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Does Body Mass Index Modify Memory, Reasoning, and Speed of Processing Training Effects in Older Adults

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Abstract

Objective—To describe 10-year trajectories of cognitive performance by body mass index (BMI) class and to investigate BMI differences in response to memory, reasoning, and speed of processing training in older adults.

Methods—This is a secondary analysis of the multisite, randomized trial Advanced Cognitive Training for Independent and Vital Elderly. There were 701 older adults with normal weight, 1,081 with overweight, and 902 with obesity (mean age 73.6) randomized to memory training, reasoning training, speed of processing training, or no-training control group. Participants completed memory, reasoning, and speed of processing tests. Baseline sociodemographic, health, and chronic disease measures were included as covariates in analyses.

Results—The 10-year trajectories of memory, reasoning, or speed of processing performance did not differ by BMI status among the participants randomized to the untrained control arm. The training effect on the reasoning and speed of processing outcomes did not differ by BMI status. The training effect on the memory outcome in participants with a BMI indicating obesity, however, was just 38% of that observed in participants with normal-weight BMI.

Conclusions—These analyses of data from the largest trial of cognitive training ever conducted suggest that older adults with obesity may be less responsive to memory training.

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Introduction

Obesity in middle age is associated with higher rates of many chronic diseases (1) and is a substantial risk factor for dementia in late life (2). Data from the Swedish Twin Registry, for example, have shown that midlife obesity defined as body mass index (BMI) of 30 kg/m² or greater at around age 43 years was associated with a 3.9 greater odds of dementia approximately 30 years later (3).

Adults with obesity have elevated levels of circulating proinflammatory cytokines, and there is growing evidence that, over time, systemic inflammation leads to changes in brain structure and function (4,5). Despite this evidence, published studies are somewhat inconsistent regarding the relationship between obesity and cognitive function in older adults (6,7). Many of these studies, however, have had to rely upon just a one-time measure of cognitive function (e.g., Refs. 8 to 11). Few studies have been able to explore whether change in cognitive function over time is associated with obesity, and perhaps no study has investigated whether obesity modifies interventions designed to improve cognitive function in older adults.

Cognitive activity or training is an evidence-based intervention for improving cognitive function. A recent analysis found that self-reported frequency of cognitive activity in adulthood was positively associated with cognitive function independent of age, neuropathology, or years of education (12). The authors concluded that “more frequent cognitive activity can counterbalance the cognitive loss associated with neuropathology” (12). Moreover, the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) randomized controlled trial (13) and others (14,15) have shown that short-term, targeted cognitive training improved cognitive function in older adults ($d = 0.25$ – 1.46). More importantly, emerging evidence indicates that cognitive training may reduce 10-year dementia incidence (16).

Given the high significance of both obesity and cognitive dysfunction to public health and the growing evidence of a link between obesity status and brain function, we evaluated whether obesity was associated with cognitive change in the participants of the ACTIVE randomized controlled trial. The ACTIVE study enrolled 2,802 cognitively normal adults residing in communities and aged 65 years and older who were randomized to one of three cognitive training interventions or to a no-contact control arm. Using the longitudinal data from ACTIVE, we examined 10-year trajectories of cognitive function by BMI class among those randomized to the no-contact control arm. In addition, we investigated whether older adults with normal weight, overweight, and obesity responded differently to cognitive training.

Methods

Data source and study sample

ACTIVE was a multisite, randomized, controlled clinical trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00298558) identifier NCT00298558) (17,18). Recruitment occurred in six metropolitan areas using a variety of sampling strategies. Adults residing in communities and aged 65 years and older were

eligible. Persons were excluded if they had significant cognitive dysfunction (score <23 on the Mini-mental State Examination, MMSE) (19); functional impairment (dependency or regular assistance in activities of daily living on Minimum Data Set Home Care) (20); self-reported diagnoses of Alzheimer's disease (AD), stroke within the past 12 months, or certain cancers; current chemotherapy or radiation therapy; or poor vision, hearing, or communicative ability that would have interfered with the interventions or outcome assessments. Enrollment resulted in a sample of 2,802 individuals (average age 74 years, average education 13 years, 74% white and 26% African-American, and 76% women). Details of randomization and follow-up can be seen in the CONSORT diagram in Figure 1. Eligible participants were randomly assigned to one of three treatment arms (memory, reasoning, or speed training) or a no-contact control group. Screening and baseline assessment took place before randomization. Outcome assessments were conducted immediately following and 1, 2, 3, 5, and 10 years after the intervention. Study procedures were approved by the institutional review boards at the collaborating institutions, and all subjects gave informed consent to participate.

