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RESEARCH ARTICLE

Sex differences in risk of Alzheimer's disease in adults with Down syndrome

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Abstract

Introduction: Adults with Down syndrome (DS) older than 40 have Alzheimer's disease (AD) neuropathology and high risk for dementia, but little is known about the relationship of sex to AD risk in this population.

Methods: Using nonparametric methods and Cox proportional hazards models we analyzed differences in incidence of dementia, by sex, presence of an apolipoprotein E (*APOE*) ε4 or ε2 allele, and dementia duration and decline in 246 adults over 40 with DS.

Results: There was no significant sex difference in risk of AD or rate of cognitive decline. *APOE* ε4 allele significantly increased risk of AD irrespective of sex. No significant interactions were found between sex and *APOE* status on AD risk. Among those who died, dementia duration was significantly longer in women.

Discussion: This study showed no effect of sex nor interaction between sex and APOE for risk of AD in adults with DS; however, women had longer dementia duration.

KEYWORDS
Alzheimer's disease, apolipoprotein ε2 allele, apolipoprotein ε4 allele, cognitive decline, dementia duration, Down syndrome, sex differences in Alzheimer's disease

1 | BACKGROUND

Adults with Down syndrome (DS) are at high risk for Alzheimer's disease (AD) and virtually all adults develop AD-associated neuropathology by 40 years of age.[1] In less than a century, life expectancy for individuals with DS has increased from an average of 12 years[2] to ≈ 60 years of age[3] and a large increase in AD among adults with DS can be expected. The high risk of AD in those with DS is thought to be

due to the early and increased deposition of amyloid beta (Aß) in the brain from overexpression of the gene for the precursor of Aß, which is triplicated on chromosome 21.[4] Although there are neuropathological, neurochemical, and neurophysiological parallels between AD in adults with DS and late-onset AD (LOAD) in the neurotypical population,[3] the mean age of onset of AD is in the early 50s in adults with DS,[5,6] two to three decades earlier than in the general population. In addition, there is considerable variation in age at onset of dementia in adults with DS, ranging from under 40 to over 70 years of age,[3] suggesting that factors other than triplication of the gene for the precursor of Aß may modify risk or affect clinical progression. These factors may provide potential targets for intervention to delay or prevent onset of AD.

Major known risk factors for LOAD are age; the presence of an Apolipoprotein ε4 allele (*APOE ε4*), which has been associated with an increased risk for LOAD;[7] and sex, where the risk of AD appears to be greater in women compared to men, independent of the longer life expectancy for women.[8] The literature is inconsistent with respect to the differential effects of sex on AD, with several studies finding either no difference between men and women in incidence of AD[9] or a significant effect of age and sex on risk of AD, as the incidence of AD is higher in women in the older age range.[10,11] Several lines of investigation have shown a protective role for estrogen in LOAD[12,13] and the loss of estrogen has been identified as an important factor in the increased risk of AD in women after menopause.[14,15] Sex may also have an effect on rate of cognitive decline after onset of AD[16] and it appears that women with AD have worse cognitive impairment than men at baseline[17] and may decline faster.[18] A recent review on the differential effect of sex on AD highlights knowledge gaps in many aspects of risk factors of progression and biomarkers for AD in the general population and the need for further study.[19]

Several risk factors for AD in DS have also been identified, including age and the presence of an *APOE ε4*;[20-22] however, much less is known about the relationship of sex to risk of AD or to rates of progression in adults with DS, and the few existing reports have been inconsistent.[23,24] One community-based study of ≈ 100 individuals with DS[23] found that men had an earlier onset and an almost three-fold greater risk for AD than women; however, another similarly powered study[24] found that females had a higher risk for developing AD. Even less is known about the interaction of these risk factors and risk for AD in the DS population.

