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RESEARCH ARTICLE

Examination of metabolic syndrome in Down syndrome and association with dementia

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Abstract

INTRODUCTION: In the neurotypical population, metabolic syndrome (MetS) is associated with Alzheimer's disease (AD). However, this has not been well studied in adults with Down syndrome (DS).

METHODS: The prevalence of MetS and its subcomponents was examined in adults with DS using the Alzheimer Biomarkers Consortium – Down Syndrome data (ABC-DS, $N = 389$). Logistic regression was used to examine the relationship between MetS and AD at baseline visits.

RESULTS: Prevalence of MetS, diabetes, hypertension, and hyperlipidemia was low with DS, even though the prevalence of obesity was elevated. Obesity was positively associated with AD in adults with DS (odds ratio = 2.79, $P = 0.021$), but there was no association between MetS and AD in DS.

DISCUSSION: The prevalence of MetS was low in adults with DS. Although MetS was not associated with AD, obesity, a subcomponent of MetS, was associated with AD in adults with DS. This may inform targeted treatments in the future.

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KEYWORDS
Alzheimer's disease, dementia, diabetes, Down syndrome, hyperlipidemia, hypertension, metabolic syndrome, obesity

Highlights

- There was a low prevalence of metabolic syndrome (MetS) in adults with Down syndrome (DS).
- Overall MetS was not associated with dementia in adults with DS.
- Obesity, a subcomponent of MetS, had a high prevalence in adults with DS.
- Obesity was positively associated with dementia in adults with DS.

1 | INTRODUCTION

Metabolic syndrome (MetS) is defined by a combination of subcomponents including elevated fasting glucose, elevated triglycerides, reduced high-density lipoprotein-cholesterol (HDL-C), elevated blood pressure, and elevated waist circumference.[1] In the neurotypical population, the co-existence of MetS subcomponents is more frequent than would be expected by chance, and the combined effect of these co-occurring signs of metabolic dysfunction adds substantial cardiovascular risk beyond that of individual risk factors.[2] Although MetS is a known risk factor for clinical Alzheimer's disease (AD) in the neurotypical population,[3,4] the relationship between MetS and AD in individuals with Down syndrome (DS) has not yet been studied in a sufficiently large cohort.

Adults with DS are at a high risk of developing Down syndrome–associated Alzheimer's disease (DS-AD), thought to be due to triplication of chromosome 21, including the amyloid precursor protein (*APP*) gene, which leads to overproduction of amyloid beta peptides.[5,6] For this high-risk population, the relationship between various risk factors and DS-AD is less than clear. To date, many studies have investigated general cardiovascular risk in DS, but a limited number of studies have investigated the prevalence of MetS in DS. Some prior studies report higher prevalence of MetS in adults with DS,[7,8] while others report the opposite.[9,10] Luchsinger and colleagues examined metabolic correlates of obesity in adults with DS and found a relative lack of metabolic risk factors, with the exception of high leptin levels.[11] Prior studies that investigated the prevalence of MetS in adults with DS had relatively small sample sizes, ranging from 48 to 139 individuals.[12,13] It is important to note that adults with DS exhibit a unique set of phenotypes that are less commonly observed in the neurotypical population. Despite having a higher prevalence of obesity, they tend to have relatively lower prevalence of type 2 diabetes and cardiovascular risk factors (e.g., hypertension and atherosclerosis).[5,14,15] This set of distinctive and unusual phenotypes in adults with DS offers a unique opportunity to characterize the relation between subcomponents of MetS and DS-AD.

We examined one of the largest cross-sectional studies of adults with DS ($N = 389$) to understand the relationship between MetS (and its subcomponents) and DS-AD. Specifically, we investigated whether (1) the prevalence of MetS in a large cohort of adults with DS is elevated or not in comparison to published data from the neurotypical population, given their high prevalence of obesity; and (2) the presence of MetS is associated with the presence of DS-AD in adults with DS at baseline visits, given that prior studies in neurotypical adults have shown a positive association between MetS and AD.

2 | METHODS

2.1 | Alzheimer Biomarkers Consortium – Down Syndrome

2.1.1 | Study participants

The Alzheimer Biomarkers Consortium – Down Syndrome (ABC-DS) is a multidisciplinary, multi-site, longitudinal study examining biomarkers of DS-AD in a large cohort of adults with DS, ages 25 years and older ($N = 503$ participants at baseline visit). We downloaded data from the LONI Image & Data Archive database on September 7, 2024. ABC-DS participants were seen at 16-month intervals, at which time they underwent cognitive testing as well as medical and neurological assessments. In addition, blood was collected to provide plasma-based DS-AD biomarkers, and caregivers completed questionnaires regarding DS-AD symptoms, psychological well-being, and daily functioning. For the present study, we used the baseline data to estimate cross-sectionally the prevalence of MetS in a cohort of adults with DS. Because some were missing subcomponent data, we restricted our analysis to 389 ABC-DS study participants who (1) had a baseline visit; (2) had data recorded for all of MetS subcomponents (i.e., hyperlipidemia, hypertension, diabetes, and obesity); and (3) had a valid consensus diagnosis for cognitive status. Full details regarding inclusion and exclusion criteria for the ABC-DS study were described previously along with procedures for consensus diagnosis.[16]