ACTIVE training focused on memory, reasoning, and speed of processing because prior research indicated these abilities show early age-related decline and are related to activities of daily living. Interventions were conducted in small groups in 10-, 60-, and 75-min sessions over 5 to 6 weeks. Memory training focused on improving verbal episodic memory through instruction and practice in strategy use. Reasoning training focused on improving the ability to solve problems that contained a serial pattern. Speed training focused on visual search and the ability to process increasingly more information presented in successively shorter inspection times.

Eligibility and demographic data (age, gender, race, education, and marital status) were gathered in telephone and in-person screenings. Health history (self-report of type 2 diabetes, myocardial infarction, angina, congestive heart failure, stroke, hypertension, high cholesterol, and current alcohol use), physical function status (Short-Form 36) (21), MMSE (19), and cognitive measures (see below) were gathered via in-person examinations in individual and small-group formats. Depressive symptoms were measured with a 12-item version of the Center for Epidemiologic Studies-Depression scale (22) via self-report questionnaire at baseline.

Obesity was determined from BMI (in kg/m^2) computed from measured height and weight data obtained at baseline. We created normal (18.5–24.9), overweight (25–29.9), and obesity (> 30) classes based on World Health Organization criteria (23). There were a limited number of underweight respondents ($n = 30$) and respondents with missing BMI ($n = 88$). These persons were excluded from the analyses.

Cognitive outcomes

Cognitive outcomes include four cognitive performance measures used in prior investigations of ACTIVE data (9). These measures of basic mental ability were gathered at each occasion of measurement (baseline, immediate post-training, 1-year, 2-year, 3-year, 5-year, and 10-year follow-up). First, memory ability was measured using the Hopkins Verbal Learning Test (total of the three learning trials) (24), Rey Auditory-Verbal Learning Test

(total of the five learning trials) (25), and River-mead Behavioral Memory Test (immediate recall) (26). Second, reasoning ability was measured using letter series (total correct) (27), letter sets (total correct) (28), and word series (total correct) (29). Third, speed of processing ability was measured using three tasks of Useful Field of View (UFOV) (30) and the Digit Symbol Substitution (DSS) test. Scores of each test were transformed using the Blom transformation (31,32), and the composite scores were created by averaging the individual Blom-transformed test scores. The Blom transformation was used to standardize the individual tests in each cognitive domain to have equal weights on the composite score and to reduce the skewness in the measures. In addition to the main analysis where Blom-transformed cognitive outcomes were used, a sensitivity analysis was carried out using cognitive outcomes calculated without using Blom transformation. A nearly identical pattern of findings was obtained. The UFOV cognitive outcome measure was scored based on the presentation time needed to correctly perform the task 75% of the time; a higher score indicates poorer cognitive performance. For memory and reasoning composite scores and the DSS, a higher score indicates better cognitive performance.

Statistical analysis

We first present descriptive data for each of the covariates and cognitive measures by BMI class. Continuous variables are summarized using means and standard deviations. Differences across the three BMI classes were evaluated using the nonparametric Kruskal-Wallis test. Categorical variables are presented using frequencies and proportions. Their association with BMI class was assessed using the Pearson χ^2 test.

To evaluate whether the patterns of cognitive performance over time differed by BMI class among the control group respondents, we used a repeated measures mixed-effects model. The dependent variables were the Blom-transformed cognitive outcomes at baseline, immediate post-test, and 1, 2, 3, 5, and 10 years. Fixed effects included time (treated as a categorical variable to allow a nonlinear longitudinal pattern), BMI class, and an interaction between time and BMI class. A significant time by BMI class interaction indicates a difference in the longitudinal patterns of cognitive performance across the BMI classes. Fixed effects also included the baseline covariates.

