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THE MODERATING ROLE OF GLUCOREGULATION IN POSTPRANDIAL COGNITIVE RESPONSE TO BEVERAGES VARYING IN CARBOHYDRATE CONTENT: A RANDOMIZED, COUNTERBALANCED, CROSSOVER TRIAL (98 pp.)

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Research examining the role of carbohydrates in postprandial cognition has yielded inconsistent results. Some studies demonstrate significant cognitive improvement following caloric intake, while others do not. Interindividual differences in glucoregulation partially explain this inconsistency. Prior work suggested persons with artificially dichotomized "better" glucoregulation perform best after caloric intake with more carbohydrates, while individuals with "poorer" glucoregulation perform best after lower carbohydrate intake. Recent works utilizing more rigorous statistical methodology (i.e., continuous measures of glucoregulation and linear mixed modeling) imply the role of glucoregulation in postprandial cognition might vary by cognitive domain. However, these studies examined young adults and children, and considered only fasting blood glucose. Work in animal models indicates the role of glucoregulation in postprandial cognition may vary by age, and it may also differ based on how it is measured. The current study examined the role of glucoregulation in postprandial cognition among adults using multiple glucoregulation indices (including fasting plasma glucose and response to a glucose excursion challenge) across three ecologically valid beverage conditions. It was hypothesized that participants with poorer glucoregulation would demonstrate better cognitive response following low-carbohydrate beverages, with the opposite pattern occurring for participants with better glucoregulation. Differences in these relationships across cognitive domains and

glucoregulation indices were also examined. Healthy, overnight-fasted adults (n=44) attended three morning sessions in a randomized, counterbalanced, repeated-measures design. After baseline cognitive testing (CNS Vital Signs) and blood draw, participants ingested 8oz of 2% milk, apple juice, or water. Re-testing occurred 30, 90, and 150 min post-ingestion. Complex attention, working memory, processing speed, executive functioning, and simple attention composite scores from the CNS Vital Signs test battery were analyzed using linear mixed modeling. Results showed partial support for study hypotheses. At 30 minutes, participants with higher fasting glucose showed better complex attention scores after ingesting milk or water compared to juice, and milk facilitated processing speed and executive function compared to water for participants with larger glucose responses. These relationships reversed at 150 minutes. There were no findings that suggested juice was beneficial or detrimental for performance based on glucose response. The role of glucoregulation in postprandial cognition among adults varies based on the aspect of glucoregulation in question, as well as cognitive domain. Replication using an oral glucose tolerance test to measure glucose response, as well as cognitive measures that incorporate both speed and accuracy, is recommended for future research.

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Introduction

Overview

Research on postprandial cognition (i.e., cognitive performance immediately following caloric intake) has yielded mixed results. Although prior work typically suggests that caloric intake is beneficial for cognition (Benau, Orloff, Janke, Serpell, & Timko, 2014; Galioto & Spitznagel, 2016), the degree of inconsistency across studies has led researchers to consider potential moderators of these cognitive benefits, such as macronutrient make-up of the food that is consumed (e.g., carbohydrate content) and interindividual differences of the participants (e.g., glucoregulation, or the body's ability to regulate glucose; Ceriello, 2010). While multiple studies have demonstrated an interplay between carbohydrate content and glucoregulation (e.g., Anderson, Hawkins, Updegraff, Gunstad, & Spitznagel, 2017; Anderson et al., 2018; Craft, Murphy, & Wemstrom, 1994; Lamport, Chadwick, Dye, Mansfield, & Lawton, 2014; Nabb & Benton, 2006a; Nabb & Benton, 2006b), these studies have various methodological limitations that hinder insight into the role of this interplay in postprandial cognition.

Below is presented a brief summary of the literature on postprandial cognition, with greater detail regarding inconsistent findings. This summary is followed by description of work that has spurred further consideration of glucose-related moderators of postprandial cognition, particularly carbohydrate content and glucoregulation. After discussion of limitations of work in this field to date, a study that incorporates key methodological improvements to address these

limitations and provide greater insight about when and what type of caloric intake provides acute cognitive benefits is presented.

Postprandial Benefit for Cognition

A large body of research has evaluated the acute cognitive impact of caloric intake, generally suggesting cognitive benefits. In a recent systematic review, Galioto and Spitznagel (2016) examined 34 studies of postprandial cognition among adults. Although many studies suggested acute cognitive benefits following caloric intake, and no detrimental cognitive effects were observed, other studies showed equivocal results. Despite this inconsistency, the overall pattern of results suggested cognitive performance may be optimized following caloric intake, particularly on memory tasks. Another systematic review (Benau et al., 2014) aggregated experimental work on the cognitive effects of caloric intake versus short-term fasting in healthy adults. This review included ten studies across multiple cognitive domains, including reaction time, psychomotor speed, attention, learning and recall, working memory, executive function, and verbal fluency (i.e., cued word production). Although results were mixed, they typically indicated either no effect or a beneficial impact of caloric intake on cognition, especially for psychomotor speed and executive function.

Other work has demonstrated acute benefits of caloric intake in other age groups. Pollitt and Mathews (1998) reviewed observational studies of morning caloric intake and academic performance among children and adolescents, ultimately concluding that skipping breakfast was associated with poorer academic performance. A more recent and systematic review among children and adolescents (Adolphus, Lawton, Champ, & Dye, 2016) considered 24 experimental studies of the impact of caloric intake on cognition. The researchers considered five cognitive

domains: attention, memory, language, executive function, and psychomotor function. As with systematic reviews focused on adults (Benau et al., 2014; Galioto & Spitznagel, 2016), findings varied across studies, but generally indicated that caloric intake facilitated cognitive performance. These benefits were particularly salient for tests of attention, executive function, and memory (Adolphus et al., 2016).

Of note, while a consensus of studies suggests acute postprandial cognitive benefits over fasting in general (Adolphus et al., 2016; Benau et al., 2014; Galioto & Spitznagel, 2016; Pollitt & Mathews, 1998), recent work (e.g., Mattson, Moehl, Ghena, Schmaedick, & Cheng, 2018) postulates that intermittent fasting should optimize cognitive performance. In a narrative review, Mattson and colleagues (2018) discuss the neural sequelae of intermittent metabolic switching – the intentional alternation between ketosis (i.e., an increased presence of ketones in the body to provide energy, often induced through fasting; Gershuni, Yan, & Medici, 2018) and recovery (caloric intake) – and hypothesize about the potential cognitive benefits of this dietary plan. While they describe that intermittent fasting increases the expression of neurochemicals that facilitate brain health, the researchers also note that there is no experimental work assessing the effects of intermittent metabolic switching on cognitive performance in humans (Mattson et al., 2018). The notion that intermittent fasting is more beneficial for cognition than caloric intake thus remains hypothetical.

In sum, reviews of research examining change in cognition from pre- to postprandial conditions reveal findings that are not fully consistent; however, these studies typically show that caloric intake has either no effect or a positive impact on cognition relative to fasting. This pattern of results implies that, while caloric intake may acutely benefit cognition, other factors, such as macronutrient profile, might determine the magnitude of these benefits.

The Glucose Facilitation Effect

Brief History of Inquiry

One potential mechanism for acute postprandial cognitive effects is the glucose facilitation effect, an acute improvement in cognition that is observed following the administration of glucose (Gold, 2014; Smith, Riby, Van Eekelen, & Foster, 2011). This effect was first suggested by Lapp (1981), who examined the effects of a carbohydrate-focused meal versus fasting on immediate cued recall in adolescents. The participants who ingested the meal, all of whom showed postprandial increases in blood glucose resulting in levels above 130 mg/dl at the time of testing, demonstrated better performance than participants in the fasting control condition, whose blood glucose levels were below 80 mg/dl. Lapp (1981) hypothesized that this difference in performance was caused by differences in blood glucose at the time of testing. Subsequent studies in animal models complemented these findings. Messier and White (1984) showed that a sucrose solution (a carbohydrate that the body converts to glucose; Dashty, 2013) improved memory in an avoidance learning paradigm among rats when compared to a saccharin solution (i.e., a sweetened control beverage to control for any effects of pleasurable taste on performance). Work by Gold (1986) revealed similar findings; injecting rats with a glucose solution improved memory in an avoidance learning paradigm compared to the injection of saline. Thus, several studies suggested a positive impact of increased blood glucose on memory in both animals and humans.

Studies of this facilitative effect of glucose continued in humans. Parsons & Gold (1992) found that 25g glucose improved delayed recall performance among older adults. A study in young adults (Benton & Sargent, 1992) revealed that eating a meal improved spatial memory and immediate recall relative to fasting, and that greater blood glucose at the time of testing

correlated with better spatial memory in both the meal and fasting conditions. Benton & Parker (1998) showed that the ingestion of 50g glucose improved memory performance as the task progressed, especially among participants who had not eaten breakfast before testing. These results suggested that both glucose administration and meal consumption could benefit memory, and that the effect of either intervention on blood glucose could play a role in postprandial cognitive performance.

Subsequent research on the glucose facilitation effect considered cognitive domains other than memory, suggesting additional benefits. Studies in adults revealed benefits of glucose administration for working memory (Kennedy & Scholey, 2000), verbal fluency (Kennedy & Scholey, 2000; Riby et al., 2006), and even visual tracking while simultaneously learning a word list (Scholey, Sünram-Lea, Greer, Elliott, & Kennedy, 2009). Eventually, a review of the glucose facilitation effect (Smith et al., 2011) concluded that glucose consumption acutely facilitated performance in several cognitive domains, including verbal episodic memory, verbal fluency, visuospatial ability, working memory, and facial recognition. Research has continued since this review, with studies suggesting benefits of glucose administration for attention (Jones, Sünram-Lea, & Wesnes, 2012; Stollery & Christian, 2013) and executive function (Brandt, Gibson, & Rackie, 2013). Together, the literature indicates that glucose may improve performance on tasks of several cognitive domains.

Carbohydrate Metabolism in the Body and Brain

Although many studies of the glucose facilitation effect specifically consider glucose consumption, ingesting carbohydrates in general (e.g., lactose, sucrose, maltose, fructose, or galactose) ultimately introduces glucose into the body (Dashty, 2013). Many carbohydrates are

converted to glucose in the small intestine, including maltose, lactose, and sucrose. Portions of lactose and sucrose in the small intestine are also converted to galactose and fructose, respectively. Glucose, galactose, and fructose are then transported to the liver, where the remaining fructose and galactose can be converted to glucose. Glucose is either released into peripheral blood circulation or stored in the liver as glycogen (Dashty, 2013), a compound that can be converted to glucose as the body's glucose supply dwindles (Roach, Depaoli-Roach, Hurley, & Tagliabracci, 2012). When humans ingest carbohydrates, approximately one third of the resulting glucose remains in the liver, leaving the remaining two thirds to enter circulation (Moore, Coate, Winnick, An, & Cherrington, 2012).

A portion of the glucose that enters circulation travels to the brain and facilitates its function (Moore et al., 2012; Philips & Rothstein, 2017). To enter the brain, glucose first crosses the blood-brain barrier, the epithelial cells of the central nervous system that regulate the passage of ions and molecules between the brain and peripheral blood circulation (Daneman & Prat, 2015). As glucose cannot passively diffuse across this barrier, it is transported across via glucose transporter proteins (Patching, 2017). Upon entering the brain, glucose may be taken up by neurons (Vannucci, Maher, & Simpson, 1997), as well as astrocytes and oligodendrocytes, and converted to lactate (Caravas & Wildman, 2014; Philips & Rothstein, 2017). These three cell types can then convert lactate to adenosine triphosphate (ATP), the primary energy compound of the body (Thomas, Alhasawi, Appanna, Auger, & Appanna, 2015). Astrocytes and oligodendrocytes may also release lactate for neurons to utilize in additional ATP production (Philips & Rothstein, 2017). Thus, the entry of glucose into the brain can result in increased ATP in neurons and other brain cells, providing energy for brain activity.

In addition to revealing that carbohydrates can ultimately increase glucose in the brain (and thus energy levels), this information suggests a likely mechanism for the glucose facilitation effect and postprandial cognition. The brain utilizes approximately 50% of the body's glucose under fasting conditions (Baron, Brechtel, Wallance, & Edelman, 1988), highlighting its significant energy demands. The resulting ATP from glucose facilitates the activity of sodium and potassium channels on neuronal membranes, which are integral in the firing of action potentials (Philips & Rothstein, 2017). This information complements work demonstrating that the brain utilizes glucose as cognitive tasks progress (Lamport et al., 2009). The use of glucose during task performance is even detectable in the periphery, as prior work has demonstrated that peripheral blood glucose levels decline throughout performance of cognitive tasks, compared to blood glucose levels in time-matched control conditions (Scholey, Harper, & Kennedy, 2001). Given that neurons have minimal capacity for energy storage (Amiel, 1994; Peters et al., 2004; Philips & Rothstein, 2017), this combination of findings suggests that consuming carbohydrates may replenish an energy supply that decreases throughout task performance (Scholey, Laing, & Kennedy, 2006; Smith et al., 2011), thereby providing acute postprandial cognitive benefits.

Carbohydrate Content and Postprandial Cognition

Given the role of carbohydrates in the replenishment of energy in the brain, a multitude of studies have examined the role of carbohydrate content in postprandial cognition. The results of these studies have varied substantially, with some studies indicating positive effects, some suggesting no effect, and others even indicating a detrimental impact of carbohydrates. While some studies of recall memory found no benefit of carbohydrates, (Azari, 1991; Benton & Owens, 1993), other studies have (e.g., Craft et al., 1994). This discrepancy continues even when

similar age groups are evaluated: Manning and colleagues (1997) observed facilitation of recall performance after carbohydrate administration for older but not younger adults, but Stollery & Christian (2013) found that a similar dose of carbohydrates benefited recall performance in their young adult sample. Studies of other cognitive domains have also yielded variable results. One study found that a higher-carbohydrate condition improved accuracy in a working memory paradigm compared to conditions with less carbohydrate and more protein (Fischer, Colombani, Langhans, & Wenk, 2002). However, work from the same research group found that a lower-carbohydrate meal yielded better working memory than a higher-carbohydrate meal (Fischer, Colombani, Langhans, & Wenk, 2001). A third study demonstrated *worse* working memory performance following a higher- versus lower-carbohydrate meal (Jones, Sünram-Lea, & Wesnes, 2012). Regarding attention, some research suggests no effect of carbohydrate intake (Kaplan, Greenwood, Winocur, & Wolever, 2001), while other work indicates that carbohydrate consumption may be detrimental (Bachlechner et al., 2017). Thus, even though carbohydrates ultimately yield an important fuel source for the brain (Dashty, 2013; Philips & Rothstein, 2017), a thorough understanding of their postprandial cognitive impact remains elusive.

To clarify the relationship between carbohydrate intake and postprandial cognition, several researchers have reviewed the topic (Boyle et al., 2018; Edefonti et al., 2014; Galioto & Spitznagel, 2016; Hawkins et al., 2018). However, as foreshadowed above, these reviews were ultimately inconclusive due to highly variable findings across studies. While Edefonti and colleagues (2017) stated that a meal lower in carbohydrates may be more acutely beneficial for cognitive performance compared to a higher-carbohydrate meal in an update of their 2014 review (i.e., the addition of two new studies), they also noted that results generally remained mixed. The literature thus far generally demonstrates that carbohydrate content alone has an

inconsistent impact on postprandial cognition, even though glucose is imperative for neuronal function (Philips & Rothstein, 2017; Thomas et al., 2015). This continued inconsistency indicates a need to consider additional factors that affect postprandial cognitive performance.

Glucoregulation and Cognition

Measuring Glucoregulation

Another potential explanatory factor for inconsistent results in the postprandial cognition literature is glucoregulation, the body's ability to regulate blood glucose. Researchers typically consider two components of glucoregulation in postprandial cognition studies: fasting glucose and response to a glucose excursion challenge (henceforth 'glucose response'). Higher fasting glucose is considered poorer glucoregulation, with values above 100 and 126 mg/dl denoting impaired fasting glucose and type 2 diabetes, respectively (American Diabetes Association, 2014). Glucose response is typically measured following ingestion of a glucose bolus (i.e., a dose provided all at once), which is often provided as a glucose drink (e.g., Kaplan, Greenwood, Winocur, & Wolever, 2000). Once an individual has consumed this bolus, glucose response can be indexed in several ways, including but not limited to the glucose area-under-the-curve (e.g., Kaplan et al., 2000), incremental area-under-the-curve (iAUC; Brouns et al., 2005), the difference between baseline glucose and postprandial glucose after a specific duration (e.g., 60 minutes; Craft et al., 1994), or a single postprandial blood glucose measurement (e.g., Lamport et al., 2014; see **Figure 1**). Clinically impaired glucose response or type 2 diabetes can be diagnosed following ingestion of a standardized 75g glucose beverage (American Diabetes Association, 2014). At two hours post-ingestion, a postprandial blood glucose of 140 mg/dl or greater denotes impaired glucose response, and values at 200 mg/dl or higher indicate type 2

diabetes (American Diabetes Association, 2014). Regardless of the method utilized to assess glucose response, a larger value is considered poorer glucoregulation.

The Relationship between Glucoregulation and Cognition

The relationship between glucoregulation and cognition is well-documented, especially for type 2 diabetes. A systematic review by van den Berg and colleagues (2009) examined studies between 1990 and 2008 that considered the impact of type 2 diabetes on cognition. Inclusion in the review required that each study assess at least one cognitive domain using two validated neuropsychological tests, or at least two cognitive domains with one or more validated tests. Cognitive domains considered in the review included general intelligence, memory, processing speed, attention, cognitive flexibility, visuospatial ability, and language. Results from 27 studies indicated that type 2 diabetes was associated with poorer cognition, particularly processing speed, attention, and memory, with these domains generally showing small to moderate effect sizes (Cohen, 1992). A recent meta-analysis of 24 studies (Palta, Schneider, Biessels, Touradji, & Hill-Briggs, 2014) yielded complementary results. The researchers considered studies as far back as 1980 that utilized neuropsychological tests of motor function, executive function, processing speed, verbal memory, visual memory, and attention. Analyses indicated poorer cognition in type 2 diabetes across all domains, with a small effect size in the attention domain and small to moderate effect sizes in the remaining domains (Cohen, 1992).

Glucoregulation is associated with cognition among nondiabetic individuals as well. One study (Yaffe et al., 2004) found that adults with impaired fasting glucose demonstrated poorer cognitive performance relative to participants with normal fasting glucose. Di Bonito and colleagues (2007) found that adults with impaired fasting glucose had worse performance on the

Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975), a brief test of general cognition. Rolandsson and colleagues (2008) examined the relationship between glucoregulation and memory performance in 411 nondiabetic individuals age 35 to 85. Results showed that higher fasting glucose was associated with poorer memory performance, particularly among women. A more recent study in nondiabetic younger adults (Hawkins et al., 2016) assessed the relationship between fasting glucose and cognitive performance. Results indicated that higher fasting glucose was associated with poorer inhibitory control.

While these studies demonstrate a relationship between fasting glucose and cognition among nondiabetics, research on the relevance of glucose response has yielded more mixed results. Lamport and colleagues (2009) reviewed the relationship between glucose response and cognitive performance among nondiabetic adults. They described that across studies, individuals with larger glucose responses demonstrated poorer verbal memory, though they also indicated that the methodology for characterizing glucose response varied between studies (e.g., glucose response was indexed via glucose AUC, specific postprandial glucose values, or the difference between baseline and latter postprandial glucose; Lamport et al., 2009). The authors indicated that this relationship between glucose response and cognitive performance was primarily observed among healthy participants. Studies comparing healthy participants to persons with clinically impaired glucose response typically found no effect, a pattern that the researchers attributed to the difference in sensitivity of the cognitive tests used across these two types of studies. Studies involving participants with both healthy and clinically impaired glucose response typically involved tests that were less difficult (e.g., the Mini-Mental Status Exam; Folstein et al., 1975), and thus less sensitive to interindividual differences than tests from studies with only healthy samples. Subsequent work from this group supported this explanation (Lamport et al.,

2014), demonstrating that adults with impaired glucose response had worse memory and psychomotor function than adults with normal glucose response. This pattern of findings implies that while more sensitive tests are required to observe the relationship between glucose response and cognition in a nondiabetic population, such a relationship does exist.