2.1.2 | MetS definition

We used a modified version of the American Heart Association's definition of MetS to identify prevalence of MetS at baseline visit in ABC-DS

given that fasting laboratory data and waist circumference data were not available, and laboratory data at the time of writing has been collected only for a subset of individuals. The American Heart Association defines MetS as having three of the five following: *elevated fasting glucose* greater than or equal to 100 mg/dL (including diabetes); *triglycerides* greater than or equal to 1.69 mmol/L (or on triglyceride treatment); *HDL-C* in men less than 1.03 mmol/L, and in women less than 1.29 mmol/L (or on HDL treatment); *blood pressure* greater than or equal to 130/85 mmHg (or on antihypertensive medication); and *waist circumference* in men greater than or equal to 102 cm, or 88 cm in women.[1] In the current study, we considered a participant as having MetS if the individual had at least three of the four following MetS subcomponents as per medical chart review: health history of diabetes, health history of hyperlipidemia, health history of hypertension, and obesity as determined by body mass index (BMI) greater than or equal to 30 (BMI = weight in kg / height in m^2). Height and weight measurements were taken from physical and neurological exams, which were performed at baseline visit. BMI has a strong correlation with waist circumference [17]; as such, we used BMI as a proxy measure for waist circumference. Conversely, we classified those with two or fewer MetS subcomponents as not having MetS. When we refer to MetS throughout the study, we are referring to MetS and its subcomponents (i.e., hyperlipidemia, hypertension, diabetes, and obesity).

2.1.3 | AD definition

DS-AD was defined based on consensus diagnosis in ABC-DS.[16] Given that DS-AD neuropathology is almost universal in adults with DS by the age of 40 years,[5,6] those with dementia in ABC-DS were most likely to have dementia of the Alzheimer's type, although etiology of dementia was discussed at consensus conferences. Using consensus diagnosis in ABC-DS, participants were classified clinically as cognitively stable (CS), mild cognitive impairment (DS-MCI), DS-AD, or "undetermined" based on review of medical history, neurologic exam findings, informant interviews, and participant performance on testing, independent of biomarker profiles.[16] "Undetermined" indicates that changes in functioning have occurred, but assessment of symptoms of DS-AD is confounded by other factors that might also affect functioning including medical illness or other factors. We classified participants from the CS and DS-MCI groups together as the reference group (those without DS-AD) and those with DS-AD were classified as the risk group. We excluded the participants who were classified as "undetermined" in this analysis ($N = 21$).

2.2 | Statistical analysis

2.2.1 | Descriptive statistics

All statistical analyses were performed using R software, version 4.3.2.[18] We determined the prevalence of MetS in ABC-DS. Baseline demographic characteristics and clinical characteristics are presented.

RESEARCH IN CONTEXT

1. **Systematic review**: Metabolic syndrome (MetS) is a known risk factor for Alzheimer's disease (AD) in the neurotypical population. However, MetS and its association with dementia has not been well studied in adults with Down syndrome (DS), who are known to have high prevalence of obesity and low prevalence of cardiovascular risk factors.
2. **Interpretation**: Our study found a low prevalence of MetS in adults with DS, and no association between overall MetS and dementia. However, obesity, a subcomponent of MetS, was positively associated with dementia.
3. **Future directions**: This cross-sectional study proposes a framework for disparate relationships between each MetS subcomponent and dementia in adults with DS. Future studies will be needed to examine the longitudinal relationships between MetS subcomponents and dementia.

For baseline characteristics, we separated the cohort by consensus diagnosis of dementia (CS, DS-MCI, and DS-AD). We applied a Kruskal–Wallis test for continuous traits to take into account potential non-normality. For categorical traits, we applied a chi-squared test or a Fisher's exact test when a cell had fewer than five subjects. Statistical significance was defined as $p < 0.05$.

2.2.2 | Associations of MetS and baseline characteristics with prevalent DS-AD

To illustrate the effects of age and sex on adiposity, we showed changes in BMI as a function of age at visit, stratified by sex (Figure 1). The figure presents the relationship by locally estimated scatterplot smoothing and 95% confidence bands. This plot identifies critical windows of weight gain or loss, highlighting trends that may impact the relationship between MetS and DS-AD.

We first used a univariate logistic regression analysis to examine the association between age and MetS by dividing age into tertiles (older, middle, and younger) to assess meaningful changes in DS-AD risk due to age. We also used a univariate logistic regression analysis with MetS as the outcome and with sex as the predictor to understand how MetS differs based on baseline demographic characteristics. We created bar graphs (Figures 2 and 3) to show the proportion of individuals with MetS in each age tertile, and the proportion of females and males with MetS, respectively.