APOE plays a central role in plasma lipoprotein metabolism and lipid transport within tissues, binds to the Aβ peptide, and plays a role in clearing this peptide from the brain.[7] The *APOE* ε4 allele has been associated with higher levels of total and low-density lipoprotein (LDL) cholesterol, and with increased risk for cardiovascular disease and diabetes; the *APOE* ε2 allele has been associated with decreased risk for AD.[25] The presence of an *APOE ε4 allele* in the neurotypical population is not only a risk factor for AD but may also confer greater risk of AD to women than men.[26-28] This interaction may be further modified by age, as women in the younger age brackets (65–75 years of age) have greater risk for AD than men.[29] Although the effect of the *APOE* ε4 haplotype on risk of AD in adults with DS has been confirmed,[20-22] the interaction of sex and *APOE* ε4 in DS has not been studied. Therefore, a larger study could provide a more reliable determination of sex-related risk for AD and any sex-related effect of *APOE ε4* in individuals with DS.

In our analysis of a cohort of adults with DS, we address four questions related to effects of sex, and the presence of an *APOE ε4* or ε2 allele, on risk for AD: (1) Is there a sex difference in the risk for development of AD? (2) Is there a sex difference in risk for AD in those who carry the ε4 or ε2 alleles? (3) Is there a sex difference in the duration of AD? (4) Is there a sex difference in rate of cognitive decline after the onset of AD?

HIGHLIGHTS

- No sex difference in Alzheimer's disease (AD) risk in adults with Down syndrome (DS).
- Apolipoprotein ε4 increases risk for AD in DS without sex difference.
- Rate of cognitive decline of AD in adults with DS showed no sex difference.
- Women with DS have longer duration of AD than men with DS.

RESEARCH IN CONTEXT

1. **Systematic review:** Alzheimer's disease (AD) is prevalent in adults with Down syndrome (DS) with many parallels with late onset AD (LOAD) in the neurotypical population. Careful review of the literature using traditional (eg, PubMed) sources indicated that sex differences in the risk for AD in DS are not fully understood. Prior studies had a mix of prevalent and incident cases of AD or had low numbers of participants.
2. **Interpretation:** Our study of only incident cases of AD in a large cohort of adults with DS (N = 246) with long follow-up (≈8.5 years) demonstrates longer duration of AD in women versus men with DS, but no sex differences in risk for AD while accounting for the role of apolipoprotein E (*APOE*) genotype and other covariates, including presence of an *APOE ε4* allele.
3. **Future directions:** The role of genetic, hormonal, and environmental factors on the longer duration of AD in women with DS deserves further investigation.

TABLE 1 Demographic characteristics of the cohort by dementia status

Characteristic N (%)	Total N = 246	Cognitively stable N = 91 (37%)	Demented N = 155 (63%)
Age at first visit: Mean years (S.D.)	46.7 (5.2)	45.5 (4.8)	47.3 (5.3)*
Sex: N (%)			
Male	151 (61.4)	54 (35.8)	97 (64.2)
Female	95 (38.6)	37 (38.9)	58 (61.1)
Level of intellectual disability N (%)			
Mild/moderate	150 (61.0)	55 (60.4)	95 (61.3)
Severe/profound	96 (39.0)	36 (39.6)	60 (38.7)
Apolipoprotein genotypes: N (%)	N = 184	N = 58	N = 126
APOE ε4 allele	38 (20.7)	9 (15.5)	29 (23.0)
APOE ε2 allele	30 (16.3)	9 (15.5)	21(16.7)
Hypothyroidism: N (%)	139 (57.2)	47 (52.8)	92 (59.7)
High cholesterol: N (%)	75 (30.5)	29 (31.6)	46 (29.7)
BMI (SD)	30.2 (6.6)	30.8 (6.6)	30.2 (6.3)
Diabetes: N (%)	8 (3.3)	5 (5.5)	3 (1.9)

*$P < .05$

Abbreviations: APOE, apolipoprotein E; BMI, body mass index; SD, standard deviation.

2 | METHODS

2.1 | Study population

The study sample consisted of 246 adults with DS 40 years of age and older, who were selected from among 758 adults who were consecutively evaluated at a Partners Neurology specialty clinic for adults with DS, where information was collected from both the patients and care providers or family members. Individuals were excluded from the analysis if they had a diagnosis of prevalent dementia, were under 40 years of age at the first visit, had no follow-up visits after the initial visit, or lacked standardized testing that was used in the determination of dementia.