Finally, we investigated whether participants in the three BMI classes responded differently to cognitive training. We used a repeated measures mixed-effects model to investigate baseline, post-test, and 1-year outcomes. Fixed effects of the model included time (treated as a categorical variable), BMI class, training group (memory, reasoning, speed, and control), and all of the two-way and three-way interaction terms between these three variables. Since prior research has shown that cognitive training only improves the targeted cognitive ability, we only evaluated the difference in the cognitive outcome targeted by the training. That is, we only evaluated the memory training effect on memory outcome, reasoning training effect on reasoning outcome, and speed training effect on UFOV and DSS. The net training effects immediately post-training and at 1 year were defined as the mean improvement from baseline for subjects in a training arm relative to the mean improvement for subjects in the control arm and were estimated based on the mixed-effects model. Following prior research of the ACTIVE study, we presented results as effect sizes, defined as the net training effect

divided by the intra-subject standard deviation, so that different cognitive outcomes could be compared. Baseline covariates included in the models to obtain adjusted training effects were age, female sex, minority race, married, years of education, current smoker, alcohol use, Short-Form 36 physical functioning, Center for Epidemiologic Studies-Depression scale score, hypertension, type 2 diabetes, stroke, congestive heart failure, ischemic heart disease, and high cholesterol.

A sensitivity analysis that included MMSE score and visual acuity as additional covariates resulted in *P* values essentially the same as those reported below. Further sensitivity analyses investigated change in BMI to 2-, 3-, 5-, and 10-year follow-up. Subjects with normal weight at baseline had relatively stable BMI during the study period. Subjects who were overweight at baseline showed an average BMI decline of 0.07 per year (95% CI: 0.03–0.1) while subjects with obesity at baseline showed an average decline of 0.22 per year (95% CI: 0.18–0.26). Similar to the main results shown in Figure 2 below, there were no differences in cognitive function across BMI classes at specific follow-up visits. Attrition, whether by death, study withdrawal, or family refusal, did not differ by BMI class at 1 year. By 10-year follow-up, death had occurred in 24.5% of subjects with normal weight versus 20.5% of subjects who were overweight or had obesity. This difference was not statistically significant (*P* = 0.156). All analyses were conducted using SAS 9.3 (SAS Institute Inc, Cary, NC).

Results

Baseline data are shown in Table 1 by BMI class for the full sample. At baseline, the subgroup with obesity was younger, had fewer mean years of education, was more likely female, minority, and married, was less likely to smoke or drink alcohol, and had lower physical function, greater depressive symptoms, and a higher prevalence of hypertension, diabetes, ischemic heart disease, and high cholesterol. The group classified as overweight was more similar to the normal-weight group in terms of demographic characteristics but more similar to the group with obesity in disease status. Baseline cognitive scores did not differ by BMI class with the exception that older adults who were overweight and had obesity had *better* UFOV scores compared with those with normal weight. To reiterate, normal cognition was required to be enrolled in ACTIVE.

There were 671 control group participants included in the analysis of 10-year change. These participants are embedded within the numbers shown in Table 1. Prior publications have shown that the control group participants did not differ from other arms at baseline (13). We show in Figure 2 the 10-year change for each of the cognitive outcomes—memory composite (panel A), reasoning composite (panel B), UFOV (panel C), and DSS (panel D)—adjusted for the covariates. As prior reports from ACTIVE have shown, the control arm participants showed improvements in the early follow-up period across all four cognitive measures. This was followed by considerable decline in the later years for each of the four outcomes. In neither the adjusted nor unadjusted models was there a statistically significant difference in change over the 10-year follow-up period by BMI class. This was true for all four cognitive measures.