We first used univariate logistic regression to examine the relationship between MetS and dementia status by treating dementia status as a binary variable (DS-AD vs. DS-MCI or CS). Subsequently, we used multivariable logistic regression to examine the relationship between

TABLE 1 Baseline characteristics for ABC-DS participants.[a]

Characteristic	Total	CS	DS-MCI	DS-AD	*p*-value
N	389	303	51	35	
Mean age (years) ± SD	42.61 ± 10.13	39.58 ± 8.85	52.90 ± 6.74	53.91 ± 5.99	<0.001*
Range of age: Min-Max	25–81	25–72	40–81	40–67	
Sex					
Female (%)	177 (45.50%)	143 (47.19%)	15 (29.41%)	19 (54.29%)	0.034*
Male (%)	212 (54.5%)	160 (52.8%)	36 (70.6%)	16 (45.7%)	
Racial group					0.393
White	374 (96.1%)	293 (96.7%)	48 (94.1%)	33 (94.3%)	
Non-White	15 (3.9%)	10 (3.3%)	3 (5.9%)	2 (5.7%)	
APOE ε4 alleles (*N*, %)					0.024*
2	6 (1.6%)	5 (1.7%)	1 (2.0%)	0 (0%)	
1	86 (22.9%)	57 (19.5%)	15 (30.6%)	14 (42.4%)	
0	283 (75.5%)	231 (78.8%)	33 (67.4%)	19 (57.6%)	
Mean BMI (kg/m^2) ± SD	31.7 ± 7.4	32.5 ± 7.6	27.4 ± 5.2	30.4 ± 6.2	<0.001*
MetS (*N*, %)					0.869
Present	12 (3.1%)	9 (3.0%)	2 (3.9%)	1 (2.9%)	
Absent	377 (96.9%)	294 (97.0%)	49 (96.1%)	34 (97.1%)	
Hyperlipidemia (*N*, %)					<0.001*
Present	125 (32.1%)	79 (26.1%)	27 (52.9%)	19 (54.3%)	
Absent	264 (67.9%)	224 (73.9%)	24 (47.1%)	16 (45.7%)	
Hypertension (*N*, %)					0.009*
Present	18 (4.6%)	9 (3.0%)	6 (11.8%)	3 (8.6%)	
Absent	371 (95.4%)	294 (97.0%)	45 (88.2%)	32 (91.4%)	
Diabetes (*N*, %)					0.4416
Present	17 (4.4%)	12 (4.0%)	4 (7.8%)	1 (2.9%)	
Absent	372 (95.6%)	291 (96.0%)	47 (92.2%)	34 (97.1%)	
Obesity (*N*, %)					<0.001*
Present	206 (53.0%)	173 (57.1%)	13 (25.5%)	20 (57.1%)	
Absent	183 (47.0%)	130 (42.9%)	38 (74.5%)	15 (42.9%)	

Abbreviations: ABC-DS, Alzheimer Biomarkers Consortium – Down Syndrome; AD, Alzheimer's disease; APOE, apolipoprotein E; BMI, body mass index; CS, cognitively stable; DS, Down syndrome; MCI, mild cognitive impairment; MetS, metabolic syndrome; SD, standard deviation.

[a]For continuous traits, we applied a Kruskal-Wallis test to account for non-normality. For categorical traits, we applied a chi-squared test or a Fisher's exact test when a cell had fewer than five subjects.

*Indicates statistically significant at $p < 0.05$.

MetS and dementia status (DS-AD vs. DS-MCI or CS), while adjusting for baseline characteristics (age, sex, *APOE ε4* carrier status). Age was examined per 5-year increase. We classified participants as carriers (if they had one or two copies) versus non-carriers of *APOE ε4*.

3 | RESULTS

The baseline demographic and clinical characteristics of the ABC-DS cohort are shown in Table 1. The cohort consisted of 389 adults with DS, with a mean age of 42.6 years (age range 25–81 years). As expected, mean age was higher in groups with greater cognitive impairment. The overall cohort was 45.5% female. The proportion of females was lower in the DS-MCI group compared to the CS and DS-AD groups. The majority of study participants (96.1%) were reported to be white. The mean BMI was 31.7 kg/m^2 (BMI range 16.8–69.2 kg/m^2). Mean BMI was lowest in the DS-MCI group. The percentage of *APOE ε4* carriers increased in groups with greater cognitive impairment, as expected. The prevalence of DS-AD in this cohort was 9.0%, MetS overall was 3.2%, hyperlipidemia was 32.1%, hypertension was 4.6%, diabetes was 4.4%, and obesity was 53.0%. MetS prevalence and diabetes prevalence were not significantly different across varying levels of cognitive impairment. Hyperlipidemia and hypertension prevalence increased with greater levels of cognitive impairment. Obesity

