


RESEARCH ARTICLE

Exploring semantic verbal fluency patterns and their relationship to age and Alzheimer's disease in adults with Down syndrome

Farah Mgaieth¹  | R. Asaad Baksh^{1,2} | Carla M. Startin^{1,2,3,4} | Sarah Hamburg² | Rosalyn Hithersay^{1,2,3} | Sarah Pape^{1,5} | Henrik Zetterberg^{6,7,8,9,10,11} | Nicholas J. Ashton^{5,6,12,13} | Miren Tamayo-Elizalde¹ | Fedal Saini¹ | Mina Idris¹ | The LonDownS Consortium² | Andre Strydom^{1,2,3,5}

¹Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

²The LonDownS Consortium, London, UK

³Division of Psychiatry, University College London, London, UK

⁴School of Psychology, University of Roehampton, London, UK

⁵South London and Maudsley NHS Foundation Trust, London, UK

⁶Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden

⁷Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden

⁸Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK

⁹UK Dementia Research Institute at UCL, London, UK

¹⁰Hong Kong Center for Neurodegenerative Diseases, Hong Kong, China

¹¹Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, University of Wisconsin–Madison, Madison, Wisconsin, USA

¹²Institute of Psychiatry, Psychology and Neuroscience Maurice Wohl Institute Clinical Neuroscience Institute, King's College London, London, UK

¹³Centre for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway

Correspondence

Farah Mgaieth, Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), 16 De Crespigny Park, Denmark Hill SE5 8AF, London.
E-mail: farah.mgaieth@kcl.ac.uk

Funding information

National Institute for Health Research networks (mental health, dementias, and neurology) and participating NHS trusts; Wellcome Trust Strategic Award, Grant/Award Number: 098330/Z/12/Z; Medical Research Council, Grant/Award Numbers: MR/S011277/1, MR/S005145/1,

Abstract

Introduction: Adults with Down syndrome (DS) are at ultra-high risk of developing Alzheimer's disease (AD), characterized by poor episodic memory and semantic fluency in the preclinical phase in the general population. We explored semantic fluency performance in DS and its relationship to age, AD, and blood biomarkers.

Methods: A total of 302 adults with DS at baseline and 87 at follow-up from the London Down Syndrome Consortium cohort completed neuropsychological assessments. Blood biomarkers were measured with the single molecule array technique in a subset of 94 participants.

Results: Poorer verbal fluency performance was observed as age increases. Number of correct words declined in those with AD compared to those without over 2 years

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2023 The Authors. *Alzheimer's & Dementia* published by Wiley Periodicals LLC on behalf of Alzheimer's Association.

MR/R024901/1; the Swedish Research Council, Grant/Award Number: #2022-01018; European Union's Horizon Europe research and innovation programme, Grant/Award Number: 101053962; Swedish State Support for Clinical Research, Grant/Award Number: #ALFGBG-71320; Alzheimer Drug Discovery Foundation, Grant/Award Number: #201809-2016862; AD Strategic Fund and the Alzheimer's Association, Grant/Award Numbers: #ADSF-21-831376-C, #ADSF-21-831381-C, #ADSF-21-831377-C; European Union Joint Programme – Neurodegenerative Disease Research, Grant/Award Number: JPND2021-00694; Alzheimer's Society, Grant/Award Number: AS-CP-18-0020; Jérôme Lejeune Foundation; European Commission, Grant/Award Number: 848077; Bluefield Project; Olav Thon Foundation; Erling-Persson Family Foundation; Stiftelsen för Gamla Tjänarinnor; European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie, Grant/Award Number: 860197; UK Dementia Research Institute, Grant/Award Number: UKDRI-1003; Hjärfonden, Grant/Award Number: #FO2022-0270

and was negatively correlated with neurofilament light ($r = -0.37, P = .001$) and glial fibrillary acidic protein ($r = -0.31, P = .012$).

Discussion: Semantic fluency may be useful as an early indicator of cognitive decline and provide additional information on AD-related change, showing associations with biomarkers in DS.

KEYWORDS

Alzheimer's disease, animal subcategories, Down syndrome, glial fibrillary acidic protein, intrusions, neurofilament light, repetitions, semantic verbal fluency

1 | INTRODUCTION

Down syndrome (DS; trisomy of chromosome 21) is a developmental disability estimated to be present in ≈ 6 million people worldwide.^{1,2} Adults with DS are at an increased risk of early-onset Alzheimer's disease (AD)³ due to APP triplication with 90% eventually developing clinical features of AD in their lifetime.^{4,5}

DS is characterized by impairment in multiple cognitive domains^{6,7} and identifying whether decline during adulthood is attributable to normal aging or AD can be challenging.⁸ While combining history, physical examination, and cognitive testing remains the best approach to diagnose AD in DS, there is still a need for tests sensitive to early AD decline.⁹ There is some evidence to suggest that in people with DS, executive functioning abilities precede the typical memory loss found in sporadic AD.¹⁰

One measure closely related to executive functioning that is relatively easy to assess is verbal fluency,¹¹ a common test which engages cognitive processes and use of retrieval strategies.¹² In the general population, AD is reported to be associated with deficits in verbal fluency, especially semantic fluency,¹³ with poorer performance predicting incident dementia 4 to 6 years before clinical diagnosis.^{14,15} In adults with DS, deficits in verbal fluency are also associated with age and AD¹⁶⁻²⁰ with changes in performance suggested to be detected from the age of 35 to 39²¹ and observed to be a strong predictor of AD over the age of 40.¹⁷

While verbal fluency has been identified as a robust measure of cognitive decline and dementia onset in people with DS, the associations with the development of underlying neuropathology has not been established. Plasma biomarkers such as neurofilament light (NFL) and

glial fibrillary acidic protein (GFAP) are associated with AD and show promise as diagnostic/prognostic biomarkers of AD in DS.²²⁻²⁶ In DS, NFL levels have been found to be predictive of AD^{26,27} and higher GFAP levels have been observed in response to abnormal brain amyloid beta ($A\beta$) accumulation.²⁸ Determining the relationship between verbal fluency and these plasma biomarkers would help illustrate how this task reflects changes in underlying neuropathology.

