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Childhood Metabolic Biomarkers Are Associated with Performance on Cognitive Tasks in Young Children

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Abstract

Objective: To evaluate the hypothesis that metabolic measures (fasting glucose, insulin and Homeostatic Model of Assessment for Insulin Resistance [HOMA-IR] levels) are inversely associated with performance on cognitive tasks using data from young (4- to 6-year-old), typically developing, healthy children.

Study design: Data were obtained from children participating in the Healthy Start study, a pre-birth cohort in Colorado. HOMA-IR, glucose and insulin values were centered and scaled using the study sample means and standard deviations (SD). Thus, they are reported in number of SD units from the mean. Fully corrected T-scores for inhibitory control (Flanker task), cognitive flexibility (Dimensional Change Card Sort test), and receptive language (Picture Vocabulary test) were obtained via the NIH Toolbox cognition battery.

Results: Children included in this analysis (n = 137) were 4.6 years-old, on average. Per 1 SD unit, fasting glucose (B = - 2.02, 95% CI: −3.54, −0.49), insulin (B = −1.67, 95% CI: −2.96, -0.38), and HOMA-IR values (B = −1.79, 95% CI: −3.09, −0.49) were each significantly and inversely associated with inhibitory control ($P < .05$ for all, respectively). Fasting glucose levels were also inversely associated with cognitive flexibility (B = −1.96, 95% CI: −3.71, −0.21, p = 0.03).

Conclusion(s): Our data suggest that metabolic health may impact fluid cognitive function in healthy, young children.

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Keywords

insulin resistance; cognition; childhood; executive function

Cognitive functions, such as attention, memory, language, inhibitory control and cognitive flexibility contribute significantly to academic [1, 2] and professional success [3], as well as health-related quality of life [4]. Both perinatal and postnatal exposures can disrupt the cognitive developmental trajectory leading to delay or underdevelopment of cognitive skills [5–7]. The increasing prevalence of metabolic abnormalities [8] and overt type 2 diabetes in children and youth [9] is of particular concern for child cognition, given the established link between poor metabolic health and cognitive decline in adults [10–14].

Although limited data exists for healthy, young children, several studies have found a significant association between indicators of poor metabolic health, specifically fasting glucose levels and insulin resistance, and poorer performance on cognitive tests in youth [15, 16]. These data highlight metabolic health as an understudied factor in the progression or disruption of child cognitive development and brings peripheral metabolism into focus as an early life course issue for developmental morbidity.

Hallmarks of poor metabolic health, such as impaired glucose tolerance (elevated blood glucose levels) and insulin resistance have been observed in typically developing, young children, suggesting that poor metabolic health may begin early in the life course. Although most pronounced in children with obesity [17], indicators of poor metabolic health are also found in 4–6% of children without obesity [8, 18, 19], implicating a broader risk group for negative cognitive outcomes. However, to date, no study has investigated the association between metabolic markers and cognition in young, typically developing children. Therefore, we tested the hypothesis that higher levels of fasting blood glucose, insulin and estimated insulin resistance would be significantly and inversely associated with performance on cognitive function tests in healthy, young children.

METHODS

Data used in this analysis were obtained from participants enrolled in the ongoing Healthy Start study, a pre-birth longitudinal cohort of ethnically diverse children, ages 4 to 6 years old, living in Colorado. Mother-offspring dyads participating in the Healthy Start study have been followed from early pregnancy (<24 weeks of gestation). Information on pregnancy and birth characteristics have been reported elsewhere [20, 21]. Written informed consent was obtained from the mother or legal guardian of the child. The Healthy Start protocol was approved by the Colorado Multiple Institution Review Board.

Study Visit Procedures

Mother-offspring dyads participating in the Healthy Start study were invited to the University of Colorado for an in-person research visit. Prior to arriving for the in-person research visit children fasted for at least 8 hours. During the in-person visit, trained research professionals drew blood on the child participant and made direct measurements of child weight, height, body composition via air displacement plethysmography (PeaPod, Cosmed,

Italy) and anthropometry (eg, skin folds, waist circumference, etc.). Child body mass index (BMI) was calculated as weight (kg) divided by height (m^2) and BMI-for-age z-scores were derived using the Centers for Disease Control growth charts [22]. The participant's mother or parent/guardian was also asked to report on self, child, and household demographics.