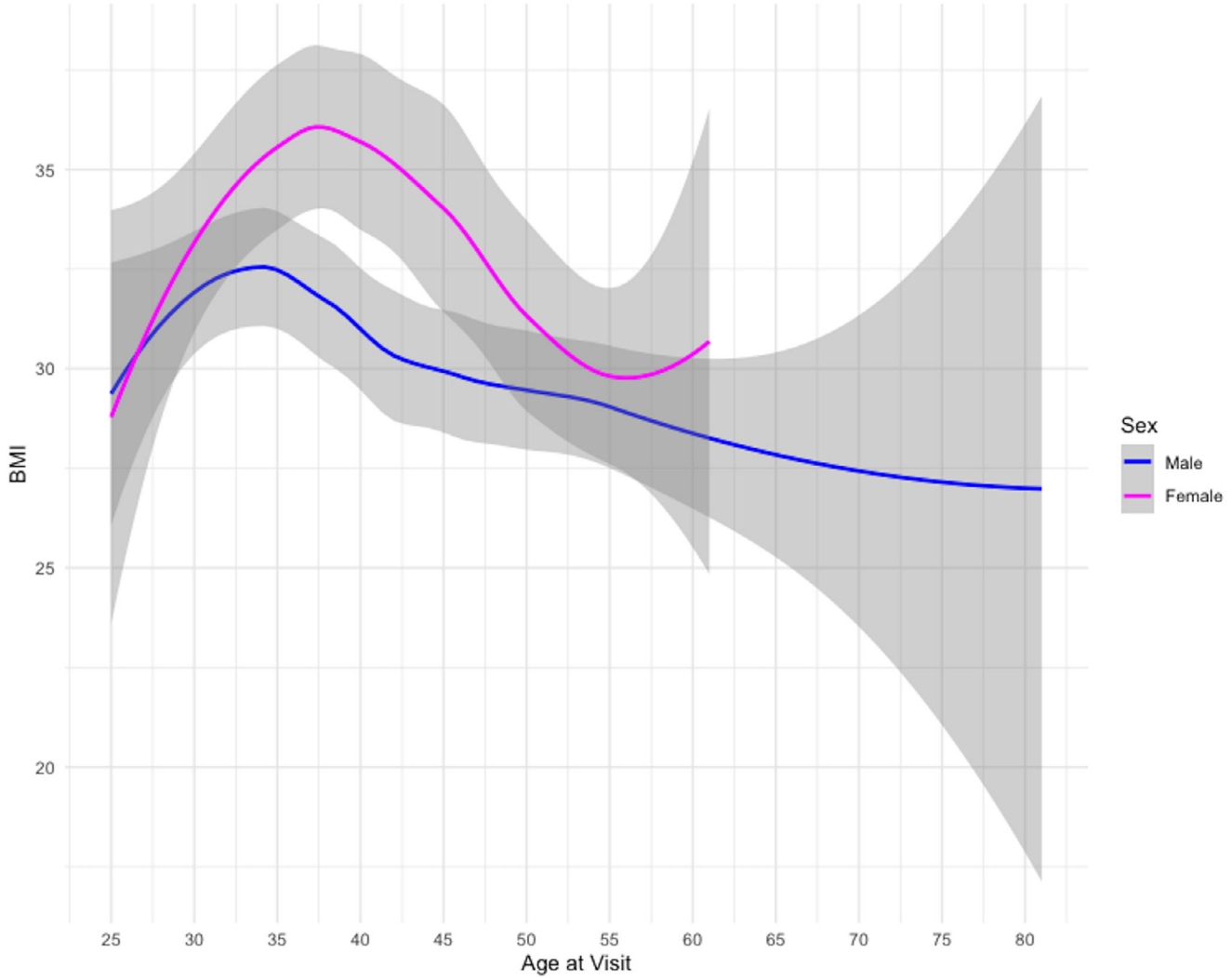

FIGURE 1 Change in BMI by age at visit, stratified by sex. Lines represent average BMI across age at visit among adults with Down syndrome, shown separately for males (blue) and females (pink). Shaded areas indicate 95% confidence intervals. BMI, body mass indes.

prevalence was lower in the DS-MCI group compared to the other two groups.

We then examined the role of age in MetS, since age is a significant risk factor for cognitive performance. Figure 1 shows an inverse U-shaped distribution in body mass index (BMI) by age, stratified by sex. Because adiposity differs by age and sex, this figure pinpoints key periods of weight gain and loss that reveal patterns that may shape the relationship between MetS and DS-AD. In both males and females, BMI initially rises with age with its peaks being between age 35 and 40 for both females and males. Subsequently, the curves for BMI in both females and males decrease in an inverse U-shaped fashion. However, the peak in mean BMI for females had a sharper increase and slightly later peak compared to the peak in mean BMI for males and continued to remain elevated for longer compared to males.

Table 2 presents the association of MetS with age group in tertiles using univariate logistic regression analysis to detect threshold effects such as a step change in MetS among various age groups (older age was considered 48–81 years, middle age 37–47 years, and younger age 25–36 years). MetS and all subcomponents differed significantly based on age tertile, as expected.

Specifically, as shown in Figure 2, MetS prevalence increased with higher age group, with the younger age group having no individuals with MetS. The prevalence of hyperlipidemia and hypertension increased with higher age group. Diabetes prevalence was similar in middle and older age groups; however, the younger age group had no individuals with diabetes. Obesity prevalence, on the other hand, decreased with higher age group. When the effects of sex on MetS were examined using logistic regression, neither MetS nor its subcomponents differed significantly by sex with the exception of obesity, which was elevated significantly for female sex, as presented in Table 2. Figure 3 shows a graph of MetS risk factors by sex, indicating that obesity is present in a higher proportion of females than males; however, other MetS subcomponents and MetS overall are present in similar proportions in both females and males.

