. All the cognitive scores increased with increasing SES and parental educational level ($p < 0.001$ for all; data not shown). The cognitive performance of urban children was better than rural children in all the tests except verbal ability and attention and concentration ($p < 0.01$ for all). Scores for tests of visuospatial ability and fluid reasoning increased with increasing maternal age ($p < 0.001$ for both). Children of multiparous mothers performed less well in tests of long-term storage and retrieval ability, planning and fluid reasoning, and verbal abilities ($p < 0.01$ for all) compared with primiparous children. Children examined in the morning ($n = 465$) performed better compared with those examined in the afternoon ($n = 40$; p for difference = 0.03). There were no associations

of maternal BMI, height, and season of birth with cognitive outcomes.

Associations between birth measurements and cognitive outcomes. Multiple linear regression analyses describing the associations between birth measurements and cognitive performance are presented in Table 3. The regression coefficient (β) is the SD change in outcome per SD increase in birth measurements. Birthweight and head circumference were positively associated with learning ability/long-term storage and retrieval and visuospatial ability test scores, adjusted for the children's age, sex, and gestation (model 1). The associations were similar in boys and girls. These effects remained similar after adjusting for SLI and parental education (model 2) and on further adjustment for maternal age, BMI, height, parity, time of testing, and urban/rural residence (model 3). The associations were diminished after adjusting for the children's current head circumference (model 4). The associations did not change even after excluding children born to GDM mothers. There were no associations with the other cognitive measures. There were differences between the association of scores for learning ability/long-term storage and retrieval and the other cognitive tests in relation to head circumference at birth [$\beta = 0.7$ (95% CI: 0.20–1.26); $p = 0.007$] and birthweight [$\beta = 0.5$ (95% CI: -0.04–1.02); $p = 0.071$] and, similarly, for the association of birthweight with verbal-ability scores [$\beta = 0.5$ (95% CI: -0.02 to 1.08; $p = 0.059$).

DISCUSSION

This is the first study from India examining associations between neonatal birth measurements and cognitive perfor-

Table 2. Characteristics of the study cohort

Birth measurements	Boys (n = 239) Mean (SD)	Girls (n = 266) Mean (SD)	p*
Birthweight (kg)	2.955 (0.433)	2.860 (0.420)	0.01
Head circumference (cm)	34.2 (1.3)	33.6 (1.2)	<0.0001
Gestational age (wk)	39.5 (1.2)	39.7 (1.1)	0.09
Measurements at the time of cognitive testing			
Age (y)	9.7 (0.3)	9.7 (0.3)	0.7
Height (cm)	131.4 (5.5)	130.4 (5.9)	0.057
BMI (kg/m ²)	14.6 (1.7)	14.7 (2.0)	0.6
Head circumference (cm)	50.8 (1.4)	50.5 (1.5)	0.064
Tests of cognitive function			
Atlantis (score)	67.6 (17.9)	68.2 (16.8)	0.7
Word order (score)	16.2 (2.6)	16.7 (2.5)	0.02
Pattern reasoning (score)†	9 (4, 13)	11 (6, 14)	0.004
Verbal fluency (score)			
Test 1—animals	11.9 (3.2)	12.3 (3.4)	0.2
Test 2—first names	14.8 (4.1)	17.5 (5.2)	<0.0001
Kohs block design (score)†	77.5 (63.7–88.3)	76.4 (63.7–88.5)	0.6
Coding-WISC-III (score)	30.4 (7.5)	35.1 (8.1)	<0.0001
Maternal characteristics at recruitment in pregnancy			
Age (y)	23.9 (4.2)		
Parity, N (%)			
0	256 (50.7)		
1	170 (33.7)		
2 or more	79 (15.6)		
Height (cm)	154.3 (5.3)		
BMI (kg/m ²)†	23.2 (21.0, 26.0)		
Glucose tolerance test, N (%)			
Normal	450 (93.6)		
Abnormal	31 (6.4)		
Parent's current socioeconomic status			
Standard of living index (score)	36.5 (8.2)		
Maternal education, N (%)			
<10 y of education	177 (35.1)		
10 y of education	155 (30.8)		
>10 y of education	172 (34.1)		
Paternal education, N (%)			
<10 y of education	187 (37.1)		
10 y of education	199 (39.5)		
>10 y of education	118 (23.4)		
Residence, N (%)			
Urban	368 (72.9)		
Rural	137 (27.1)		

* p value for the difference between boys and girls derived using *t* test.