Turning to weight class differences in responses to cognitive training, Figure 3 shows the effect of memory training on memory composite (panel A), reasoning training on reasoning composite (panel B), and speed of processing training on UFOV (panel C), and DSS (panel D) scores. The panels show the adjusted differences between groups immediately post-training and at 1 year. In the case of memory training, older adults with obesity had a statistically significant lower training effect on memory composite score compared with adults with normal weight at post-training that carried through to 1 year. This was true in both the unadjusted ($P=0.023$) and adjusted ($P=0.006$) models. As shown in Figure 3B, reasoning training had a significant training effect at both post-training and 1 year. However, the training effect did not differ for older adults with normal weight, overweight, or obesity. Similarly, the significant training effect of the speed of processing training on the UFOV outcome did not differ by BMI class. Speed of processing training did not have a significant training effect on the DSS outcome, nor did it have a different training effect on DSS by BMI class.

Discussion

We investigated trajectories of cognitive performance in older adults with normal weight, overweight, and obesity who received no cognitive training (i.e., control arm), and we compared response to training in those who received either memory, reasoning, or speed of processing training relative to those in the control arm. In this sample, which excluded those who had cognitive impairment at baseline, there were no significant differences in 10-year trajectories of cognitive performance by BMI class. In addition, we did not discover any differences in effect sizes across BMI classes for reasoning or speed of processing training. We did, however, observe differences by BMI class in the effect size of memory training on memory performance at post-training and 1 year. These differences were rather large. In fact, the effect size for the participants with obesity was 0.38 that observed in the participants with normal weight.

Epidemiological studies have generally shown BMI to be associated with cognitive decline and dementia but these studies have included older adults with and without cognitive impairment at baseline or have investigated BMI in middle age for its effects on late life cognitive outcomes (6,7). A prior investigation using the baseline data of ACTIVE found no association between BMI and baseline cognitive performance (9). But, as noted, older adults with cognitive impairment were not eligible to participate in the ACTIVE study. Even so, we were surprised to find no BMI class differences in the 10-year trajectories of cognitive performance within the control arm. The obesity paradox refers to the often reported finding that obesity is protective of mortality in later life (33). Selective survival and physiological reserve are two explanations for this paradox. It is likely that older adults with obesity with no cognitive impairment are a select subgroup that does not represent all older adults with obesity. Repeat assessments in representative sample of older adults with obesity may reveal different and important findings.

This is the first report of response to cognitive training by BMI class. The largest effect sizes within the ACTIVE study were from speed of processing training including evidence of reduced 10-year dementia incidence (16). In this domain, we did not find any BMI

differences in response to speed training. Similarly, response to reasoning training does not appear to vary by BMI. Given the high prevalence of obesity in the older adult population, this is good news for those disseminating or participating in cognitive training. The obesity group's lower response to memory training warrants some concern. The overweight group also showed a trend of reduced response to memory training suggesting the possibility of a dose-response relationship between BMI and memory training. If confirmed, additional investigation into the source of this reduced response and how best to address it would be important work given that 71% of the older adult population is either overweight or has obesity (34).

These memory training results may be indicative of a relation of obesity to impaired neural plasticity. There is strong evidence of an effect of obesity on inflammation and evidence of an effect of inflammation on cognitive function. The hypothalamus, in particular, is affected by obesity-related systemic inflammation. In a review, Miller and Spencer (2014) noted that the hypothalamus is responsible for a wide range of physiological functions that are inter-related with attention, learning, and memory (35). Dysregulation of the hypothalamic-pituitary-adrenal axis, for example, leads to chronic hypersecretion of glucocorticoids, which adversely affects the hippocampus and is associated with memory impairments (35).

Response to memory training may be a more sensitive marker of the functioning of the neural substrate than overall levels of performance. If so, it may present another linkage between obesity and age-related neurodegeneration including AD. Using data from existing meta-analyses, Norton et al. estimated that the population-attributable risk of obesity to AD in the United States is more than 7% (2). Given this impact, further exploration of the linkage between obesity and systemic and central inflammatory and trophic responses to cognitive and physical training seems warranted.

