Type 2 Diabetes Interacts With Alzheimer Disease Risk Factors to Predict Functional Decline

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Objective: The current study examined the interactive effect of type 2 diabetes and Alzheimer disease (AD) risk factors on the rate of functional decline in cognitively normal participants from the Alzheimer's Disease Neuroimaging Initiative.

Methods: Participants underwent annual assessments that included the Functional Activities Questionnaire, an informant-rated measure of everyday functioning. Multilevel modeling, controlling for demographic variables and ischemic risk, examined the interactive effects of diabetes status (diabetes, n = 69; no diabetes, n = 744) and AD risk factors in the prediction of 5-year longitudinal change in everyday functioning. One model was run for each AD risk factor, including: objectively-defined subtle cognitive decline (Obj-SCD), and genetic susceptibility [apolipoprotein E ε4 (APOE ε4) as well as cerebrospinal fluid β-amyloid (Aβ), total tau (tau), and hyperphosphorylated tau (p-tau).

Results: The 3-way diabetes×AD risk factor×time interaction predicted increased rates of functional decline in models that examined Obj-SCD, APOE ε4, tau, and p-tau positivity, but not Aβ positivity.

Conclusions: Participants with both diabetes and at least 1 AD risk factor (ie, Obj-SCD, APOE ε4, tau, and p-tau positivity) demonstrated faster functional decline compared with those without both risk factors (diabetes or AD). These findings have implications for early identification of, and perhaps earlier intervention for, diabetic individuals at risk for future functional difficulty.

Key Words: diabetes, Alzheimer disease, everyday functioning, subtle cognitive decline

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Type 2 diabetes mellitus (DM) is a growing public health concern, as over 30 million adults in the United States have diabetes (12.2% of all US adults).[1] There is consistent evidence that DM is a risk factor for cognitive decline and dementia[2–4] and a significant portion of older Medicare beneficiaries with dementia have coexisting diabetes (37%).[5] However, the specific relationship between DM and Alzheimer disease (AD) is not well understood. Research has shown that people with DM are at greater risk for developing amnestic mild cognitive impairment (MCI)[2] and AD, as well as vascular dementia.[6] Although DM increases the risk of a clinical diagnosis of AD, there does not appear to be a clear relationship between DM and β-amyloid (Aβ) pathology, which is a defining feature of AD.[4,7–9] Indeed,

prior work from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study showed that DM was associated with cerebrospinal fluid (CSF) total tau (tau) and hyperphosphorylated tau (p-tau), but not CSF or positron emission tomography (PET) measures of Aβ.[10]

Research on the interactive effects of DM and risk factors for AD-related dementia [eg, apolipoprotein E (APOE) ε4 allele, MCI] shows that those with both DM and an AD risk factor such as MCI have poorer cognitive outcomes,[11,12] reduced brain volume and glucose metabolism,[13] and more severe AD pathology[14] relative to having either DM or an AD risk factor alone. However, there is minimal research on cognitively normal (CN) individuals with DM, or how DM in combination with AD risk factors predicts longitudinal changes in everyday functioning. Further, our recent work has shown that objectively-defined subtle cognitive decline (Obj-SCD), operationally defined using sensitive neuropsychological scores, may be a promising indicator of those at risk for future progression to MCI and dementia.[15] It is currently unknown whether subtle cognitive changes in those with DM are predictive of faster functional decline.

Everyday functioning is a key feature that differentiates MCI from dementia, whereas MCI may have very mild functional changes,[16] more significant functional impairment is needed for a diagnosis of dementia.[17,18] Cognitive performance, particularly in the domains of memory and executive functioning, have been shown to predict changes in everyday functioning.[19–21] In addition, CSF Aβ and p-tau significantly predict decline on the Functional Activities Questionnaire (FAQ)[22] in cognitively unimpaired older adults, with p-tau being the most sensitive predictor of functional decline.[23] Everyday functioning may be a particularly relevant outcome with regard to tracking disease severity in the context of DM, as DM has been shown to be an independent risk factor for functional disability.[24–26] Further, as individuals with DM often need to be able to manage complex medication regimens and medical appointments, mild declines in everyday function may result in a feedback loop such that cognitive and functional declines impact medication management, which in turn lead to greater cognitive and functional difficulties.[27]

To our knowledge, there are no studies that examine the interaction of DM with different AD risk factors to predict everyday functioning in those without MCI or dementia, despite the common cooccurrence of both DM and AD.[5] Taken together, the current study aimed to examine the moderating effect of DM on AD risk factors in predicting functional decline in older adults without a neurocognitive disorder to determine whether DM and AD risk factors act synergistically to promote functional impairment beyond their independent contributions.