The study population was composed of 95 (38.6%) females and 151 (61.4%) males, who were 40 to 66 years old, and nondemented at the time of the initial visit (mean 46.7 ± 5.2). The 246 participants were classified into two main groups by level of intellectual disability (LID) before the onset of dementia based on IQ scores, historical designation, or clinical determination to account for the potential influence of LID on cognitive scores: (1) N = 150 mild/moderate (IQ 40–70, at least good activities of daily living [ADL] skills, language with at least short sentences) and (2) N = 96 severe/profound (IQ < 40, at least some help needed for ADL skills, language in short phrases or nonverbal, Table 1). Institutional Review Board approval for a medical records review was obtained from Massachusetts General Hospital.

2.2 | Clinical assessments

Regular assessments were conducted every 2 years for those 40 to 50 years old if they did not show any decline from the previous assessment, and yearly for those showing some decline from the previous visit or anyone over 50. The average duration of follow-up for the study sample was 8.4 ± 4.9 years. Clinical assessments involved evaluation of: (1) medical status (including risk factors for dementia such as body mass index [BMI], LID, hypothyroid status, as well as risk factors for cerebrovascular disease including diabetes or hypercholesterolemia, which could contribute to cognitive dysfunction; (2) educational and vocational history, functional ability; and (3) cognition, including scores on the Test of Severe Impairment (TSI,[30] which includes 24 items assessing language, memory, executive function, and motor performance), scores on the 1-minute Verbal Fluency Tests (animals and foods)[31] and scoring of cognitive and non-cognitive/social realms on the Dementia Questionnaire for People with Learning Disabilities (DLD, a 50 item questionnaire covering the areas of short-term and long-term memory, spatial and temporal orientation, speech, practical skills, mood, activities and interest, and behavioral disturbance).[32] Higher scores on the TSI and Verbal Fluency Tests were associated with better performance; higher scores on the DLD indicated worsening performance.

2.3 | Determination of dementia of the Alzheimer type

Based on information from all available sources, dementia was determined based on a decline in function in two or more areas that was sustained for at least 1 year. Decline in scores on the TSI and on the Verbal Fluency Tests, and worsening function on the DLD were also factored.

2.4 | Apolipoprotein E (*APOE*) genotyping

APOE genotyping was done using standard methods.[33] Of the 246 participants, 186 had genotyping. As those with *APOE ε2* and *APOE ε4* have opposing effect on risk of AD in the general population, two participants with *APOE ε2/ε4* genotype were excluded.

2.5 | Statistical analysis

The Kaplan Meier curve is a non-parametric statistic used to estimate the time to event (or survival time) from a defined starting point and is typically used for exploratory analysis before regression models.[34] The unadjusted Kaplan Meier curve was used prior to conducting the Cox regression models, to assess the effect of sex on age at onset of AD from the age at the initial visit, and the effect of sex on duration from onset of AD to death. We conducted statistical analyses based on data

from those individuals who were AD-free at baseline and used age of AD onset as the outcome variable.

We also conducted a longitudinal data analysis to identify sex differences in cognitive decline after onset of AD for the following five cognitive measures: TSI, Verbal Fluency Test-Animals (VFTA), Verbal Fluency Test-Foods (VFTF). Dementia Questionnaire for People with Learning Disabilities (DLD) related to cognitive functions (DLD-Cog) and non-cognitive social domains (DLD-Soc). Using the mixed-effect model with the cognitive measure as the outcome, we fitted the model with covariates including onset age of AD, sex, time since AD onset, and the interaction term of sex and time since AD onset: $Y_{ij} = \beta_0 + \beta_1 W_i + \beta_2 X_i + \beta_3 t_{ij} + \beta_4 X_i t_{ij} + b_{0i} + b_{1i} t_{ij} + \varepsilon_{ij}$ where Y_{ij} is the outcome variable measured at t_{ij} for the ith individual; W_i = age at onset of AD; X_i = sex indicator; t_{ij} = time since age of AD onset; $\beta_0, \beta_1, \beta_2, \beta_3, \beta_4$: fixed effects; b_{0i}, b_{1i}:random effects; ε_{ij}: error term.

