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RESEARCH ARTICLE

Age of Alzheimer's disease diagnosis in people with Down syndrome and associated factors: Results from the Horizon 21 European Down syndrome consortium

Frode Kibsgaard Larsen[1,2] | **R. Asaad Baksh**[3,4] | **Eimear McGlinchey**[5,6] | **Ellen Melbye Langballe**[1,7] | **Bessy Benejam**[8] | **Jessica Beresford-Webb**[9,10] | **Mary McCarron**[5] | **Antonia Coppus**[11] | **Segolene Falquero**[12] | **Juan Fortea**[8,13,14] | **Johannes Levin**[15,16,17] | **Sandra V. Loosli**[15,18] | **Ruth Mark**[19] | **Anne-Sophie Rebillat**[12] | **Shahid Zaman**[9,10] | **Andre Strydom**[3,4,20]

[1]The Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust, Tønsberg, Norway

[2]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway

[3]Institute of Psychiatry, Psychology, and Neuroscience, Department of Forensic and Neurodevelopmental Sciences, King's College London, London, UK

[4]The London Down Syndrome (LonDownS) Consortium, London, UK

[5]Trinity Centre for Ageing and Intellectual Disability, Trinity College Dublin, Lincoln Gate, Dublin, Ireland

[6]Global Brain Health Institute, Trinity College Dublin & University of California, San Francisco, California, USA

[7]Department of Geriatric Medicine, Oslo University Hospital, Oslo, Norway

[8]Barcelona Down Medical Center, Fundació Catalana Síndrome de Down, Barcelona, Spain

[9]Department of Psychiatry, University of Cambridge, The Old Schools, Cambridge, UK

[10]Cambridgeshire & Peterborough NHS Foundation Trust, Fulbourn Hospital, Cambridge, UK

[11]Department of Primary and Community Care, Radboud University Medical Center, Nijmegen, The Netherlands

[12]Institute Jerome Lejeune, Paris, France

[13]Sant Pau Memory Unit, Department of Neurology, Hospital of Sant Pau, Sant Pau Research Institute, Barcelona, Spain

[14]Centro de Investigación Biomédica en Red en Enfermedades Neurodegenerativas (CIBERNED), Monforte de Lemos, Madrid, Spain

[15]Department of Neurology, Ludwig-Maximilians-Universität München, Munich, Germany

[16]German Center for Neurodegenerative Diseases, Munich, Germany

[17]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

[18]Department of Neurology, University Hospital Zurich, Zurich, Switzerland

[19]Cognitive Neuropsychology, Tilburg University, Tilburg, The Netherlands

[20]South London and the Maudsley NHS Foundation Trust, London, UK

Correspondence
Frode Kibsgaard Larsen, The Norwegian National Centre for Ageing and Health, P.box 2136, N-3103 Tønsberg, Norway.
Email: Frode.larsen@aldringoghelse.no

Abstract

INTRODUCTION: People with Down syndrome (DS) have high risk of developing Alzheimer's disease (AD). This study examined mean ages of AD diagnosis and

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associations with co-occurring conditions among adults with DS from five European countries.

METHODS: Data from 1335 people with DS from the Horizon 21 European DS Consortium were used for the analysis.

RESULTS: Mean ages of AD diagnosis ranged between 51.4 (SD 7.0) years (United Kingdom) and 55.6 (SD 6.8) years (France). Sleep-related and mental health problems were associated with earlier age of AD diagnosis. The higher number of co-occurring conditions the more likely the person with DS is diagnosed with AD at an earlier age.

DISCUSSION: Mean age of AD diagnosis in DS was relatively consistent across countries. However, co-occurring conditions varied and impacted on age of diagnosis, suggesting that improvements can be made in diagnosing and managing these conditions to delay onset of AD in DS.

KEYWORDS
age of diagnosis, Alzheimer's disease, co-occurring conditions, Down syndrome

Highlights

- Mean age of AD diagnosis was relatively consistent between countries
- Sleep problems and mental health problems were associated with earlier age of AD diagnosis
- APOE ε4 carriers were diagnosed with AD at an earlier age compared to non-carriers
- Number of co-occurring conditions was associated with earlier age of AD diagnosis
- No differences between level of intellectual disability and mean age of AD diagnosis