METHODS

Data used in the preparation of this article were obtained from the ADNI database (www.adni.loni.usc.edu). ADNI was launched in 2003 as a public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information on ADNI (www.adni-info.org). This study was approved by the Institutional Review Boards at each of the participating institutions, and written informed consent was obtained from all participants or authorized representatives at each site.

Participants

The specific enrollment inclusion/exclusion criteria for ADNI as well as detailed MCI and dementia criteria have been described elsewhere.[17,28–30] Participants were included in the current study if they were considered to be CN and had a FAQ score at their baseline visit (N = 813). Participants were excluded if they met Jak/Bondi comprehensive neuropsychological criteria for MCI[28,29] or ADNI's criteria for dementia.[17,30] In addition to a baseline visit, participants had follow-up visits that occurred at 6 (n = 756), 12 (n = 693), 24 (n = 682), 36 (n = 459), 48 (n = 388), and 60 months (n = 211).

Jak/Bondi neuropsychological MCI criteria were defined by: (1) performance > 1 SD below the demographically adjusted (age, education, sex) mean on 2 neuropsychological measures within the same cognitive domain *or* (2) performance > 1 SD below the demographically adjusted mean on at least 1 measure across all 3 sampled cognitive domains.[15,28,29] Six neuropsychological test scores were used in the Jak/Bondi diagnostic criteria for MCI.[29] There were 2 measures in 3 cognitive domains: *memory* [Rey Auditory Verbal Learning Test (AVLT) delayed free recall correct responses and AVLT recognition (hits minus false positives)], *language* [30-item Boston Naming Test total correct, Animal Fluency total score], and *attention/executive function* (Trail Making Test Part A and Part B times to completion). The neuropsychological demographically adjusted *z*-scores were based on regression coefficients derived from a sample of ADNI's CN participants who did not progress to MCI for the duration of their study participation (ie, "robust" controls; N = 385).[31,32] Participants without dementia that did not meet Jak/Bondi criteria for MCI were considered CN.

The dementia criteria used in ADNI[30] were: (1) subjective memory complaint reported by the subject, study partner, or clinician; (2) abnormal memory function defined by scoring below the education-adjusted cutoffs on the Logical Memory delayed recall subscale from the Wechsler Memory Scale–Revised; (3) Mini-Mental State Examination (MMSE) score <27; (4) Clinical Dementia Rating = 0.5 or 1.0; and (5) met NINCDS/ADRDA criteria for probable AD.[17]

Materials and Procedure

Functional Assessment

The FAQ[22] is an informant-rated questionnaire measuring functional difficulty over the preceding 4 weeks. It is part of the Uniform Data Set compiled by the National Alzheimer's Coordinating Center as a measure of functioning on instrumental activities of daily living (IADL).[33] The FAQ has good reliability with item-total correlations ≥ 0.80 and effectively distinguishes between CN individuals and those with dementia (0.85 to 0.98 sensitivity, 0.71 to 0.91 specificity),[22,34] as well as between MCI and early dementia (0.80 sensitivity, 0.87 specificity).[34] An FAQ total score of > 5 has been shown to best distinguish between MCI and early dementia.[34]

The measure includes 10 IADL items: (1) writing checks, paying bills, balancing a checkbook; (2) assembling tax records, business affairs; (3) shopping; (4) playing a game of skill; (5) heating water, making coffee; (6) preparing a balanced meal; (7) keeping track of current events; (8) paying attention and understanding a television program or book; (9) remembering appointments, dates, medications; (10) traveling out of the neighborhood. Difficulty on each item was rated as 0 (normal or never did, but could do now); 1 (has difficulty, but does by self or never did, but would

have difficulty now); 2 (requires assistance); or 3 (dependent). The total FAQ score was included in analyses; if an FAQ item was missing (eg, skipped by the participant), the FAQ score for that occasion was considered missing. The FAQ was completed at the baseline assessment as well as at each follow-up visit.