Given the disparate relationships of MetS subcomponents with age (with obesity having an early peak in young age followed by a steep

TABLE 2 Effects of age and sex on MetS and its subcomponents.

Parameter	MetS	Hyperlipidemia	Hypertension	Diabetes	Obesity
Age tertile (older, middle, younger)					
OR	3.05	2.85	4.67	2.40	0.70
p	0.014*	<0.001*	<0.001*	0.012*	0.005*
Sex (M = 0, F = 1)					
OR	0.59	0.96	0.58	0.48	1.67
p	0.395	0.848	0.294	0.182	0.013*

Abbreviations: MetS, metabolic syndrome; OR, odds ratio.
*Indicates statistically significant at $p < 0.05$.

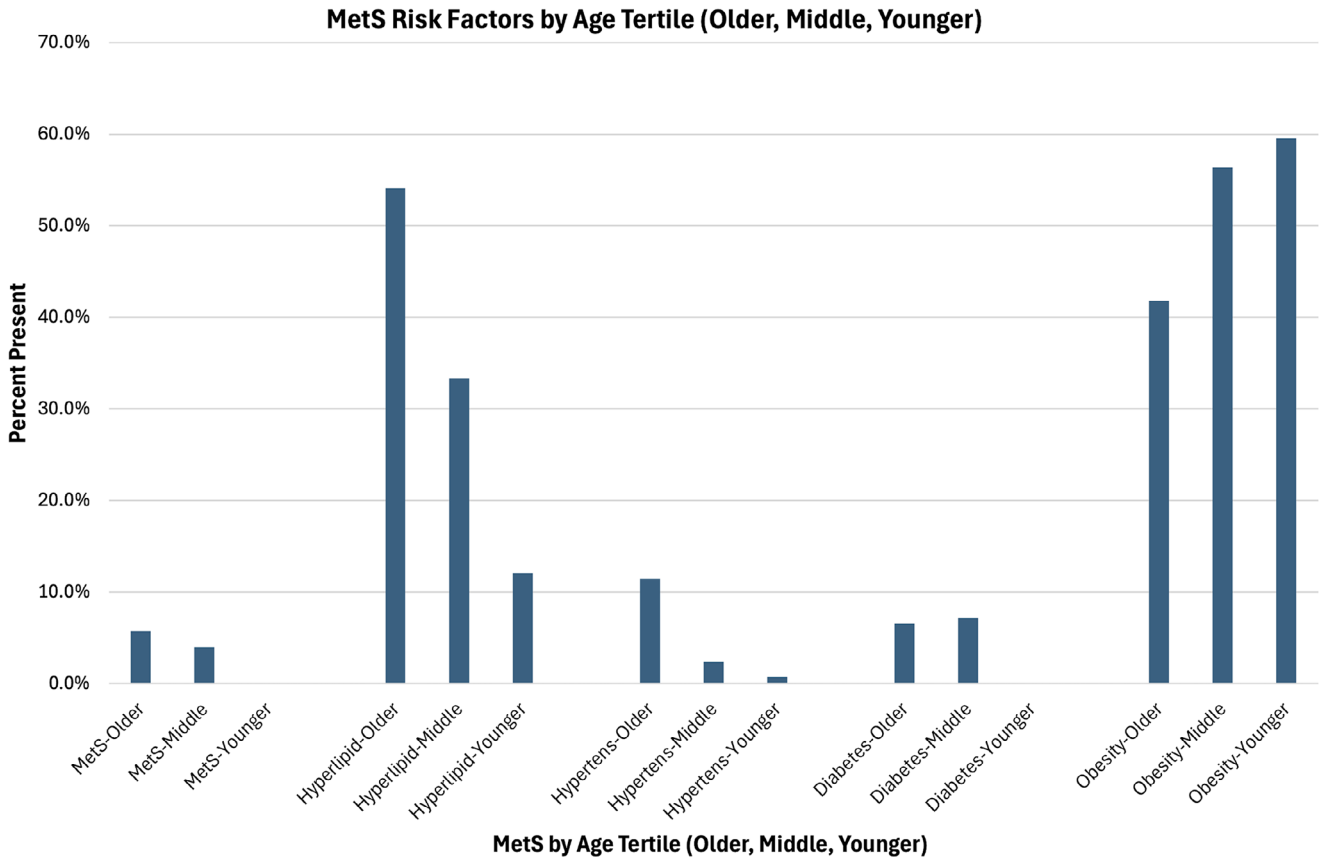

FIGURE 2 MetS risk factors by age tertile (older, middle, younger). Bars represent the percentage of individuals with each MetS risk factor, including overall MetS, hyperlipidemia, hypertension, diabetes, and obesity, stratified by age tertile (older, middle, and younger). Older age was considered 48–81 years, middle age 37–47 years, and younger age 25–36 years. MetS, metabolic syndrome.

decline, whereas hyperlipidemia and hypertension increase with age), we examined which MetS subcomponents were associated with AD risk. The relations between DS-AD and MetS are shown in Table 3. In the univariate model, hyperlipidemia and hypertension were associated with increased odds of DS-AD; however, only hyperlipidemia was significant at $p < 0.05$. A subsequent multivariable logistic regression analysis revealed that the significant association observed for hyperlipidemia was no longer significant when age was included in the model along with sex and *APOE ε4* carrier status. Of MetS and its subcomponents, obesity was the only subcomponent that was significantly associated with DS-AD risk in the multivariable model, in which obesity was associated with a 2.8-fold increase in DS-AD risk.