The ACTIVE study was a large and well-thought-out trial, but it was not designed to investigate the role of obesity in cognition or cognitive responses to cognitive training. Our secondary analysis relies on statistical modeling to adjust for differences in baseline characteristics between the ACTIVE participants with obesity and the participants with normal weight. The study was not powered to investigate differences by obesity either. Future research that randomized adults and older adults with obesity to cognitive training conditions would be valuable. Furthermore, research that included a more representative sample of adults with obesity (e.g., those with some existing cognitive impairment) would be valuable in determining the generalizability of the training effects. With these limitations in mind, our findings hold both good and concerning news. Some forms of cognitive training may have similar effects regardless of an older adult's obesity status while others may not.

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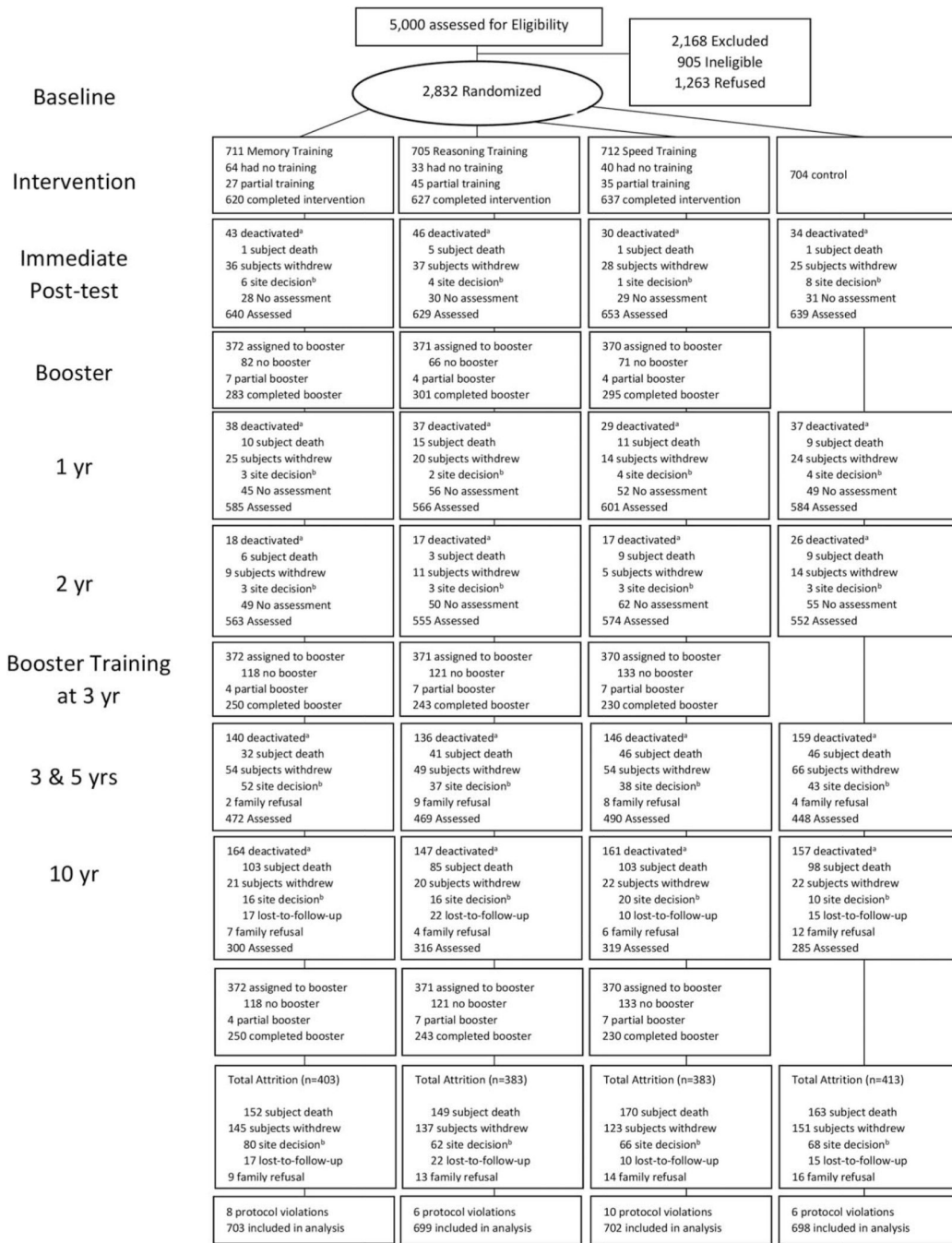


Figure 1. CONSORT diagram of 10-year effects of the Advanced Cognitive Training for Independent and Vital Elderly trial on cognition and everyday functioning in older adults.

