**Title**: Evaluating the joint impact of physical activity and obesity on cognitive function in adults with Down syndrome

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**Introduction**: Lifetime incidence of Alzheimer’s disease (AD) in adults with Down syndrome (DS) exceeds 90%, with most experiencing cognitive decline by their mid-50s1. Emerging research suggests that dementia-related cognitive decline may be modifiable 2. In adults with and without DS, obesity and low levels of moderate-to-vigorous physical activity (MVPA) have independently been associated with poor cognitive performance 3,4. Previous work indicates that high MVPA might reduce risk type 2 diabetes and cardiovascular disease even in the presence of obesity 5, however this has yet to be investigated in the context of cognition or in DS. The purpose of this analysis was to investigate the joint association of MVPA and obesity on cognition in persons with DS.

**Method**: Seventy-five adults with DS (age 39.1 years; 46.7% female; 54.7% with obesity) participated in the Alzheimer Biomarker Consortium-Down Syndrome (ABC-DS) study and an optional 7-day accelerometer protocol. Cognitive function was assessed using the ABC-DS cognitive battery, which includes the modified Cued Recall Test, Stroop Cat and Dog Test, Dementia Questionnaire for People with Learning Disabilities (DLD), and the Down Syndrome Mental Status Examination (DSMSE). Body mass index (BMI) was used to categorize participants into obesity (BMI ≥30 kg/m²) and no obesity (BMI <30 kg/m²) and median split of MVPA was used to create four groups: No Obesity/High MVPA, No Obesity/Low MVPA, Obesity/High MVPA, and Obesity/Low MVPA. Generalized linear models adjusted for age, cognitive impairment, gender, premorbid intellectual disability, and APOE-4 status were used to compare cognitive scores across groups.

**Results**: Scores on each assessment by group are presented in table 1.

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| **Table 1.** | **No Obesity/High MVPA (n=19)** | **No Obesity/Low MVPA (n=15)** | **Obesity/High MVPA (n=19)** | **Obesity/Low MVPA (n=22)** |
| Modified Cued Recall Total Score | 30.5±7.8 | 26.0±11.3 | 32.6±8.2 | 28.8±9.0 |
| Cued Recall Intrusions | 3.2±4.8 | 5.5±6.5 | 1.1±3.7 | 2.3±4.2 |
| DLD Sum of Cognitive Score | 3.3±4.5 | 9.5±10.4 | 2.6±3.6 | 7.1±7.7 |
| DLD Sum of Social Score | 3.6±3.5 | 6.9±5.6 | 3.2±3.6 | 7.3±6.5 |
| Cat and Dog Task Errors | 2.4±4.0 | 4.3±9.6 | 1.1±3.7 | 2.3±4.2 |
| DSMSE | 62.5±16.0 | 56.9±16.0 | 66.5±14.4 | 59.9±13.8 |

The Obesity/High PA group has fewer Cued Recall Intrusions than the No Obesity/Low MVPA group (*p*=0.018). DLD Cognitive and Social Scores were better in both High MVPA groups when compared with each Low MVPA group (all *p*<0.05), with low scores indicating better outcomes. Obesity/High MVPA group had fewer Cat Dog Task Switching errors compared with the Obesity/Low MVPA group (*p*=0.004). There were no differences in the DSMSE or modified Cued Recall total score between groups.

**Discussion:** Physical activity may have a stronger influence than obesity on cognitive function related to AD in individuals with DS. Future research should prioritize physical activity as a potential intervention to prevent or delay AD in this population.

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