Current research primarily investigates whether the number of correct words can be predictive of decline in semantic fluency tests.^{15,29,30} Less is known about whether errors including repetitions and intrusions, and the variety of animal subcategories, could be used as cognitive markers of preclinical AD in DS. The measure of subcategories is helpful to assess the ability to access a range of subcategories as well as productivity (e.g., to identify the ability to use different subcategories when one is exhausted) and may be sensitive to decline due to AD. In the general population, patients with mild cognitive impairment accessed fewer subcategories compared to healthy older adults.³¹⁻³³

In the non-DS population, results regarding the number of errors as markers for cognitive decline have been inconsistent; one study³⁴ demonstrated that errors generated showed little difference between those who remain cognitively healthy and those who developed dementia. Yet others have indicated that a high number of repetitions can help in the early identification of cognitive impairment.³⁵ In DS, the occurrence of intrusions in memory recall tasks have been shown to predict memory decline,³⁶ suggesting these may warrant further attention in this population.

We aimed to explore the potential association between semantic fluency performance and age using longitudinal data from a large DS

cohort study. We were interested in the number of correct words, intrusions, repetitions, and subcategories produced in adults with DS. People with AD are more impaired on semantic fluency than healthy controls;¹³ we thus investigated the ability of these measures to detect differences in participants with and without AD. Finally, we aimed to explore the relationship between verbal fluency and two plasma biomarkers for AD: NfL and GFAP.

2 | METHODS

2.1 | Participants

A total of 327 participants were recruited from the London Down Syndrome Consortium (LonDownS) cohort (from which 25 participants were excluded) and completed baseline assessments, and 87 participants aged ≥ 36 at baseline completed follow-up assessments 2 years later. Participants aged ≥ 16 years at baseline with sufficient hearing to comfortably engage with the cognitive tests (with the threshold being the Whisper Test at conversational level), and with mild to moderate intellectual disability (ID) were eligible. Full details regarding participants and the assessments can be found in Startin et al.³⁷

Participants aged ≥ 36 were expected to have AD neuropathology and thus to present with varying degrees of cognitive decline over time with those 16 to 35 years likely to perform near their cognitive peak. Baseline assessments (Time 1, T1) were completed between October 2013 and September 2015, with follow-up assessments ≈ 2 years later (Time 2, T2). Only older adults participated in follow-up assessments, as young adults < 36 years old should not show significant change in cognitive functioning. For more information regarding participants and the rationale behind the selection of the age groups, refer to Firth et al.²⁰

Ethical approval was obtained from the North West Wales Research Ethics Committee (13/WA/0194).

2.2 | Procedure

Outcomes used in the current analysis include a semantic verbal fluency task, cognitive tests, ID severity score, a dementia diagnosis, and measures of NfL and GFAP.

Each participant was administered a semantic verbal fluency task at baseline (T1) and, where relevant, at follow-up (T2), and instructed to name as many different animals as possible in 60 seconds. The total number of correct words generated was recorded along with the number of errors including intrusions (i.e., non-relevant words to the semantic group) and repetitions (i.e., correct words that were repeated such as the same words, the same words with different endings, or the same words coupled with a descriptive word, such as “dog” and “cute dog”). Sex-specific and age-specific words of the same animal species were given credit and not considered a repetition if their phonemic was different (e.g., lion and lioness, cat and kitten). The number of animal subcategories (i.e., the number of subcategories produced within

RESEARCH IN CONTEXT

- 1. Systematic Review:** We reviewed the literature using standard search engines (e.g., PubMed and GoogleScholar). Few studies have investigated whether poor semantic fluency performance can be a predictor of Alzheimer's disease (AD) in Down syndrome (DS) and have supported these findings with plasma biomarkers for AD. However, studies have identified that deficits in verbal fluency performance could be used as cognitive markers of preclinical AD.
- 2. Interpretation:** This study indicates that the simple verbal fluency task may provide valuable additional information on early cognitive change due to AD in DS and there is a relationship between verbal fluency performance and measures of neurodegeneration and astrocytic activation.
- 3. Future Directions:** These findings contribute to our understanding of the mechanisms of typical age-related declines in verbal fluency in adults with DS and provide evidence for its use as an early indicator of cognitive decline.

the higher category “animals”) was also recorded and assessed using the following categories: wild animals, domestic animals, aquatic animals, reptiles, birds, and arthropods. Three members of the research team met on two occasions to first define subcategories and finally to revise them to ensure they were consistent and culturally appropriate. For example, although snakes could be both wild and domesticated, we agreed that most people would consider snakes to be wild animals. These categories were then consistently applied for all participants. While no credit was given for the word “animal,” exemplars such as bird, reptile, fish, and shellfish were given credit and counted toward the number of correct words.

General cognitive abilities were assessed at the two time points using raw scores from the verbal and non-verbal subscales of the Kaufman Brief Intelligence Test Second Edition (KBIT-2).³⁸ Additionally, abilities and behaviors associated with cognitive decline over the last 2 months were assessed with the Dementia Questionnaire for People with Learning Disabilities (DLQ).³⁹

ID level was defined according to the International Classification of Diseases 10th Revision diagnostic system⁴⁰ and based on parental/caregiver report of the individual's best level of functioning. ID was classified into three levels: mild, moderate, and severe ID. These levels correspond, respectively, to the general functional abilities associated with intelligence quotient levels of 50 to 69, 35 to 49, and < 35 .