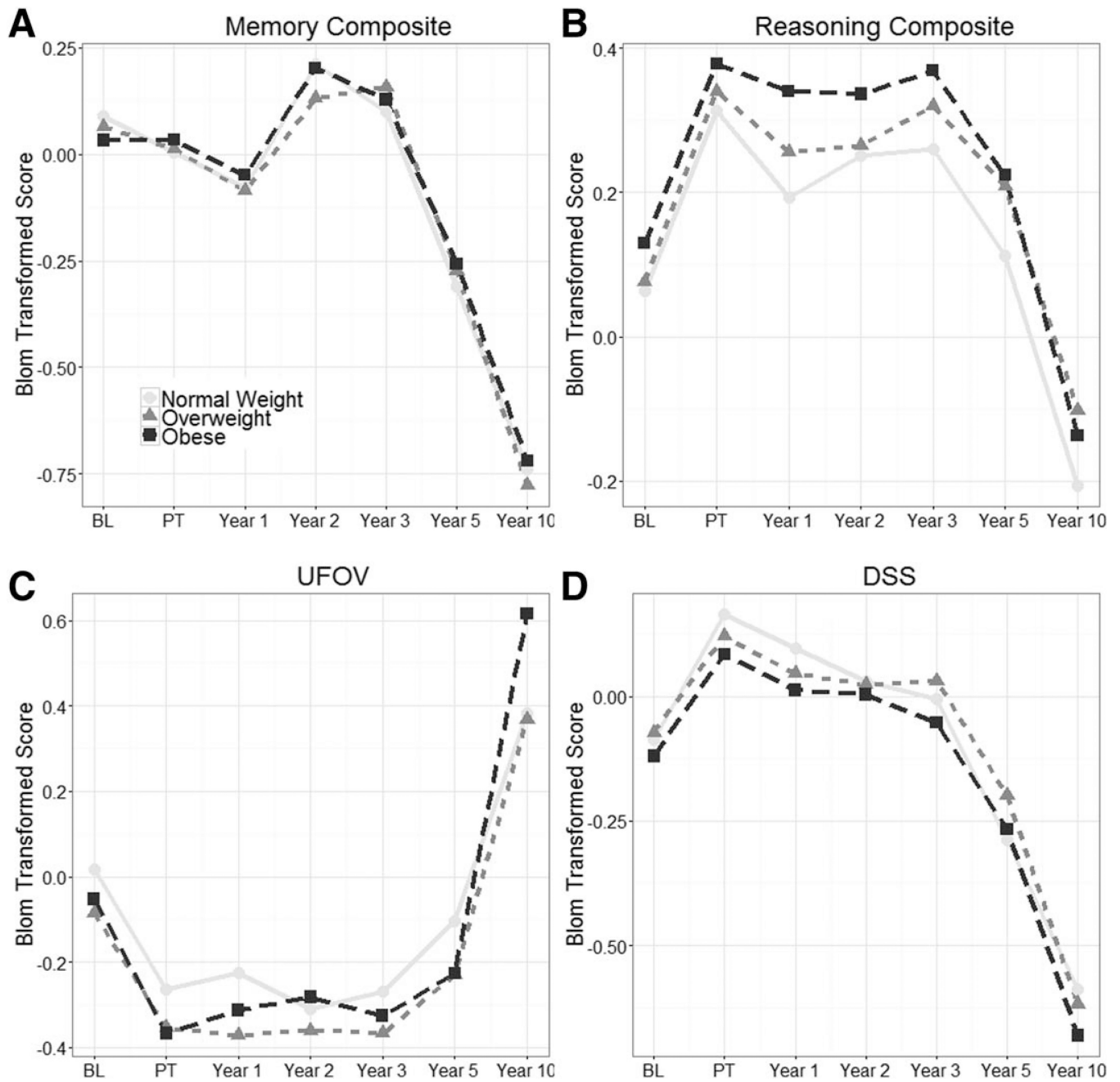


Figure 2. Ten-year trajectories for memory, reasoning, and speed of processing in control arm participants by normal ($n = 177$), overweight ($n = 277$), and obesity ($n = 217$) body mass index classes.