The analyses properly accounted for both left truncation and right censoring to ensure unbiased analytical results.[36] The terminology "left truncation" refers to a type of sampling bias which occurs when the data sample includes only individuals who were AD-free at baseline, as the data sample truncates (excludes) those who were diagnosed with AD at baseline (prevalent cases). "Right censoring" refers to the sampling constraint where age of AD onset cannot be observed due to limited follow-up time.

3 | RESULTS

3.1 | Baseline characteristics

The mean age of the cohort at the initial assessment was 46.7 ± 5.2 years with no statistical difference between men and women (mean ages 46.4 ± 4.9 years vs 47.1 ± 5.7 years, $P = .26$). Among the 246 participants in the study, 91 (37%) remained cognitively stable while 155 (63%) developed dementia over the course of follow-up: 97 men and 58 women (64.2% vs 61.1%, $P = .61$). Participants who developed dementia were significantly older at the initial assessment than those who remained cognitively stable (mean age 47.3 ± 5.3 vs 45.5 ± 4.8 years, $P = .008$; Table 1). Although the mean years of follow-up was 8.5 years for the whole group, those with incident dementia were followed significantly longer than those who remained dementia-free (9.5 ± 4.7 vs 6.9 ± 4.8 years, $P < .01$). When the cohort was divided into a cognitively stable group and a demented group, the following characteristics were not significant between the two groups: (1) mild/moderate LID (60.4% vs 61.3%), severe/profound LID (38.6% vs 38.7%; $P = .89$); (2) history of hypothyroidism (52.8% vs 59.7%, $P = .14$); (3) hypercholesterolemia (31.6% vs 29.7%, $P = .72$); (4) BMI (30.7 vs 30.2, $P = .52$); and (5) diabetes (5.5% vs 1.9%, $P = .13$).

3.2 | Relation of sex to risk for AD

Among the 155 individuals with dementia in the study, there was no statistical difference in the mean age of AD onset between men and women (53.9 ± 5.7 vs 53.1 ± 5.9, $P = .39$). The estimated hazard curves for males and females showed that women had higher risk of developing AD, but the difference was not significant (Figure 1). Cox regression analyses adjusted for LID were conducted based on sample size N = 246 to examine the relationship of sex to risk of developing AD. Overall, there was no significant effect of sex on risk for AD (hazard ratio [HR] 1.26, confidence interval [CI]: 0.90 to 1.76, $P = .18$). Although women had a higher incidence of hypothyroidism than men in the cohort (F 68.1%, M 53.5%, $P = .033$), there were no significant differences between men and women in the incidence of the other medical comorbidities. Similarly, the effect of sex on risk for AD did not change when the comorbid conditions (hypothyroidism, obesity-BMI > 30, high cholesterol, and diabetes were added to the analyses (HR = 1.22, CI: 0.85 to 1.75, $P = .28$).

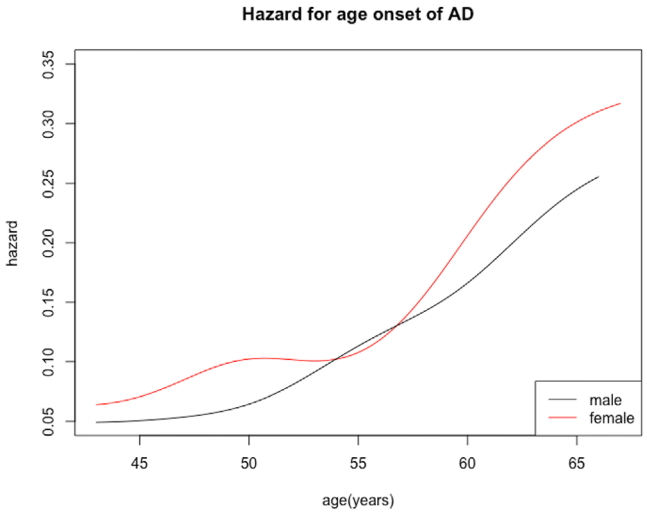

FIGURE 1 Risk of developing Alzheimer's disease in males (blue) and females (red) with Down syndrome after age 40. Females had higher risk than males, but the difference was not significant