Dementia diagnoses were made by specialists using comprehensive assessments and were extracted from patients' medical history. These assessments were used to identify symptoms of decline in cognition,

adaptive functioning, or behavior indicative of early dementia-related change. Information regarding potential comorbidities (e.g., seizures) were collected in a semi-structured informant interview and physical health check.

In participants where blood samples were able to be collected, venipuncture of the antecubital fossa was generally performed on the same day as neurocognitive assessment. Plasma samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes using a closed Vacutainer system with a butterfly needle. Samples were centrifuged at $2000 \times g$ at 4°C for 10 minutes; aliquoted into $250 \mu\text{L}$ cryotubes; and stored at the Social, Genetic and Developmental Psychiatry Centre, King's College London at -80°C until analysis. NfL and GFAP concentrations were measured with automated the single molecule array (Simoa) technique using Quanterix at the Clinical Neurochemistry Laboratory, University of Gothenburg. Repeatability for NfL was 4.5% and for GFAP 3.9%. Precision was 6% for NfL and 4.1% for GFAP. Additional details of the sample collection are described in the supplementary methods in supporting information.

2.3 | Statistical analysis

Descriptive statistics were used to summarize the sample and its characteristics. Because age in DS is strongly associated with AD, linear regressions were performed to determine an association with age as a continuous variable and verbal fluency ability adjusting for sex, ID severity, verbal knowledge (KBIT-2), and AD diagnosis, and to investigate changes in verbal fluency performance within subjects at baseline and follow-up. We tested associations between NfL and GFAP samples, and verbal fluency ability with Spearman's rank correlation tests and partial correlation tests adjusting for age, sex, and ID severity. Furthermore, an adjusted logistic regression model was used to identify differences in verbal fluency ability between those with and without AD, adjusting for sex, ID severity, verbal knowledge (KBIT-2 scores), and age.

Statistical significance was set at $P < .05$. All statistical analyses were performed using the statistical software packages SPSS (version 25.0; SPSS Inc.).

3 | RESULTS

The analysis included 302 participants at baseline (T1) and 87 participants at follow-up (T2) with demographic characteristics and mean scores for both younger and older adult groups presented in Table 1. From the original cohort, 25 participants (8 with AD, 14 males, mean age = 46.48, standard deviation [SD] = 14.53) were excluded from the following analysis due to the inability to produce any words during the verbal fluency task at baseline. However, participants who were able to produce words at baseline but unable to produce any at follow-up were included in the analysis because it might be indicative of cognitive decline. Additionally, 83 participants were lost to follow-up (mean age = 50.31, SD = 8.56) including 21 with a diagnosis of AD (constitut-

ing 56.7% of those with AD at baseline), 41 males (49.4%), and 7 who died between baseline and follow-up.

3.1 | Verbal fluency and age at baseline

Linear regression was performed to ascertain the relationship between the number of correct words, intrusions and repetitions, and age adjusting for sex, verbal knowledge, ID severity, and AD diagnosis at T1 (across both groups of participants). As shown in Table 2, the number of correct words had a statistically significant relationship with age, with fewer words as age increases (adjusted R square = 19.5%). Neither intrusion nor repetition scores were significantly associated with age (unadjusted results can be found in the [supplementary tables](#) in supporting information). However, because the number of errors made may be associated with the total number of words produced, intrusions and repetitions were also calculated in relation to the number of correct words proportionally. We used linear regression to assess whether a higher proportion of errors were made with aging. Adjusting for the same covariates as previously, the number of intrusions was significantly associated with age, but not the number of repetitions ($\beta = 6.5$, 95% confidence interval (CI) [0.29, 12.73], $P = .04$; $\beta = 3.35$, 95% CI [-4.32, 11.01], $P = .39$, respectively), suggesting that the number of intrusion errors proportionally increased as age increased. The number of total animal subcategories (analyzed separately) was also significantly associated with age ($\beta = -1.27$, 95% CI [-2.47, -0.06], $P = .039$) with a decrease in the number of animal subcategory production as participants aged. When subcategories were analyzed independently (e.g., wild animals), only the number of domestic animals was associated with age ($\beta = -1.17$, 95% CI [-1.81, -0.52], $P = .001$). Additional details of the results are included in the supporting information.

3.2 | Verbal fluency performance and its relationship to NfL and GFAP levels

Blood samples were collected from a subset of participants with NfL levels available for 94 participants (mean age 41.54; $M = 19.509$ pg/mL, $SD = 18.39$) and GFAP levels available for 76 participants (mean age 41.67; $M = 122.535$ pg/mL, $SD = 91.51$). NfL levels and the number of correct words were significantly negatively correlated ($r = -0.367$, $P = .001$) as well as GFAP levels and the number of correct words ($r = -0.313$, $P = .012$). There were no significant correlations between either biomarker and the number of intrusions (NfL $r = -0.053$, $P = .641$; GFAP $r = -0.175$, $P = .167$, respectively) or repetitions (NfL $r = -0.025$, $P = .82$; GFAP $r = 0.136$, $P = .283$, respectively). Adjusted for sex, ID severity, and age, the number of correct words remained significantly correlated with NfL levels ($r = -0.265$, $P = .048$) but not with GFAP levels ($r = -0.193$, $P = .15$).