Together, these studies demonstrate a relationship between cognition and glucoregulation, whether glucoregulation is measured as glucose response or fasting glucose. Given the relevance of glucose for postprandial cognition (Gold, 2014; Smith et al., 2011), this relationship is undoubtedly implicated in the impact of carbohydrate content on postprandial cognition.

Considering Glucoregulation in Postprandial Cognition

Impact of "Good" versus "Poor" Glucoregulation

As implied above, research shows that glucoregulation influences postprandial cognition. Craft and colleagues (1994) tested older and younger adults' cognitive performance following provision of a 50g carbohydrate beverage, comparing it to performance following an artificially-sweetened control beverage. The researchers further divided the younger and older adult groups into "good" and "poor" glucoregulatory groups based on their glucose response to the beverage (i.e., a median split of the baseline to 60-minute blood glucose difference score within each age group). Although the results indicated that younger participants with poor glucoregulation and older participants with good glucoregulation showed improvements in memory (i.e., paragraph recall) after consuming the beverage, closer inspection reveals that these two groups demonstrated average glucose response values closer to the center of the measure's overall distribution, compared to the younger good and older poor glucoregulators. This highlights the

potentially misleading nature of median splits when considering the role of glucoregulation in postprandial cognition, as they may obscure such information. Use of continuous glucoregulation measures in future work will likely provide more interpretable results.

More recent work from another research team further demonstrates a role of differences in glucose response in postprandial cognition. Lamport and colleagues (2014) examined the impact of carbohydrate content on postprandial cognition in a randomized, crossover design, considering participants' glucose response and waist circumference as potential moderators. Their test battery included tests of psychomotor function, executive function, and verbal and spatial memory. The researchers found that participants with impaired glucose response and higher waist circumference showed impaired learning after fasting or consuming a 75g glucose beverage, but not a 37g-carbohydrate meal. In addition, this group of participants demonstrated poorer delayed recall performance after the 75g-carbohydrate meal. These results suggest that among participants with worse glucoregulation, a meal consisting of more carbohydrates may have yielded too much glucose for optimal performance.

As with glucose response, several studies indicate that fasting glucose moderates the effect of carbohydrate content on postprandial cognition, even among healthier samples. Nabb and Benton (2006a; 2006b) conducted two studies that examined the effect of carbohydrate content on postprandial cognitive performance. In one study (Nabb & Benton, 2006a), the researchers recruited 168 healthy young adult females and assigned them to meal conditions varying in carbohydrate content. Participants were further separated based upon their fasting glucose levels; specifically, the researchers divided participants into two groups using a fasting glucose cutoff of 108 mg/dl to ensure an adequate number of participants in each group for statistical purposes. Findings demonstrated the moderating role of fasting glucose, such that

participants with higher fasting glucose demonstrated poorer recall memory following 30g- and 50g-carbohydrate meals compared to a 15g-carbohydrate meal. In the second study (Nabb & Benton, 2006b), the researchers randomly assigned 189 young adult females to meal conditions varying in carbohydrate content. Participants were again divided into two groups based on their fasting glucose; however, in this study, the authors noted that a cutoff of 90 mg/dl better ensured adequate group sizes for statistical analyses. Results showed that participants with lower fasting glucose made more errors during a sustained attention task after a 24g-carbohydrate meal, but made faster decisions during a choice reaction time task and were more accurate in a sustained attention paradigm following a 59g-carbohydrate meal. Together, these two studies show that fasting glucose is an important determinant of whether one's cognitive performance will improve or decline following a meal; specifically, persons with lower fasting glucose benefit most from higher-carbohydrate caloric intake, while the opposite pattern occurs in individuals with higher fasting glucose.

Examining the Role of Glucoregulation as a Continuous Index

While these two studies yielded crucial information, they have two noteworthy methodological limitations. First, these studies utilized an artificially dichotomized glucoregulation variable, as the authors divided participants into groups based on their fasting glucose values (Nabb & Benton, 2006a; Nabb & Benton, 2006b). The cutoffs were essentially arbitrary, being chosen for statistical convenience. This artificial dichotomization is problematic, because it introduces unnecessary error and reduces statistical power and replicability (McClelland, Lynch, Irwin, Spiller, & Fitzsimons, 2015), raising the question of whether these cutoffs would generalize to other samples. Second, these two studies, along with nearly all prior

work studying postprandial cognition in adults (as reviewed by Galioto & Spitznagel, 2016), relied on analysis of variance (ANOVA) to analyze their data. Linear mixed modeling is more appropriate, as it better accommodates the correlated error structure inherent in within-subject, repeated-measures designs (Peugh, 2010).

To account for these concerns, a recent study assessed the role of glucoregulation in postprandial cognition using a continuous glucoregulation measure. In a randomized, counterbalanced, crossover experiment, Anderson and colleagues (2017) recruited 86 healthy young adults (average age of 21.09 years), all of whom attended three morning laboratory sessions after fasting for at least eight hours. At each session, participants ingested 8oz of one of three beverages: 1% dairy milk (12g carbohydrate), apple juice (29g carbohydrate), or water (control condition). Participants then completed computerized complex attention and executive function tasks 30, 90, and 120 minutes post-ingestion to determine the duration of any potential effects. Analyses entailed linear mixed modeling (Peugh, 2010) and the regions of significance technique (Preacher, Curran, & Bauer, 2006), which, along with a continuous glucoregulation measure, allowed identification of specific fasting glucose values at which differences appeared between beverage conditions. At 30 minutes post-ingestion, participants with fasting glucose above 105.80 mg/dl demonstrated better accuracy on a speeded working memory task after milk versus juice, while participants with fasting glucose below 76.85 mg/dl benefited more from juice relative to milk. In addition, participants with fasting glucose above 107.69 mg/dl made fewer commission errors during an inhibitory control task after drinking milk compared to water, with the opposite occurring in participants with fasting glucose below 70.85 mg/dl; this effect occurred across all three timepoints. Crucially, the use of advanced statistical methods, consideration of baseline glucoregulation, and avoiding artificial dichotomization yielded

additional insights (including fasting glucose threshold values specific to each task and beverage comparison) relative to a prior study in essentially the same sample (Galioto et al., 2015), a difference that raises the question of whether similar findings involving a moderating role of glucoregulation have been obscured in other postprandial cognition work.

A separate study from the same research group (Anderson et al., 2018) yielded conceptual replication of these results. In this study, 84 school-age children (average age of 10.18 years) attended two morning laboratory sessions after fasting for at least eight hours. After fasting glucose measurement and baseline cognitive testing, participants ingested 8oz of either 1% dairy milk or fruit juice in a randomized, counterbalanced, crossover manner. Participants completed cognitive testing again 30, 90, and 120 minutes post-ingestion. The beverages and cognitive tests in this study were chosen to match those utilized in the college-age sample (Anderson et al., 2017). Using similar statistical methods as the previous study, the researchers showed that glucoregulation also moderated the effect of carbohydrate content on postprandial cognition among children – participants with fasting glucose above 89.91 mg/dl demonstrated faster performance during an inhibitory control task after ingesting the lower-carbohydrate beverage (milk) compared to the beverage higher in carbohydrates (fruit juice). This effect was present across all three timepoints. Notably, the fasting glucose threshold at which these differences in performance became apparent differed between the two studies, highlighting age as a factor requiring further consideration in glucoregulation and postprandial cognition research.

Age and Glucoregulation

As with these two studies (Anderson et al., 2017; Anderson et al., 2018), prior research has indicated that the role of glucoregulation in postprandial cognition may differ across age

groups. Several studies have demonstrated that older adults with worse glucoregulation benefit cognitively from a 50g glucose bolus (e.g., Kaplan et al., 2000; Messier, Tsiakas, Gagnon, Desrochers, & Awad, 2003), a finding that conflicts with the notion that persons with poorer glucoregulation should benefit more from meals with lower carbohydrate content. Work in animal models suggests this discrepancy may be due to differences in the brain's efficiency of glucose utilization across the lifespan: McNay & Gold (2001) found that extracellular glucose concentrations in the hippocampus evidenced larger decreases in older versus younger rats during the same test of spatial memory. Although the methodology utilized in the studies by Anderson and colleagues (2017; 2018) yielded additional insights compared to past work, the differing role of glucoregulation across the lifespan calls into question whether these insights would generalize to other age groups. This uncertainty is validated at least in part by the differences in findings (especially the fasting glucose thresholds) across the two studies, despite using the same cognitive tests and beverages (Anderson et al., 2017; Anderson et al., 2018). A detailed characterization of the role of glucoregulation in postprandial cognition thus requires further study using similar statistical methodology in other age groups.

Considering other Glucoregulation Indices

In addition to examining only child and young adult samples, the two studies by Anderson and colleagues (2017; 2018) included a single measure of glucoregulation – fasting glucose. Several studies demonstrate the relevance of glucose response for cognition (Lamport et al., 2009; Rolandsson et al., 2008), as well as postprandial cognition (Craft et al., 1994; Lamport et al., 2014). However, no study has considered glucose response as a continuous moderator of postprandial cognition, as the two studies by Anderson and colleagues (2017; 2018) were the

first to consider glucoregulation in general in such a study. In addition, studies that have considered the relationship between glucose response and cognition have indexed glucose response in a variety of ways, such as glucose AUC, specific postprandial blood glucose values, or the difference between baseline and latter postprandial glucose (Lamport et al., 2009). It is possible that considering fasting glucose and several methods of characterizing glucose response could yield a different pattern of results (Boyle et al., 2018). This methodological choice could prove informative: if some measures of glucoregulation can predict postprandial cognitive benefits while others cannot, such a discrepancy may provide insight into the underlying physiology of these cognitive benefits, as well as inconsistent results across prior work.

The Current Study

In summary, caloric intake typically facilitates cognition (Adolphus et al., 2016; Benau et al., 2014; Galioto & Spitznagel, 2016; Pollitt & Mathews, 1998), and the glucose facilitation effect likely plays a role in this phenomenon (Brandt et al., 2013; Jones et al., 2012; Smith et al., 2011; Stollery & Christian, 2013). However, despite the necessity of glucose for brain function (Caravas & Wildman, 2014; Philips & Rothstein, 2017; Thomas et al., 2015), carbohydrate content alone has shown inconsistent impact on postprandial cognition in prior works (Boyle et al., 2018; Edefonti et al., 2014; Galioto & Spitznagel, 2016; Hawkins et al., 2018), and some work indicates that carbohydrate intake can even have a negative impact on cognition (e.g., Jones et al, 2012). This inconsistency is explained at least partially by interindividual differences in glucoregulation; persons with better glucoregulation typically perform best after ingesting more carbohydrates, while individuals with poorer glucoregulation usually perform best after fewer carbohydrates (Anderson et al., 2017; Anderson et al., 2018; Lamport et al., 2014; Nabb &

Benton, 2006a; Nabb & Benton, 2006b). Advanced statistical methods and the use of continuous glucoregulation measures have further demonstrated the importance of glucoregulation in postprandial cognition, as well as a need for further evaluation of this phenomenon in other age groups (Anderson et al., 2017; Anderson et al., 2018). No other postprandial cognition studies thus far have considered components of glucoregulation other than fasting glucose as continuous moderators, which could provide mechanistic insight. In addition, many prior studies that evaluated the role of glucoregulation in postprandial cognition did so using conditions that are not isocaloric (e.g., Craft et al., 1994; Nabb & Benton, 2006a; Nabb & Benton, 2006b), or conditions with particularly high amounts of carbohydrate achieved using carbohydrate beverages (e.g., Craft et al., 1994; Lamport et al., 2014); these methodological choices could potentially confound conclusions and reduce generalizability of findings. The present study assessed the role of glucoregulation in postprandial cognition using two isocaloric, ecologically valid beverages and a water control condition. Specific aims and hypotheses were as follows:

Aim 1: Determine the role of fasting plasma glucose in postprandial cognitive response to beverages varying in carbohydrate content.

Hypothesis 1: Participants with higher fasting glucose – as measured via blood draw – will demonstrate better working memory, processing speed, executive function, complex attention, and simple attention composite scores on the CNS Vital Signs test battery after ingesting low-carbohydrate beverages (2% milk and/or water) versus fruit juice.

Aim 2: Determine the role of plasma glucose incremental area-under-the-curve following a glucose excursion challenge in postprandial cognitive response to beverages varying in carbohydrate content.

Hypothesis 2: Participants with a larger plasma glucose incremental area-under-the-curve – as measured via blood draw following fruit juice ingestion – will demonstrate better working memory, processing speed, executive function, complex attention, and simple attention composite scores on the CNS Vital Signs test battery after ingesting low-carbohydrate beverages (2% milk and/or water) versus fruit juice.

Aim 3: Determine the role of postprandial plasma glucose 30 minutes after a glucose excursion challenge in postprandial cognitive response to beverages varying in carbohydrate content.

Hypothesis 3: Participants with a larger postprandial response to a glucose excursion challenge – as measured via blood draw 30 minutes following fruit juice ingestion – will demonstrate better working memory, processing speed, executive function, complex attention, and simple attention composite scores on the CNS Vital Signs test battery after ingesting low-carbohydrate beverages (2% milk and/or water) versus fruit juice.

Aim 4: Determine the role of change in plasma glucose from baseline to 30 minutes after a glucose excursion challenge in postprandial cognitive response to beverages varying in carbohydrate content.

Hypothesis 4: Participants with a larger plasma glucose change from baseline to 30 minutes following fruit juice ingestion – as measured via blood draw – will demonstrate better

working memory, processing speed, executive function, complex attention, and simple attention composite scores on the CNS Vital Signs test battery after ingesting low-carbohydrate beverages (2% milk and/or water) versus fruit juice.

Aim 5 (exploratory): Ascertain specific glucoregulation values at which differences in postprandial cognition become apparent between beverages varying in carbohydrate content.

In two prior studies of the role of glucoregulation in postprandial cognition, Anderson and colleagues (2017; 2018) utilized continuous glucoregulation measures, linear mixed modeling (Peugh, 2010), and the regions of significance technique (Preacher et al., 2006). This allows pinpointing of specific fasting glucose values at which significant differences are observable between beverage conditions. The current study utilized the same methodology to extract such values for the glucoregulation indices described above.

Aim 6 (exploratory): Evaluate differences in the role of glucoregulation in postprandial cognition based on glucoregulation index.

Prior work has suggested that employing several methods of assessing glucoregulation may reveal additional aspects of the relationship between glucoregulation and cognition (Lamport et al., 2009), as well as the role of glucoregulation in postprandial cognition (Boyle et al., 2018). The present study thus involved examination of results to determine whether findings differed substantially across glucoregulation indices.

Methods

The present study utilized archival data from a randomized, counterbalanced, crossover trial, conducted from December 2014 to August 2015 in Chicago and Glen Ellyn, IL, United States. The trial followed Good Clinical Practice Guidelines, the Declaration of Helsinki, and the United States 21 Code of Federal Regulations. The trial was approved by the Schulman Institutional Review Board (Cincinnati, OH) prior to data collection, and use of trial data for secondary analyses was approved by the Kent State University Institutional Review Board. Information regarding the sample, design, measures, and procedures of the study is provided below.

Participants

Participants in this project were 70 healthy men and premenopausal women who were 18 to 49 years of age and had a body mass index (BMI) between 18.5 and 34.9 kg/m^2. Exclusion criteria included the following: 1) type 1 or 2 diabetes mellitus; 2) history of cardiac, renal, hepatic, endocrine, pulmonary, biliary, pancreatic, gastrointestinal, or neurologic disorders; 3) history of cancer in the past 2 years; 4) sensitivity, allergy, or taste aversion to any study beverage ingredients; 5) history of eating disorders or alcohol abuse; 6) use of weight loss medications, supplements, programs, meal replacement products, or medications that influence carbohydrate metabolism; 7) recent reported weight change of 4.5 kg (~10 lb); 8) recent use of psychotropic medications or any medications or dietary supplements that influence cognition;

and 9) color blindness. Of the 70 participants who were enrolled, 21 were excluded because they did not complete testing in all study conditions, 3 participants were excluded due to insufficient blood glucose data, and 2 additional participants were excluded because preliminary data screening suggested that they provided inadequate effort throughout the protocol, resulting in 44 participants for data analysis (see **Figure 2**).

Measures

Cognitive Function

Postprandial cognitive response was assessed using the CNS Vital Signs (CNSVS; Gualtieri & Johnson, 2006; www.cnsvs.com). The CNSVS is a repeatable, computerized neuropsychological test battery that includes tasks of several cognitive domains. These tasks resemble common pencil-and-paper tests utilized in clinical neuropsychological practice, such as the Stroop Color Word Test (Golden & Freshwater, 2002). The CNSVS tasks demonstrate generally moderate to high correlations (Cohen, 1992) with traditional tests of the same domain, and CNSVS scores differ significantly between healthy and clinical populations (Gualtieri & Johnson, 2006). In addition, the CNSVS has been previously used to detect relationships between cognitive performance and several dietary variables and manipulations, such as sceletium tortuosum extract supplementation (Zembrin; Chiu et al., 2014), supplementation with a mix of natural ingredients and vitamins (i.e., SuperUlam; Udani, 2013), lutein and zeaxanthin supplementation (Renzi-Hammond et al., 2014), and seafood intake (Masley, Masley, & Gualtieri, 2012). The sensitivity of the CNSVS to such relationships and effects implies that its use is appropriate for postprandial cognition studies as well. The present study utilized domain composite scores derived from the following CNSVS tasks:

Stroop Test (Stroop). The CNSVS Stroop is comprised of three subtests. In the first, participants respond as quickly as possible to color words that appear on the screen (i.e., Blue, Green, Yellow, and Red). In the second subtest, participants must respond only when the word and its printed color are congruent (e.g., 'Blue' is printed in blue). In the third, participants must respond only when the word and color are *in*congruent (e.g., 'Blue' is printed in red, green, or yellow).

Symbol Digit Coding (SDC). The CNSVS SDC entails matching numbers on the keyboard one at a time to a set of pre-determined symbols. Participants are shown several individual screens containing eight random symbols at the top of the screen, with empty boxes below them. They must then type in the number that corresponds to the currently highlighted symbol.

Shifting Attention Test (SAT). The CNSVS SAT involves matching figures on a computer screen by shape or color. Participants are shown three figures at a time on individual screens; they must choose one of the figures at the bottom of the screen to match the figure presented at the top, based on guidelines (i.e., shape or color) that change at random.

Continuous Performance Test (CPT). The CNSVS CPT requires participants to respond as quickly as possible to a target stimulus over a span of five minutes. Specifically, participants are shown a series of individual letters and instructed only to respond to the letter 'B' while refraining from responding to any other letter.

4-Part Continuous Performance Test (4PCPT). The CNSVS 4PCPT is comprised of four subtests. In the first, participants respond as quickly as possible to any stimulus presented on the screen. In the second subtest, participants must respond only to pre-determined stimuli, ignoring others. In the third, participants must respond to stimuli only when they match the immediately

preceding stimulus (i.e., “one-back”). In the fourth, participants are instructed to respond only when the current stimulus matches the one presented two occasions prior (i.e., “two-back”).

Composite scores. Neuropsychological tests commonly yield a multitude of outcomes, a phenomenon that can prove problematic when drawing conclusions based on statistical analyses. For example, just three subtests from the Automated Neuropsychological Assessment Metrics–4 (www.vistalifesciences.com), a battery used in prior work (Anderson et al., 2017; Anderson et al., 2018), can yield 15 different cognitive outcomes. If a study were to utilize all 15 outcomes and an α of .05, there would be a 75% chance of finding a significant effect, even if all true effect sizes in the population were zero. The CNSVS test battery is similar in that each of its subtests produces a plethora of outcomes, such as number of omission errors, commission errors, and correct responses, as well as reaction times. The inflation of type I error resulting from this phenomenon implies a need to reduce the number of outcomes to maintain a reasonable error rate.

In addition to a need to manage type I error, past postprandial cognition work indicates a tendency to characterize findings by cognitive domain. Reviews of postprandial cognition (Adolphus et al., 2016; Benau et al., 2014; Edefonti et al., 2014; Edefonti et al., 2017; Galioto & Spitznagel, 2016; Hawkins et al., 2018) typically classify results by cognitive domain, rather than describing the specific tests from each study. A method of characterizing neuropsychological test results that both manages type I error and caters to this system of classification would thus be useful.