Diabetes Classification

DM classification was determined via the ADNI medical history database[13] or the presence of glucose-lowering agents.[10] Consistent with previous work in ADNI,[13] the following search terms were used to identify participants with DM at baseline from medical history: diabetes, diabetic, insulin, insulin-dependent diabetes mellitus, and noninsulin dependent diabetes mellitus. Those with type 1 diabetes were excluded. The majority of the participants classified as DM were classified based on their medical history (n = 51); a smaller proportion (n = 18) were classified based the presence of a diabetes medication; 7 participants were prescribed insulin. A subset of individuals who also underwent FDG-PET have blood glucose values (n = 642); however, the length of the fast before the blood draw varied (some participants had a 4-h fast, others had an 8-h fast, some may have been longer), so these values were not used for diabetes classification.

AD Risk Factors

Obj-SCD is thought to be part of the preclinical AD trajectory[35,36] and has been previously shown to predict progression to MCI and dementia.[15] Consistent with our recent work, Obj-SCD status was determined by the following criteria: (1) 1 impaired total test score (>1 SD below demographically adjusted mean) in 2 different cognitive domains (memory, language, attention/executive), or (2) 2 impaired neuropsychological process scores from the AVLT (learning slope, retroactive interference, intrusion errors), or (3) 1 impaired total test score and 1 impaired process score.[15] Neuropsychological process scores quantify error-types or other aspects of an individual's performance that allow one to determine the approach by which an individual achieved the total score on a neuropsychological measure. The process scores used in the Obj-SCD definition have previously been shown to predict progression from CN to MCI or dementia in ADNI.[37] A determination of Obj-SCD status was available for 754 participants (DM− n = 693, DM+ n = 61) with nonmissing neuropsychological data.

APOE ε4 positivity was based on presence of at least 1 ε4 allele. A subset of participants underwent a lumbar puncture (N = 586; DM− n = 536, DM+ n = 50) and CSF biomarkers of AD were measured using Elecsys immunoassays. Biomarker positivity was determined by cutoff scores proposed by Schindler et al[38] β-amyloid positivity (Aβ+) <1098 pg/mL, total tau positivity (tau+) >242 pg/mL, and hyperphosphorylated tau positivity (p-tau+) >19.2 pg/mL.

Statistical Analyses

Baseline demographic and clinical characteristics by DM status were examined using independent *t* tests (for continuous variables), Mann-Whitney tests (for nonparametric variables), or χ^2 test (for categorical variables).

Multilevel modeling (MLM) was used to examine whether there were differential rates of functional difficulty (FAQ) over time by DM and AD risk status. The Time variable included 7 assessment visit time points over 5 years and was modeled as a continuous parameter. Both linear and quadratic effects of Time were examined, but including the quadratic term for Time did not improve model-fit based on −2 log likelihood, Akaike information criterion, and Bayesian information criterion. Covariates included demographic variables (age, education, sex), variables that are related to everyday functioning, including: the Geriatric Depression Scale to adjust for depressive symptoms and the MMSE to adjust for global cognition, as well as the Hachinski Ischemia Scale (HIS) to adjust for ischemic risk as this differed between DM+ and DM− groups. Pulse pressure (systolic blood pressure−diastolic blood pressure) was considered for inclusion to adjust for arterial stiffness but was removed for parsimony in the final analyses as it was not a significant predictor in any of the models and did not differ between DM+ and DM− groups. The random effect of intercept and slope were included in the model. All available data (full information maximum likelihood) were included, which reduces bias relative to other methods (eg, list-wise deletion).[39] Variables were centered around their respective mean before being entered in the model. One MLM was run for each AD risk factor (Obj-SCD, APOE, Aβ, tau, p-tau), and all main effects, 2-way, and 3-way interactions were examined for DM, AD risk factor, and Time. Each AD risk factor was included as a dichotomous variable based on presence of the risk factor (for Obj-SCD and APOE ε4) or the positivity threshold described in the methods (Aβ, tau, p-tau). The 3-way DM×AD risk factor×Time interaction is discussed in the Results section as this is the primary outcome of interest. Sensitivity analyses, excluding participants with incident dementia, were then completed to examine the extent to which incident dementia cases are driving the results. Given the small sample of those with both DM and an AD risk factor, and α of 0.05 was used to determine statistical significance.