1 | BACKGROUND

Down syndrome (DS) is the most common genetic cause of intellectual disability, characterized by trisomy 21 in approximately 95% of cases, and estimated with a population prevalence in Europe of 5.6 per 10,000.[1,2] Alzheimer's disease (AD) neuropathology is present in virtually everyone with DS by the age of 40 due to three copies of the amyloid precursor protein (APP) gene located on chromosome 21, leading to overproduction and accumulation of amyloid-beta (Aβ)[3] and with an associated lifetime risk of over 95%.[4] Age-specific risk for AD has been estimated to 23%-55% at age 40-49 and 75%-88% by age 60-69,[3,5,6] with a mean age of diagnosis of 53.8 years.[7]

The variation in co-occurring conditions and levels of intellectual disability among people with DS is substantial.[8–10] Lifelong conditions common in this population include: congenital heart defects, immunological dysfunctions, hypothyroidism, musculoskeletal dysfunction, vision and hearing impairment, sleep apnea,[11] and depression and anxiety.[12] Distinct patterns of age-related co-occurring conditions differ from both the general population and people with intellectual disability with other etiologies than DS.[13]

DS is considered a form of genetically determined AD, similar to autosomal dominant forms in other populations without DS.[14–17] In addition to the high genetic risk of AD in people with DS, the increase in life expectancy over the past decades,[3] has led to an increase in age-related co-occurring conditions.

Individuals with both DS and AD have higher rates compared with those of the same age without AD of hypothyroidism, sensory impairments, depression, anemia, weight loss, and epilepsy.[18,19] While previous studies have reported on these commonly co-occurring conditions, less is understood about their relationship with age of onset of AD in DS.

The influence of apolipoprotein E (*APOE*) ε4 can vary across age, sex, ethnicity, and nationality.[20–23] The association between *APOE* ε4 allele and increased risk and earlier age of onset in sporadic AD is well established.[24] This association is not as clear for age of onset in autosomal dominant AD.[22,23,25] AD in DS is an autosomal dominant form of AD and the connection between APOE ε4 and DS shows that APOE ε4 carriers has an earlier decline in episodic memory, earlier clinical diagnosis of symptomatic AD and earlier changes in AD biomarkers.[23]

Diagnosing AD in DS is complex due to the pre-existing intellectual disability, early cognitive decline, lack of diagnostic criteria and

various assessment procedures,[26–29] which may give rise to variability in diagnoses between clinicians and health systems. While our primary interest in this study was an exploration of the association between rates of co-occurring conditions and AD diagnosis, much can be gained from examining the rate of co-occurring conditions and age of AD diagnosis across different countries to inform public health policies, guide international collaborative research, and improve health surveillance. Researchers can investigate commonalities and differences between countries to identify novel risk factors, environmental influences, and clinical practices that may inform targeted screening and interventions. The need to harmonize diagnostic processes across countries has been recognized, and this has led to the establishment of research collaboration of the Horizon 21 European Down syndrome Consortium (H21DSC).[6,30] The H21DSC consists of 12 sites across Europe focused on clinical progression of the early stages of AD in DS, identifying and refining cognitive outcome measures, alongside harmonization of assessments and procedures and working together to identify feasible interim markers of disease progression by exploring the relationship between fluid biomarkers, neuroimaging, and the development of cognitive decline in DS.[6]

The aim of the current study was to examine the rates of co-occurring conditions and their relationship with AD diagnosis across different European countries. The goal was to identify whether there are differences in inter-country mean age of diagnosis as well as to identify conditions that should be targeted for better management to improve healthier aging in people with DS.

RESEARCH IN CONTEXT

1. **Systematic review**: The literature was retrieved using traditional electronic databases (e.g., PubMed, MEDLINE, Google Scholar) and snowball sampling. Several studies have used national or regional data to investigate age of Alzheimer's disease (AD) diagnosis in people with Down syndrome (DS) and associated factors, but few have included multi-country samples.
2. **Interpretation**: Despite differences in health services, the results of this novel, multi-country study consistently found a mean age of AD diagnosis in people with DS ranging from 51 to 56 years, suggesting that clinical diagnoses are reliably applied in people with DS. Sleep problems, mental health problems, and apolipoprotein E (*APOE*) ε4 carriers are factors strongly associated with age at AD diagnosis.
3. **Future directions**: AD diagnosis in people with DS is a reliable measure but there is a need for better identification and management of co-occurring conditions. Our findings have clinical and practical implications for the provision of health care and future research.

2 | METHODS

2.1 | Participants

A cross sectional sample of 1335 people with DS from six centers in five countries were included in this study. Participants were from the United Kingdom (the London Down Syndrome Consortium [LonDownS], the Cambridge Dementia in Down's Syndrome [DiDS] cohort), Germany (AD21 study group, Munich), France (TriAL21 for Lejeune Institute, Paris), Spain (the Down Alzheimer Barcelona Neuroimaging Initiative (DABNI), and the Netherlands (the Rotterdam Down syndrome study), all members of the H21DSC. Results are reported at country level to reflect potential differences in health care systems; therefore, the two samples in the United Kingdom were combined. Informed consent was obtained from participants in all sites.[31] The study was performed according to the Declaration of Helsinki and regulations for data privacy. All data were anonymized according to good clinical practice guidelines and general data protection regulations prior to analysis.