Based on this information, cognitive outcomes in the proposed study will consist of composite scores produced from the CNSVS. Prior work indicates that the test-retest reliability of CNSVS domain composite scores range from .65 to .87, values that rival traditional tests

(Gualtieri & Johnson, 2006). The five subtests described above can be used to create the following composites: 1) working memory ([4PCPT part 4 correct responses] - [4PCPT part 4 errors]), 2) processing speed ([SDC correct responses] - [SDC errors]), 3) executive function ([SAT correct responses] - [SAT errors]), 4) complex attention ([Stroop commission errors] + [SAT errors] + [CPT commission errors] + [CPT omission errors]), and 5) simple attention ([CPT correct responses] - [CPT commission errors]). These five composites will serve as primary outcomes in the proposed study.

Plasma Glucose

Blood samples were collected via intravenous blood draw and stored in vials containing ethylenediaminetetraacetic acid. These samples were then centrifuged at -4 °C for 10 min within 10 min of collection, after which plasma was separated and stored in microcentrifuge tubes at -80 °C. Plasma glucose was assessed via glucose oxidase assay (Thermo Fisher Scientific, USA).

Fasting glucose values at each session will be used as a measure of glucoregulation. The iAUC (Brouns et al., 2005) of postprandial glucose in the juice condition will be used as a second glucoregulation measure. The iAUC will be used instead of the area-under-the-curve, because the iAUC is less confounded by fasting glucose: two individuals may evidence equivalent postprandial iAUCs, but one may have higher fasting glucose, resulting in a larger area-under-the-curve despite the same postprandial glucose response (Brouns et al., 2005). The glucose iAUC from the juice condition (henceforth solely ‘iAUC’) will be used because this beverage provides the largest glucose challenge among the three beverage conditions.

The remaining glucose response indices will entail the 30-minute postprandial glucose value (Glu30) and change in blood glucose from baseline to 30 minutes in the juice condition

(ΔGlucose). In a review of the relationship between glucoregulation and cognition (Lamport et al., 2009), studies that utilized postprandial blood glucose values as glucoregulation measures consistently selected timepoints with the greatest variability in blood glucose. Preliminary examination of glucose values in the juice condition of the proposed study revealed that the 30-minute timepoint best met this criterion, prompting its use.

Procedures

Participants first underwent in-person screening, consisting of inclusion/exclusion criteria assessment, height and weight measurement, and two CNSVS practice sessions to diminish the role of practice effects in future sessions (Beglinger et al., 2005). Participants then attended three testing visits after fasting overnight (8-12 hours) and avoiding alcohol consumption and vigorous physical activity for at least 24 h. Participants also refrained from tobacco use (1 hr) and caffeine intake (8-12 hr) before test sessions. After providing fasting blood samples and completing baseline cognitive testing (CNSVS), participants then ingested one of the following 8oz beverages per session in randomized, counterbalanced order: 2% milk (122 kcal, 12g carbs, 8g protein, 5g fat), 100% apple juice (120 kcal, 29g carbs, 0g protein, 0g fat), or water (0 kcal, 0g carbs, 0g protein, 0g fat). Participants were required to ingest the beverage within 15 minutes. They then completed cognitive testing 30, 90, and 150 minutes post-ingestion, and provided blood samples for assessing plasma glucose 30, 60, 90, 120, 150, and 180 minutes post-ingestion. See **Figure 3** for a depiction of overall study procedures, and **Figure 4** for a depiction of procedures during the testing visits.

Statistical Analyses

Preliminary Analyses

Data analysis began with screening for outliers and examination of plasma glucose and neuropsychological test score distributions to ensure statistical assumptions were sufficiently met. Variables that did not meet statistical test assumptions were transformed in accordance with established convention (Tabachnick & Fidell, 2006). Participant sex and BMI were examined as covariates given their demonstrated relevance for postprandial cognition (Anderson et al., 2017). Visit number was also assessed as a covariate. Covariates were retained if they improved model fit as evidenced by a significant likelihood ratio test ($\alpha = .05$).

Primary Analyses

All statistical evaluation of specific aims and hypotheses utilized an α of .05. Details about the evaluation of each aim and hypothesis is provided below.

Aim 1: Determine the role of fasting plasma glucose in postprandial cognitive response to beverages varying in carbohydrate content.

Hypothesis 1: Participants with higher fasting glucose – as measured via blood draw – will demonstrate better working memory, processing speed, executive function, complex attention, and simple attention composite scores on the CNS Vital Signs test battery after ingesting low-carbohydrate beverages (2% milk and/or water) versus fruit juice.

Linear mixed models (Peugh, 2010) were used to assess the role of fasting glucose in postprandial cognitive response to 2% milk, fruit juice, and water. Working memory, processing speed, executive function, complex attention, and simple attention composites were each

examined in their own models, controlling for performance at baseline. Differences between these three beverage conditions were examined using dummy coding, with water serving as the reference condition; models were then re-examined with juice as the reference condition to assess differences between the milk and juice conditions. Each model included random effects for beverage condition and the intercept, accounting for heterogeneity in performance and the effects of each beverage by allowing these effects to vary between participants. Nonsignificant interactions – so long as they were not components for significant higher-order interactions – were removed from the final model to allow accurate model interpretation. This hypothesis was considered supported if analyses revealed a significant interaction involving fasting glucose and beverage condition, with the low-carbohydrate beverages (milk and water) promoting better performance among participants with higher fasting glucose and juice facilitating optimal performance in participants with lower fasting glucose. Significant interactions were probed using the Regions of Significance technique (Preacher et al., 2006) to determine specific fasting glucose values at which beverage conditions differed in cognitive response. Of note, findings from these analyses have been published elsewhere (Anderson et al., 2021).

Aim 2: Determine the role of plasma glucose incremental area-under-the-curve following a glucose excursion challenge in postprandial cognitive response to beverages varying in carbohydrate content.

Hypothesis 2: Participants with a larger plasma glucose incremental area-under-the-curve – as measured via blood draw following fruit juice ingestion – will demonstrate better working memory, processing speed, executive function, complex attention, and simple attention

composite scores on the CNS Vital Signs test battery after ingesting low-carbohydrate beverages (2% milk and/or water) versus fruit juice.

This hypothesis was examined in the same manner described above. It was considered supported if analyses indicated a significant interaction involving iAUC and beverage condition, with the low-carbohydrate beverages (milk and water) promoting better performance among participants with a greater glucose iAUC and juice facilitating optimal performance in participants with a smaller glucose iAUC. Significant interactions were probed using the Regions of Significance technique (Preacher et al., 2006). Although specific threshold iAUC values were not considered be as informative as their fasting glucose counterparts, the Regions of Significance technique could still demonstrate that these thresholds differ between cognitive domains, which would be informative for future postprandial cognition work.

Aim 3: Determine the role of postprandial plasma glucose 30 minutes after a glucose excursion challenge in postprandial cognitive response to beverages varying in carbohydrate content.

Hypothesis 3: Participants with a larger postprandial response to a glucose excursion challenge – as measured via blood draw 30 minutes following fruit juice ingestion – will demonstrate better working memory, processing speed, executive function, complex attention, and simple attention composite scores on the CNS Vital Signs test battery after ingesting low-carbohydrate beverages (2% milk and/or water) versus fruit juice.

This hypothesis was also examined via linear mixed modeling. It was deemed supported if analyses indicated a significant interaction involving beverage condition and Glu30, with the low-carbohydrate beverages (milk and water) promoting better performance among participants

with a higher Glu30 and juice facilitating optimal performance in participants with a lower Glu30. Significant interactions were probed using the Regions of Significance technique (Preacher et al., 2006), which could allow demonstration of varying thresholds across cognitive domains.

Aim 4: Determine the role of change in plasma glucose from baseline to 30 minutes after a glucose excursion challenge in postprandial cognitive response to beverages varying in carbohydrate content.

Hypothesis 4: Participants with a larger plasma glucose change from baseline to 30 minutes following fruit juice ingestion – as measured via blood draw – will demonstrate better working memory, processing speed, executive function, complex attention, and simple attention composite scores on the CNS Vital Signs test battery after ingesting low-carbohydrate beverages (2% milk and/or water) versus fruit juice.

This hypothesis was examined in the same manner described above. It was considered supported if analyses indicated a significant interaction involving beverage condition and ΔGlucose, specifically if low-carbohydrate beverages (milk and water) promote better performance among participants with a larger ΔGlucose and juice facilitates optimal performance in participants with a smaller ΔGlucose. Significant interactions were probed using the Regions of Significance technique (Preacher et al., 2006), which could allow demonstration of varying thresholds across cognitive domains. Of note, findings from these analyses have been published elsewhere (Anderson et al., 2021).

Reliable Change

To determine whether change in performance from baseline to 30 minutes post-ingestion could be classified as practically significant, as well as whether beverage conditions differed in this regard, reliable change indices (Jacobson & Truax, 1991) were calculated for each participant in each beverage condition via the following formula:

$$RC = \frac{x_2 - x_1}{s_{diff}}$$

where RC denotes the reliable change index, x_2 denotes a participant's performance at 30 minutes, x_1 denotes the participant's baseline performance, and s_{diff} denotes the standard error of difference between the two scores. This latter index was calculated via the following formulas:

$$s_{diff} = \sqrt{2(S_E)^2} \qquad S_E = s_1\sqrt{1 - r_{xx}}$$

where S_E is the standard error of measurement, s_1 is the standard deviation of baseline performance in the respective condition, and r_{xx} is the test-retest reliability of the composite. Reliable change indices above 1.96 or below -1.96 were characterized as reliable increases and decreases in score respectively, with index values between these thresholds characterized as "no change" (Jacobson & Truax, 1991); threshold values of $\pm$ 1.96 were used to maintain an α of .05.

Given the nested nature of the data, chi-square analyses were deemed inappropriate for determining whether reliable change distributions differed between beverage conditions (McHugh, 2013). Instead, mixed effects multinomial logistic regression, which accounts for this nested nature, (Raudenbush & Bryk, 2002) was deemed optimal, with beverage condition dummy coded as described above and reliable change category serving as the outcome of interest.

Statistical Power

Several factors complicate power analyses for the current study. A typical a priori power analysis utilizes standardized effect sizes based on past work. To date, there is no universally-accepted standardized effect size for linear mixed models (Peugh, 2010). This lack of a universally-accepted standard means that power analyses for linear mixed models must utilize unstandardized effect sizes, which requires the existence of previous work that used the same measures as the current study. Such work does not exist, as the only studies that considered the role of continuous glucoregulation indices in postprandial cognition utilized a different cognitive test battery (Anderson et al., 2017; Anderson et al., 2018). To circumvent similar difficulties, other researchers have developed software that uses pilot data to calculate required sample sizes for future a priori power analyses (Green & MacLeod, 2015). However, this would not be appropriate for the proposed study, because using this software with the data that is currently available would not provide any additional information compared to simply conducting the analyses. Other power analysis software for linear mixed modeling (e.g., Westfall, Judd, & Kenny, 2014) only accommodates specific experimental designs, none of which are consistent with that of the present study. These challenges indicate that power considerations for the current study must be undertaken in a nontraditional manner.

The two studies thus far that considered continuous glucoregulation indices in postprandial cognition using linear mixed modeling may provide insight as to whether the current sample size will yield adequate power. The first study (Anderson et al., 2017) included 86 college-age participants who each completed nine testing sessions for a total of 774 cognitive measurements. The second study (Anderson et al., 2018) involved 84 participants ages 8 to 12, each with eight testing sessions, yielding 672 cognitive measurements. At an α of .05, the first study detected a hypothesis-supporting effect with 54.5% of its cognitive outcomes (Anderson et

al., 2017), while the second study found such an effect among only 33.3% of its cognitive outcomes (Anderson et al., 2018). While this difference could be due to differences in the number of measurements, past work indicates it may partially be explained by previously-mentioned changes in the efficiency of glucose utilization across the lifespan (McNay & Gold, 2001); these changes may increase the size of the hypothesized effects as age increases, which would explain why the college-age study yielded more hypothesis-supporting effects.

This role of age in the relationship between glucoregulation and postprandial cognition, in combination with other information, holds crucial implications for the statistical power of the present study. Analyses in the present study involved 44 participants who completed 12 cognitive assessments each, resulting in 528 measurements total. While the sample size of the current study is smaller than that of the two prior studies, the present work also entails more measurements per participant, a change that increases statistical power (Brysbaert & Stevens, 2018). In addition, the average age of this sample is older than that of the college-age sample, which implies that the effect size will be larger. In summary, based on the age of the participants, as well as the increased number of measurements per participant compared to past work, the sample size and number of measurements in the current study suggest sufficient statistical power to detect the hypothesized effects.

Results

Descriptive and Preliminary Analyses

See **Table 1** for final sample demographics. One participant was removed from processing speed analyses due to several outlying scores, and two participants had one outlying trial each for the executive function domain, prompting removal of these trials from analyses to preserve accurate parameter estimation.

Preliminary analyses revealed no statistically significant differences in fasting glucose between beverage conditions. Complex attention scores were log transformed to correct for positive skew. Simple attention and working memory scores were inverse transformed to correct negative skew. Executive function scores were square-root transformed to correct for negative skew. With these transformations, higher scores reflect better performance for simple attention, working memory, and processing speed, whereas lower scores reflect better performance for complex attention, executive function. Untransformed descriptive statistics for cognitive outcomes are presented in **Tables 2 through 6.**

Primary Analyses

Aim 1: Determine the role of fasting plasma glucose in postprandial cognitive response to beverages varying in carbohydrate content.

Complex attention. Neither demographic covariates improved prediction of complex attention scores, though controlling for session number improved model fit ($\chi^2(1) = 4.89$, $p = .03$). The final model revealed a Beverage*Fasting Glucose*Time interaction involving the juice and water conditions ($b = -1.28*10^{-4}$, $SE_b = 5.27*10^{-5}$, $p = .02$), as well as a trend toward a second Beverage*Fasting Glucose*Time interaction comparing the milk and juice conditions ($b = -1.05*10^{-4}$, $SE_b = 5.86*10^{-5}$, $p = .07$). At 30 minutes, participants with lower fasting glucose performed best following juice, while those with higher fasting glucose performed best after water (see **Figure 5a**). At 90 minutes, there was little to no effect of fasting glucose on the difference in performance between the juice and water conditions (see **Figure 5b**). The pattern of results at 150 minutes was the reverse of that observed at 30 minutes, such that performance for participants with lower fasting glucose was best after water, and complex attention for those with higher fasting glucose was best after juice (see **Figure 5c**). The trend toward a Beverage*Fasting Glucose*Time interaction involving the milk and juice conditions mirrored these findings. That is, participants with higher fasting glucose performed better following milk at 30 minutes, and participants with lower fasting glucose performed better following juice at 30 minutes, with reversal of this pattern at 150 minutes (see **Figure 6**). There were no regions of significance for these interactions. No other significant interactions emerged. Other than participants' performance worsening across visits ($b = .02$, $SE_b = .007$, $p = .04$), no significant main effects were found.

Processing speed. Accounting for BMI significantly improved model fit ($\chi^2(1) = 6.40$, $p = .01$). After removal of all nonsignificant interactions, higher BMI was associated with poorer performance ($b = -0.43$, $SE_b = 0.16$, $p = .01$), and participants' processing speed improved over

time, regardless of beverage condition ($b = 1.31*10^{-2}$, $SE_b = 6.62*10^{-3}$, $p = .048$). No other main effects or interactions were observed in the final model.

Executive function. Accounting for BMI ($\chi^2(1) = 5.67$, $p = .02$) significantly improved model fit. After removal of all nonsignificant interactions, higher BMI was associated with poorer executive function ($b = 4.56*10^{-2}$, $SE_b = 1.91*10^{-2}$, $p = .02$). Higher fasting glucose was also associated with better executive function, regardless of beverage condition ($b = -9.99*10^{-3}$, $SE_b = 4.89*10^{-3}$, $p = .04$), and participants trended toward better performance following juice versus water ($b = -0.18$, $SE_b = 0.10$, $p = .07$). No other significant effects were observed in the final model.

Working memory. Controlling for BMI significantly improved model fit ($\chi^2(1) = 5.05$, $p = .02$). After removal of nonsignificant interactions, the final model for working memory indicated that greater BMI was associated with poorer performance ($b = -0.01$, $SE_b = 4.65*10^{-3}$, $p = .03$). No other significant effects were found.

Simple attention. Adjusting for visit number significantly improved prediction of simple attention performance ($\chi^2(1) = 12.54$, $p < .001$). The final model for simple attention showed that participants' performance worsened across visits ($b = -.03$, $SE_b = .01$, $p < .001$). There were no covariates that improved model fit for simple attention, and there were no significant main effects or interactions for simple attention.

Aim 2: Determine the role of plasma glucose incremental area-under-the-curve following a glucose excursion challenge in postprandial cognitive response to beverages varying in carbohydrate content.

Complex attention. Accounting for visit number improved model fit ($\chi^2(1) = 3.86$, $p = .049$). None of the other demographic variables improved model fit. The final model revealed that participants' complex attention scores worsened across visits ($b = .02$, $SE_b = .007$, $p = .04$). No significant main effects or interactions were observed.

Processing speed. Inclusion of BMI significantly improved model fit ($\chi^2(1) = 7.55$, $p = .01$). Analyses revealed a significant Beverage*iAUC*Time interaction ($b = 1.11*10^{-4}$, $SE_b = 4.20*10^{-5}$, $p = .01$). At 30 minutes, participants whose plasma glucose iAUC after juice was above 575.04 mg*min/dl showed significantly faster processing speed after consuming milk versus water (see **Figure 7a**). At 90 minutes, there was minimal relationship between plasma glucose iAUC and the difference in performance between the milk and water conditions (see **Figure 7b**). At 150 minutes, participants with a smaller plasma glucose iAUC performed better after milk, and those with a larger plasma glucose iAUC performed better following water, though performance between conditions did not differ significantly at any level of plasma glucose iAUC (see **Figure 7c**). While greater BMI was associated with poorer performance ($b = -.43$, $SE_b = .15$, $p = .01$), no other significant effects emerged.

Executive Function. Adding BMI significantly improved model fit ($\chi^2(1) = 4.32$, $p = .04$). Results showed a Beverage*iAUC*Time interaction comparing the milk and water conditions ($b = 7.00*10^{-6}$, $SE_b = 3.30*10^{-6}$, $p = .04$). At 30 minutes, participants with a large plasma glucose iAUC performed better after drinking milk versus water (see **Figure 8a**). At 90 minutes, there was minimal relationship between plasma glucose iAUC and the difference in performance between the milk and water conditions (see **Figure 8b**). At 150 minutes, participants with a smaller plasma glucose iAUC performed better after milk, while those with a larger iAUC

performed better after water (see **Figure 8c**). There were no regions of significance for this interaction.

Working memory. None of the covariates improved prediction of working memory performance, and no significant main effects or interactions were observed.

Simple attention. None of the covariates improved prediction of simple attention performance, and no significant main effects or interactions were observed.

Aim 3: Determine the role of postprandial plasma glucose 30 minutes after a glucose excursion challenge in postprandial cognitive response to beverages varying in carbohydrate content.

Complex attention. Accounting for visit number improved model fit ($\chi^2(1) = 3.86$, $p = .0495$). None of the other covariates improved model fit. The final model revealed that participants' complex attention scores worsened across visits ($b = .02$, $SE_b = .007$, $p = .04$). No other significant effects were observed.

Processing speed. Adjusting for BMI significantly improved model fit ($\chi^2(1) = 6.83$, $p = .01$). Analyses demonstrated a Beverage*Glu30*Time interaction involving the water and milk conditions ($b = -2.41*10^{-3}$, $SE_b = 9.80*10^{-4}$, $p = .01$). At 30 minutes, participants with higher Glu30 performed better after ingesting milk compared to water (see **Figure 9a**). At 90 minutes, there was little to no relationship between Glu30 and difference in performance between the milk and water conditions (see **Figure 9b**). At 150 minutes, participants with lower Glu30 performed better after milk, water appeared better for performance among participants with higher Glu30 (see **Figure 9c**). There were no regions of significance for these relationships. While greater

BMI was associated with poorer performance (b = -.41, SE_b = .15, p = .01), there were no other significant effects.