RESULTS

Table 1 shows the baseline characteristics of the total sample and split by DM status. At baseline, there were significant differences ($P < 0.05$) between DM− and DM+ groups on sex, HIS, and blood glucose values but no other demographic, clinical, cognitive, or AD risk factor variables. Notably, there were not differences between DM− and DM+ groups on baseline FAQ score. The baseline characteristics by AD risk factor status are included in Supplementary Digital Content 1 (http://links.lww.com/IJG/A278). Across all participants (n = 813), there were 355 (43.7%) who progressed to MCI or dementia at any point during the 5-year follow-up interval; 70 of these 355 participants progressed to dementia during this interval.

Before the running the MLMs, *t* test and χ^2 tests were performed to examine whether there were demographic (eg, age, sex, education) or clinical characteristics (eg, Geriatric Depression Scale, MMSE, HIS, FAQ, DM status) that differed between participants who were present or missing at the 5-year follow-up visit. Across these variables, there were no significant differences between these groups (all $Ps > 0.05$).

An initial MLM including the main effect of DM and the 2-way DM×Time interaction on functional difficulty (without the AD risk factor main effect and interactions) found that after adjusting for relevant covariates, there was not a significant main effect of DM on level of functional difficulty [$F_{1, 842.60} = 3.57$, $P = 0.059$, $r = 0.065$], but there

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TABLE 1. Baseline Demographic, Clinical, and AD Risk Variables by DM Status

	Mean (SD)				
	Total Sample (N = 813)	DM− (N = 744)	DM+ (N = 69)	*t*, *U*, or χ^2	*P*
Age	73.62 (6.91)	73.72 (6.99)	72.60 (6.02)	$t = 1.28$	0.200
Education	16.26 (2.71)	16.30 (2.72)	15.77 (2.59)	$t = 1.56$	0.120
Female [n (%)]	377 (46.4)	353 (47.4)	24 (34.8)	$\chi^2 = 4.07$	**0.044**
FAQ	1.20 (2.62)	1.17 (2.58)	1.48 (3.04)	$U = 25{,}924.00$	0.869
GDS	1.20 (1.32)	1.21 (1.34)	1.17 (1.16)	$U = 26{,}252.00$	0.743
HIS	0.58 (0.67)	0.57 (0.68)	0.71 (0.57)	$U = 29{,}656.50$	**0.016**
PP	60.16 (14.75)	60.15 (14.92)	60.29 (12.86)	$t = 1.28$	0.939
MMSE	28.63 (1.52)	28.65 (1.48)	28.35 (1.89)	$U = 23{,}556.50$	0.239
Obj-SCD+ [n (%)]	260 (34.5)	233 (33.6)	27 (44.3)	$\chi^2 = 2.81$	0.094
APOE ε4+ [n (%)]	269 (33.2)	242 (32.7)	27 (39.1)	$\chi^2 = 1.19$	0.275
Aβ+ [n (%)]	271 (46.2)	250 (46.6)	21 (42.0)	$\chi^2 = 0.40$	0.529
tau+ [n (%)]	243 (41.5)	226 (42.2)	17 (34.0)	$\chi^2 = 1.26$	0.262
p-tau+ [n (%)]	323 (55.1)	300 (56.0)	23 (46.0)	$\chi^2 = 1.84$	0.175
Blood glucose	100.42 (17.21)	99.40 (15.56)	110.91 (27.24)	$t = -3.14$	**0.003**

Bold values indicate statiscally significant ($P < 0.05$).

Blood glucose (mg/dL) was available for 642 participants (DM− n = 585, DM+ n = 57), but the fasting period varied (as little as 4 h). The subset of participants with Obj-SCD values is n = 754 (DM− n = 693, DM+ n = 61) and the subset with Aβ, tau, and p-tau values is n = 586 (DM− n = 536, DM+ n = 50).