Cognitive Function Assessment

The National Institutes of Health (NIH) Toolbox cognition battery was used to assess cognitive function in children participating in the Healthy Start study. The NIH Toolbox employs an online interface to deliver a battery of tests assessing cognitive subdomains including executive functions (e.g. set-shifting or cognitive flexibility, working memory, and attention/inhibitory control), language (i.e. receptive), and processing speed for individuals ranging in age from 3 to 85 years old [23]. Due to the young age of child participants, only cognitive flexibility, attention/inhibitory control, and receptive language were measured via the Dimensional Card Sort test, Flanker Inhibitory Control and Attention Test, and Picture Vocabulary test, respectively. These tests were administered to participating children on an iPad during the in-person research visit with a trained professional research assistant providing instruction and supervision. The Spanish-language version of the NIH Toolbox was used with Spanish-only speaking children.

Fully corrected T-scores for age and sex based upon the normative population were generated for each completed test and used for the analysis.

Metabolic Biomarker Analysis

Fasting blood samples were analyzed by the Colorado Clinical and Translational Sciences Institute core laboratory. Blood glucose was measured via the Hexokinase method (Beckman Coulter) and insulin was measured via chemiluminescence immunoassay (Beckman Coulter).

The Homeostatic Model for Assessment of Insulin Resistance (HOMA-IR) was derived from fasting blood glucose and insulin values [24] and used in the present analyses as an estimate for insulin resistance. HOMA-IR, glucose and insulin values were centered and scaled using the study sample means and standard deviations for each measure and used in all statistical models.

Statistical Analyses

Descriptive characteristics of the study sample were derived and are reported as means and frequencies. To test the association between childhood metabolic biomarkers glucose, insulin, and HOMA-IR and performance on tests for cognitive flexibility, inhibitory control, and receptive language we employed multiple univariate linear regression modeling. One model was run for each metabolic biomarker and cognitive outcome pair, resulting in nine total models. Covariates were defined *a priori* and included ethnicity (Hispanic vs non-Hispanic), APGAR-5 score at birth, birthweight z-score (for age and sex), maternal education (Bachelor's degree or higher vs. all others) and smoking in pregnancy (yes vs. no). Ethnicity was not included as a covariate in models with receptive language as the outcome.

Finally, covariates with a p-value greater than 0.1 were removed from the final models in a backward-stepwise manner.

Given that children with obesity are more likely to be dysmetabolic [17], we additionally tested the association between child BMI z-score and the cognitive outcomes of interest, controlling for the aforementioned *a priori* covariates. All analyses were performed in SAS version 9.4 (SAS Institute Inc., Carey, NC).

RESULTS

Healthy Start children included in the present analysis had completed the in-person research visit at 4–6 y/o as of April 2018 (N = 479), had data on fasting glucose and insulin levels (n = 337), and complete data on all three cognitive function tests (n = 155). Children were excluded from the study sample if they were born preterm (<37 weeks of gestation) (n = 11). This resulted in a study sample of n = 144. Missing information on covariates minimally reduced the final sample size for complete case analysis to n = 137.

Children included in the study sample were 47% female, 4.6 years-old, on average, and predominantly non-Hispanic white (60%). Children had an average BMI z-score of 0.2, waist-tohip ratio of 1.0, and 21% fat mass. Further, on average, fasting glucose, insulin and HOMA-IR values were all within normal range (Table I).

Fasting glucose, insulin, and HOMA-IR values were significantly and inversely associated with inhibitory control ($p < 0.01$ for all, respectively). On average, a one standard deviation higher value of fasting glucose corresponded with a 2-point lower difference in Flanker test scores ($B = -2.02$, $SE = 0.77$). Similarly, a one standard deviation higher value in either fasting insulin or HOMA-IR corresponded with a 1.7- and 1.8-point lower difference in Flanker test scores ($B = -1.67$, $SE = 0.65$; $B = -1.79$, $SE = 0.66$, respectively). Fasting glucose levels were also inversely associated with cognitive flexibility ($B = -1.96$, $SE = 0.88$, $p = 0.03$). No significant associations were found with receptive language (picture vocabulary test). Child BMI z-score was not associated with any of the measured cognitive outcomes. Table 2 includes further details. The Figure displays example scatter plots of observed neurocognitive test scores by metabolic measures and the fitted regression line.