† Transformed variable; values are median and interquartile range.

mance in 9- to 10-y-old healthy children born at full-term. We found that birthweight and head circumference at birth were positively associated with two tests of cognitive function measuring learning, long-term storage, and retrieval and visuospatial ability, after controlling for a range of potential confounders. The associations were reduced after adjusting for current (9.5 y) head circumference, suggesting that cognitive performance may be influenced by prenatal environmental or genetic factors that determine both head size at birth and postnatal head growth.

Strengths of the study were that in a large sample of children, we had standardized anthropometric measurements at birth, a battery of cognitive function tests specifically adapted for, and validated in, a South Indian population, and collected data on a variety of potential confounding factors including gestational age, parity, parents' education, rural/

urban residence, SLI, and seasonality at birth. Unlike a number of earlier studies, which focused on low birthweight or preterm babies, our findings relate to healthy full-term babies. A limitation of the study was loss to follow-up (14%), which could have introduced selection bias. However, birth measurements were similar in children who participated in the study and in those lost to follow-up. Another limitation was non-availability of information about the children's current diet and other possible parental confounders such as maternal psychosocial stress or parents' intellectual ability. A hospital-based study in India, where patients choose their healthcare facilities based on what they can afford, will not be representative of the whole population. The families visiting HMH would be representative of the "middle-class" section of society and would not include either the very poor or the very wealthy.

Table 3. Associations between birth measurements and cognitive tests: multiple linear regression analysis

Birth measurements	Cognitive tests		
	Atlantis (SD), β (95% CI)	Word order (SD), β (95% CI)	Pattern reasoning (SD), β (95% CI)
Birthweight (SD)			
Model 1	0.1 (0.03 to 0.22)**	0.1 (−0.03 to 0.16)	0.1 (−0.003 to 0.18)
Model 2	0.1 (−0.001 to 0.18)	0.02 (−0.07 to 0.11)	0.03 (−0.05 to 0.12)
Model 3	0.1 (0.02 to 0.21)*	0.03 (−0.06 to 0.13)	0.04 (−0.05 to 0.14)
Model 4	0.06 (−0.04 to 0.16)	−0.02 (−0.12 to 0.08)	0.005 (−0.09 to 0.10)
Head circumference (SD)			
Model 1	0.2 (0.07 to 0.26)**	0.1 (0.01 to 0.19)*	0.06 (−0.04 to 0.15)
Model 2	0.1 (0.03 to 0.21)**	0.05 (−0.04 to 0.15)	−0.01 (−0.09 to 0.08)
Model 3	0.1 (0.04 to 0.23)**	0.07 (−0.02 to 0.16)	0.001 (−0.09 to 0.09)
Model 4	0.08 (−0.02 to 0.19)	0.004 (−0.10 to 0.11)	−0.06 (−0.16 to 0.04)

Model 1 adjusted for sex, gestation, and child's age at the time of study; model 2 adjusted for model 1 parameters + SLI, parent's education; model 3 adjusted for model 2 parameters + parity, maternal age, BMI, height at pregnancy, urban/rural residence, and time of testing; and model 4 adjusted for model 3 parameters + child's current head circumference.

* $p \leq 0.05$; ** $p \leq 0.01$.