AD indicates Alzheimer disease; APOE ε4+, apolipoprotein E ε4 positive; Aβ+, β-amyloid positive; DM, type 2 diabetes mellitus; FAQ, Functional Activities Questionnaire; GDS, Geriatric Depression Scale; HIS, Hachinski Ischemia Scale; MMSE, Mini-Mental State Examination; Obj-SCD+, Objectively-defined subtle cognitive decline positive; PP, pulse pressure; p-tau+, hyperphosphorylated tau positive; tau+, total tau positive.

was a significant interaction such that those with DM had an increased rate of functional difficulty over Time [$F_{1,\,790.78} = 6.00$, $P = 0.015$, $r = 0.087$]. However, in the models where the AD risk factor and associated interactions were included, this 2-way DM×Time interaction becomes nonsignificant and seems to be moderated by the AD risk factors (via the 3-way interaction).

Figure 1 shows the FAQ trajectories by DM and AD risk factor status, and Table 2 shows the parameter estimates for each of the AD risk factor MLMs. The 3-way DM×AD risk factor×Time interactions were significant for the Obj-SCD, APOE ε4, tau, and p-tau models. Specifically, the DM×Obj-SCD×Time [$F_{1,\,663.00} = 3.96$, $P = 0.047$, $r = 0.077$], DM×APOE ε4×Time [$F_{1,\,775.44} = 12.52$, $P < 0.001$, $r = 0.126$], DM×tau×Time [$F_{1,\,539.51} = 6.29$, $P = 0.012$, $r = 0.108$], and DM×p-tau×Time [$F_{1,\,555.97} = 4.15$, $P = 0.042$, $r = 0.086$] interactions showed that participants who had both DM and 1 of these 4 AD risk factors had a fastest rate of functional decline over 5 years compared with those without both risk factors. The 3-way DM×Aβ×Time interaction was nonsignificant [$F_{1,\,554.81} = 0.35$, $P = 0.555$, $r = 0.025$]. By the 5-year follow-up, only those with both DM and an AD risk factor had predicted FAQ scores above the threshold that best distinguishes MCI and dementia (FAQ > 5).

As the 3-way interaction that included Aβ was not significant, the 2-way interactions involving Aβ were examined. The 2-way DM×Aβ interaction was also not significant [$F_{1,605.24} = 0.10$, $P = 0.758$ $r = 0.013$], suggesting that those participants who had DM and were Aβ+ were not functioning disproportionally worse than those without these risk factors at baseline (ie, the functional decline did not already occur). The 2-way Aβ×Time interaction was significant [$F_{1,\,562.54} = 28.72$, $P < 0.001$, $r = 0.221$], suggesting that independent of DM status, those who were Aβ+ had a faster decline in everyday functioning compared with those who were Aβ-.

Sensitivity analyses were then conducted to determine to what extent these results can be explained by those who progressed to dementia (n = 70) within 5 years. Therefore, these MLMs were re-run excluding the 70 participants who progressed to dementia. The pattern of findings was largely similar in that the 3-way DM×APOE ε4×Time [$F_{1,\,632.59} = 9.61$, $P = 0.002$, $r = 0.122$] and DM×tau×Time [$F_{1,\,417.11} = 5.27$, $P = 0.022$, $r = 0.112$] interactions remained significant and the DM×Aβ×Time interaction remained nonsignificant [$F_{1,\,414.85} = 0.15$, $P = 0.702$, $r = 0.019$]. The 3-way DM×Obj-SCD×Time [$F_{1,\,1468.13} = 3.17$, $P = 0.075$, $r = 0.046$] and DM×p-tau×Time [$F_{1,\,402.92} = 2.52$, $P = 0.113$, $r = 0.079$] interactions, which were previously on the cusp of statistical significance, no longer reach significance once those with incident dementia are excluded from analyses.