DISCUSSION

We found that higher blood biomarkers of poor metabolic health are related to lower cognitive flexibility and inhibitory control in healthy, young children. These results contribute to the larger body of literature in children with overt type 1 and type 2 diabetes that demonstrates consistent and negative effects of poor metabolic health on cognition. Furthermore, these results are consistent with studies in older children in which elevated blood biomarkers, suggestive of poor metabolic health, were found to be associated with lower cognitive performance on inhibitory control, attention, working memory, and language tests [15, 16, 25]. Our analysis also revealed that child BMI was not associated with cognitive functions, suggesting that insulin and glucose may be the underlying factors contributing to metabolically-related neurodevelopmental outcomes, possibly via their signaling roles in the brain. Importantly, our data contribute evidence from an early life stage

to support a potential life course trajectory for the impact of metabolic health on cognitive development in typically developing children.

Executive functions, including cognitive flexibility and inhibitory control, encompass measurably distinct but functionally interrelated skills that govern goal-directed behavior. Cognitive flexibility, also referred to as set-shifting, is defined as an individual's ability to switch or shift between tasks or mental states. Embedded within cognitive flexibility is one's ability to inhibit previous mental states or stop an ongoing task in favor of moving on to a new task, which requires inhibitory control. Delay or impairment of cognitive flexibility and inhibitory control processes are found in developmental disorders such as attention-deficit/hyperactivity disorder [26, 27] and autism spectrum disorder [27, 28]. Cognitive flexibility and inhibitory control impairments are also observed in children with psychiatric conditions including bipolar disorder [29]. Executive functions are therefore critical to healthy functioning in children. Cognitive flexibility and inhibitory control are considered "fluid" skills; they do not rely on practiced, or familiar skills. Receptive vocabulary, a crystallized skill, one specifically taught and practiced was not related to metabolic status in this analysis, suggesting that it is the more unique and novel fluid skills that are impacted by glucose, insulin and insulin resistance.

The importance of understanding the effects of metabolic health on cognition in children is 2-fold. First, from birth through adolescence the brain is maturing and refining its neural circuitry thus driving cognitive development of executive functions. However, during this growth period the brain is also vulnerable to insult. For example, animal models have demonstrated detrimental effects of hyperglycemia during critical postnatal developmental windows, specifically in the neonatal period, on brain structure and neurochemistry in brain regions involved in cognitive function [30–32]. Further, several studies have shown white matter alterations that persist over time among young children with type 1 diabetes, as compared with their metabolically healthy counterparts [33, 34]. These studies also showed a significant association between glucose control and extent of white matter abnormalities. Beyond developmentally sensitive periods, adults with metabolic dysfunction (e.g. pre-diabetes, hyperlipidemia, hyperglycemia, etc.) and type 2 diabetes show reductions in tissue volume and altered neural function in brain regions that sub-serve executive function [35, 36]. Together, the animal and adult human data suggest that disruption of neural structure and function may result from metabolic abnormalities and could underlie the cognitive deficits observed in patients with metabolic syndrome and diabetes of any type. Thus, children with altered glucose-insulin metabolism may also be at risk for disrupted cognitive development via underlying brain structural and functional changes.

Finally, from the life course perspective, early and sustained exposure to metabolic dysregulation may have a cumulative, detrimental impact on learning and cognitive development. This is most clearly demonstrated among youth with type 1 and type 2 diabetes who show progressively weaker performance on cognitive tasks as a function of disease duration, specifically processing speed [37, 38]. The inverse relationship between type 1 diabetes duration and cognitive functioning has also been shown in adults with long-standing disease [39, 40]. Further, among a large French cohort of adults without overt diabetes, the cumulative burden of metabolic conditions (e.g. obesity, hyperglycemia) was

significantly associated with lower cognitive scores [41]. Thus, either through increased exposure time to elevated glucose, or increased burden from multiple indicators of poor metabolic health, individuals who are exposed in childhood may be at risk for suboptimal cognitive outcomes throughout their lifetime.