Because those aged ≥ 36 have significantly higher NfL and GFAP levels than younger individuals, the number of correct words and the relationship to these plasma biomarkers was explored in both age groups. In younger individuals (16–35 years old), the number of

TABLE 1 Demographic data and mean (SD) neuropsychological scores for younger adult and older adult groups.

		Young adults (aged 16–35)		Older adults (aged 36–74)		
		Baseline	Baseline	Follow-up		
Participants	Age	26.08 (5.39)	49.59 (7.95)	50.90 (7.30)		
	N	132 (43.7%)	170 (56.3%)	87 (51.2% of baseline)		
	<i>Ethnicity</i>					
	White	112 (37.1%)	162 (53.6%)	82 (94.3%)		
	Other ethnicity	20 (6.6%)	8 (2.6%)	5 (5.7%)		
	<i>ID level</i>					
	Mild	54 (40.9%)	80 (47.1%)	44 (50.6%)		
	Moderate	78 (59.1%)	90 (52.9%)	43 (49.4%)		
	Sex: male	59 (44.7%)	91 (53.5%)	50 (57.5%)		
Dementia diagnosis	0 (0.0%)	37 (21.8%)	23 (26.4%)			
Tests	<i>Verbal fluency</i>					
	Correct words	10.63 (5.27)	8.31 (5.01)	7.02 (5.95)		
	Wild animals	3.79 (3.21)	2.93 (2.78)	2.67 (3.12)		
	Domestic animals	3.73 (2.22)	3.18 (2.19)	2.40 (2.39)		
	Aquatic animals	0.73 (1.17)	0.46 (0.92)	0.34 (0.73)		
	Reptiles	0.79 (1.11)	0.43 (0.77)	0.31 (0.65)		
	Birds	1.17 (1.37)	1.00 (1.23)	1.13 (1.74)		
	Arthropods	0.40 (0.84)	0.26 (0.85)	0.17 (0.59)		
	Repetitions	1.01 (1.50)	1.01 (1.64)	0.87 (1.39)		
	Intrusions	0.23 (0.65)	0.28 (0.70)	0.55 (1.04)		
	Total number of subcategories	3.40 (1.38)	2.94 (1.36)	2.29 (1.76)		
	KBIT-2 raw verbal	n = 131; 36.34 (14.78)	n = 163; 30.32 (16.12)	n = 73; 30.86 (18.76)		
	KBIT-2 raw non-verbal	n = 131; 15.81 (5.54)	n = 163; 12.70 (6.13)	n = 75; 12.41 (6.62)		
	DLD (cognitive scores)	n = 97; 5.51 (6.15)	n = 99; 10.55 (9.64)	n = 83; 13.79 (12.86)		
DLD (social scores)	n = 101; 8.25 (5.73)	n = 100; 10.43 (6.95)	n = 83; 12.37 (10.52)			

Note: Baseline includes young and older adults and excludes participants unable to produce any words. Follow-up includes older adults only and those unable to produce any words at follow-up. Adults < 36 years old were not included in the follow-up.

Abbreviations: DLD, Dementia Questionnaire for People with Learning Disabilities; ID, intellectual disability; KBIT-2, Kaufman Brief Intelligence Test Second Edition; SD, standard deviation.

TABLE 2 Relationship between verbal fluency performance and age.

	β	95% CI	P-value
Number of correct words	-0.38	(-0.75, -0.01)	.049*
Intrusions	0.69	(-1.49, 2.86)	.53
Repetitions	-0.29	(-1.55, 0.97)	.66
Sex (female)	3.55	(0.67, 6.44)	.016*
Intellectual disability (mild)	-5.33	(-8.40, -2.25)	.001***
Verbal knowledge	-0.13	(-0.26, -0.01)	.037*
AD diagnosis (with)	-11.31	(-16.08, -6.55)	.001***

Note: Linear regression included sex, verbal knowledge, intellectual disability severity and AD diagnosis as covariates, and age as an outcome.

Abbreviations: AD, Alzheimer's disease; CI, confidence interval.

*p < .05; ***p < .001.

correct words was not significantly correlated with NfL (M = 8.920 pg/mL, SD = 4.40; r = 0.098, P = .57) nor were GFAP (M = 68.260 pg/mL, SD = 27.73; r = -0.016, P = .93) levels. However, in the older adult group, the number of correct words was significantly negatively correlated with NfL (M = 26.383 pg/mL, SD = 20.66; r = -0.398, P = .007) and there was a weaker negative correlation with GFAP (M = 157.933 pg/mL, SD = 101.07; r = -0.317, P = .064) levels, as shown in Figure 1.

3.3 | Verbal fluency and AD diagnosis

A logistic regression model was able to distinguish groups with and without dementia with the number of correct words being a significant predictor (P = .02) adjusting for age, sex, verbal knowledge, and