3.3 | Relationship of sex to *APOE* genotype

Among the 246 participants in the study, 184 had *APOE* genotypes for analysis after excluding two individuals with the *APOE-ε2/ε4* genotype. Of the 184 adults with DS who were genotyped, 115 (62.5%) were men and 69 (37.5%) were women. These percentages were very similar to the sex distribution of the whole cohort (61.4% men and 38.6% women). When further divided for the subanalyses, 40 individuals carried the *APOE ε4* allele: 17 (58.6%) men and 12 (41.4%) women, and 30 carried the *APOE ε2* allele: 21 (55.3%) men and 17 (44.7%) women. Age at onset of AD was significantly lower in those with the *APOE ε4* allele compared to those with the reference *APOE-ε3/ε3* (50.6 ± 5.1 vs 54.6 ± 5.8, $P < .001$), and there was no difference between men and women who carried the *APOE ε4* allele with respect to their mean age of AD onset (M: 50.47 ± 4.9; F: 50.67 ± 5.5).

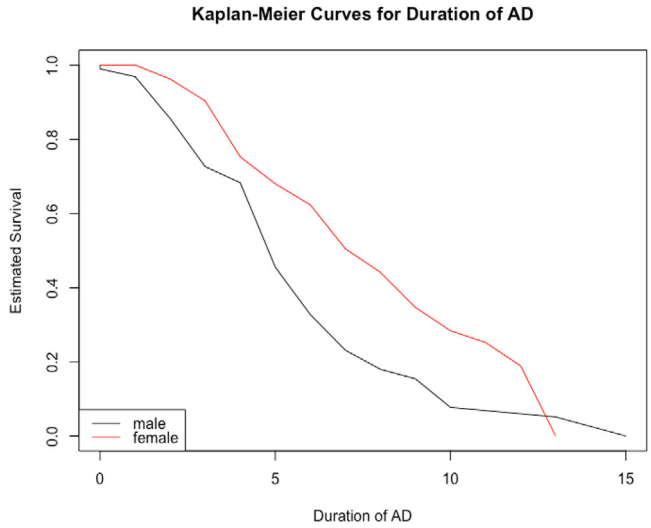

FIGURE 2 Duration of Alzheimer's disease (AD) in males (blue) and females (red) with Down syndrome from AD onset until death. Mean duration in males 51 ± 3.1 years versus females 6.73 ± 3.3 years ($P = .02$)

We used a Cox regression model that included *APOE ε3/ε3* as the baseline hazard group and examined the effects of *APOE ε4*, *APOE ε2*, and LID on risk of developing AD. Those with *APOE ε4* were divided by sex (21 M, 17 F) and further subdivided for "younger" age at first visit (<45) and "older" age at first visit (>46). There were 14 (66.7%) men and 10 women (58.8%) in the "younger" group, of whom 12 (85.7%) men and 7 (70%) women developed AD. In the "older" group at first visit, 7 (33.3%) men and 5 (71%) women developed AD. Analysis of the *APOE ε4* group with respect to a younger (<45) versus an older (>46) age at first visit by sex did not show a significant difference in incidence of AD: 12 of 14 (85.7%) younger men versus 7 of 10 (70%) younger women; $P = .37$. The interaction between sex and *APOE ε4* was not significant, so the interaction term was not included in this Cox model. The analysis showed that the presence of *APOE ε4* compared to the reference group *APOE ε3/ε3* increased the hazard for developing AD (HR = 1.72, CI: 1.09 to 2.70, $P = .02$). The presence of *APOE ε2* did not significantly decrease the hazard for developing AD (HR = 0.88, CI: 0.53 to 1.46, $P = .61$) and inclusion of LID did not affect the hazard for developing AD (HR = 0.77, CI: 0.53 to 1.12, $P = .18$).