Despite the mounting evidence of a detrimental impact of poor metabolic health on cognitive function, the mechanisms underlying this relationship are incompletely understood, especially among children. However, human studies have highlighted the role of insulin signaling in the brain as important for cognition [42–44]. Insulin signaling in the brain is facilitated by insulin receptors (IR), insulin-like growth factor (IGF) receptors, and insulin receptor substrate proteins, all of which are important for neuron signaling processes [45–47]. In the brain, insulin signaling predominates in structures that are central to cognitive function, especially executive functioning, such as the prefrontal cortex, nucleus accumbens, and hippocampus, among others [48, 49]. Importantly, administration of insulin via intranasal spray or intravenously modulates neuronal activity in these specific brain regions [50–52], demonstrating their insulin sensitivity. Further, lower peripheral insulin sensitivity in adults is associated with reduced neuronal activity in these insulin-sensitive brain regions [44, 53]. Metabolic dysregulation has also been shown to reduce the expression and function of IR and IGF-1 receptors in the brain [54]. These data may be interpreted as abnormal peripheral metabolism impeding neuronal activity in insulin-sensitive regions via disrupted insulin signaling, providing biologic plausibility for our current findings. Additional research in the pediatric-aged population is needed to establish the timing of brain insulin signaling disruption and its relationship to cognitive development.

We demonstrate an inverse association between metabolic markers and cognitive performance on executive function tests in healthy, young children. The Healthy Start cohort, from which the present data was derived, is a well-characterized group of 4 to 6-year-old children allowed us to account for important confounders such as maternal smoking in pregnancy and education level. However, a limitation of the current analysis was that working memory, a third executive function skill [55], was not assessed due to the older age requirement (7 years-old and older) of the working memory test included in the NIH Toolbox cognition battery (List-Sorting Working Memory). Despite this limitation, future analyses will investigate the relationship between peripheral metabolic markers and the full executive function skill set as the Healthy Start cohort is ongoing and executive function will be assessed again when participants are older and more able to complete this demanding task.

Our study provides evidence that peripheral metabolic health is related to cognition in youth and extends the window of potential harm to the early life course. Additional studies are needed to confirm our findings as well as help to establish a possible mechanism for this relationship.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

HOMA-IR	Homeostatic Model of Assessment for Insulin Resistance
CI	Confidence Interval
BMI	Body Mass Index
SD	Standard Deviation

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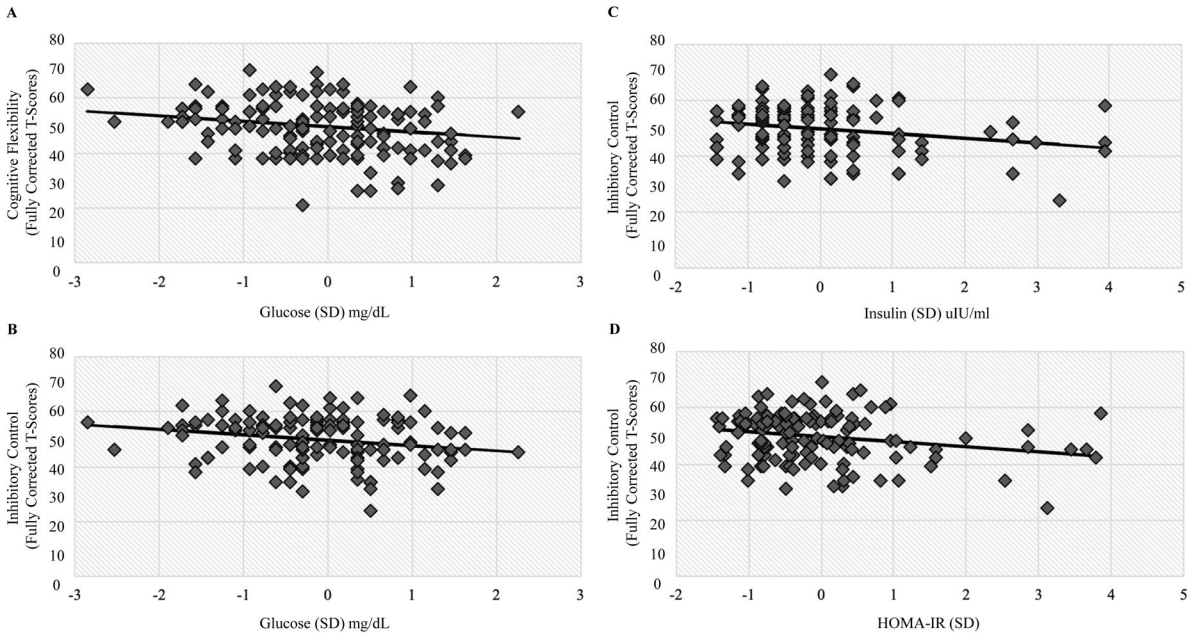

Figure.

Observed NIH Toolbox scores for cognitive flexibility and inhibitory control by standard deviation of fasting blood glucose (A and B), insulin (C), and HOMA-IR (D) values overlaid by the fitted regression line.