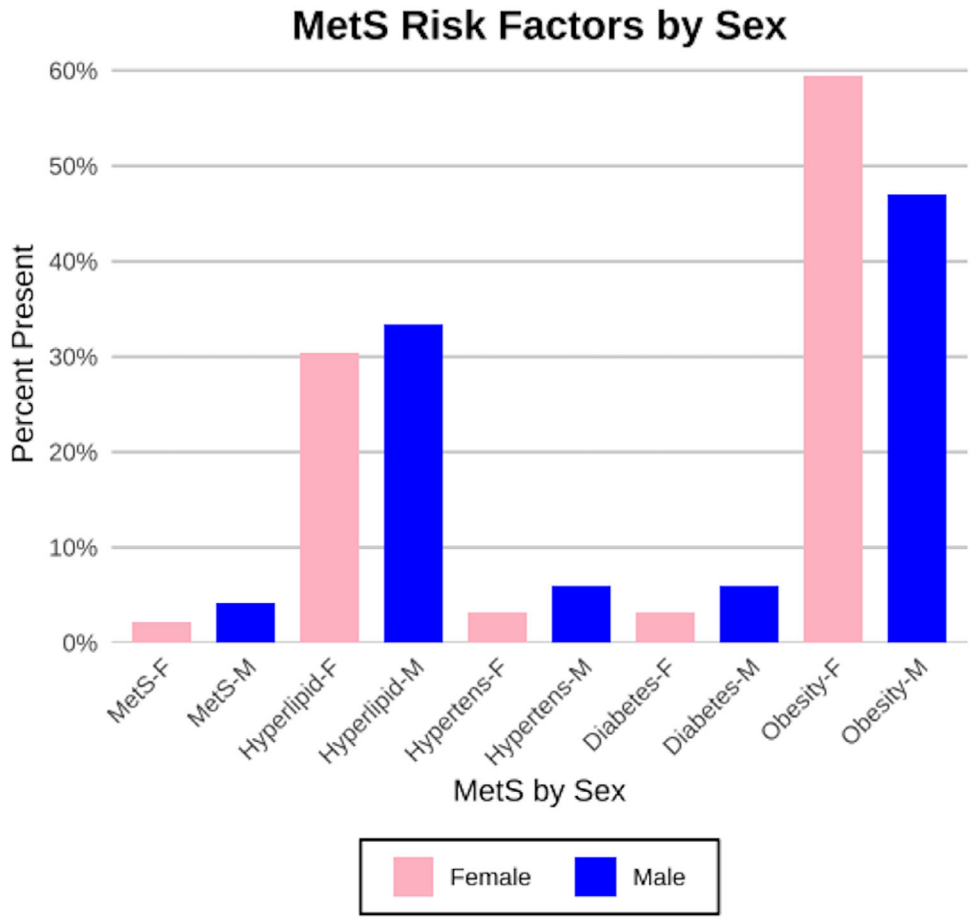

FIGURE 3 MetS risk factors by sex. Bars represent the percentage of individuals with each MetS risk factor, including overall MetS, hyperlipidemia, hypertension, diabetes, and obesity, shown separately for females (pink) and males (blue). MetS, metabolic syndrome.

TABLE 3 Effects of MetS and its subcomponents on DS-AD.[a]

	MetS counts			Univariate		Multivariable	
Parameter	Total (*N*)	Present (*N*)	Present (%)	OR	*p*-value	OR	*p*-value
MetS	389	12	3.1%	0.92	0.935	0.67	0.721
DS-AD	35	1	2.9%				
CS and DS-MCI	354	11	3.1%				
Hyperlipidemia	389	125	32.1%	2.78	0.004*	1.02	0.966
DS-AD	35	19	54.3%				
CS and DS-MCI	354	106	29.9%				
Hypertension	389	18	4.6%	2.12	0.255	0.36	0.273
DS-AD	35	3	8.6%				
CS and DS-MCI	354	15	4.2%				
Diabetes	389	17	4.4%	0.62	0.649	0.51	0.539
DS-AD	35	1	2.9%				
CS and DS-MCI	354	16	4.5%				
Obesity	389	206	53.0%	1.20	0.603	2.79	0.021*
DS-AD	35	20	57.1%				

(Continues)

TABLE 3 (Continued)

	MetS counts			Univariate		Multivariable	
Parameter	Total (*N*)	Present (*N*)	Present (%)	OR	*p*-value	OR	*p*-value
CS and DS-MCI	354	186	52.5%				

Abbreviations: APOE, apolipoprotein E; CS, cognitively stable; DS, Down Syndrome; DS-AD, Down syndrome–associated Alzheimer's disease; MCI, mild cognitive impairment; MetS, metabolic syndrome.