2.2 | Data collection and measurements

For each cohort, the sites obtained a comprehensive medical history and administered clinical assessments and cognitive tests—the different questionnaires and tests used are summarized elsewhere.[31] The authors harmonized interpretation of clinical diagnoses to ensure that data were comparable between sites and countries.

2.2.1 | Alzheimer's disease (AD) diagnosis

AD diagnoses were based on an agreed clinical consensus which were applied to all cohorts. Data across countries included age of assessment and age of AD diagnosis. Participants from the Netherlands were assigned to AD or No AD, all other sites were assigned to the following AD decline group:

1. **No cognitive decline**—that is, no clinical record of diagnosis of AD, and no symptoms of AD reported by carers.
2. **Cognitive concern associated with other causes**—some reports of cognitive OR activities of daily living (ADL) change, but most likely due to another condition such as an acute/active physical illness or new onset/ active mental health problem, or life event. Requires clinical surveillance and follow-up.
3. **Possible/prodromal AD**—individual presents with moderate/early but typical AD-like symptoms, but these are not sufficient to meet criteria for ICD-10, DSM-IV AD, or DSM-5 major neurocognitive disorder (but may meet criteria for DSM-5 mild neurocognitive disorder); the symptoms are thought not to be (mainly) due to another cause of decline (otherwise they would have been classified in category 2).

4. **Definite AD**—the individual has been diagnosed with AD by their own clinicians after comprehensive work-up OR they present with clear symptoms of AD after comprehensive (research) assessment. Both significant cognitive change AND decline in ADLs are present, which are judged not to be (mainly) due to other problems (i.e., AD may be diagnosed in the presence of treated/well-managed comorbidities).

2.2.2 | Clinical co-occurring conditions

Clinical diagnoses of common DS related co-occurring conditions were collected at each study site. These included diagnoses of epilepsy/seizures, sleep problems including obstructive sleep apnea (OSA) or other sleep disorders, hypothyroidism, and data on current mental health diagnosis including depression, anxiety, or psychosis. The threshold for mental health variables was a mental health condition that required treatment including psychological therapy without medication. Any current psychotropic medication prescription data was also collected including prescriptions for anti-depressants, anti-psychotics, hypnotics, and benzodiazepines. Current or history of sensory problems (hearing and/or vision) were recorded, as were data on any other medical morbidity associated with DS; this could include any additional and current acute or chronic physical illness requiring treatment/intervention not including disability such as mobility issues. The severity of intellectual disability in the United Kingdom, the Netherlands, and France was established based on the criteria outlined in ICD-10, while Germany and Spain used the criteria specified in DSM-5. These criteria are broadly similar.

2.2.3 | Apolipoprotein E status

Apolipoprotein E (APOE) status was also included in the analysis coded as non-$\varepsilon 4$ carriers, $\varepsilon 4$ carriers, and $\varepsilon 2$:$\varepsilon 4$ carriers. All sites except Germany contributed *APOE* genotyping data.

2.3 | Statistical analysis

Descriptive statistics were used to present participant characteristics by country and statistical testing was performed using Fisher's exact test for frequency data and the Kruskal–Wallis test for continuous data. Linear regression models were fitted to cross-sectionally estimate factors associated with the age of AD diagnosis in people with DS across the five countries. Due to missing data across the countries, as shown in Table 1 Demographic characteristics of participants, four separate linear regressions were fitted with differing variables to maximize the covariates examined and the inclusion of as many countries as possible in the analysis.

Model 1 consisted of sex, level of intellectual disabilities (mild, moderate and severe) and country (Spain, Germany, France, The Netherlands and the United Kingdom). Model 2 consisted of the variables in Model 1 and common DS morbidities (sleep problems, hypothyroidism, epilepsy/seizures) and current or history of sensory problems. Model 3 included Model 2 variables, with the addition of current mental health diagnosis and psychotropic medication prescriptions. The inclusion of these new variables excluded The Netherlands from Model 3 as data on mental health diagnosis and medication were missing in this dataset. Finally, Model 4 examined the effect of *APOE* status on age of AD diagnosis, similarly to the previous models, Model 4 included Model 2 variables and *APOE* status. Model 4 did not include Germany as *APOE* status was not available for participants. Spain was used as the reference group for all models as this country had the most AD cases. In a sub-analysis we examined the impact of the total number of morbidities (sleep problems, hypothyroidism, epilepsy/seizures, current mental health diagnosis, and any other medical morbidity) on the age of AD diagnosis, adjusting for sex, level of intellectual disabilities, current or history of sensory problems, country, and *APOE* status. This analysis used data from the United Kingdom and France as these were the only countries with data on all the variables of interest. In this model, France was the reference group.