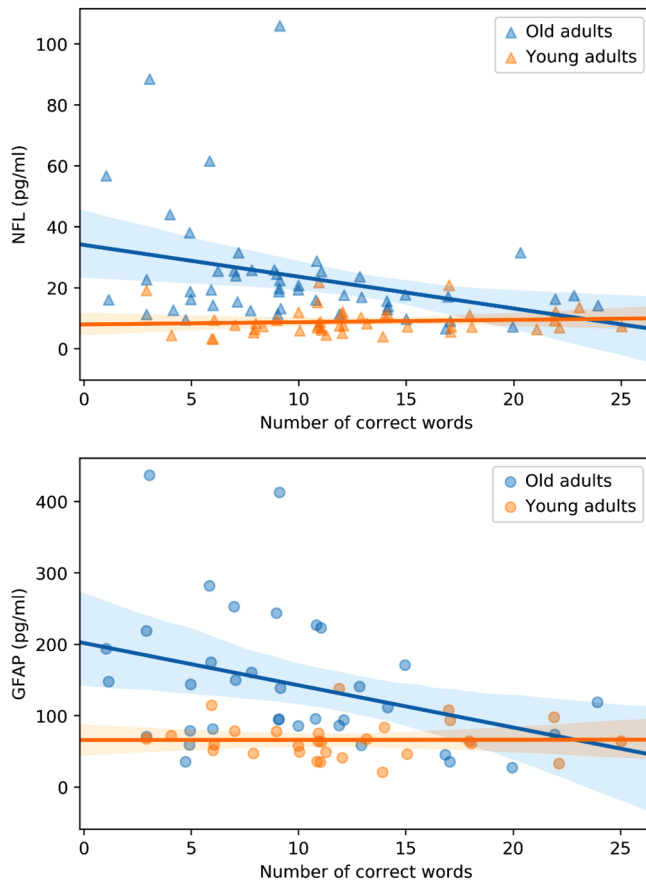


FIGURE 1 Correlation of the number of correct words with plasma biomarkers, and the relationship in both younger adults (≤ 35 years old) and older adults (≥ 36 years old). The graphs demonstrate that there is a relationship between the number of correct words and plasma biomarker levels mainly in older adults. NFL, neurofilament light; GFAP, glial fibrillary acidic protein.

ID severity as presented in Table 3 (unadjusted results can be found in the [supplementary tables](#)). Using the same covariates and analyzed separately, the number of total animal subcategories did not predict the presence of AD ($\beta = 0.11$, $\text{exp}[\beta] = 1.12$, 95% CI [0.76, 1.66], $P = .57$).

3.4 | Longitudinal change in verbal fluency performance over 2 years

To understand the progression of verbal fluency over time and whether it may be a predictor for cognitive decline, we examined the effect of age at T2 on verbal fluency with a linear regression model. To do so, we subtracted scores at T1 from T2 for each subject to obtain a change score for the numbers of correct words, intrusions, repetitions, and total number of subcategories. While the number of intrusions, repetitions, and subcategories did not differ over time, the number of correct words generated significantly decreased after 2 years when accounting for sex, ID, verbal knowledge, and AD diagnosis at T2 (Table 4; unadjusted results and covariates are supplied in the [supplementary tables](#)).

TABLE 3 Prediction of presence of Alzheimer's disease by verbal fluency performance.

	β	Exp(β)	95% CI exp(β)	P-value
Number of correct words	0.17	1.18	(1.03, 1.36)	.02*
Intrusions	0.43	1.54	(0.76, 3.11)	.23
Repetitions	-0.30	0.74	(0.52, 1.06)	.10
Sex (female)	-0.06	1.06	(0.39, 2.27)	.89
Intellectual disability (mild)	0.66	1.93	(0.74, 5.00)	.18
Verbal knowledge	0.04	1.04	(1.00, 1.09)	.05
Age	-0.08	0.92	(0.89, 0.96)	.001***

Note: Logistic regression included sex, verbal knowledge, intellectual disability severity, and age as covariates, and Alzheimer's disease as an outcome.

Abbreviation: CI, confidence interval.

* $p < .05$; *** $p < .001$.

TABLE 4 Longitudinal change in verbal fluency performance (Time 2 - Time 1).

	β	95% CI	P-value
Number of correct words	-0.18	(-0.31, -0.05)	.007**
Intrusions	-0.00	(-0.05, 0.04)	.97
Repetitions	0.02	(-0.04, 0.08)	.50
Subcategories	-0.01	(-0.06, 0.04)	.63

Note: Linear regression included sex, verbal knowledge, intellectual disability severity, and AD diagnosis as covariates, and age at Time 2 as an outcome.

Abbreviations: AD, Alzheimer's disease; CI, confidence interval.

** $p < .01$.

4 | DISCUSSION

Using data from 302 adults with DS at baseline, we investigated whether various semantic verbal fluency outcomes were associated with age and AD in this population. To our knowledge, this is the first in-depth study of verbal fluency performance in adults with DS using a standardized approach and including the number of correct words, repetitions, intrusions, and animal subcategories generated. A significant decline in verbal fluency as age increases was observed, using the metrics of the number of correct words, animal subcategories, and intrusions proportionate to the number of correct words, controlling for sex, verbal knowledge, ID severity, and AD diagnosis. Adjusting for AD, we were able to demonstrate that verbal fluency is sensitive to significant changes relative to aging as well as dementia-related changes. This is in line with previous work¹⁹ showing poorer performance on the number of correct words in older adults with DS. A decline in the number of subcategories was also observed potentially reflecting poorer abstract thinking ability and difficulty using more complex strategies during word generation. The findings on intrusions are also consistent with a previous study that found the production of intrusions made during a working memory task was a characteristic of middle-aged

adults with DS.³⁶ In this line of investigation in the general population, intrusions in a semantic verbal fluency task were found to be a trait of mild AD.⁴¹ However, in that study, a healthy older group committed more repetitions than the younger group, but the older group did not commit more repetitions than those with mild AD, suggesting that this might also be a feature of aging rather than a distinctive feature of AD. Our analysis did not demonstrate a higher proportion of repetitions to the number of correct words in adults with DS with increasing age. Given the association of intrusions with AD in the general population, a high number of intrusions proportional to the number of correct words might be an early sign of cognitive decline in people with DS.