[a]The multivariable model includes MetS (or its subcomponents) as the predictor and DS-AD diagnosis as the outcome, adjusting for age (per 5-year increase), sex, and *APOE ε4* carrier status.

*Indicates statistically significant at $p < 0.05$.

4 | DISCUSSION

This study has shown that adults with DS have low prevalence of MetS at 3.1%, even though over 50% of the study participants were considered to be obese. While some MetS subcomponents (i.e., hyperlipidemia, hypertension, and diabetes) increased with age, the prevalence of obesity initially increased and then decreased with age. Hyperlipidemia and hypertension were higher in groups with greater cognitive impairment, but obesity was higher in the CS and DS-AD groups, yet low in the DS-MCI group. Although MetS was not significantly associated with DS-AD, obesity, a subcomponent of MetS, was significantly positively associated with DS-AD. This cross-sectional study suggests that given the early-life peak in obesity in adults with DS, and the association of obesity with DS-AD, early-life obesity in adults with DS, particularly in young women with DS who have a higher prevalence of obesity compared to men with DS, could potentially be a targetable modifiable environmental risk factor for DS-AD. Furthermore, the findings of this study show that MetS in adults with DS may not be a unified syndrome as it is in the neurotypical population, given that the cardiovascular subcomponents of MetS increase with age, whereas obesity peaks early in life and then declines. Future studies may further investigate these striking differences in MetS in adults with DS compared to the neurotypical population.

Our study shows that MetS subcomponents remain disparate in adults with DS, in that although hyperlipidemia and hypertension rise with increased age, obesity has an initial rise followed by a steep decline with increased age. This is in contrast to the neurotypical population, in which MetS subcomponents tend to cluster together and tend to increase with age.[5] Given the opposite directionality of obesity and cardiovascular risk factors in adults with DS, MetS in adults with DS does not behave as a unified syndrome the same way that it does in the neurotypical population. As such, future studies of MetS and DS-AD should focus separately on early to mid-life effects of obesity on cognitive impairment, versus mid- to late-life effects of other cardiovascular risk factors such as hyperlipidemia and hypertension on cognitive impairment. Failure to separately examine the cardiovascular and metabolic subcomponents could obscure opportunities for early intervention in adults with DS.

We observed that MetS as a whole did not increase the risk of DS-AD in this cohort of adults with DS; however, some of the subcomponents of MetS were associated with DS-AD. Specifically, there was a higher prevalence of hyperlipidemia and hypertension in those who were more cognitively impaired as determined by consensus diagnosis of dementia. However, the prevalence of obesity was lower in the DS-MCI group compared to the CS group, and higher in the DS-AD group compared to the DS-MCI group. This finding may be in line with an earlier study using a smaller subset of the ABC-DS data, which showed that unintentional weight loss occurs alongside amyloid beta deposition in adults with DS, and thus may be a useful early sign of DS-AD.[19] However, another possible reason for the lower prevalence of obesity in the DS-MCI group may be that the proportion of females was lower in the DS-MCI group compared to the CS and AD groups, and that women with DS tend to have higher prevalence of obesity.[20] When longitudinal data become available, future studies may examine the change in memory test scores and AD biomarkers as BMI increases in males and females with DS.

The increase in prevalence of hyperlipidemia and hypertension across varying levels of cognitive impairment may at least in part be explained by age. We found that both hyperlipidemia and hypertension are both positively associated with age in adults with DS, while obesity is negatively associated with age. Obesity in adults with DS also differs by sex in that females have a sharper rise in BMI prior to age 40 compared to males, and BMI in females remains elevated for longer compared to males. This peak in BMI occurs earlier in adults with DS compared to the neurotypical population, in which BMI tends to increase while individuals are between 40 and 59 years of age as per National Health and Nutrition Examination Survey (NHANES) data from 2021 to 2023.[21] Ultimately, the rise in obesity in early to mid-life in adults with DS and mid- to late-life peak in cardiovascular subcomponents of MetS suggests that clinicians and researchers should prioritize treating early-life obesity in young adults, particularly young women, with DS, over cardiovascular risk factors, highlighting the need for age-, sex-, and disease-specific interventions rather than viewing MetS as a unified syndrome in this population.

This study showed that adults with DS experience low prevalence of MetS, despite prevalent obesity. That is, we observed only one individual who had both MetS and DS-AD in this relatively large cohort of adults with DS. This is in contrast to the neurotypical population, in which 41.8% of US adults have MetS according to the NHANES.[22] Our study found that, despite the lack of association between MetS and DS-AD, there was an association between obesity, a subcomponent of MetS, and increased odds of DS-AD (OR = 2.79, $p = 0.021$). This suggests that although treatment of overall MetS may not modify DS-AD risk, targeted treatments for obesity in adults with DS (such

as glucagon-like peptide 1 (GLP-1) agonists, diet, and exercise) could potentially be beneficial in modifying DS-AD risk. The potential mechanisms underlying the observed phenomena are complex and likely to involve multiple components, including diet, decreased metabolic rate, hormonal differences in leptin and adiponectin, beta amyloid, and other factors. To further address these questions, a longitudinal study is warranted.