The outcome variable in the regression models (age at AD diagnosis) was log transformed to avoid violation of normality and covariates were back transformed for reporting and presented as exp(β) with 95% confidence intervals (95% CIs). R version 4.1.3 used for statistical analysis.[32]

3 | RESULTS

Age, sex, level of intellectual disabilities, AD diagnosis status, mean age of AD diagnosis, and prevalence of co-occurring conditions across the five countries are shown in Table 1.

There were significant differences in the sex of participants between countries ($p = 0.003$) with the highest proportion of females in France (52.7%) and the lowest in the Netherlands (37.2%). Differences in level of intellectual disability of participants were also found ($p < 0.001$). The Netherlands had the highest proportion of people with a severe level of intellectual disabilities (38.4%) and Germany the lowest (14.3%).

3.1 | AD status

AD diagnosis status differed between countries ($p < 0.001$) with the lowest rate in the Netherlands at 15.6% and highest in Spain and Germany at 28%. A diagnosis of possible or prodromal AD was highest in the United Kingdom (11.8%) and lowest in France (4.3%), ($p < 0.001$).

Mean age at assessment differed between countries ($p < 0.001$) with those in Germany having an assessment earliest at an average of 37.5 years, followed by United Kingdom at 40.9 years, Spain at 45.2 year, France at 49.9 years, and those in the Netherlands having the highest average age at assessment at 51.7 years. These differences were seen also in average age of AD diagnosis ($p = 0.002$) where those in the United Kingdom were diagnosed on average youngest at 51.4 years,

TABLE 1 Demographic characteristics of participants divided by country.

Variable	Spain	France	Germany	The Netherlands	UK	*p*-Value of comparison
n	311	188	42	417	377	
Sex						
Male	169 (54.3)	89 (47.3)	25 (59.5)	262 (62.8)	197 (52.3)	0.003
Female	142 (45.7)	99 (52.7)	17 (40.5)	155 (37.2)	180 (47.7)	
Mean age at assessment (SD)	45.19 (10.83)	49.86 (7.43)	37.48 (13.6)	51.69 (5.05)	40.91 (13.51)	<0.001
Level of ID						
Mild	63 (20.3)	20 (10.9)	21 (50.0)	54 (12.9)	137 (37.0)	<0.001
Moderate	160 (51.4)	124 (67.4)	15 (35.7)	203 (48.7)	175 (47.3)	
Severe	88 (28.3)	40 (21.7)	6 (14.3)	160 (38.4)	58 (15.7)	
AD diagnosis	87 (28.0)	48 (25.5)	12 (28.6)	65 (15.6)	64 (17.1)	<0.001
Mean age of AD diagnosis (SD)	53.47 (5.53)	55.6 (6.8)	53.62(5.24)	55.13 (4.15)	51.4 (7.02)	0.002
AD decline rating						
No cognitive decline	181 (58.2)	104 (55.3)	22 (52.4)		219 (58.9)	<0.001
Cognitive concern other causes	18 (5.8)	28 (14.9)	4 (9.5)		45 (12.1)	
Possible/ prodromal AD	25 (8.0)	8 (4.3)	4 (9.5)		44 (11.8)	
Definite AD	87 (28.0)	48 (25.5)	12 (28.6)		64 (17.2)	
Current mental health diagnosis						
Yes	28 (9.0)	67 (35.6)	12 (29.3)		83 (22.8)	<0.001
Currently prescribed psychotropic medication						
Yes	126 (50.0)	66 (35.1)	7 (17.5)		75 (20.1)	<0.001
Epilepsy/seizures diagnosis						
Yes	61 (19.6)	35 (18.6)	7 (17.1)	87 (24.4)	57 (16.9)	0.15
Sleep problems						
Yes	30 (10.1)	88 (46.8)	4 (9.8)	43 (12.4)	38 (11.4)	<0.001
Hypothyroidism						
Yes	145 (46.8)	103 (54.8)	22 (53.7)	88 (23.5)	147 (40.8)	<0.001
Current or history of sensory problems (hearing and/or vision)						
Yes	148 (61.9)	69 (36.7)	7 (17.5)	337 (82.4)	318 (84.6)	<0.001
Any other medical comorbidity						
Yes		82 (43.6)	32 (80.0)		287 (76.5)	<0.001
APOE status						
Non-e4	238 (79.6)	142 (77.2)		305 (73.1)	268 (71.1)	0.04
e4 carriers	57 (19.1)	39 (21.2)		94 (22.5)	101 (26.8)	
e2: e4	4 (1.3)	3 (1.6)		18 (4.3)	8 (2.1)	