Executive function. Accounting for BMI ($\chi^2(1) = 6.01$, p = .01) significantly improved model fit. After removal of all nonsignificant interactions, higher BMI was associated with poorer executive function ($b = 5.21*10^{-2}$, $SE_b = 2.05*10^{-2}$, p = .02). Participants demonstrated better executive function scores after ingesting juice versus water (b = -0.23, SE_b = 0.10, p = .02). No other significant effects were observed in the final model.

Working memory. BMI significantly improved prediction of working memory performance ($\chi^2(1) = 6.09$, p = .01). The final model revealed a positive relationship between Glu30 and working memory performance ($b = 3.62*10^{-3}$, $SE_b = 1.20*10^{-3}$, p = .005), and a negative relationship between BMI and working memory performance ($b = 1.08*10^{-2}$, $SE_b = 4.30*10^{-3}$, p = .02). There were no other significant main effects, and no significant interactions.

Simple attention. None of the covariates improved prediction of simple attention performance. There was a trend toward performance declining over time ($b = -5.01*10^{-4}$, $SE_b = 2.65*10^{-4}$, p = .06). No significant main effects or interactions were observed.

Aim 4: Determine the role of change in plasma glucose from baseline to 30 minutes after a glucose excursion challenge in postprandial cognitive response to beverages varying in carbohydrate content.

Complex attention. Accounting for visit number improved model fit ($\chi^2(1) = 3.87$, p = .0491). None of the other covariates improved model fit. The final model revealed that participants' complex attention scores worsened across visits (b = .02, SE_b = .007, p = .04). No other significant effects were observed.

Processing speed. Accounting for BMI significantly improved model fit ($\chi^2(1) = 7.83$, $p = .01$). Analyses revealed a Beverage*ΔGlucose*Time interaction involving the water and milk conditions ($b = -3.12*10^{-3}$, $SE_b = 1.17*10^{-3}$, $p = .01$). At 30 minutes, participants with ΔGlucose above 20.21 mg/dl performed significantly better after ingesting milk compared to water (see **Figure 10a**). At 90 minutes, there was little to no relationship between ΔGlucose and difference in performance between the milk and water conditions (see **Figure 10b**). At 150 minutes, participants with lower ΔGlucose performed better after milk, water appeared better for performance among participants with higher ΔGlucose (see **Figure 10c**). There were no regions of significance at 90 or 150 minutes. While greater BMI was associated with poorer performance ($b = -.43$, $SE_b = .15$, $p = .01$), there were no other significant effects.

Executive function. Accounting for BMI ($\chi^2(1) = 5.21$, $p = .02$) significantly improved model fit, and after removal of all nonsignificant interactions, higher BMI was associated with poorer executive function ($b = 4.75*10^{-2}$, $SE_b = 2.01*10^{-2}$, $p = .02$). Participants also demonstrated better executive function scores after ingesting juice versus water ($b = -0.23$, $SE_b = 0.10$, $p = .02$). No other significant effects were observed in the final model.

Working memory. None of the covariates improved prediction of working memory performance, and no significant main effects or interactions were observed.

Simple attention. None of the covariates improved prediction of simple attention performance. There was a trend toward performance declining over time ($b = -5.01*10^{-4}$, $SE_b = 2.66*10^{-4}$, $p = .06$). No significant main effects or interactions were observed.

Reliable Change

Reliable change indices were calculated for the complex attention, processing speed, and executive function composites based on test-retest reliability estimates provided in recent work (Littleton, Register-Mihalik, & Guskiewicz, 2015). A review of the literature reveals no test-retest reliability estimates for the simple attention and working memory composites.

See **Figure 11** for visual depiction of reliable change categories for complex attention, processing speed, and executive function. Nearly all subjects failed to demonstrate reliable change from baseline to 30 minutes, precluding analyses of any differences in reliable change between beverage conditions due to insufficient power (Peduzzi, Concato, Kemper, Holford, & Feinstein, 1996). While reliable changes in performance were more frequent following water and juice, the number of increases and decreases were essentially equivalent in both conditions.

Discussion

The current study evaluated the role of glucoregulation in postprandial cognition among adults using two isocaloric, ecologically valid beverages and a water control condition, as well as multiple indices of glucoregulation. It was hypothesized that participants with poorer glucoregulation would demonstrate better cognitive performance after ingesting low-carbohydrate beverages (2% milk or water) compared to a beverage higher in carbohydrates (fruit juice). While some analyses provided support for predictions, results were generally not consistent with hypotheses. Participants with higher fasting glucose demonstrated better complex attention scores at 30 minutes after ingesting water compared to juice; however, this relationship reversed at 150 minutes. Individuals with lower fasting glucose demonstrated better complex attention at 30 minutes in the juice condition, but poorer complex attention at 150 minutes in this same condition compared to water. Complex attention findings were also in the predicted direction when comparing performance in the juice and milk conditions at 30 minutes, but opposite of predictions at 150 minutes. Analyses involving other glucoregulation measures yielded a different pattern of results. Participants with an iAUC above 575.04 mg*min/dl or ΔGlucose above 20.21 mg/dl showed better processing speed scores at 30 minutes after ingesting milk versus water, though this relationship reversed and had no regions of significance for either glucoregulation measure at 150 minutes. Processing speed results were similar when Glu30 was considered as a moderator, though there were no regions of significance regardless of timepoint. Several details of these results warrant further discussion.

Partial Support for the Hypothesized Role of Fasting Glucose in Postprandial Cognition

Analyses of the role of fasting glucose in postprandial complex attention revealed some support for hypotheses, with caveats. Beverages with fewer carbohydrates (i.e., milk and water) yielded better performance than juice at 30 minutes among participants with higher fasting glucose, a conceptual replication of past work (Anderson et al., 2017; Anderson et al., 2018). However, this relationship reversed at the extended postprandial timepoint (150 minutes), a phenomenon that was not identified in previous work, potentially due to the latest assessment occurring at 120 minutes in these earlier studies (Anderson et al., 2017; Anderson et al., 2018). Findings comparing milk and juice were only a trend, a difference in statistical significance that likely reflects the greater difference in carbohydrates between water and juice compared to that between milk and juice. Together, these findings suggest that calories consisting of fewer carbohydrates may be beneficial for complex attention among persons with higher fasting glucose in the short-term, but optimal for individuals with lower fasting glucose in the long-term, relative to calories with more carbohydrates.

Although analyses of the complex attention domain indicated some support for predictions about fasting glucose, findings from other domains did not. No role of fasting glucose in postprandial cognition was observed when considering processing speed, working memory, or simple attention scores. While higher fasting glucose was associated with better executive function scores, there was no evidence that fasting glucose altered the impact of study beverages on these scores. The lack of findings in these domains, particularly executive function and working memory, contrasts with findings from recent postprandial cognition studies among college students (Anderson et al., 2017) and children (Anderson et al., 2018) that utilized nearly identical beverage manipulations. One potential explanation for this difference is variability in

how these cognitive domains were measured across studies. In both prior works, most significant findings that involved a moderating role of fasting glucose in postprandial executive function and working memory pertained to outcomes that incorporated response speed, specifically reaction time during tasks of these domains or a combination of reaction time and accuracy (e.g., correct responses per minute). Given that all of the cognitive outcomes in the present study considered only response accuracy, it may be the case that cognitive outcomes involving response speed are more sensitive to the interaction between glucoregulation and calorie intake. As the present study utilized a comparatively older sample than these two previous studies (Anderson et al., 2017; Anderson et al., 2018), it is also possible that differences in glucose utilization across the lifespan impacted results, as even greater glucose could be required to replenish the brain's energy supply following performance of the same task by older versus younger subjects (McNay & Gold, 2001). Future studies may wish to consider these factors, perhaps by utilizing cognitive outcomes that account for both response speed and accuracy and by including calorie conditions that yield greater plasma glucose.

Partial Support for the Hypothesized Role of Response to a Glucose Excursion Challenge in Postprandial Cognition

As with the hypothesis pertaining to fasting glucose, analyses evaluating the moderating role of glucose response revealed only partial support for hypotheses about the role of these glucoregulation indices. Participants with a larger iAUC demonstrated better processing speed and executive function scores in the short-term after milk versus water. However, this relationship reversed in the long-term, with water proving more beneficial for these same participants at 150 minutes, and milk becoming optimal for participants with a smaller iAUC at

this extended timepoint. Glu30 and ΔGlucose demonstrated similar moderating roles in the prediction of processing speed scores, but no significant roles for executive function scores. Although milk's facilitation of performance in these two domains at 150 minutes compared to water for persons with a smaller glucose response is consistent with study hypotheses (given that milk has greater carbohydrate content than water), the reversal of this pattern of results at 30 minutes is not. Further, there were no findings that suggested juice proved beneficial for participants with better glucoregulation or detrimental for participants with poorer glucoregulation. Thus, this pattern of results requires a different explanation: why would milk initially prove beneficial compared to water in persons with larger glucose responses, and why might there be a lack of findings involving juice when considering glucose response as a moderator?

Differences in Findings Across Glucoregulation Measures

Consideration of the qualities of dairy milk and comparison of glucoregulation measures may help answer these questions. Compared to juice, milk ingestion results in a more stable postprandial glucose response (Galioto et al., 2015), potentially due to the insulinotropic effects of dairy protein (Hoyt, Mickey, & Cordain, 2005). Past work indicates that fasting glucose and glucose response measures are not always correlated (Awad, Gagnon, Desrochers, Tsiakas, & Messier, 2002), likely because glucose response measures consider postprandial aspects of glucoregulation. If the consumption of carbohydrates ultimately replenishes glucose in the brain (Scholey et al., 2006; Smith et al., 2011), and the most relevant glucoregulation measures for the executive function and processing speed domains in the current study were the measures that considered changes in postprandial plasma glucose, it is understandable that a beverage with

qualities that both increase and stabilize postprandial plasma glucose (i.e., milk) may interact with these glucoregulation measures to influence postprandial cognition when compared to a control condition. Therefore, the more important qualities of caloric intake when considering measures of glucose response as moderators may be those qualities that influence the stability of the postprandial glucose profile (e.g., insulinotropic effects), rather than solely carbohydrate content. Research that further considers such qualities is needed to confirm this hypothesis.

Notably, consideration of iAUC as a moderator revealed an interaction when predicting executive function scores, whereas Glu30 and ΔGlucose did not. It is possible that this difference occurred because the iAUC incorporates more information about the postprandial glucose curve than the other two glucose response indices: for example, two individuals could have a similar change in plasma glucose from baseline to 30 minutes, but differences in their plasma glucose after 30 minutes that result in a larger or smaller iAUC. This additional information may have yielded additional predictive power in analyses of the executive function domain in the current study. Given that the iAUC was able to capture essentially the same processing speed interaction as the other two glucose response measures, as well as yield a threshold glucoregulation value in Regions of Significance analyses, this raises the question of whether the iAUC may be a superior glucoregulation measure compared to Glu30 or ΔGlucose. Additional studies that compare these glucoregulation measures will likely answer this question.

While the glucose response measures appeared most relevant for processing speed and executive function, fasting glucose was most relevant for complex attention; consideration of neuroanatomy may provide insight into this difference. Previous research demonstrates that different neuroanatomical regions are implicated in different cognitive functions. For example, performance on tasks of executive function are most often associated with the prefrontal cortex

(Chung, Weyandt, & Swentosky, 2014) and other frontal system areas, such as the anterior cingulate cortex (Manza et al., 2016), while working memory performance is commonly associated with the prefrontal cortex, as well as the hippocampus (Blumenfeld, 2010). Studies of glucose metabolism reveal differing glucose concentrations and rates of glucose utilization across neuroanatomical regions (Dienel, 2012; Nugent et al., 2014), as well as selective glucose utilization by regions most implicated in task performance (Frahm, Krüger, Merboldt, & Kleinschmidt, 1996; McNay, Fries, & Gold, 2000; McNay et al., 2010). It is possible that different glucoregulation indices play a larger role in postprandial cognition for different cognitive domains as a result of these differences in glucose utilization and concentration across neuroanatomical regions – some domains may require a smaller but more stable release of glucose (e.g., milk in the case of processing speed and executive function in the current study), whereas others may require a larger increase in blood glucose when an individual's fasting glucose levels are below an optimal level (e.g., juice for complex attention in the present study). Further study incorporating neuroimaging could provide insight into this possibility.

The difference in role of the glucoregulation measures examined in the current study has important implications for the field of postprandial cognition, as it could suggest different causes for results. Theoretically, if a group of individuals evidenced the same response to a glucose excursion challenge, but demonstrated interindividual variability in fasting glucose, the same beverage could still yield varying postprandial glucose levels among these participants despite a similar typical response to a glucose excursion challenge, assuming any other glucoregulation components were held constant. This difference in postprandial glucose among this hypothetical sample is relevant for postprandial cognition work, because past research has demonstrated relationships between blood glucose and cognition independent of beverage consumption

(Hawkins et al., 2016; Rolandsson et al., 2008). This information suggests that such a difference in postprandial blood glucose would also result in differences in cognitive performance. Alternatively, if fasting glucose and other glucoregulation components were held constant, but typical glucose response varied between participants, one could anticipate variations in both change in glucose over time and postprandial glucose among this sample, another relevant factor for postprandial cognition given that the rate at which blood glucose changes after caloric intake has been implicated in postprandial cognition as well (Sünram-Lea & Owen, 2017). When considered in the context of contrasting findings between glucoregulation indices in the current study, this information suggests that researchers should consider the role that their chosen glucoregulation measure(s) could have in their results, as different glucoregulation measures could yield different findings.

Lack of Reliable Change Across Beverage Conditions

The results of reliable change analyses in the current study revealed little to no reliable change in complex attention, processing speed, or executive function scores from baseline to 30 minutes following milk, juice, or water, to the extent that statistical comparisons between beverage conditions could not be completed due to insufficient power (Peduzzi et al., 1996). The number of cases that demonstrated reliable increases (n = 14) were nearly canceled out by the number of cases that showed reliable decreases (n = 9). In addition, the total number of reliable change cases strongly suggests that these cases reflect type I error rather than genuine change: 390 instances of possible change and 24 actual instances of change yields an overall change rate of approximately 6%, a percentage that nearly matches the type I error rate of 5%. This information suggests that ingestion of these beverages alone does not result in any practically

significant changes in complex attention, processing speed, or executive function. This lack of practically significant change highlights the importance of considering glucoregulation in postprandial cognition work, particularly given that other analyses in the current study revealed a significant role of glucoregulation for these three cognitive domains.

Few Identifiable Glucoregulation Thresholds for Differences Between Conditions

Although an exploratory aim of the present study entailed comparison of glucoregulation values at which differences in cognitive performance appeared between beverage conditions, analyses frequently failed to identify such values, preventing this comparison. While the current study had sufficient power to detect interactions between beverage condition and glucoregulation indices, it is possible that there was an insufficient number of participants to allow delineation of the desired threshold values. Past work that utilized the same beverages and statistical techniques yielded these glucoregulation values with fewer measures per participant, but with more participants overall (Anderson et al., 2017; Anderson et al., 2018). This difference in findings suggests future studies that wish to obtain these threshold glucoregulation values would benefit from including more participants than the current study.

While there were few glucoregulation thresholds in the current study, the Regions of Significance technique still provided other useful information. These analyses revealed that, for the interactions in models predicting processing speed scores, the glucose response measures that incorporated baseline performance (i.e., iAUC and ΔGlucose) yielded threshold glucoregulation values, while Glu30 did not. This difference between the glucoregulation indices raises the question of whether accounting for baseline glucose may provide more precise parameter estimates compared to only considering postprandial glucose values. If future studies can

replicate such findings, it could mean that incorporating baseline glucose values in glucose response measures will lead to more accurate prediction of what caloric intake will best facilitate cognitive performance.

Limitations and Strengths

The findings of the current study must be considered in the context of its limitations. Although the present study utilized beverages that are high in ecological validity, these beverages also contain compounds other than carbohydrates that could impact cognition, such as flavonoids in apple juice (Bell, Lamport, Buter, & Williams, 2015). Such compounds may have introduced additional variability in cognitive performance that could obscure the role of glucoregulation in postprandial cognition. In addition, while ecologically valid beverages were used in the current study, other work indicates a trend toward increased portion sizes in Western cultures (Nielsen & Popkin, 2003), which suggests that the 8oz servings used in this study may underestimate typical portions. While the present study had sufficient power to detect interactions between beverage condition and glucoregulation, more participants were likely required to ascertain threshold glucoregulation values using Regions of Significance (Preacher et al., 2006), though this technique still provided greater resolution for the probing of interactions than other techniques (e.g., Simple Slopes; Preacher et al., 2006), even at the current number of participants. Even though reliable change analyses suggested a lack of reliable change in cognitive performance from baseline to 30 minutes in the current study, test-retest reliability estimates were only available for three out of the five composites used for the current study (Littleton et al., 2015). As such, it is possible that the remaining two indices had different distributions of reliable change. The CNSVS composites in the present study did not account for

response speed, which may have prevented detection of effects relevant for the evaluation of study aims.

The present study also has several strengths compared to past work. Although it is possible that typical servings are larger than those utilized in this study (Nielsen & Popkin, 2003), these beverages are still of greater ecological validity than those used in many other studies, such as pure carbohydrate beverages (e.g., Parsons & Gold, 1992; Lamport et al., 2014). The current study considered several measures of glucoregulation, which successfully demonstrated differences in findings across these measures that could be relevant for the postprandial cognition literature. In addition, the consideration of multiple cognitive domains within this study revealed a difference in the importance of different glucoregulation measures for each domain, which could also prove relevant for future research. The use of rigorous statistical methodology, particularly the combination of linear mixed modeling (Peugh, 2010), continuous glucoregulation measures, and the Regions of Significance technique may have also demonstrated the potential superiority of some glucoregulation measures over others – continued use of these methods could yield similar benefits when evaluating the role of glucoregulation in future postprandial cognition studies.

Considerations for Future Work

When considered in the context of the postprandial cognition literature, the findings, strengths, and limitations of the current study suggest additional considerations for future research. As described above, utilizing measures of a cognitive domain that incorporate response speed may yield results that differ from those of the current study. This complements suggestions from other researchers, specifically to utilize multiple measures of a cognitive domain within the

same study to ensure that findings truly depend on the domain assessed rather than other aspects of cognitive tests (Philippou & Constantinou, 2014). While the currently study demonstrated a role of glucose response measures based upon ingestion of 8oz of fruit juice, replication of this work using of a 75g glucose beverage to generate these measures may increase generalizability, given that such a methodology is more standard for evaluating these constructs (American Diabetes Association, 2014). Future studies may also benefit from having only two beverage conditions, given that analyses revealed a detrimental impact of successive visits on cognitive performance for some cognitive outcomes. Finally, although the current study considered several aspects of glucoregulation, additional glucoregulation measures, such a glycated hemoglobin (Ceriello, 2010) or homeostasis model assessment (HOMA; Matthews et al., 1985), warrant further investigation.

Conclusions

In summary, the present study evaluated the role of glucoregulation in postprandial cognition following dairy milk, fruit juice, and water among healthy adults. It was hypothesized that participants with poorer glucoregulation would demonstrate better cognitive performance after ingesting water or dairy milk compared to juice. While participants with higher fasting glucose performed initially performed better on a complex attention task after ingesting milk or water compared to juice, this relationship reversed at an extended postprandial timepoint. In addition, results for analyses that considered a moderating role of glucose response revealed that milk initially proved beneficial compared to water in participants with worse glucoregulation, with this relationship also reversing at an extended postprandial timepoint. The role of glucoregulation in postprandial cognition among adults varies based on the aspect of glucoregulation under consideration, as well as the way in which it is measured. Future studies should utilize several measures of cognitive domains, incorporate speed and accuracy into cognitive assessments, consider additional aspects of glucoregulation, and replicate these findings using standard measures of glucose response.