3.4 | Relationship of sex to duration of dementia

We used Kaplan-Meier curves to estimate the distribution of duration of AD for men and women from onset of AD to death (Figure 2). Among those who died, the mean duration of AD was significantly longer for females than for males (6.7 ± 3.3 vs 5.1 ± 3.1 years, $P = .02$). Next, a Cox regression analysis was conducted to analyze the sex effect on duration of AD adjusted for onset age of AD. In the Cox model, women with DS had significantly longer duration from onset of dementia to death than men with DS (HR = 0.60, CI: 0.39 to 0.92, *P*-value = .02). The result of these two approaches was highly consistent and both approaches concluded that women tended to have longer duration of AD than men from onset to death, even though the mean age of AD onset in those who died showed no significant difference between men and women (53.5 ± 5.5 vs 53.7 ± 5.9 years, $P = .89$). Although there was a trend for women to die later than men (60.0 ± 5.9 vs 58.6 ± 5.8 years, $P = .14$), this did not reach statistical significance (Table 2).

TABLE 2 Relation of sex to AD onset age, age at death, and dementia duration among those who died

Characteristic	Males N = 61	Females N = 33	*P*
Age of AD onset: mean years (SD)	53.5 (5.5)	53.8 (5.9)	.39
Age of AD death: mean years (SD)	58.6 (5.8)	60.0 (5.9)	.14
Dementia duration: mean years (SD)	5.1 (3.1)	6.7 (3.2)	.02 *

Abbreviations: AD, Alzheimer's disease; SD, standard deviation.

3.5 | Relationship of sex to cognitive decline

When scores on the TSI, VFTA, or VFTF was the outcome marker, the value of the outcome marker decreased for increasing age of AD onset and the decrease was significant ($P = .001$, .000, .000, respectively). The value of these outcome markers decreased significantly over time from the onset of AD ($P = .003$, .014, and .003, respectively). However, both the sex effect at onset age of AD and the sex effect for the rate of change of TSI, VFTA, or VFTF outcome marker values over time were not significant (0.990, 0.700, 0.590; 0.555, 0.991, 0.713). When either DLD-Cog or DLD-Soc scores was the outcome marker, the value of the outcome marker increased significantly with increasing age of AD onset ($P = .001$ and .002, respectively). The value of the DLD-Cog or DLD-Soc outcome marker increased with increasing time from onset of AD and this increase was significant ($P = .005$ and .000, respectively). The sex effect at age of AD onset and the sex effect for rate of change of these marker values of cognitive and social domains were not significant (0.332, 0.977; 0.337, 0.338).

3.6 | Potential contribution of comorbid conditions to risk of dementia

We evaluated the potential contribution of medical comorbid conditions to the risk for dementia, including LID, hypothyroid status, BMI as a marker for obesity, hypercholesterolemia, and diabetes. We did not include hypertension, which is a common comorbid condition in the neurotypical population, because hypertension is quite rare in individuals with DS. Although there was a high incidence of hypothyroidism, the presence of hypothyroidism did not have a

significant effect on risk for developing AD (HR = 1.26, CI: 0.89 to 1.79, $P = .19$), even when adjusting for the other covariates (BMI, LID, and age).