Notes: Percentage in parentheses unless otherwise stated.
Abbreviations: *APOE*, apolipoprotein E; ID, intellectual disability; UK, United Kingdom;

with Spain (53.5 years) and Germany (53.6 years) at similar ages and The Netherlands (55.1 years) and France (55.6 years) diagnosed on average approximately 2 years later.

3.2 | Co-occurring conditions and *APOE* status

There were significant differences between countries in the prevalence of co-occurring conditions ($p < 0.001$). A mental health condition was diagnosed in 9% of participants in Spain compared to 35.6% in France, 29.3% in Germany, and 22.8% in the United Kingdom. Half of participants in Spain were prescribed psychotropic medication compared to 17.5% in Germany, 20.1% in the United Kingdom, and 35.1% in France, ($p < 0.001$). Participants in France had the highest level of diagnosed sleep problems (including OSA) at 46.8% compared to 9.8%–12.4% in all other countries. No significant difference was found in epilepsy diagnosis between the five countries ($p = 0.15$) where the United Kingdom had the lowest at 16.9% and the Netherlands the highest at 24.4%.

3.3 | Factors associated with age of AD diagnosis

Table 2 presents the results of four linear regression models conducted to examine the factors associated with the age of AD diagnosis in people with DS across the five European countries.

Model 1 examined the association between age at AD diagnosis and sex, level of intellectual disabilities, and country. Being female was associated with a younger age of diagnosis (exp(β) = 0.97 (95% CI 0.94-1.00) than males. Compared to people with DS in Spain, participants in France (exp(β) = 1.04 (1.00-1.08) were more likely to be diagnosed at a later age and being from the United Kingdom was significantly associated with a younger age of diagnosis (exp(β) = 0.96 (0.92-0.99). Model 2 added sleep problems, hypothyroidism, epilepsy, and history of sensory problems, none of which were associated with age of AD diagnosis.

Model 3 added mental health diagnosis and psychotropic medication, this model did not include data from the Netherlands. We found that current mental health diagnosis was associated with a younger age of AD diagnosis (expβ = 0.93, 0.89-0.98) but not use of psychotropic medication. Being from France was again associated with an older age of AD diagnosis compared to Spain (exp(β) = 1.12, 1.05-1.19)

Model 4 included *APOE* status but did not include Germany as *APOE* data were not available. Being female was associated with a younger age of diagnosis (exp(β) = 0.97, 0.94-1.00), and participants in France were diagnosed at an older age (exp(β) = 1.08, 1.03-1.13). *APOE* status was found to be significantly associated with age of AD diagnosis, with *APOE* ε4 carriers being diagnosed at a younger age than non-ε4 carriers (exp(β) = 0.93, 0.90-0.97).

Investigating the impact of the total number of co-occurring conditions on age of AD diagnosis we found that the total number of co-occurring conditions present was negatively associated with age of AD diagnosis (exp(β) = 0.97, 0.95-0.99, $p = 0.02$). In this model, as the total number of common DS morbidities increased, the age of AD diagnosis decreased. Participants in the United Kingdom were diagnosed earlier than in France (exp(β) = 0.93, 0.87-0.99, $p = 0.02$), and being an *APOE* ε4 carrier was associated with earlier AD diagnosis (exp(β) = 0.92, 0.87-0.98, $p = 0.006$). Sex, level of ID, and current or history of sensory problems were not associated with age of diagnosis (all $p > 0.05$).

4 | DISCUSSION

To our knowledge, this is one of the largest studies to examine age of AD diagnosis in people with DS and the association with co-occurring conditions and *APOE* status. While there were statistically significant differences, age of AD diagnosis was relatively stable across countries, ranging from 51 to 56 years old. We found that, compared to Spain where the mean age of AD diagnosis was 53 years old, participants in France were diagnosed slightly older at 56 years old and younger in the United Kingdom at 51 years old. Data here support recent findings from a meta-analysis that reported a mean age of diagnosis across studies of 53.8 years.[7] As expected, being an *APOE* ε4 carrier was associated with a younger age of diagnosis.