The positive associations of birthweight and/or head circumference at birth with subsequent cognitive abilities are consistent with findings from several previous studies (8–14), although some other studies found no associations (33,34). In a Finnish cohort, among the various birth measurements, head circumference had the most robust association with tests of cognitive abilities (11). Our findings suggest that, even though brain growth is relatively protected *in utero* and tends to be the last organ to experience growth restriction (35), variations in fetal growth can be associated with variations in brain growth and development. Associations in our study between birth size and learning ability, long-term storage and retrieval, and visuospatial ability but not with other cognitive domains may indicate an impact of prenatal factors and/or a greater influence of postnatal environmental processes, such as parent's educational attainment, on some aspects of cognitive measures (36). The association with visuospatial ability in our study is in agreement with an earlier study (11). Our finding that some, but not all, aspects of cognitive function are related to birth size are also supported by the fact that the intercorrelations among the various cognitive tests used in our study were modest (ranging from 0.2 to 0.3), consistent with an earlier factor analysis of KABC, suggestive of relative independence of various cognitive measures (37). Furthermore, in our study, there was some evidence of differences among the various cognitive tests in their association with birth size. These differential effects could indicate domain-specific effects; however, they could also have arisen from multiple statistical testing and/or low statistical power. Further research is needed, in this and other populations, to investigate the specificity of associations between size at birth and the different cognitive domains. While interpreting the clinical importance of our findings, it should be kept in mind that the effect size of the associations between head circumference at birth and later cognitive abilities were small.

Our findings are consistent with other studies in that the associations between birth measurements and cognitive performance were largely independent of socioenvironmental circumstances (7,9,18,38), suggesting that they are not fully explained by socioeconomic confounding. Our findings that the associa-

tions of birthweight and head circumference with cognitive abilities were reduced after adjusting for current head size is also consistent with findings from another study (10), suggesting that a common causal pathway links size at birth, postnatal head growth, and childhood cognitive function.

In conclusion, the factors associated with intellectual developments are highly complex and interrelated, but our results are consistent with the conclusion that prenatal head growth influences cognitive function, as measured at the age of 9–10 y. Head circumference has been used as a surrogate marker of brain volume in newborns and children (4) and has been used in previous studies that measured cognitive function (39), but a given head circumference is associated with a range of brain volumes because of age-dependent changes in the relationship between head circumference and brain volume (40). Although head circumference was an excellent predictor of brain volume in children up to 6 y of age, the relationship was modest in older children and adults. In addition, the brain volume is considered an imperfect measure of functional capacity of the various regions of the brain (41). Nevertheless, studies on children with attention-deficit hyperkinetic disorder, a disorder with prominent cognitive dysfunction, have shown that such children have smaller brain volume compared with healthy controls (42). In older adults, people with larger head circumference may have reduced risks of cognitive decline (43). Although studies have shown that both genetic and environmental factors may impact maximal brain growth (44,45), identification of critical early environmental influences may be important in optimizing an individual's genetic potential for intellectual abilities and, thus, on overall "capacity" in the population at large.

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Table 3. (Continued)

Cognitive tests			
Verbal fluency animals (SD), β (95% CI)	Verbal fluency first names (SD), β (95% CI)	Kohs block design (SD), β (95% CI)	Coding-WISC-III (SD), β (95% CI)
0.04 (−0.05 to 0.13)	−0.01 (−0.10 to 0.08)	0.2 (0.07 to 0.25)**	0.03 (−0.05 to 0.12)
0.01 (−0.09 to 0.10)	−0.04 (−0.13 to 0.05)	0.1 (0.02 to 0.20)*	−0.005 (−0.09 to 0.08)
0.03 (−0.07 to 0.13)	−0.05 (−0.15 to 0.05)	0.1 (0.03 to 0.22)*	−0.04 (−0.14 to 0.05)
−0.01 (−0.11 to 0.10)	−0.06 (−0.16 to 0.04)	0.09 (−0.01 to 0.19)	−0.07 (−0.17 to 0.02)
0.02 (−0.07 to 0.12)	0.02 (−0.08 to 0.11)	0.1 (0.04 to 0.23)**	0.02 (−0.07 to 0.11)
−0.02 (−0.11 to 0.08)	−0.02 (−0.11 to 0.07)	0.08 (−0.01 to 0.17)	−0.03 (−0.12 to 0.06)
−0.01 (−0.10 to 0.09)	−0.01 (−0.10 to 0.09)	0.08 (−0.01 to 0.18)	−0.05 (−0.14 to 0.04)
−0.06 (−0.17 to 0.04)	−0.05 (−0.15 to 0.06)	0.04 (−0.06 to 0.14)	−0.12 (−0.22 to −0.02)*

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