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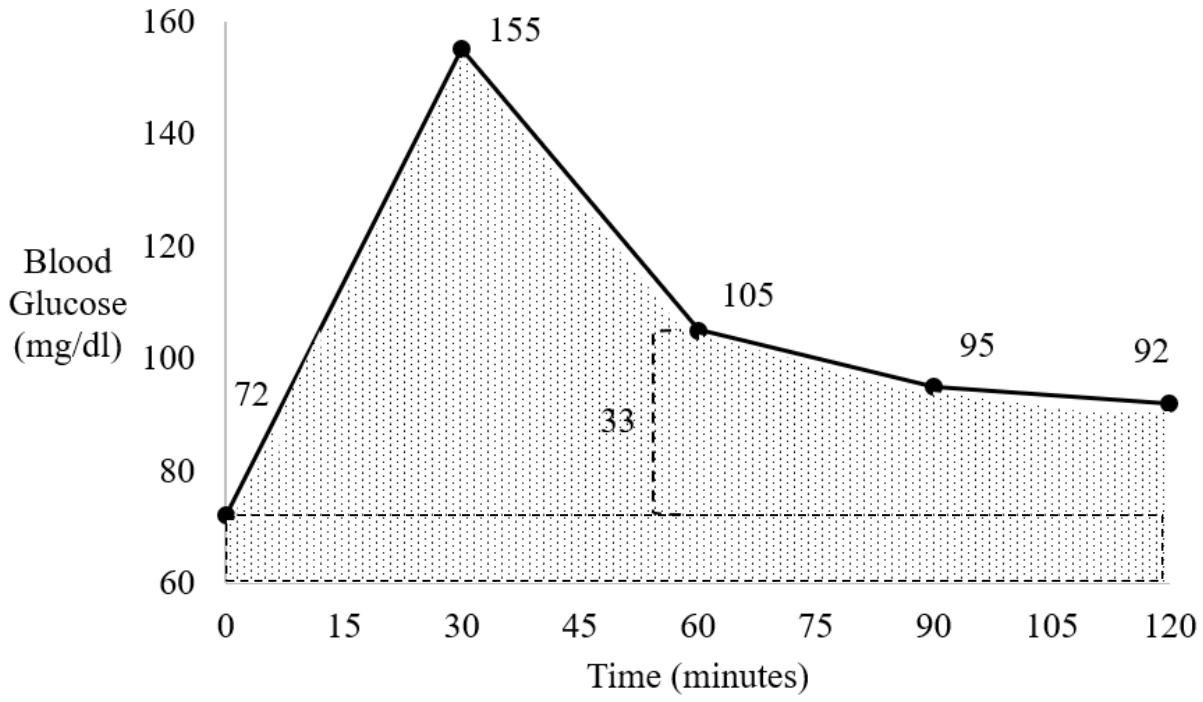


Figure 1. Example postprandial blood glucose curve, where blood glucose is assessed at baseline and every 30 minutes post-ingestion. Fasting glucose is represented at time zero (i.e., 72 mg/dl). The shaded area represents the blood glucose area-under-the-curve, an index of the individual's glucose response – subtracting the area of the dotted rectangle from the area-under-the-curve would yield the incremental area-under-the-curve (iAUC). The difference between blood glucose at 60 minutes versus zero minutes (i.e., 33 mg/dl) is depicted as another potential index of glucose response.

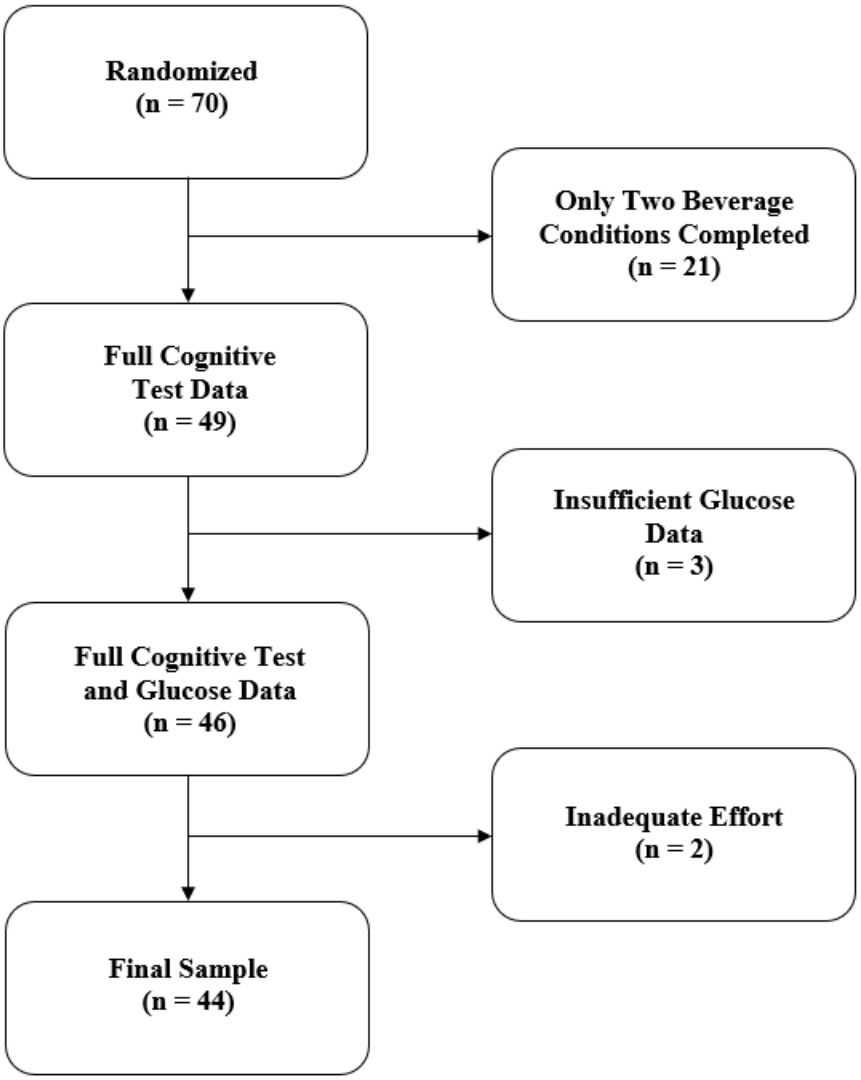


Figure 2. Flow diagram depicting exclusions from randomization to the final sample for primary analyses.

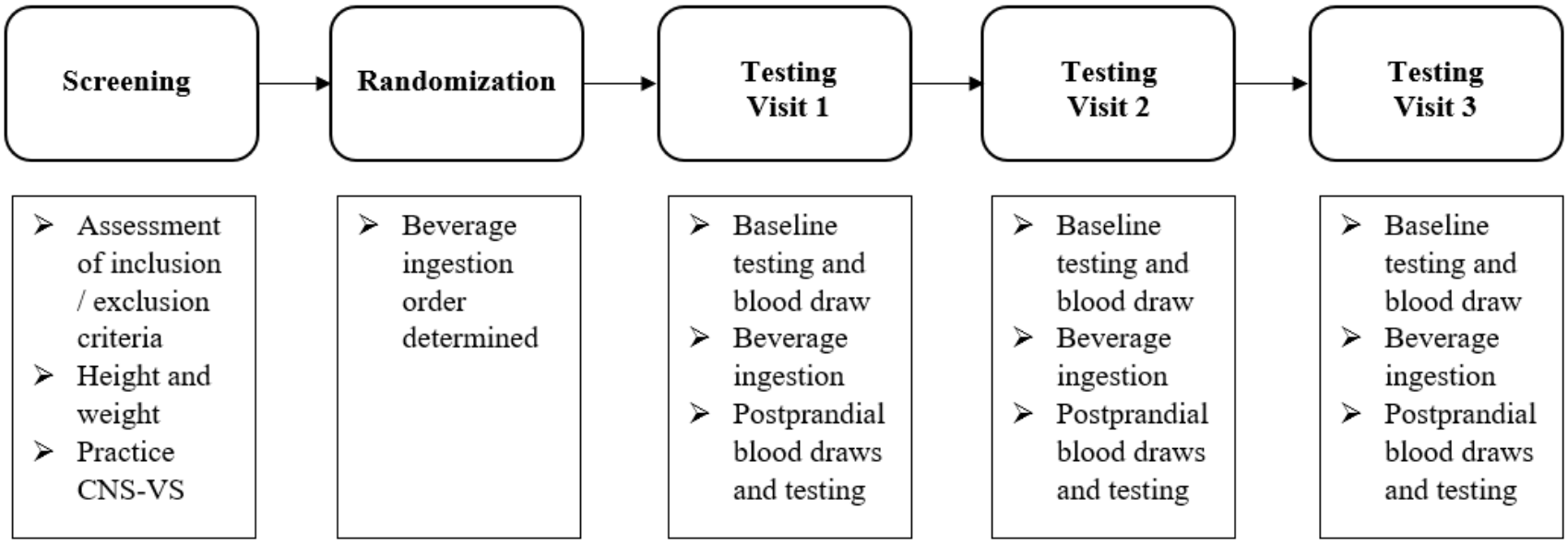


Figure 3. Diagram depicting overall study design.

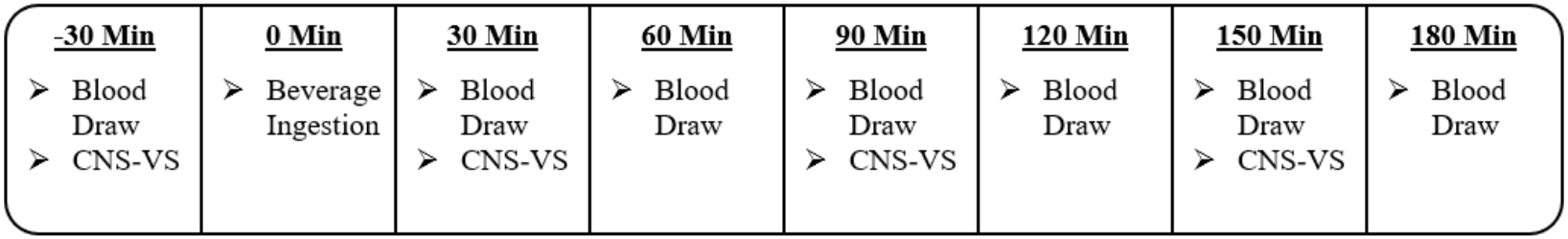
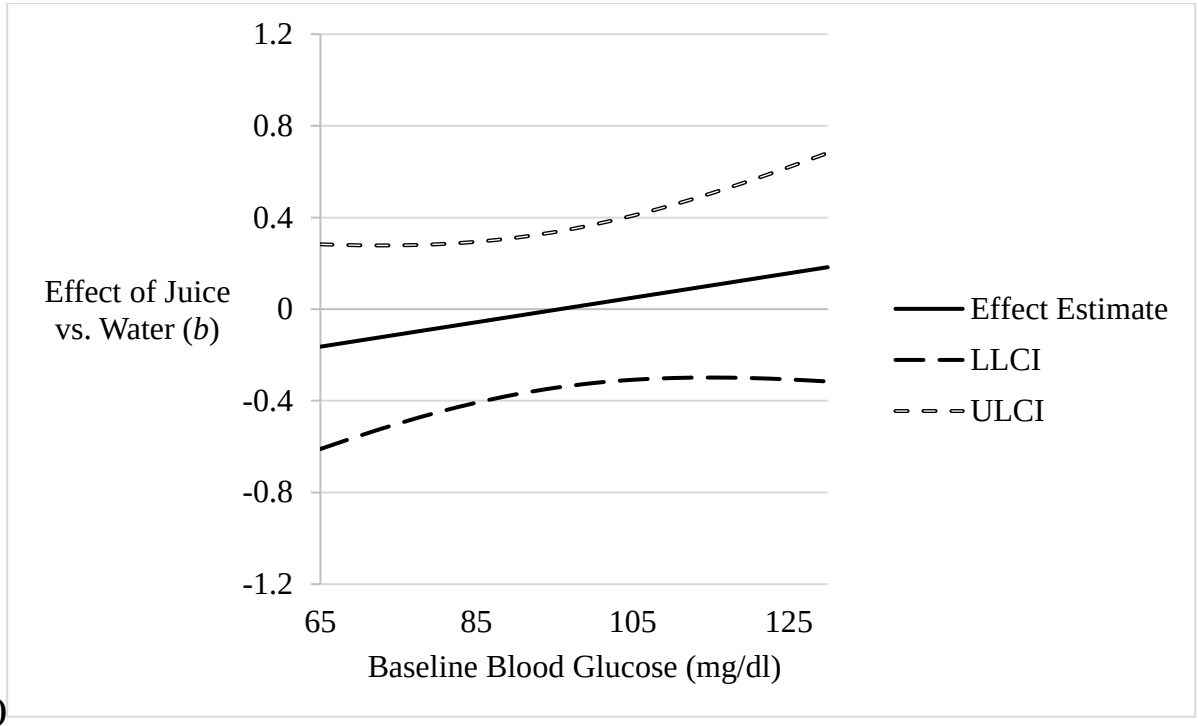
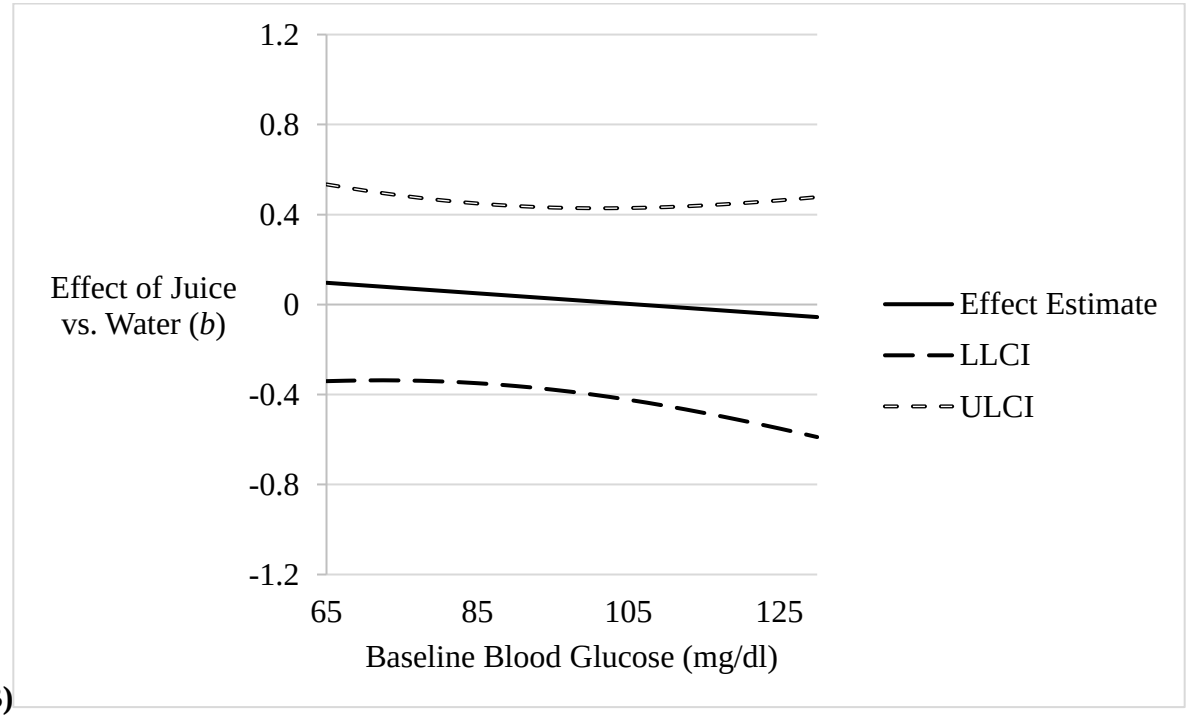


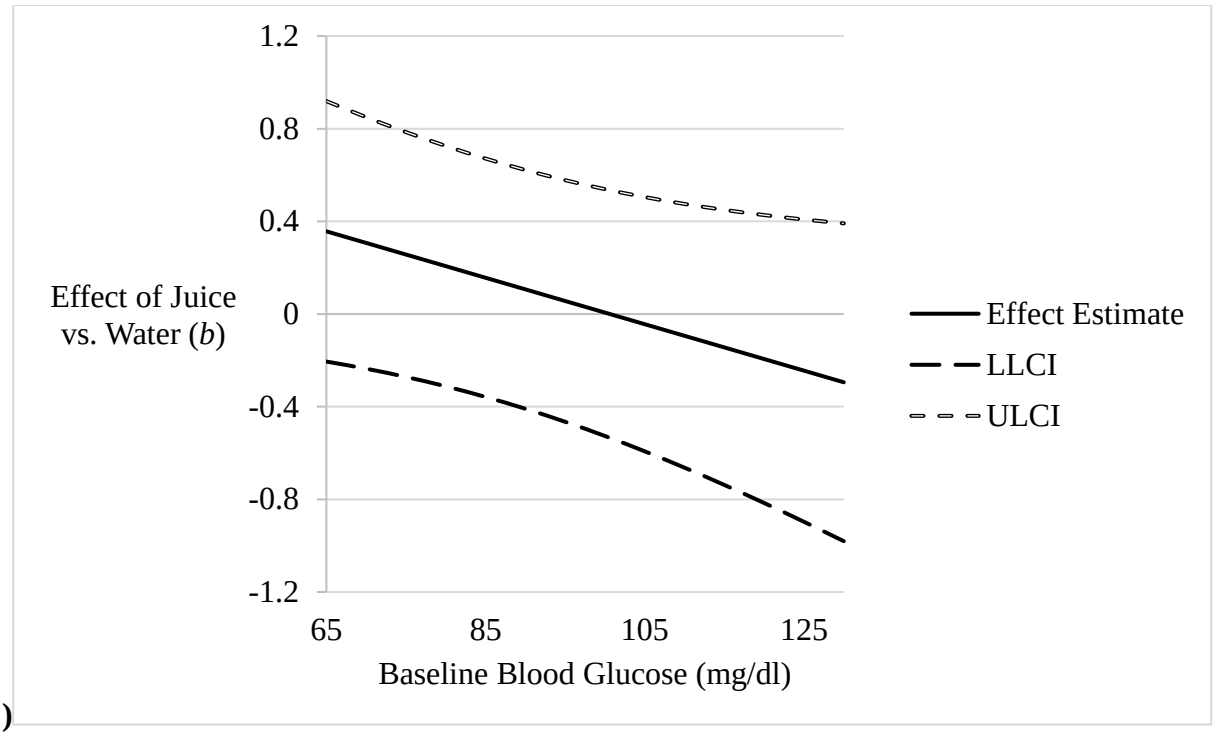
Figure 4. Diagram depicting study procedures within a testing visit.