Individuals with and without a diagnosis of AD were differentiated by the number of correct words controlling for age and other factors. This is in line with other studies which identified semantic verbal fluency to be a strong predictor of AD in DS.^{16,17} These findings are further supported by the negative association between the number of correct words and levels of NfL and GFAP, with fewer words in the verbal fluency task being correlated with elevated levels of NfL and GFAP, and driven by age (predominantly by older adults). Because these biomarkers pinpoint onset of neurodegeneration (NfL), reflect astrocytic activation (GFAP), and are predictive of dementia status in both individuals with DS and the general population,^{27,28,42,43} these findings suggest that verbal fluency ability, and especially the number of correct words, is closely associated with the underlying neurodegeneration and astrocytic injury/activation that are typical of AD.

Considering the elevated risk of developing AD with age in DS, we examined the time course of verbal fluency performance over a 2-year period in the adult group aged ≥ 36 years who are expected to have some degree of AD neuropathology.^{21,44} Although the numbers of intrusions, repetitions, and animal subcategories were not observed to significantly change over this time period, the number of correct words significantly decreased over time even when controlling for AD and verbal knowledge. This is different from the findings of Rondal and Comblain,⁴⁵ which did not show a change in the number of correct words over a 4-year period in adults with DS aged between 37 and 49 years, although their sample size was small.

4.1 | Strengths and limitations

We have used data from a large, diverse community sample of adults with DS, and standardized ratings of verbal fluency before analyzing their relationship to age, dementia diagnosis, and longitudinal change, then confirmed findings using plasma biomarkers of neurodegeneration and astrocytic injury. However, the follow-up sample was smaller and limited to 2 years of follow-up. Furthermore, there was no follow-up for younger adults (<36 years of age). Although cognitive decline in the younger group is unlikely, additional follow-up may be necessary to establish practice effects in this group. In addition, exploring verbal fluency over a longer period in older adults with DS might provide additional information regarding changes in verbal fluency and whether they can be predictive of dementia at an early stage. It is nonetheless the largest study of longitudinal change in verbal fluency

in DS to date. We took care to ensure the validity of results by only including participants with sufficient hearing, and mild to moderate ID to ensure they could comfortably engage with the cognitive tests. To ensure that participants who did not understand the task were not included in the analysis, those who did not produce any relevant words at baseline were excluded. Additionally, we adjusted for verbal knowledge throughout our analyses as it can be an important contributory factor in verbal fluency performance and prevents conflicting results due to differences in education between young and older adults.

While we have used several components of verbal fluency, including the number of errors produced, one limitation might have been the categorization of animals used to assess the ability to access a range of subcategories during word generation. A higher number of animals were included in the subcategory of wild animals compared to other subcategories such as arthropods, which may have potentially skewed the outcome. Future research should explore different subcategorizations.

5 | CONCLUSION

In summary, these findings contribute to our understanding of the mechanisms of typical age-related decline in semantic verbal fluency in adults with DS and provide evidence for its use as an early indicator of cognitive decline. Given that frontal functions and in particular executive functioning have been shown to be affected relatively early by AD in adults with DS^{46,47} but are difficult to assess in individuals with intellectual impairment, the simple verbal fluency task (used with standardized scoring) may provide valuable additional information on early cognitive change due to AD in DS.

ACKNOWLEDGMENTS

The authors would like to thank all the participants and their parents and caregivers in this study for their time. This research was supported by the National Institute for Health Research networks (mental health, dementias, and neurology) and participating NHS trusts. We would like to thank our NHS network of sites that helped to identify participants. This research was funded by Wellcome Trust Strategic Award (grant number: 098330/Z/12/Z) conferred upon The London Down Syndrome (LonDownS) Consortium; Medical Research Council grant MR/S011277/1, MR/S005145/1, and MR/R024901/1; European Commission (H2020 SC1 Gene overdosage and comorbidities during the early lifetime in Down Syndrome GO-DS21-848077); and Alzheimer's Society AS-CP-18-0020 (fellowship to S.E.P). R.A.B. was supported by a Jérôme Lejeune Foundation post-doctoral research fellowship. H.Z. is a Wallenberg Scholar supported by grants from the Swedish Research Council (#2022-01018), the European Union's Horizon Europe research and innovation programme under grant agreement No 101053962, Swedish State Support for Clinical Research (#ALFGBG-71320), the Alzheimer Drug Discovery Foundation (ADDF), USA (#201809-2016862), the AD Strategic Fund and the Alzheimer's Association (#ADSF-21-831376-C, #ADSF-21-831381-C, and #ADSF-21-831377-C), the Bluefield Project, the Olav

Thon Foundation, the Erling-Persson Family Foundation, Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Sweden (#FO2022-0270), the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 860197 (MIRIADE), the European Union Joint Programme – Neurodegenerative Disease Research (JPND2021-00694), and the UK Dementia Research Institute at UCL (UKDRI-1003). For the purposes of open access, the author has applied a Creative Commons Attribution (CC BY) license to any Accepted Author Manuscript version arising from this submission.

CONFLICTS OF INTEREST STATEMENT

HZ has served on scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave; has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). The other authors declare that they have no conflicts of interests. Author disclosures are available in the [supporting information](#).

CONSENT STATEMENT

Written informed consent was obtained from individuals who had capacity to consent. Where individuals did not have capacity to consent, a consultee was asked to approve the individual's inclusion based on their knowledge of the individual and their wishes, in accordance with the UK Mental Capacity Act 2005.