4.1 | Co-occurring conditions and association with AD

There were significant differences in the prevalence of common co-occurring conditions across countries, and differences in data collection could influence these differences. Current mental health diagnosis and sleep problems were associated with age of AD diagnosis. The number of co-occurring conditions were important for age of diagnosis where more conditions were associated with earlier age of AD diagnosis. At a systemic level, there may be explanations for differences in national health systems, and at an individual level, it may be that individuals with more co-occurring conditions see clinicians more regularly, resulting in earlier diagnosis. Longitudinal studies conducted prospectively could help to explore these issues more clearly.

4.2 | Sex differences and association with AD

In the general population, lifetime incidence of AD is higher for females than males,[33] where genome-wide association studies stratified by sex have shown differences in loci associated with AD between male and female.[34] This difference is less clear in the DS population, where some studies found no overall relationship between sex and AD diagnosis,[24,35] others identified a higher risk of AD for females in the age group 40 to 54 years but not for those under 40 years and over 55 years of age,[36] and another found sex differences in adults with DS but only over the age of 60, where males were more likely to develop AD than females.[37] In this study, being female was associated with a younger age of diagnosis in the model that included sleep problems, hypothyroidism, sensory problems, epilepsy, and *APOE* status. However, we did not stratify by age groups; therefore, it is currently unclear if there was an age group—dependent risk for diagnosis in females as previously reported.

TABLE 2 Factors associated with age of AD diagnosis across DS research groups in Europe.

	Model 1*		Model 2**		Model 3***		Model 4****	
Variable	**exp(β) (95% CI)**	***p*-Value**	**exp(β) (95% CI)**	***p*-Value**	**exp(β) (95% CI)**	***p*-Value**	**exp(β) (95% CI)**	***p*-Value**
Sex								
Male	Ref.		Ref.		Ref.		Ref.	
Female	0.97 (0.94-1.00)	0.02	0.98 (0.95-1.01)	0.11	0.97 (0.93-1.00)	0.08	0.97 (0.94-1.00)	0.03
Level of ID								
Mild	Ref.		Ref.		Ref.			
Moderate	1.01 (0.98-1.05)	0.48	1.01 (0.96-1.05)	0.79	1.01 (0.96-1.06)	0.71	1.01 (0.96-1.05)	0.82
Severe	1.02 (0.98-1.06)	0.39	1.02 (0.97-1.07)	0.47	1.01 (0.96-1.07)	0.68	1.01 (0.96-1.06)	0.60
Country								
Spain	Ref.		Ref.		Ref.		Ref.	
Germany	1.00 (0.94-1.06)	0.96	1.01 (0.94-1.08)	0.80	1.04 (0.95-1.12)	0.41		
France	1.04 (1.00-1.08)	0.04	1.07 (1.02-1.12)	0.006	1.12 (1.05-1.19)	0.0003	1.08 (1.03-1.13)	0.003
The Netherlands	1.03 (1.00-1.07)	0.08	1.02 (0.98-1.07)	0.35			1.03 (0.98-1.07)	0.24
UK	0.96 (0.92-0.99)	0.03	0.96 (0.92-1.00)	0.06	0.99 (0.94-1.05)	0.77	0.97 (0.93-1.02)	0.25
Sleep problems			0.96 (0.92-1.01)	0.10	0.95 (0.90-1.00)	0.06	0.95 (0.91-1.00)	0.04
Hypothyroidism			0.98 (0.95-1.01)	0.17	0.99 (0.95-1.02)	0.43	0.97 (0.94-1.01)	0.12
Epilepsy/seizures			0.98 (0.95-1.01)	0.23	0.98 (0.95-1.02)	0.34	0.99 (0.96-1.02)	0.54
Current or history of sensory problems			1.02 (0.98-1.06)	0.32	1.03 (0.99-1.08)	0.17	1.01 (0.97-1.05)	0.54
Current mental health diagnosis					0.93 (0.89-0.98)	0.01		
Currently prescribed psychotropic medication					1.03 (0.99-1.08)	0.18		
APOE status								
Non-ε4							Ref.	
ε4 carriers							0.93 (0.90-0.97)	0.0004
e2: ε4							1.00 (0.93-1.08)	0.93
Model statistics	R-squared: 0.10, F-statistic: 4.06 on 7 and 263 DF, *p*-value: 0.0003		R-squared: 0.12, F-statistic: 2.47 on 12 and 218 DF, *p*-value: 0.005		R-squared: 0.15, F-statistic: 2.29 on 12 and 152 DF, *p*-value: 0.01		R-squared: 0.18, F-statistic: 3.50 on 12 and 194 DF, *p*-value: 0.0001	

Notes: Spain was used as the reference group for all models as this country had the most AD cases.