1.2
0.8
0.4
0
-0.4
-0.8
-1.2
Effect of Juice vs. Water (*b*)
65
85
105
125
Baseline Blood Glucose (mg/dl)
Effect Estimate
LLCI
ULCI

(A)

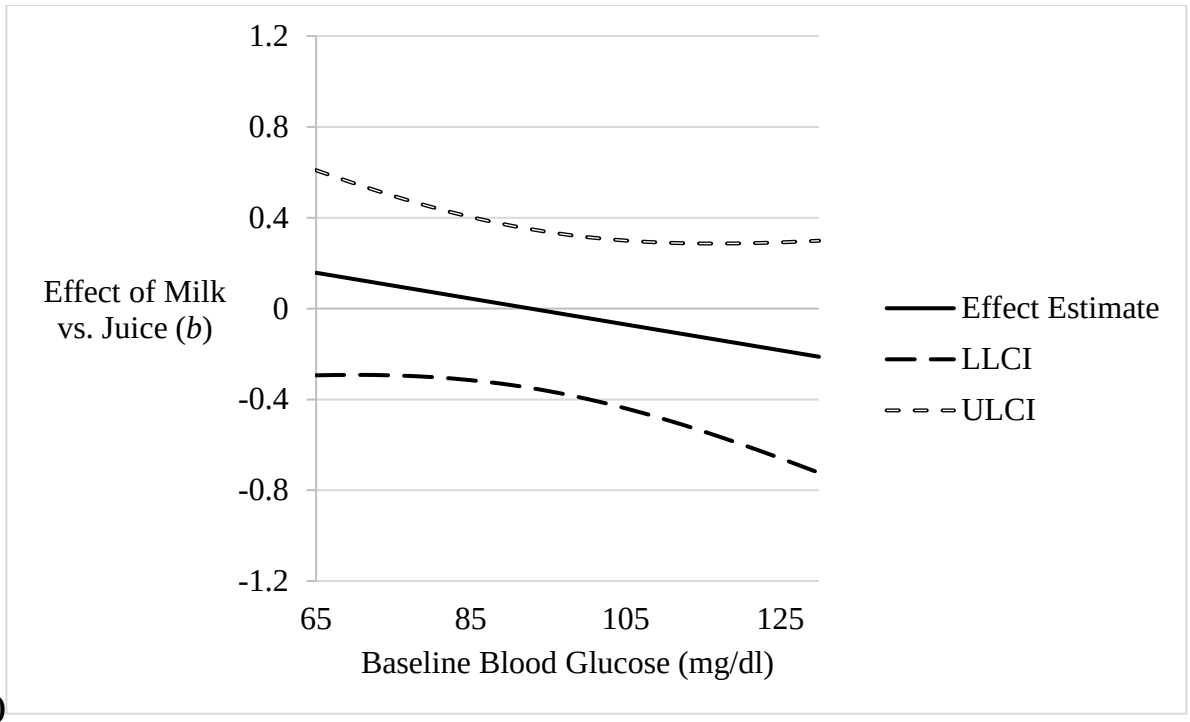

1.2
0.8
0.4
0
-0.4
-0.8
-1.2
Effect of Juice vs. Water (*b*)
65
85
105
125
Baseline Blood Glucose (mg/dl)
Effect Estimate
LLCI
ULCI

(B)

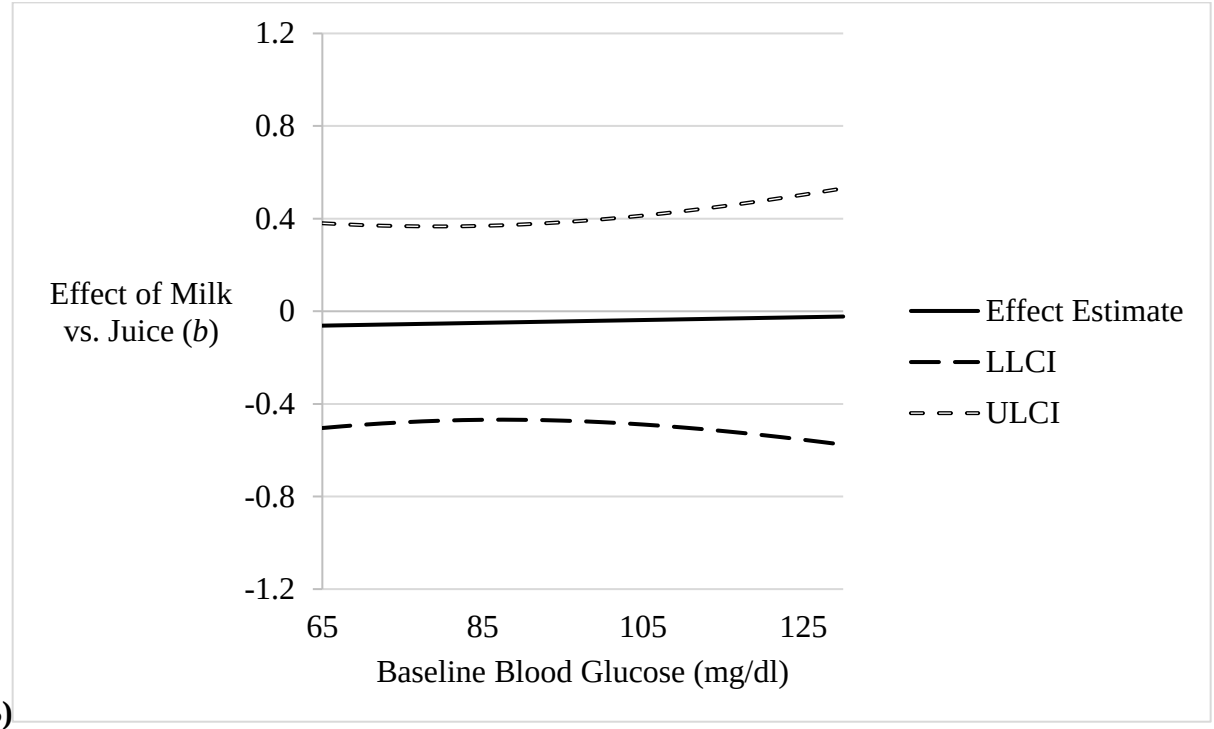


(C)

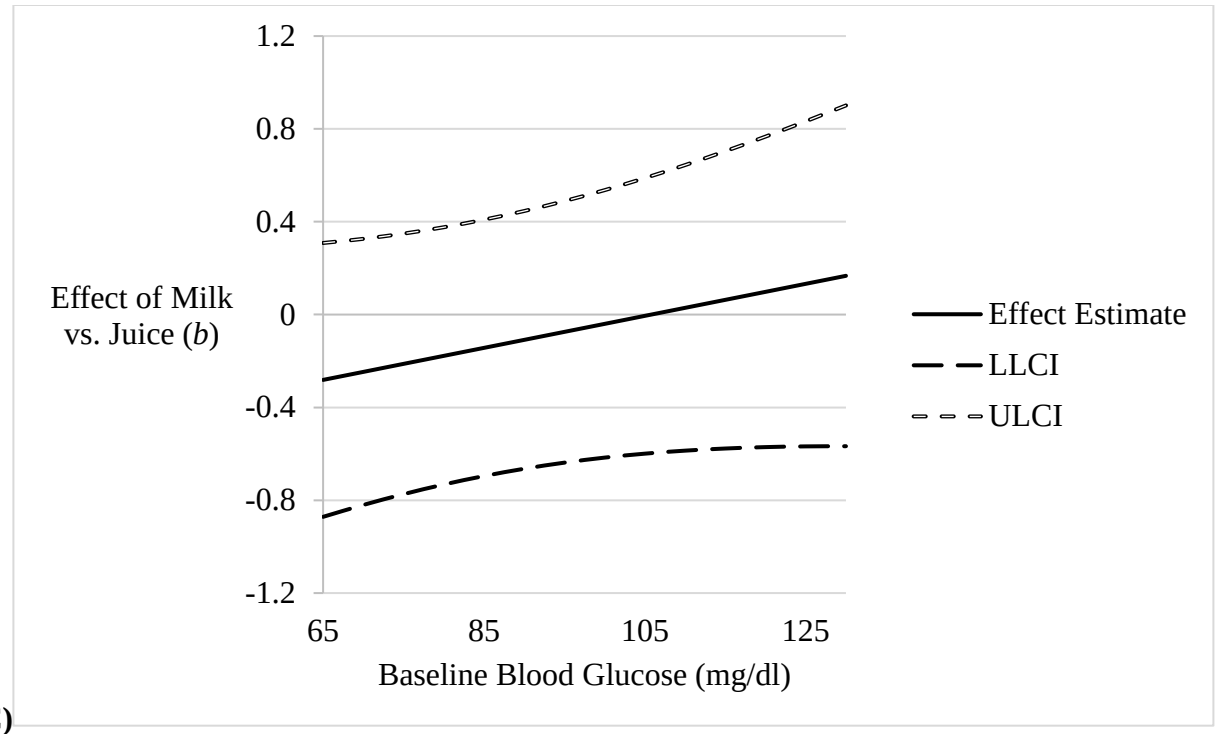
Figure 5. Visual depiction of the Beverage*Fasting Glucose*Time interaction comparing complex attention scores between the juice and water conditions (b = -1.28*10^{-4}, SE_b = 5.28*10^{-5}, p = .02). **(A)** At 30 minutes, participants with lower fasting glucose performed best following juice, while those with higher fasting glucose performed best after water. **(B)** At 90 minutes, there was little to no effect of fasting glucose on the difference in performance between the juice and water conditions. **(C)** The pattern of results at 150 minutes was the reverse of that observed at 30 minutes, such that performance for participants with lower fasting glucose was best after water, and complex attention for those with higher fasting glucose was best after juice. LLCI = Lower Limit of 95% Confidence Interval. ULCI = Upper Limit of 95% Confidence Interval.


1.2
0.8
0.4
0
-0.4
-0.8
-1.2
Effect of Milk vs. Juice (*b*)
65
85
105
125
Baseline Blood Glucose (mg/dl)
Effect Estimate
LLCI
ULCI

(A)

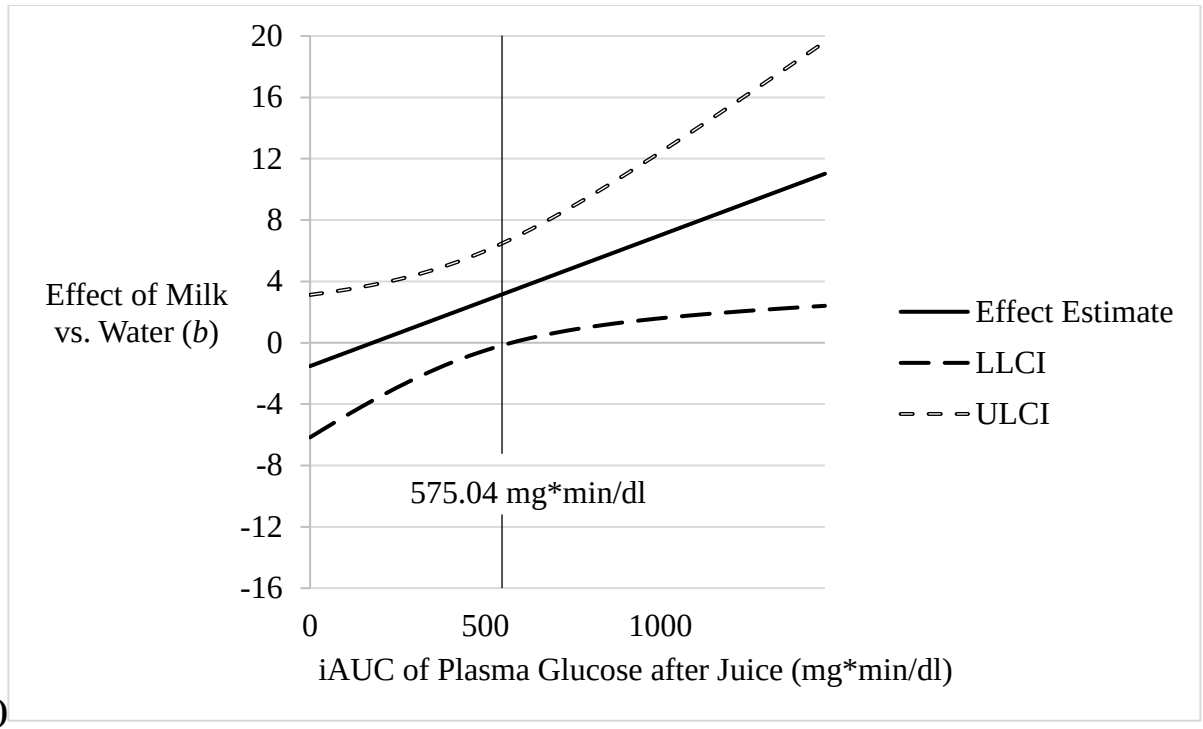

1.2
0.8
0.4
0
-0.4
-0.8
-1.2
Effect of Milk vs. Juice (*b*)
65
85
105
125
Baseline Blood Glucose (mg/dl)
Effect Estimate
LLCI
ULCI

(B)

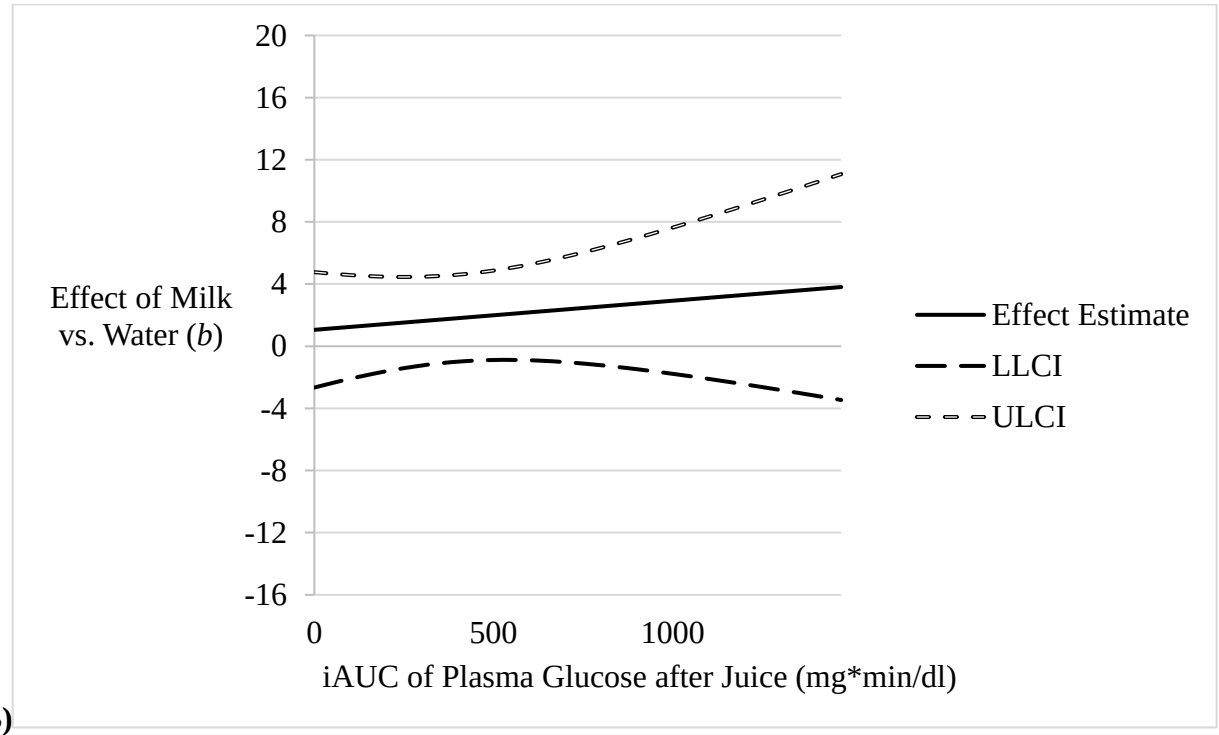


(C)

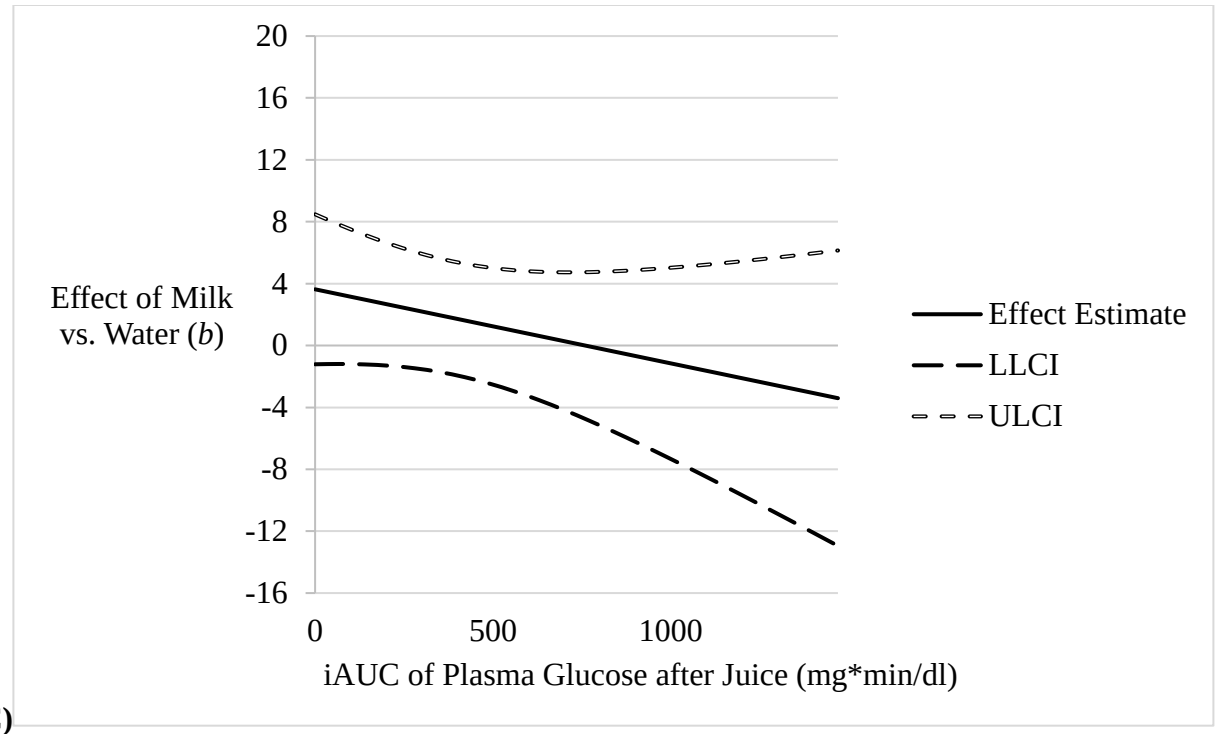
Figure 6. Visual depiction of the trend toward a Beverage*Fasting Glucose*Time interaction comparing complex attention scores between the milk and juice conditions (b = -1.05*10^{-4}, SE_b = 5.87*10^{-5}, p = .07). **(A)** At 30 minutes, participants with lower fasting glucose performed best following juice, while those with higher fasting glucose performed best after milk. **(B)** At 90 minutes, there was little to no effect of fasting glucose on the difference in performance between the milk and juice conditions. **(C)** The pattern of results at 150 minutes was the reverse of that observed at 30 minutes, such that performance for participants with lower fasting glucose was best after milk, and complex attention for those with higher fasting glucose was best after juice. LLCI = Lower Limit of 95% Confidence Interval. ULCI = Upper Limit of 95% Confidence Interval.