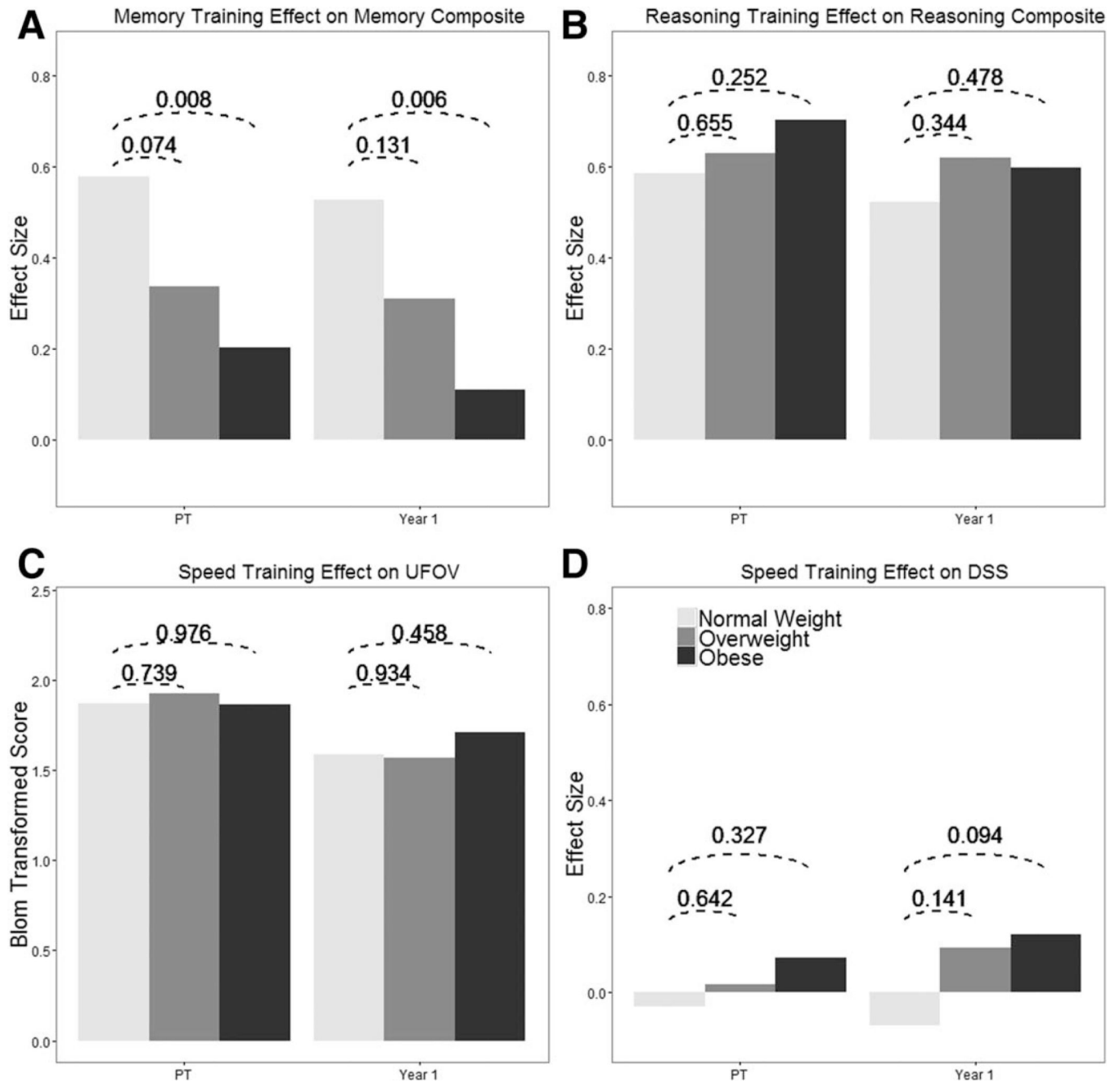


Figure 3. Adjusted effect sizes of memory, reasoning, and speed of processing training on memory, reasoning, and speed of processing outcomes by normal, overweight, and obesity body mass index classes (P values for overweight and obesity compared with normal shown inside the panels).

TABLE 1

Baseline covariate and cognition values by BMI class

Covariates	Normal (N = 701)	Overweight (n = 1,081)	Obesity (N = 902)	P	Overweight vs. normal	Obesity vs. normal	Obesity vs. overweight
Age, mean (SD)	74.6 (6.3)	73.9 (5.8)	72.2 (5.1)	<0.001	0.119	<0.001	<0.001
Female, n (%)	528 (75.3)	765 (70.8)	745 (82.6)	<0.001	0.106	0.001	<0.001
Minority race, n (%)	125 (17.8)	294 (27.2)	309 (34.3)	<0.001	<0.001	<0.001	0.002
Married, n (%)	262 (37.4)	425 (39.4)	289 (32)	0.003	1	0.073	0.002
Years of education, mean (SD)	14.1 (2.8)	13.6 (2.7)	13 (2.6)	<0.001	<0.001	<0.001	<0.001
Current smoker, n (%)	65 (9.3)	88 (8.1)	42 (4.7)	<0.001	1	0.001	0.005
Alcohol consumption, n (%)				<0.001	1	0.001	<0.001
Nondrinker	293 (42)	437 (40.6)	460 (51.1)				
Light drinker	350 (50.1)	568 (52.8)	397 (44.1)				
Heavy drinker	55 (7.9)	71 (6.6)	43 (4.8)				
SF36 physical function, mean (SD)	75.9 (21.3)	72.5 (22.3)	60.8 (24.4)	<0.001	0.002	<0.001	<0.001