Abbreviations: ID, intellectual disabilities; *APOE*, apolipoprotein E.; CI, confidence intervals; UK, United Kingdom.

*Model 1 consisted of sex, level of intellectual disabilities (ID) (mild, moderate and severe) and country (Spain, Germany, France, The Netherlands and the United Kingdom).

**Model 2 consisted of the variables in Model 1 and common DS morbidities (sleep problems, hypothyroidism, epilepsy/seizures) and current or history of sensory problems.

***Model 3 included Model 2 variables, with the addition of current mental health diagnosis and psychotropic medication prescription. The inclusion of these new variables excluded The Netherlands from Model 3 as data on mental health diagnosis and medication were missing in this dataset.

****Model 4 examined the effect of APOE status on age of dementia diagnosis, similarly to the previous models, Model 4 included Model 2 variables and APOE status. Model 4 did not include Germany as APOE status was not available for participants.

4.3 | *APOE* and association with AD

The association between *APOE* ε4 allele with increased risk in sporadic AD is well established, with increased amyloid deposition, cortical thinning, and decreased cognition,[24] and earlier age of onset. In autosomal dominant AD, the association with earlier age of onset is not as unambiguous and is mostly explained by the influence of the autosomal dominant genetic mutations that drive this rare form of AD.[24] Previous studies in populations with DS have also found an attentional disadvantage later in life,[38] greater cognitive impairment,[39] earlier age of symptom onset of 2 years,[23] and an earlier age of AD diagnosis[40] for *APOE* ε4 carriers. Data on *APOE* ε4 in this study were available for 1,293 participants across four countries. Findings here reflected those of previous studies, where *APOE* ε4 carriers received an AD diagnosis at a younger age compared to non-carriers.

4.4 | Sleep problems and association with AD

Sleep problems are more common in people with DS than in the general population, particularly in relation to OSA. The prevalence is reported up to 17% in the general population and OSA of at least moderate severity may be found in more than 40% of individuals with DS.[41–44] Evidence suggests that untreated sleep disorders impair cognitive function and may accelerate progression to AD.[45] Findings here support this, where sleep problems, which included OSA and other sleep disorders, were associated with earlier age of AD diagnosis in the model that included hypothyroidism, epilepsy, sensory problems, and *APOE* status. Animal studies suggest a bidirectional relationship between sleep problems and amyloid accumulation, whereby sleep deprivation can increase accumulation, while increased accumulation also has a disruptive effect on sleep.[46] In a study by Cody et al.,[47] individuals with DS who had mild cognitive impairment and increased accumulation of beta amyloid had higher levels of sleep problems compared to those with lower amyloid burden. As with the current study, the directionality of this relationship could not be tested.

We found that prevalence of diagnosed sleep disorders was higher in France (46.8%) compared to other countries (9.8%-12.4%) attesting to differences in practices across countries in screening for comorbidities. This speaks to the need for a harmonized approach to screening for commonly known co-occurring conditions across countries for people with DS. Screening for and improved management of treatable conditions could lead to improvement in quality of life, and with potential to delay symptoms of AD.

4.5 | Mental health problems and association with AD

In the model that included sleep problems, hypothyroidism, sensory problems, and psychotropic medication, mental health problems were significantly associated with earlier age of AD diagnosis, as was the total number of these common morbidities. Mental health problems here included depression, anxiety, and psychosis where a threshold was met for psychological therapy, but without medication. This supports previous research that found that there appears to be a stronger relationship with comorbid depression for those with DS diagnosed at an earlier age.[4] Depression in later life has been identified as a factor that could potentially contribute to 4% reduction in AD risk if treated; however, it is also recognized that this can have a bidirectional effect and be a prodrome to AD.[48] As with all modifiable risk factors, this has yet to be tested in a population with a genetic risk for AD and thus the potential for delaying symptoms onset if depression is treated is unknown. Past recommendations on differential diagnosis and active treatment of depression remain.