4 | DISCUSSION

In adults with DS, few studies have examined sex as a risk factor for AD. In our present study of incident AD in adults with DS in which 155 individuals developed dementia, there was no overall sex difference in the risk for the development of AD. These findings are consistent with several large studies in the neurotypical population that showed no difference between men and women in incidence of AD,[9,37,38] even though two thirds of prevalent cases of AD are women.[39] However, other studies of neurotypical AD indicate that age is a factor in sex differences with females having higher incidence of AD only over age 80 to 90).[10,40,41] The interaction of sex and incidence of dementia was also analyzed in the Framingham Heart Study, which took selective survival into account; findings indicated similar cumulative incidence of AD in men and women, but lifetime risk accounting for the competing risk of death, was higher in women.[42] These findings contrast with previous smaller studies in DS. Schupf et al.,[23] showed a higher risk for AD in men with DS, whereas Lai et al.[24] showed the opposite effect. Only one other study has examined sex differences in adults with DS with respect to AD risk, but this was a small autopsy study (N = 28)[43] in which the onset of AD was earlier in women than men. Nevertheless, despite the lack of an apparent sex effect on AD risk in adults with DS, there was a non-significant, marginal trend, with women showing higher risk in the estimated hazard curve. In our cohort there were fewer females (N = 95) than males (N = 151); the proportion of incident AD cases is around 60%, so the estimation efficiency might have been affected by the reduced sample size of cases. If it were possible to increase the sample size (particularly for females), there could have been a possibility of significant results. Also, from the hazard plot (Figure 1), the proportionality assumption of the proportional hazard model is not perfectly satisfied, which may also have contributed to the non-significant results.

In this study, we also found that women with DS had a significantly longer duration of dementia by almost 2 years compared to men with DS from the time of AD onset until death, even though women and men had similar mean ages at onset of AD. These results are most closely aligned with the study by Larson et al. in the neurotypical population of incident AD.[43] They found men had significantly poorer survival across all age groups compared to women. A similar finding of longer duration of AD in women has been reported in another DS study.[44] However, in that study, the age of onset of dementia was older and duration of AD was shorter, likely due to the inclusion of both incident and prevalent cases. We also did not see an effect of sex on the mean age of death, similar to what has been reported previously by Yang et al. in a mortality study in DS spanning 14 years.[45]

As expected, we found that the presence of *APOE ε4* allele was a genetic risk factor for AD in our overall DS cohort with mean age at onset of AD significantly lower in those with the *APOE ε4* allele irrespective of sex, compared to those with the ε3/ε3 genotype. This is consistent with two large meta-analyses in the general population[29,46] and in studies of DS.[47] Other studies in the neurotypical population demonstrated that women with *APOE ε4* were at higher risk for AD[26,48,49] especially those who were younger.[20] We did not find that *APOE ε4* women with DS in the younger age bracket had an increased risk for AD compared to *APOE ε4* men. However, the proportionately smaller number of women in this study may have contributed to the difference in findings. When the effect of *APOE ε2* was examined, there was a non-significant protective effect on risk for AD in our cohort. Although this finding differs from the protective *APOE ε2* effect on AD risk in the general population[25] and in DS,[24,50] this could be due to a relatively small sample size. We also evaluated the effect of sex on rate of decline on scored measures that included memory, word retrieval, temporal and spatial orientation, and behavioral parameters in the 155 adults who developed dementia and found no significant difference between men and women. Although Coppus et al.[51] showed a significant rate of decline on a social competence scale in the 53 persons with DS who developed AD, sex differences were not analyzed.

Comorbid medical conditions such as obesity, diabetes, and hypercholesterolemia are known risk factors for AD in the neurotypical population.[52] In our study, we did not find any contribution from these comorbid conditions to the risk of AD in our cohort. Likewise the presence of hypothyroidism and the difference in LID did not contribute to risk for AD. Similarly, the effect of sex on risk for AD did not change when comorbid conditions were added to the analyses. This suggests that AD in DS may have a somewhat different risk profile compared to the neurotypical population.

In summary, this is one of the largest studies of individuals with DS with incident dementia to evaluate sex differences in onset of AD. The longitudinal nature of our clinically based study with relatively large numbers of patients who were followed by a limited number of the same clinicians are strengths. While we did not find any sex differences in age of AD onset, we did find that women demonstrated longer duration of dementia compared to men; these were not related to any of the comorbid conditions studied or to the presence of an *APOE ε4* allele, but does suggest that there may be genetic, environmental, or hormonal explanations that deserve further study.

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