CES-D scale, mean (SD)	5 (5.1)	4.9 (4.9)	5.6 (5.4)	0.011	1	0.059	0.025
Disease history, n (%)							
Hypertension	273 (39.2)	544 (50.7)	548 (61)	<0.001	<0.001	<0.001	<0.001
Type 2 diabetes	44 (6.3)	121 (11.2)	175 (19.4)	<0.001	0.001	<0.001	<0.001
Stroke	34 (4.9)	76 (7.1)	70 (7.8)	0.062			
Congestive heart failure	31 (4.5)	45 (4.2)	52 (5.8)	0.214			
Ischemic heart disease	85 (12.3)	163 (15.2)	155 (17.3)	0.021	0.242	0.016	0.626
Myocardial infarction	64 (9.2)	125 (11.6)	105 (11.7)	0.205			
High cholesterol	278 (40.7)	488 (45.8)	427 (48.1)	0.013	0.106	0.011	0.954
Cognitive outcomes							
Memory composite, Blom transformed, mean (SD)	0 (0.9)	0 (0.8)	0 (0.8)	0.473			
Reasoning composite, Blom transformed, mean (SD)	0 (0.9)	0 (0.9)	0 (0.9)	0.306			
Useful field of view composite, Blom transformed, mean (SD)	0.1 (0.8)	0 (0.8)	0 (0.8)	0.004	0.007	0.011	1
Digit symbol substitution, Blom transformed, mean (SD)	-0.1 (1)	-0.1 (0.9)	-0.2 (0.9)	0.368			

Pairwise comparisons were performed for variables significantly different across BMI classes and were adjusted using Bonferroni's approach.

CES-D, Center for Epidemiological Studies Depression; SF36, Short-Form 36; SD, standard deviation.