4.6 | Level of intellectual disabilities and association with AD

There was variation between countries in level of intellectual disability of participants included in this study; however, consistent with previous research,[49] no relationship was found between level of intellectual disability and age of AD diagnosis overall, even when adjusting for common clinical variables and *APOE* status. This differs from what is expected in the general population, where the risk for AD is higher for those with lower IQ.[48] There may be cognitive, biological, and methodological explanations for this.[50] People with more severe/profound ID have lower life expectancy than those with mild/moderate ID.[49,51] This may result in a shorter age range at risk. Methodological explanations for the absence of differences may also include complexity of diagnosis in those with more severe level of ID. Additionally, those with severe ID often have a high degree disability and reduced functional ability which means that changes in skills and daily functioning are of limited use to assess symptoms of AD.[9,50,52–54]

4.7 | Limitations

Although this is the largest study of factors of age of diagnosis of AD in DS ever reported, limitations include that the populations between countries varied somewhat in terms of age and in sample size. Some within-groups analyses therefore had limited power. Different national health systems may have an impact on AD diagnosis across countries due to factors such as available resources, healthcare infrastructure, and cultural differences. We were not able to control for these factors but aimed to minimize it by using data from expert centers using comparable methods of assessment and diagnosis. Furthermore, data on some of the variables related to co-occurring conditions and *APOE* status were not available in all cohorts; this was managed by conducting a series of analyses. Finally, some potentially related factors were not measured or included in the analysis, such as education level, social interactions, or less common co-occurring conditions.

5 | CONCLUSIONS

The results of this large, multi-country study consistently support previous evidence of a mean age of AD diagnosis in the first half of the

fifth decade of life among adults with DS. Age at diagnosis was relatively consistent across Europe despite differences in health services, suggesting that clinical diagnoses are reliably applied in people with DS. As in previous studies, *APOE ε4* carriers received an AD diagnosis at a younger age compared to non-carriers. However, rates of diagnosed co-occurring conditions varied, and sleep and mental health problems were associated with an earlier age of AD diagnosis. Better identification and management of co-occurring conditions may delay onset of AD in people with DS, and our findings have clinical and practical implications by informing the development of health services, targeted healthcare guidance, future research, and treatment.

AUTHOR CONTRIBUTION

Conceived and design of the study: Andre Strydom, R. Asaad Baksh, Eimear McGlinchey, Frode Kibsgaard Larsen, and Ellen Melbye Langballe. Data cleaning, data processing, and statistical analysis: R. Asaad Baksh. Analysis and interpretation of data: Eimear McGlinchey, Frode Kibsgaard Larsen, Ellen Melbye Langballe, Andre Strydom, and R. Asaad Baksh. Initial drafts of the final manuscript: Frode Kibsgaard Larsen, Eimear McGlinchey, and R. Asaad Baksh. Revising the article critically for important intellectual content: Ellen Melbye Langballe, Andre Strydom, Frode Kibsgaard Larsen, R. Asaad Baksh, Eimear McGlinchey, Bessy Benejam, Ruth Mark, and Antonia Coppus. Performed research activities and participated in discussions: Andre Strydom, R. Asaad Baksh, Eimear McGlinchey, Frode Kibsgaard Larsen, Ellen Melbye Langballe, Jessica Beresford-Webb, Mary McCarron, Segolene Falquero, Juan Fortea, Johannes Levin, Sandra Loosli, Anne-Sophie Rebillat, and Shahid Zaman. All authors read and approved the manuscript.

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CONFLICT OF INTEREST STATEMENT

Dr. Juan Fortea reported receiving personal fees for service on the advisory boards, adjudication committees or speaker honoraria from AC Immune, Adamed, Alzheon, Biogen, Eisai, Esteve, Fujirebio, Ionis, Laboratorios Carnot, Life Molecular Imaging, Lundbeck, Perha, Roche, and, outside the submitted work. Dr. Juan Fortea report holding a patent for markers of synaptopathy in neurodegenerative disease (licensed to Adx, EPI8382175.0). Dr. Johannes Levin reports speaker fees from Bayer Vital, Biogen, EISAI, TEVA, Zambon, Merck, and Roche; consulting fees from Axon Neuroscience, EISAI, and Biogen; author fees from Thieme medical publishers and W. Kohlhammer GmbH medical publishers; and is inventor in a patent "Oral Phenylbutyrate for Treatment of Human 4-Repeat Tauopathies" (EP 23 156 122.6) filed by LMU Munich. In addition, he reports compensation for serving as chief medical officer for MODAG GmbH, is beneficiary of the phantom share program of MODAG GmbH and is inventor in a patent "Pharmaceutical Composition and Methods of Use" (EP 22 159 408.8) filed by MODAG GmbH, all activities outside the submitted work. Dr. Andre Strydom received funding from AC Immune and is an adviser to ProMIS neurosciences. All other authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

Informed consent from all participants or their legally authorized representatives was obtained in all cohorts before enrollment.

ORCID

Frode Kibsgaard Larsen https://orcid.org/0000-0003-4929-4137
R. Asaad Baksh https://orcid.org/0000-0001-6596-2145

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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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