20
16
12
8
4
0
-4
-8
-12
-16
Effect of Milk vs. Water (*b*)
575.04 mg*min/dl
0
500
1000
iAUC of Plasma Glucose after Juice (mg*min/dl)
Effect Estimate
LLCI
ULCI

(A)

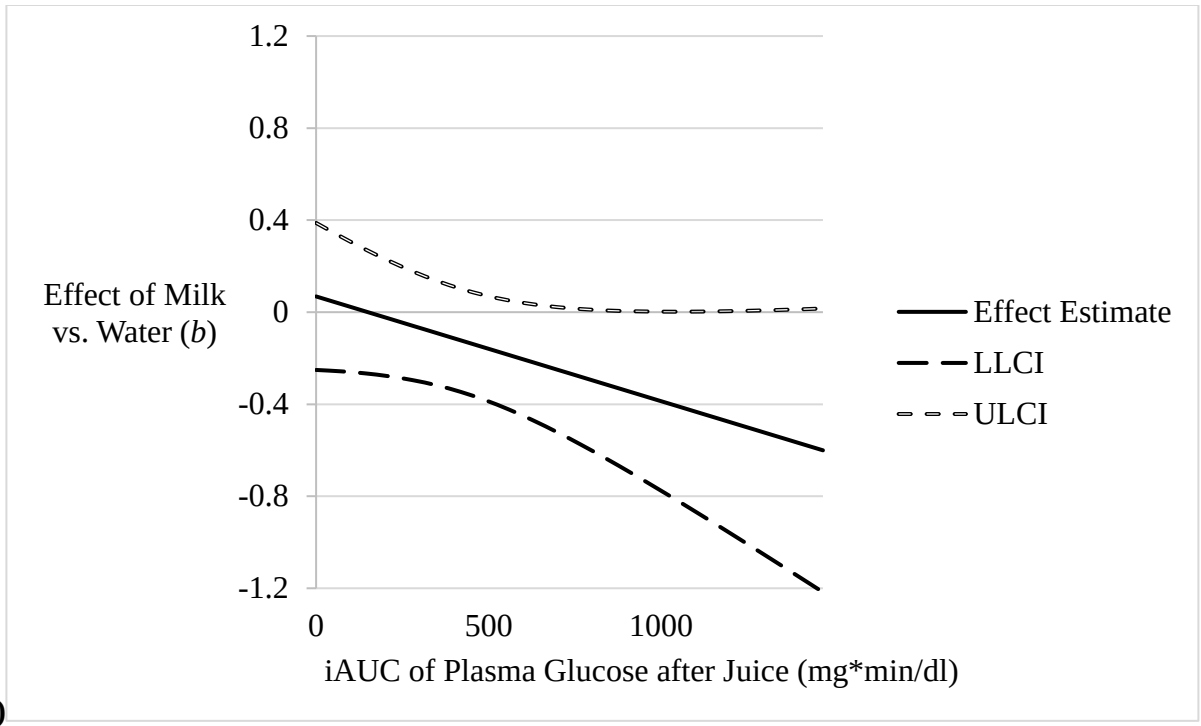

20
16
12
8
4
0
-4
-8
-12
-16
Effect of Milk vs. Water (*b*)
0
500
1000
iAUC of Plasma Glucose after Juice (mg*min/dl)
Effect Estimate
LLCI
ULCI

(B)

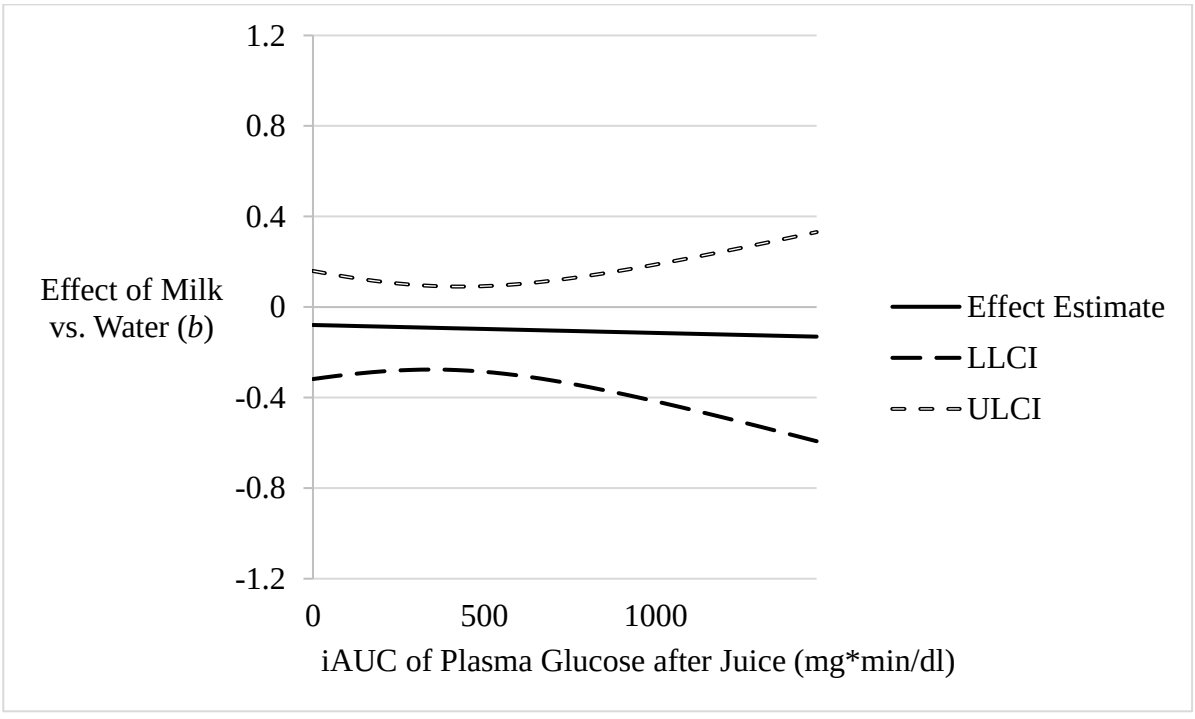


(C)

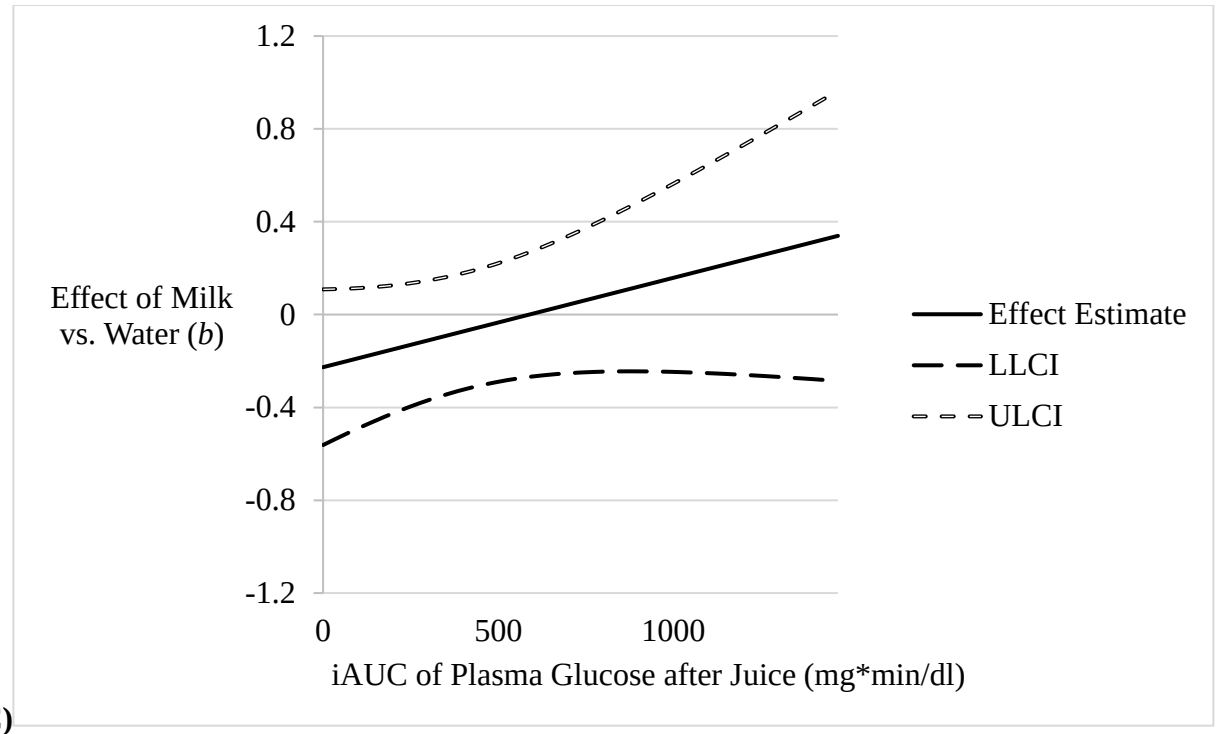
Figure 7. Visual depiction of the Beverage*iAUC*Time interaction comparing processing scores between the milk and water conditions ($b = 1.11*10^{-4}$, $SE_b = 4.20*10^{-5}$, $p = .01$). **(A)** At 30 minutes, participants whose plasma glucose iAUC after juice was above 575.04 mg*min/dl showed significantly faster processing speed after consuming milk versus water. **(B)** At 90 minutes, there was minimal relationship between plasma glucose iAUC and the difference in performance between the milk and water conditions. **(C)** At 150 minutes, participants with a smaller plasma glucose iAUC performed better after milk, and those with a larger plasma glucose iAUC performed better following water, though performance between conditions did not differ significantly at any level of plasma glucose iAUC. iAUC = Incremental Area-Under-The-Curve. LLCI = Lower Limit of 95% Confidence Interval. ULCI = Upper Limit of 95% Confidence Interval.


1.2
0.8
0.4
0
-0.4
-0.8
-1.2
Effect of Milk vs. Water (*b*)
0
500
1000
iAUC of Plasma Glucose after Juice (mg*min/dl)
Effect Estimate
LLCI
ULCI

(A)

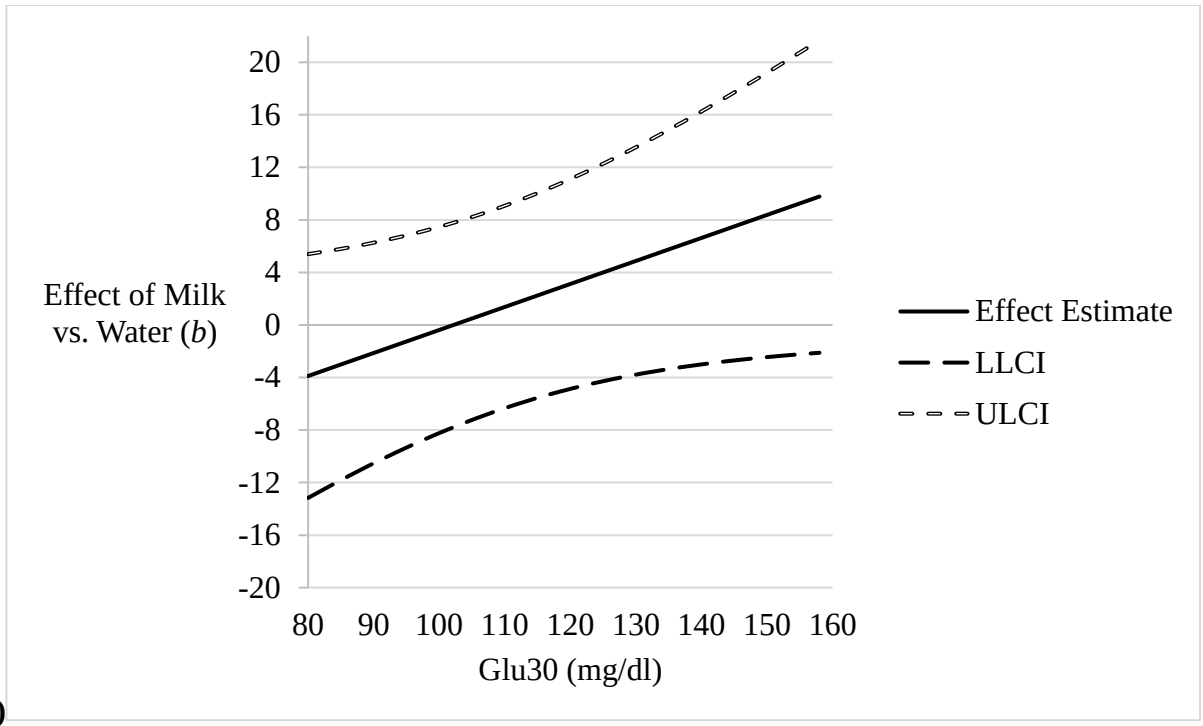

1.2
0.8
0.4
0
-0.4
-0.8
-1.2
Effect of Milk vs. Water (*b*)
0
500
1000
iAUC of Plasma Glucose after Juice (mg*min/dl)
Effect Estimate
LLCI
ULCI

(B)

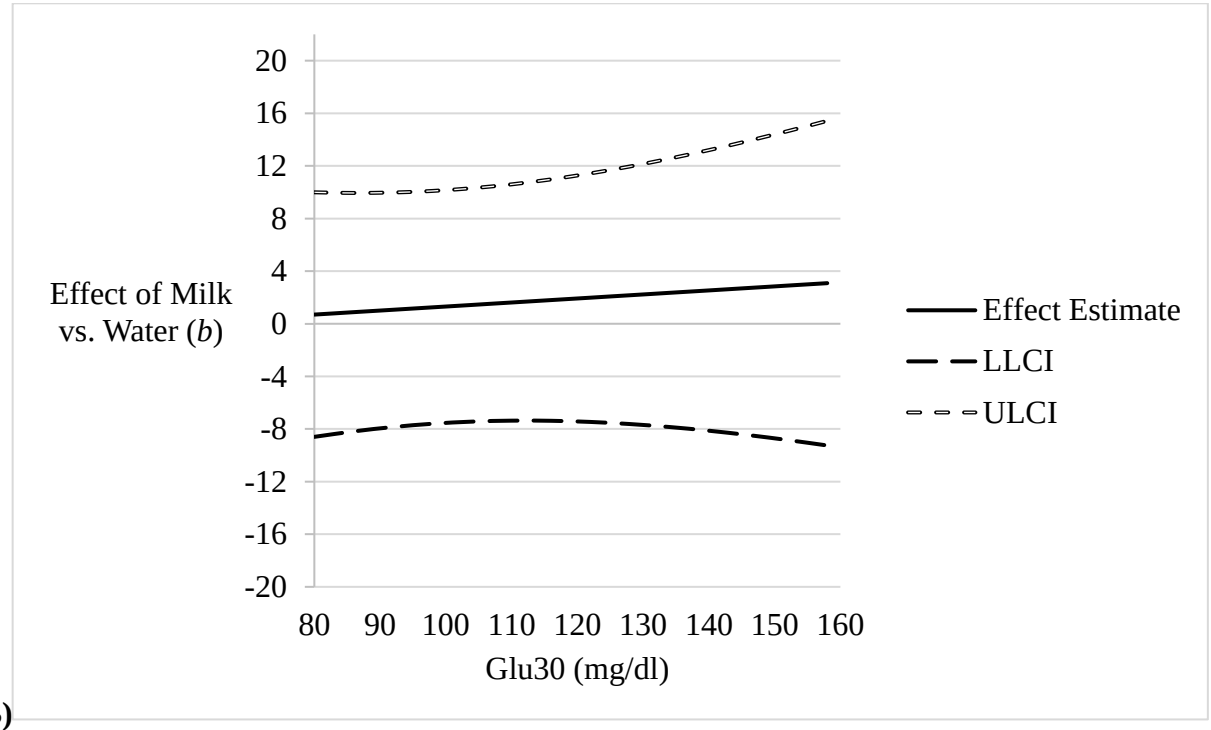


(C)

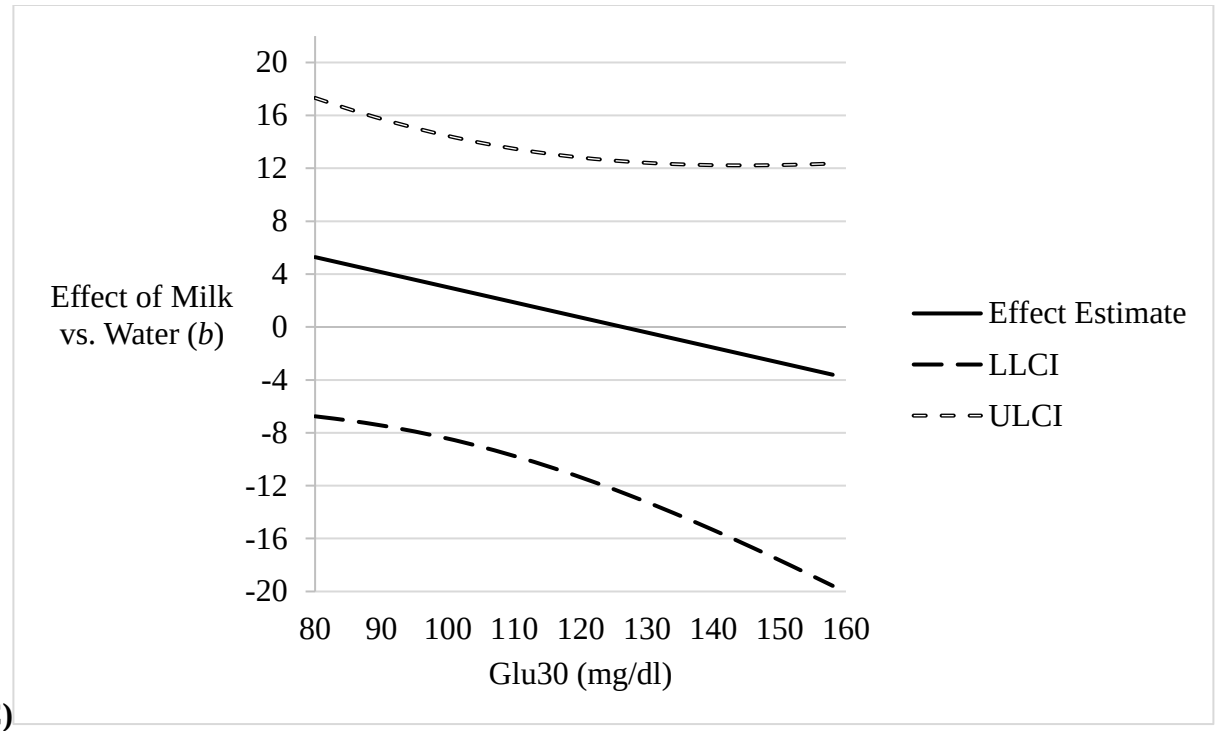
Figure 8. Visual depiction of the Beverage*iAUC*Time interaction comparing executive function scores between the milk and water conditions (b = 7.00*10^{-6}, SE_b = 3.20*10^{-6}, p = .03). **(A)** At 30 minutes, participants with a large plasma glucose iAUC performed better after drinking milk versus water. **(B)** At 90 minutes, there was minimal relationship between plasma glucose iAUC and the difference in performance between the milk and water conditions. **(C)** At 150 minutes, participants with a smaller plasma glucose iAUC performed better after milk, while those with a larger iAUC performed better after water. iAUC = Incremental Area-Under-The-Curve. LLCI = Lower Limit of 95% Confidence Interval. ULCI = Upper Limit of 95% Confidence Interval.


20
16
12
8
4
0
-4
-8
-12
-16
-20
Effect of Milk vs. Water (*b*)
80 90 100 110 120 130 140 150 160
Glu30 (mg/dl)
Effect Estimate
LLCI
ULCI

(A)

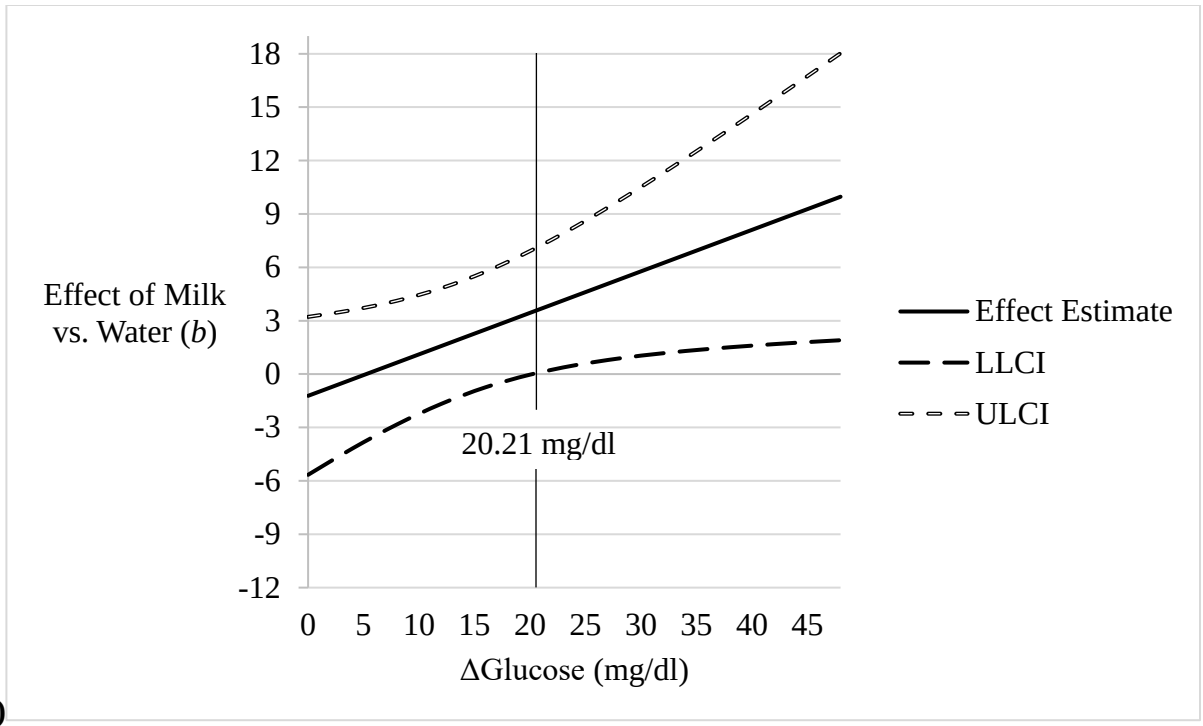

20
16
12
8
4
0
-4
-8
-12
-16
-20
Effect of Milk vs. Water (*b*)
80 90 100 110 120 130 140 150 160
Glu30 (mg/dl)
Effect Estimate
LLCI
ULCI

(B)