DISCUSSION

Our study demonstrated that CN participants who had both DM and an AD risk factor had a faster rate of functional decline relative to those with only DM or only an AD risk factor. This was true for the AD risk factors of subtle cognitive decline (Obj-SCD), genetic susceptibility (APOE ε4 positivity), as well as CSF markers of tau pathology and neurodegeneration (ie, p-tau and tau). However, DM and CSF Aβ+ did not interact to accelerate the functional decline. These preliminary findings extend previous work that has demonstrated that CSF Aβ and p-tau predict decline on functioning in cognitively unimpaired older adults[23] by examining the interactive effect of DM. In addition, DM, in combination with an AD risk factor such as cognitive impairment[11,13] or APOE ε4,[14,40] has been associated with greater atrophy, reduced glucose metabolism,[13] greater density of neurofibrillary tangles at autopsy,[14] as well as greater cognitive decline[12] and increased rates of progression to dementia;[11] however, previous work has not examined these interactions as predictors of a continuous functional outcome.

Prior work using ADNI data showed DM has a greater association with tau-related neurodegeneration (CSF tau and p-tau) than Aβ (measured by CSF and PET).[10] Although the current study did not find significant

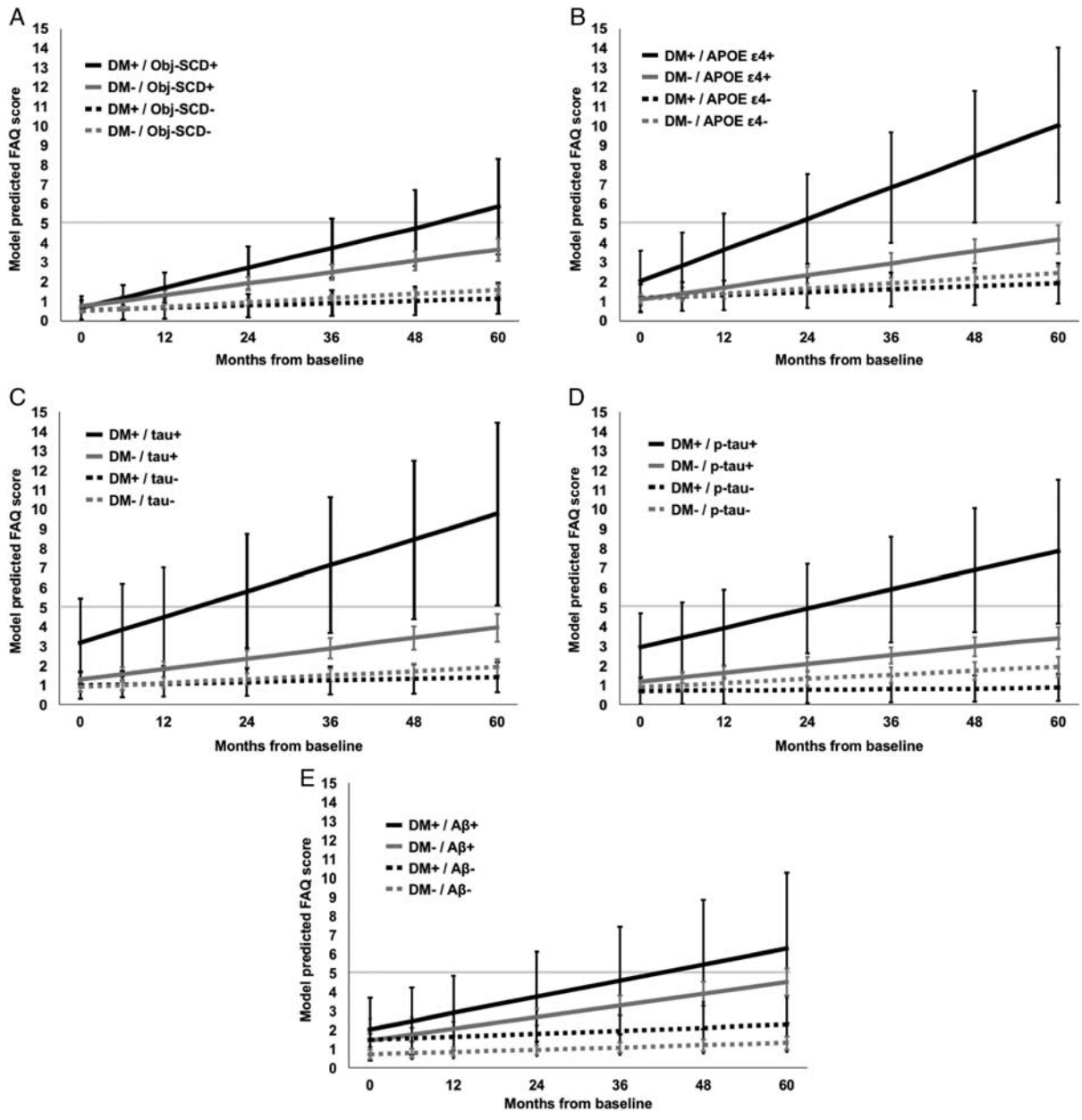

FIGURE 1. Functional Activities Questionnaire (FAQ) trajectories by diabetes mellitus (DM) and Alzheimer disease risk factor. Each panel shows a different AD risk factor: Objectively-defined subtle cognitive decline (Obj-SCD) (A); apolipoprotein E (APOE) ε4 status (B); total tau (tau) (C); hyperphosphorylated tau (p-tau) (D); β-amyloid (Aβ) (E). Error bars represent 95% confidence interval. The light gray line shows the optimal threshold for distinguishing mild cognitive impairment and dementia.