Given the relatively large sample size ($N = 389$ adults with DS), the present study improved precision and statistical power compared with earlier studies with smaller sample sizes. Another strength of this study is that we were able to use available data from ABC-DS to dissect MetS into its individual subcomponents, determine how age and sex affect MetS and its subcomponents in adults with DS, and characterize the relationship between MetS and DS-AD.

One of the limitations of the study is that we used surrogate data. The study lacked measures of fasting laboratory data for MetS and lacked a history of medication usage, such as antihypertensive medication use, statin use, etc. It used BMI (representing overall adiposity) rather than waist circumference (representing central adiposity). Consequently, some misclassifications of MetS might have weakened the true association. Lastly, the findings from the present study are based on European whites should be limited to cohorts that are predominantly white. While this is considered a limitation for generalizability to external populations, it may minimize etiologic heterogeneity, thereby enhancing statistical power.

This study was a cross-sectional examination of MetS and DS-AD. Although we did not find a cross-sectional relationship between overall MetS and DS-AD, it may be the case that when examined longitudinally, relationships between MetS and DS-AD emerge. It may also be the case that although MetS was not associated with DS-AD diagnosis, MetS may be associated with quantitative changes either in memory test scores or in DS-AD biomarkers. Future studies will be needed to examine longitudinal relationships between MetS and DS-AD, and also longitudinal changes in memory test scores and DS-AD biomarkers depending on MetS status.

5 | CONCLUSION

In this cross-sectional study of adults with DS, prevalence of MetS overall was low and was not associated with DS-AD. Individual MetS subcomponents displayed divergent relationships with age in that hyperlipidemia, hypertension, and diabetes all rose with age, whereas obesity initially rose and then declined with age. Given the opposite directionality of cardiovascular and metabolic subcomponents of MetS in adults with DS, this suggests that MetS may not be a unified syndrome in adults with DS, and that the relationships between MetS subcomponents and DS-AD are complex. This study also shows that obesity was the only MetS subcomponent that was significantly positively associated with DS-AD. Future studies may focus on targeted treatments specifically for obesity in early- to mid-life, particularly in young women with DS, as a means of potentially delaying the onset of or slowing the progression of DS-AD.

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CONFLICT OF INTEREST STATEMENT

Adam M. Brickman receives consulting fees from Cogstate, Cognito Therapeutics, Cognition Therapeutics, and IQVIA, has given a presentation to Cedara, has received support from the International Neuropsychological Society, has US Patent #9867566 and patent pending for publication #20230298170, has participated on an advisory board at University of Illinois, Urbana-Champaign, and is a section editor for *Alzheimer's and Dementia*. Bradley T. Christian receives funding from the NIA, NICHD, Eunice Kennedy Shriver Intellectual and

Developmental Disabilities Research Centers, National Center for Advancing Translational Sciences, National Centralized Repository for Alzheimer Disease and Related Dementias, DS-Connect, NIHR Cambridge Biomedical Research Centre, and Windsor Research Unit of Fulbourn Hospital in Cambridge, UK. Benjamin Handen has given a talk at University of North Carolina, and has been DSMB Chair for a Department of Defense Grant. Dina Dass receives funding from the Alzheimer's Clinical Trials Consortium, funded by the NIH/NIA. Elizabeth Head has consulted for Alzheon and Cyclotherapeutics, received royalties from Elsevier Press, and is a section editor for *Alzheimer's and Dementia*. Joseph H. Lee is a part of the external advisory board for the Alzheimer's Disease Resource Center for Minority Aging Research, University of Texas, and for the Center of Life Science, Nazarbayev University, Astana, Kazakhstan. Karen Marder receives funding from NIH, is a site investigator for Prilenia, MJ Fox, Huntington's Disease Society of America, and CHDI. Mark Mapstone is an inventor on patents related to biomarkers of neurodegenerative diseases owned by the University of Rochester, is on Scientific Advisory Boards for Brain Neurotherapy Bio, Inc, Davis Phinney Foundation for Parkinson's, Alzheon, Inc, is Chair for an NIH/NIA Data and Safety Monitoring Board (ACT Trial), and has stock options for Ireneo Health, PBC. Sharon Krinsky-McHale is an employee for the New York State Office for People with Developmental Disabilities (OPWDD). The other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Author disclosures are available in the supporting information.

Institutional Review Board (IRB) approval and informed consent (and assent when appropriate) have been obtained from all study participants or their proxy/legally authorized representative (LAR).

ETHICS STATEMENT

Institutional Review Board (IRB) approval has been obtained for this study. The majority of the participants in the ABC-DS study have European ancestry. The current study design allows recruitment of study participants with greater racial and ethnic diversity.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX 1

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