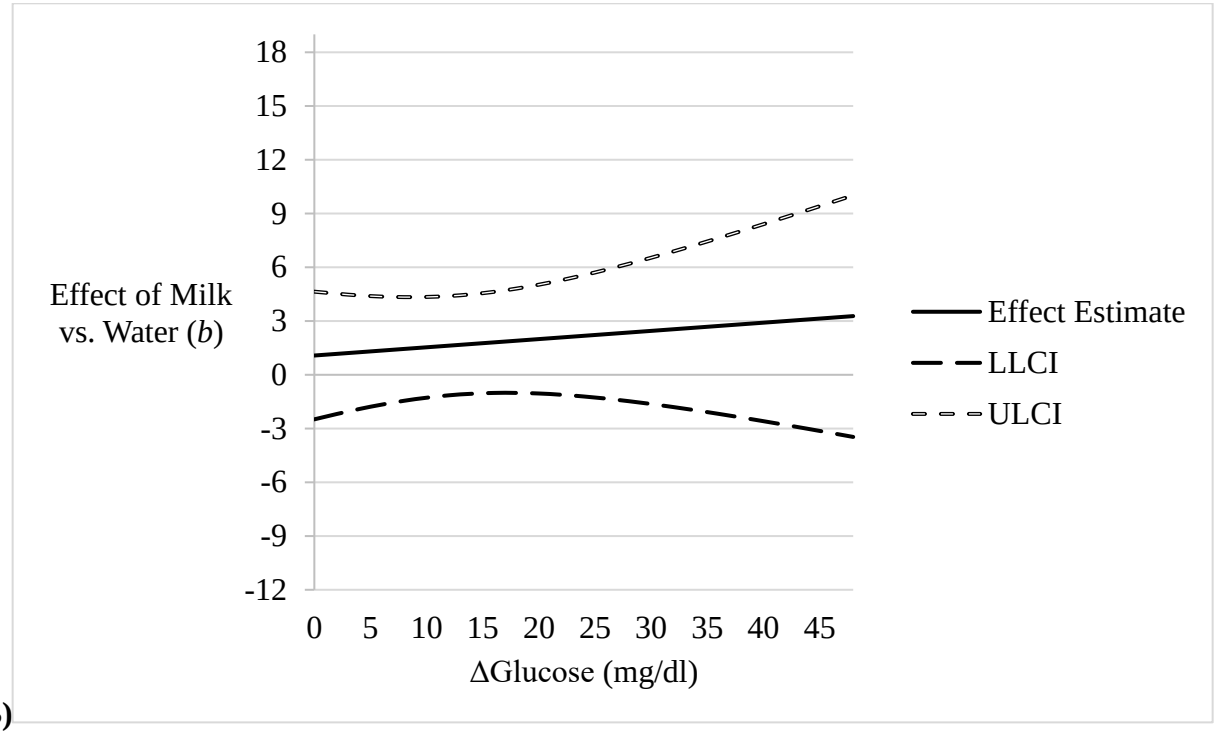


(C)

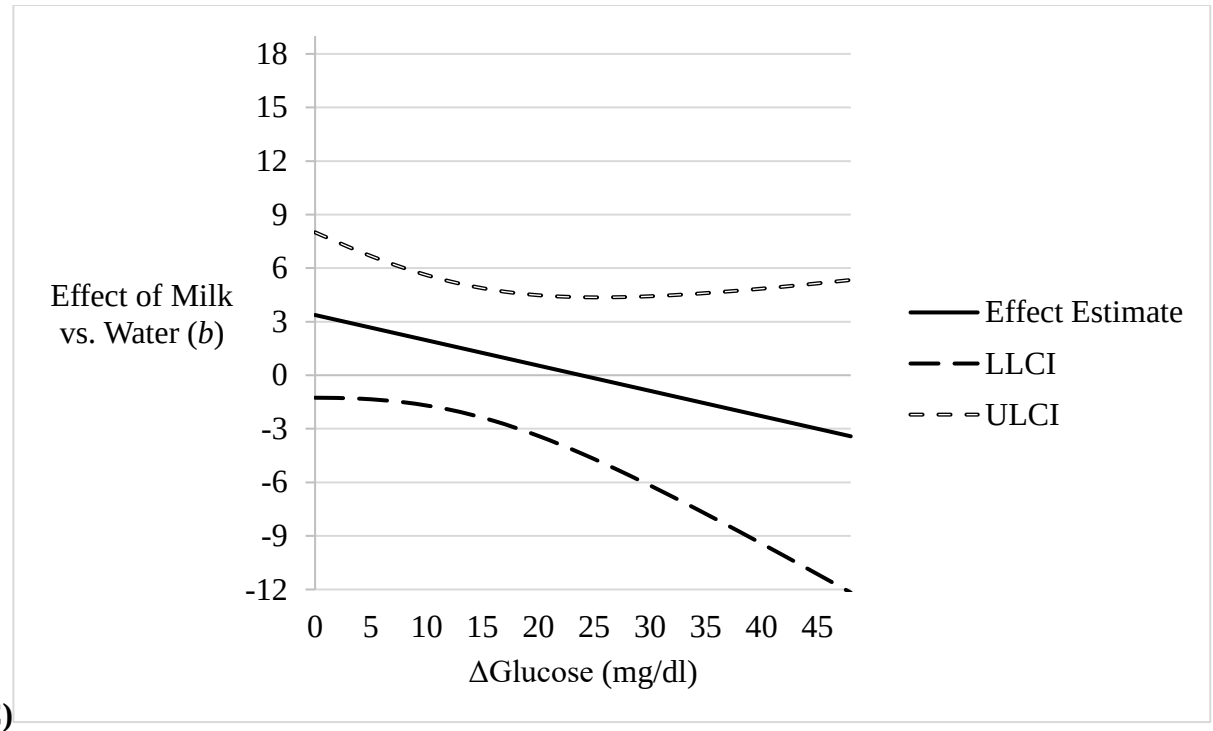
Figure 9. Visual depiction of the Beverage*Glu30*Time interaction comparing processing speed scores between the milk and water conditions (b = -2.41*10^{-3}, SE_b = 9.80*10^{-4}, p = .01). **(A)** At 30 minutes, participants with higher Glu30 performed better after ingesting milk compared to water. **(B)** At 90 minutes, there was little to no relationship between Glu30 and difference in performance between the milk and water conditions. **(C)** At 150 minutes, participants with lower Glu30 performed better after milk, water appeared better for performance among participants with higher Glu30. Glu30 = 30-minute glucose in the juice condition. LLCI = Lower Limit of 95% Confidence Interval. ULCI = Upper Limit of 95% Confidence Interval.


Effect of Milk vs. Water (*b*)
18
15
12
9
6
3
0
-3
-6
-9
-12
0 5 10 15 20 25 30 35 40 45
ΔGlucose (mg/dl)
20.21 mg/dl
Effect Estimate
LLCI
ULCI

(A)

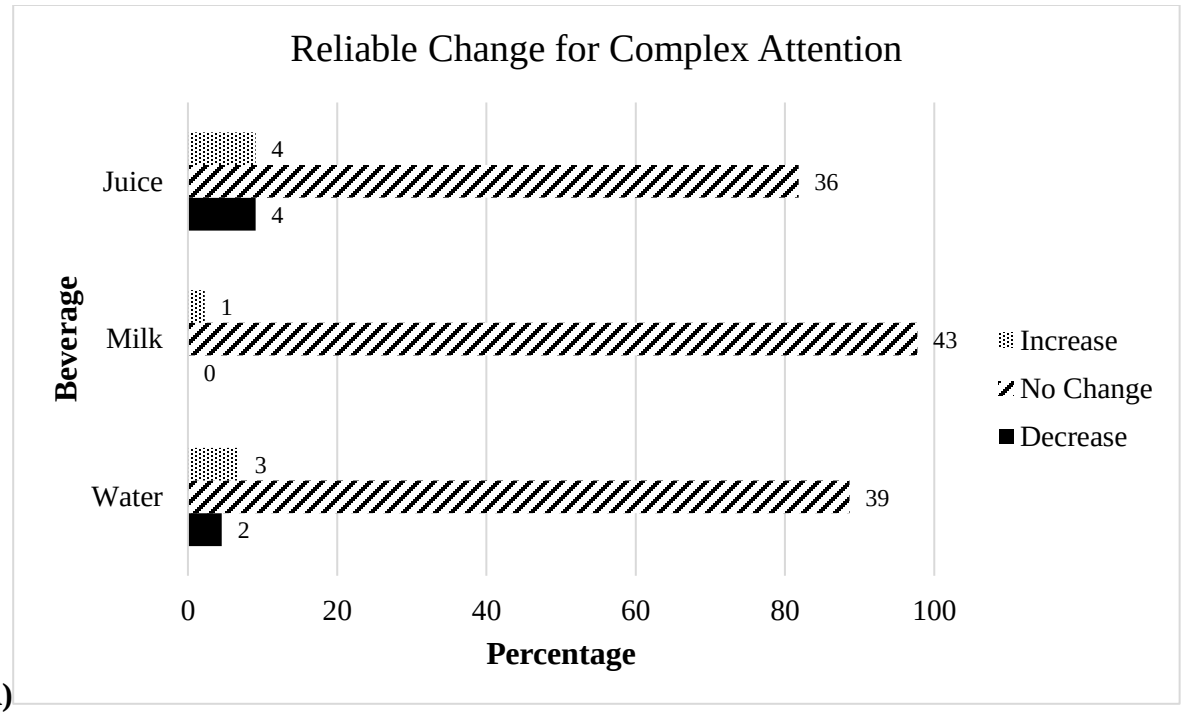

Effect of Milk vs. Water (*b*)
18
15
12
9
6
3
0
-3
-6
-9
-12
0 5 10 15 20 25 30 35 40 45
ΔGlucose (mg/dl)
Effect Estimate
LLCI
ULCI

(B)

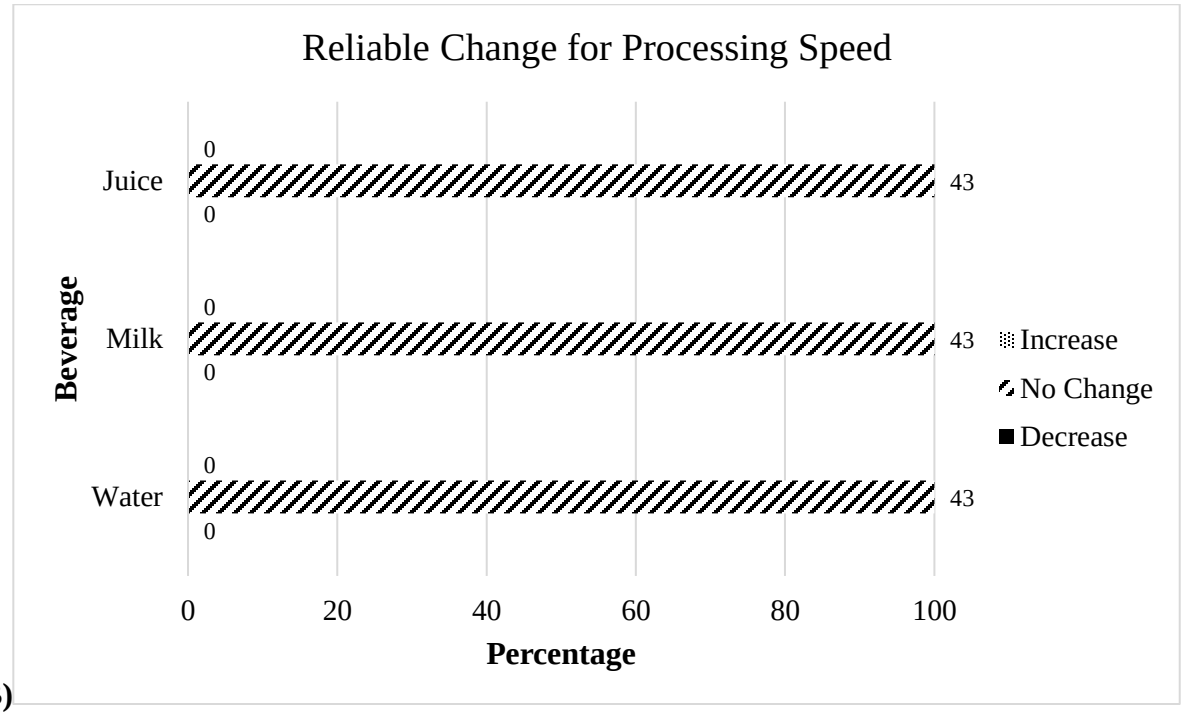


(C)

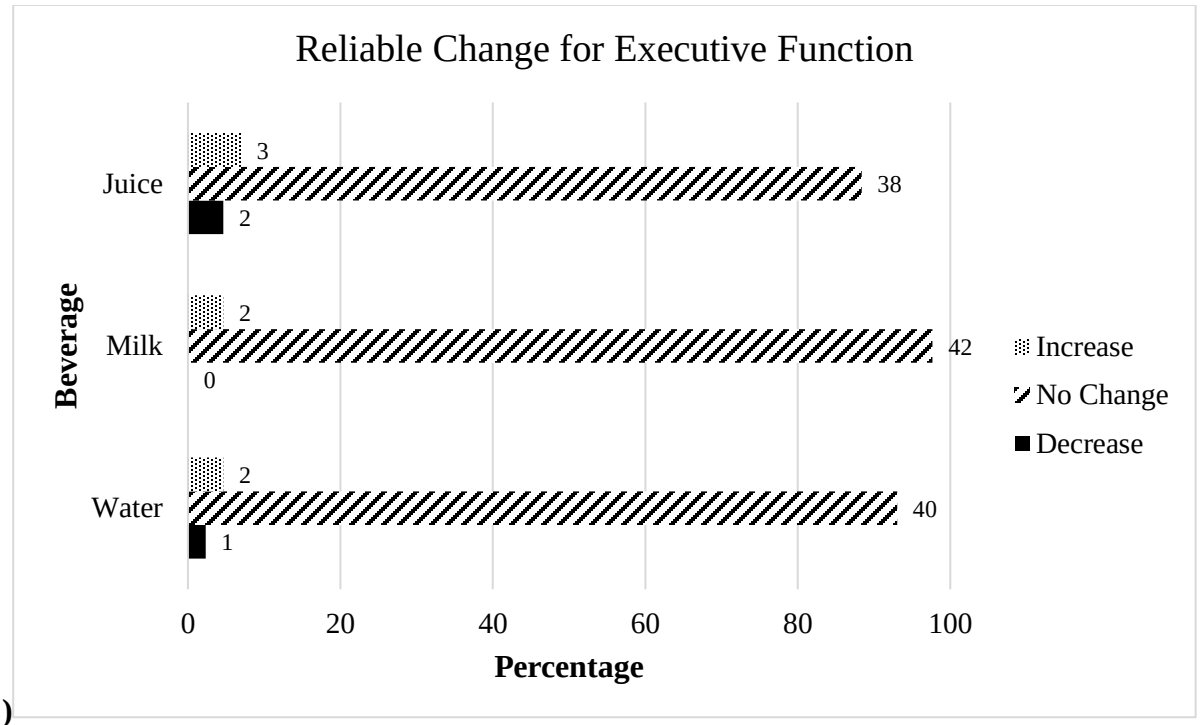
Figure 10. Visual depiction of the Beverage*ΔGlucose*Time interaction comparing processing speed scores between the milk and water conditions (b = -3.12*10^{-3}, SE_b = 1.17*10^{-3}, p = .01). **(A)** At 30 minutes, participants with ΔGlucose above 20.21 mg/dl performed significantly better after ingesting milk compared to water. **(B)** At 90 minutes, there was little to no relationship between ΔGlucose and difference in performance between the milk and water conditions. **(C)** At 150 minutes, participants with lower ΔGlucose performed better after milk, water appeared better for performance among participants with higher ΔGlucose. ΔGlucose = Change in glucose from baseline to 30 minutes in the juice condition. LLCI = Lower Limit of 95% Confidence Interval. ULCI = Upper Limit of 95% Confidence Interval.


Reliable Change for Complex Attention
Juice
Milk
Water
Beverage
4
36
4
1
43
0
3
39
2
0
20
40
60
80
100
Percentage
Increase
No Change
Decrease

(A)


Reliable Change for Processing Speed
Juice
Milk
Water
Beverage
0
43
0
0
43
0
0
43
0
0
20
40
60
80
100
Percentage
Increase
No Change
Decrease

(B)



(C)

Figure 11. Reliable change descriptives for **(A)** complex attention, **(B)** processing speed, and **(C)** executive function scores after ingestion of water, milk, and juice. Although the water and juice conditions generally demonstrated more reliable change than the milk condition, increases and decreases were approximately equal in these conditions, and there was insufficient reliable change (increase or decrease) for further statistical analysis. Bar labels are the number of participants in the category.

Table 1. Descriptive Statistics for the Final Sample (*n* = 44)

	Mean (SD)		Mean (SD)
Age (years)	30.81 (8.36)	Fasting Glucose (Milk)	97.60 (8.35)
BMI (kg/m^2)	26.50 (4.63)	Fasting Glucose (Juice)	100.35 (8.29)
iAUC (min*mg/dl)	453.27 (386.38)	Fasting Glucose (Water)	97.63 (10.63)
Sex (% female)	50%	Glu30	113.49 (19.02)
		ΔGlucose	13.14 (16.88)

Note: Fasting glucose presented in mg/dl. BMI = Body Mass Index, ΔGlucose = change in plasma glucose from baseline to 30 minutes in the fruit juice condition, Glu30 = plasma glucose 30 minutes following fruit juice ingestion, iAUC = incremental area-under-the-curve of glucose following fruit juice ingestion, SD = Standard Deviation.

Table 2. CNS Vital Signs Complex Attention Descriptives for the Final Sample (*n* = 44)

Condition	Baseline	30-min	90-min	150-min
2% Milk	7.14 (6.14)	7.07 (8.69)	7.34 (9.32)	7.70 (10.34)
Juice	5.39 (4.60)	7.11 (10.08)	6.57 (6.80)	7.57 (8.50)
Water	7.45 (9.75)	7.45 (10.54)	7.43 (9.33)	8.68 (13.96)

Note: Values are presented as Mean (Standard Deviation). Higher scores reflect worse performance.

Table 3. CNS Vital Signs Processing Speed Descriptives for the Final Sample (*n* = 44)

Condition	Baseline	30-min	90-min	150-min
2% Milk	69.70 (15.24)	72.12 (12.50)	73.28 (16.87)	73.26 (16.89)
Juice	72.34 (13.26)	72.60 (16.45)	73.79 (15.24)	74.05 (16.88)
Water	70.70 (18.04)	71.98 (13.13)	71.84 (16.42)	74.12 (16.00)

Note: Values are presented as Mean (Standard Deviation). Higher scores reflect better performance.

Table 4. CNS Vital Signs Executive Function Descriptives for the Final Sample (*n* = 44)

Condition	Baseline	30-min	90-min	150-min
2% Milk	54.23 (10.34)	55.34 (9.36)	55.50 (12.77)	55.02 (10.93)
Juice	55.11 (8.87)	56.63 (10.79)	57.59 (8.46)	56.86 (8.79)
Water	55.57 (8.15)	55.58 (7.98)	54.86 (11.58)	55.18 (10.88)

Note: Values are presented as Mean (Standard Deviation). Higher scores reflect better performance.

Table 5. CNS Vital Signs Working Memory Descriptives for the Final Sample (*n* = 44)

Condition	Baseline	30-min	90-min	150-min
2% Milk	12.43 (4.10)	12.05 (4.18)	11.75 (5.04)	11.93 (4.83)
Juice	11.52 (5.56)	11.66 (4.52)	11.91 (4.96)	11.57 (5.14)
Water	11.50 (5.59)	11.77 (5.66)	10.50 (6.25)	11.66 (3.83)

Note: Values are presented as Mean (Standard Deviation). Higher scores reflect better performance.

Table 6. CNS Vital Signs Simple Attention Descriptives for the Final Sample (*n* = 44)

Condition	Baseline	30-min	90-min	150-min
2% Milk	37.98 (3.96)	37.57 (7.15)	37.41 (6.69)	37.30 (7.29)
Juice	38.89 (2.45)	37.70 (6.41)	37.66 (6.00)	37.45 (6.46)
Water	37.18 (7.43)	37.57 (6.88)	37.82 (4.75)	37.25 (6.82)

Note: Values are presented as Mean (Standard Deviation). Higher scores reflect better performance.