Table 1

Analytic sample characteristics (N = 144).

Child age (months), mean (range)	56 (43 – 82)
Child sex (female), n (%)	70 (47)
Child race, n (%):	
NHW[1]	88 (60)
NHB[1]	29 (20)
Hispanic	27 (18)
Other	4 (2)
BMI-for-age z-score, mean (SD)	0.2 (1.1)
Weight-for-age z-score, mean (SD)	0.1 (0.9)
Waist-to-hip ratio, mean (SD)	1 (0.04)
Fat mass percent, mean (SD)	21 (6)
Mother's education, n (%):	
Less than high school	5 (8)
GED or high school diploma	11 (18)
Some college or Associate's degree	17 (28)
Bachelor's degree	11 (18)
Master's or Doctoral degree	16 (28)
Metabolic Biomarkers, mean (SD):	
Glucose (mg/dL)	82.2 (5.9)
Insulin (uIU/mL)	6.5 (3.5)
HOMA-IR	1.3 (0.8)
NIH Toolbox Scores[2], mean (SD)	
Dimensional change card sort	49 (9.5)
Flanker test	49 (8.8)
Picture vocabulary	50 (12)

1: NHW = non-Hispanic white; NHB = non-Hispanic black

2: Fully corrected T-scores (for age and sex).

Table 2

Effect estimates for the association between fasting blood biomarkers of metabolic health and performance on cognitive function tasks.

	Cognitive Domain		
	Cognitive Flexibility B (95% CI; p)	**Inhibitory Control B (95% CI; p)**	**Receptive Language B (95% CI; p)**
Glucose (SD) mg/dL[1]	−2.0 (−3.7, −0.2; 0.03)	−2.0 (−3.5, −0.5; 0.01)	−1.0 (−3.2, 1.2; 0.36)
Hispanic (yes)	−5.3 (−9.5, −1.0; 0.02)	--	--
APGAR-5	--	--	4.7 (−0.6, 10.0; 0.08)
Birthweight z-score	--	1.6 (0.1, 3.1; 0.04)	--
Maternal Education[2]	--	--	--
Gestation Smoking[3]	--	--	--
Insulin (SD) uIU/ml[1]	−0.9 (−2.4, 0.5; 0.21)	−1.7 (−3.0, −0.4; 0.01)	−0.4 (−2.3, 1.5; 0.67)
Hispanic (yes)	−6.6 (−10.8, −2.4; 0.002)	--	--
APGAR-5	−3.7 (−7.8, 0.4; 0.07)	--	4.3 (−1.0, 9.5; 0.11)
Birthweight z-score	--	1.4 (−0.1, 2.9; 0.07)	--
Maternal Education[2]	--	--	3.2 (−1.0, 7.5; 0.13)
Gestation Smoking[3]	--	--	--
HOMA-IR (SD)[1]	−1.0 (−2.5, 0.5; 0.20)	−1.8 (−3.1, −0.5; 0.01)	−0.5 (−2.5, 1.4; 0.60)
Hispanic (yes)	−6.4 (−10.7, −2.2; 0.003)	--	--
APGAR-5	−3.6 (−7.7, 0.4; 0.08)	--	4.3 (−1.0, 9.5; 0.11)
Birthweight z-score	--	1.4 (−0.1, 2.9; 0.07)	--
Maternal Education[2]	--	--	3.2 (−1.1, 7.4; 0.14)
Gestation Smoking[3]	--	--	--
BMI-for-age z-score[1]	−0.6 (−2.4, 1.2; 0.50)	−0.7 (−2.4, 1.0; 0.42)	0.7 (−1.3, 2.7; 0.49)
Hispanic (yes)	−7.0 (−11.4, −2.6; 0.002)	--	--
APGAR-5	−3.4 (−7.5, 0.7; 0.10)	--	4.5 (−0.6, 9.7; 0.08)
Birthweight z-score	--	1.5 (−0.2, 3.1; 0.09)	--
Maternal Education[2]	--	1.2 (−2.0, 4.3; 0.46)	3.4 (−0.6, 7.4; 0.09)
Gestation Smoking[3]	--	--	--

1: Unstandardized beta estimates are shown for variables included in the final models, only.

2: Maternal education categories were Bachelor's degree or higher versus all others (reference).

3: Gestational smoking categories were smoking during pregnancy, yes versus no (reference).