ORCID

Farah Mgaith  <https://orcid.org/0000-0001-7059-3209>

REFERENCES

- Wu J, Morris JK. The population prevalence of Down's syndrome in England and Wales in 2011. *Eur J Hum Genet*. 2013;21(9):1016-1019.
- Foundation GDS. Facts and FAQ About Down Syndrome. 2019. Accessed May 1, 2021. [https://www.globaldownsyndrome.org/about-down-syndrome/facts-about-down-syndrome/\(2019\)](https://www.globaldownsyndrome.org/about-down-syndrome/facts-about-down-syndrome/(2019))
- Wiseman FK, Al-Janabi T, Hardy J, et al. A genetic cause of Alzheimer disease: mechanistic insights from Down syndrome. *Nat Rev Neurosci*. 2015;16(9):564-574.
- Mccarron M, Mccallion P, Reilly E, Dunne P, Carroll R, Mulryan N. A prospective 20-year longitudinal follow-up of dementia in persons with Down syndrome. *J Intellect Disabil Res*. 2017;61(9):843-852.
- Sinai A, Mokrysz C, Bernal J, et al. Predictors of age of diagnosis and survival of Alzheimer's disease in down syndrome. *J Alzheimers Dis*. 2018;61(2):717-728.
- Nelson L, Johnson JK, Freedman M, et al. Learning and memory as a function of age in Down syndrome: a study using animal-based tasks. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29(3):443-453.
- Lukowski AF, Milojevich HM, Eales L. Cognitive functioning in children with down syndrome: current knowledge and future directions. *Adv Child Dev Behav*. 2019;56:257-289.
- Ball SL, Holland AJ, Hon J, Huppert FA, Treppner P, Watson PC. Personality and behaviour changes mark the early stages of Alzheimer's disease in adults with Down's syndrome: findings from a prospective population-based study. *Int J Geriatr Psychiatry*. 2006;21(7):661-673.
- Aschenbrenner AJ, Baksh RA, Benezam B, et al. Markers of early changes in cognition across cohorts of adults with Down syndrome at risk of Alzheimer's disease. *Alzheimers Dement (Amst)*. 2021;13(1):e12184.
- Lautarescu BA, Holland AJ, Zaman SH. The early presentation of dementia in people with down syndrome: a systematic review of longitudinal studies. *Neuropsychol Rev*. 2017;27(1):31-45.
- Troyer AK, Moscovitch M, Winocur G. Clustering and switching as two components of verbal fluency: evidence from younger and older healthy adults. *Neuropsychology*. 1997;11(1):138-146.
- Shao Z, Janse E, Visser K, Meyer AS. What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. *Front Psychol*. 2014;5:772.
- Henry JD, Crawford JR, Phillips LH. Verbal fluency performance in dementia of the Alzheimer's type: a meta-analysis. *Neuropsychologia*. 2004;42(9):1212-1222.
- Masur DM, Sliwinski M, Lipton RB, Blau AD, Crystal HA. Neuropsychological prediction of dementia and the absence of dementia in healthy elderly persons. *Neurology*. 1994;44(8):1427-1432.
- Sutin AR, Stephan Y, Terracciano A. Verbal fluency and risk of dementia. *Int J Geriatr Psychiatry*. 2019;34(6):863-867.
- Hoyo LD, Xicota L, Sánchez-Benavides G, et al. Semantic verbal fluency pattern, dementia rating scores and adaptive behavior correlate with plasma abeta42 concentrations in down syndrome young adults. *Front Behav Neurosci*. 2015;9:301.
- Pulsifer MB, Evans CL, Hom C, et al. Language skills as a predictor of cognitive decline in adults with Down syndrome. *Alzheimers Dement (Amst)*. 2020;12(1):e12080.
- Startin CM, Hamburg S, Hithersay R, et al. Cognitive markers of preclinical and prodromal Alzheimer's disease in Down syndrome. *Alzheimers Dement*. 2019;15(2):245-257.
- Ghezzi A, Salvioli S, Solimando MC, et al. Age-related changes of adaptive and neuropsychological features in persons with Down syndrome. *PLoS One*. 2014;9(11):e113111.
- Firth NC, Startin CM, Hithersay R, et al. Aging related cognitive changes associated with Alzheimer's disease in Down syndrome. *Ann Clin Transl Neurol*. 2018;5(6):741-751.
- Hithersay R, Baksh RA, Startin CM, et al. Optimal age and outcome measures for Alzheimer's disease prevention trials in people with Down syndrome. *Alzheimer's & Dementia*. 2020.
- Pape SE, Al Janabi T, Ashton NJ, et al. The reliability and validity of DSM 5 diagnostic criteria for neurocognitive disorder and relationship with plasma neurofilament light in a down syndrome population. *Sci Rep*. 2021;11(1):13438.
- Ashton NJ, Janelidze S, Al Khelifat A, et al. A multicentre validation study of the diagnostic value of plasma neurofilament light. *Nat Commun*. 2021;12(1):3400.
- Olsson B, Lautner R, Andreasson U, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. *Lancet Neurol*. 2016;15(7):673-684.
- Fortea J, Vilaplana E, Carmona-Iragui M, et al. Clinical and biomarker changes of Alzheimer's disease in adults with Down syndrome: a cross-sectional study. *Lancet*. 2020;395(10242):1988-1997.
- Carmona-Iragui M, Alcolea D, Barroeta I, et al. Diagnostic and prognostic performance and longitudinal changes in plasma neurofilament light chain concentrations in adults with Down syndrome: a cohort study. *Lancet Neurol*. 2021;20(8):605-614.
- Strydom A, Heslegrave A, Startin CM, et al. Neurofilament light as a blood biomarker for neurodegeneration in Down syndrome. *Alzheimers Res Ther*. 2018;10(1):39.
- Janelidze S, Christian BT, Price J, et al. Detection of brain tau pathology in Down syndrome using plasma biomarkers. *JAMA Neurol*. 2022;79(8):797-807.

29. Frankenberg C, Weiner J, Knebel M, et al. Verbal fluency in normal aging and cognitive decline: results of a longitudinal study. *Comput Speech Lang*. 2021;68.
30. Demetriou E, Holtzer R. Mild cognitive impairments moderate the effect of time on verbal fluency performance. *J Int Neuropsychol Soc*. 2017;23(1):44-55.
31. Price SE, Kinsella GJ, Ong B, et al. Semantic verbal fluency strategies in amnesic mild cognitive impairment. *Neuropsychology*. 2012;26(4):490-497.
32. Gocer March E, Pattison P. Semantic verbal fluency in Alzheimer's disease: approaches beyond the traditional scoring system. *J Clin Exp Neuropsychol*. 2006;28(4):549-566.
33. Bertola L, Cunha Lima ML, Romano-Silva MA, et al. Impaired generation of new subcategories and switching in a semantic verbal fluency test in older adults with mild cognitive impairment. *Front Aging Neurosci*. 2014;6:141.
34. Raoux N, Amieva H, Le Goff M, et al. Clustering and switching processes in semantic verbal fluency in the course of Alzheimer's disease subjects: results from the PAQUID longitudinal study. *Cortex*. 2008;44(9):1188-1196.
35. Pakhomov SVS, Eberly LE, Knopman DS. Recurrent perseverations on semantic verbal fluency tasks as an early marker of cognitive impairment. *J Clin Exp Neuropsychol*. 2018;40(8):832-840.
36. Kittler P, Krinsky-Mchale SJ, Devenny DA. Verbal intrusions precede memory decline in adults with Down syndrome. *J Intellect Disabil Res*. 2006;50(1):1-10.
37. Startin CM, Hamburg S, Hithersay R, et al. The LonDownS adult cognitive assessment to study cognitive abilities and decline in Down syndrome. *Wellcome Open Res*. 2016;1:11.
38. Kaufman AS, Kaufman NL. *Kaufmann brief intelligence test*. 2nd ed. Pearson Assessments; 2004. 2004.
39. Evenhuis HM. Further evaluation of the dementia questionnaire for persons with mental retardation (DMR). *J Intellect Disabil Res*. 1996;40(4):369-373. Pt.
40. World Health Organization. International statistical classification of diseases and related health problems. (11th ed.) 2019.
41. Itaguchi Y, Castro-Chavira SA, Waterloo K, et al. Evaluation of error production in animal fluency and its relationship to frontal tracts in normal aging and mild Alzheimer's disease: a combined fda and time-course analysis investigation. *Front Aging Neurosci*. 2021;13:710938.
42. Hendrix JA, Airey DC, Britton A, et al. Cross-sectional exploration of plasma biomarkers of Alzheimer's disease in down syndrome: early data from the longitudinal investigation for enhancing down syndrome research (LIFE-DSR) study. *J Clin Med*. 2021;10(9):1907.
43. Chatterjee P, Pedrini S, Stoops E, et al. Plasma glial fibrillary acidic protein is elevated in cognitively normal older adults at risk of Alzheimer's disease. *Transl Psychiatry*. 2021;11(1):27.
44. Mann DMA, Davidson YS, Robinson AC, et al. Patterns and severity of vascular amyloid in Alzheimer's disease associated with duplications and missense mutations in APP gene, Down syndrome and sporadic Alzheimer's disease. *Acta Neuropathol*. 2018;136(4):569-587.
45. Rondal J, Comblain A. Language in ageing persons with Down syndrome. *Downs Syndr Res Pract*. 2002;8(1):1-9.
46. Ball SL, Holland AJ, Treppner P, Watson PC, Huppert FA. Executive dysfunction and its association with personality and behaviour changes in the development of Alzheimer's disease in adults with Down syndrome and mild to moderate learning disabilities. *Br J Clin Psychol*. 2008;47(1):1-29.
47. Tungate AS, Connors FA. Executive function in Down syndrome: a meta-analysis. *Res Dev Disabil*. 2021;108:103802.

SUPPORTING INFORMATION

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

How to cite this article: Mgaieith F, Baksh RA, Startin CM, et al. Exploring semantic verbal fluency patterns and their relationship to age and Alzheimer's disease in adults with Down syndrome. *Alzheimer's Dement*. 2023;19:5129–5137. <https://doi.org/10.1002/alz.13097>

APPENDIX 1

Collaborators

The LonDownS Consortium principal investigators were Andre Strydom (chief investigator), Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK, and Division of Psychiatry, University College London, London, UK; Elizabeth Fisher, Department of Neurodegenerative Disease, Institute of Neurology, University College London, London, UK; Dean Nizetic, Blizard Institute, Barts and the London School of Medicine, Queen Mary University of London, London, UK, and Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore; John Hardy, Reta Lila Weston Institute, Institute of Neurology, University College London, London, UK, and UK Dementia Research Institute at UCL, London, UK; Victor Tybulewicz, Francis Crick Institute, London, UK, and Department of Medicine, Imperial College London, London, UK; Annette Karmiloff-Smith, Birkbeck University of London, London, UK (deceased); Michael Thomas, Birkbeck University of London, London, UK; and Denis Mareschal, Birkbeck University of London, London, UK. We would like to thank Tamara Al-Janabi, Division of Psychiatry, University College London, London, UK, for initial project management. Baseline data admin and data coding support was provided by Nidhi Aggarwal, Tommy Coyle, Amy Davies, Lucy Fodor-Wynne, Bryony Lowe, and Erin Rodger, all Division of Psychiatry, University College London, London, UK.