differences between those with and without DM in the proportions of those considered tau, p-tau, or Aβ+ at baseline using CSF, the interaction of DM with tau and p-tau positivity to predict functional decline is notable. DM[26] and tau-related neurodegeneration[41,42] are both risk factors for functional decline. Therefore, it follows that the presence of both risk factors would put one at additive risk for faster decline. Conversely, consistent with our own finding that Aβ predicted functional decline, independent of DM status, Aβ has been shown to predict future functional decline, but its association with DM is less clear.[42]

The mechanism for the interactive relationship between DM and tau/p-tau, including whether they are unique risk factors for functional decline or whether they share a similar underlying mechanism, is unclear. The moderating effect of DM on tau and p-tau, but not Aβ, provides support for a possible synergistic relationship between DM and tau/p-tau that may be responsible for the accelerated decline, rather than 2 independent mechanisms. In both DM and AD, there is evidence of alterations in insulin signaling and glucose metabolism, increased oxidative stress and inflammation, and formation of advanced glycation end products.[43] One

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TABLE 2. Estimates For Models Predicting Change in FAQ by DM and AD Risk Factor Status

	Obj-SCD			APOE ε4			Aβ			tau			p-tau		
	b	SE	*P*	*r*	*b*	SE	*P*	*r*	*b*	SE	*P*	*r*	*β*	SE	*P*	*r*
Intercept	1.405	0.088	**<0.001**	0.523	2.018	0.122	**<0.001**	0.499	1.936	0.138	**<0.001**	0.495	1.958	0.137	**<0.001**	0.505	1.951	0.139	**<0.001**	0.498
Age	0.028	0.013	**0.031**	0.090	0.033	0.018	0.077	0.064	0.016	0.020	0.435	0.033	0.013	0.020	0.537	0.027	0.017	0.020	0.417	0.035
Education	−0.030	0.034	0.373	−0.037	−0.066	0.048	0.172	−0.049	−0.072	0.055	0.187	−0.056	−0.067	0.054	0.211	−0.053	−0.065	0.055	0.234	−0.050
Sex	−0.486	0.178	**0.007**	−0.113	−0.910	0.253	**<0.001**	−0.128	−0.974	0.287	**0.001**	−0.142	−1.023	0.283	**<0.001**	−0.152	−0.991	0.287	**0.001**	−0.145
GDS	0.342	0.066	**<0.001**	0.213	0.356	0.093	**<0.001**	0.135	0.349	0.104	**0.001**	0.140	0.405	0.103	**<0.001**	0.165	0.381	0.104	**<0.001**	0.153
HIS	−0.059	0.132	0.656	−0.019	0.249	0.185	0.177	0.048	0.044	0.207	0.833	0.009	0.127	0.204	0.535	0.026	0.135	0.208	0.516	0.027
MMSE	−0.312	0.064	**<0.001**	−0.198	−0.633	0.086	**<0.001**	−0.255	−0.499	0.098	**<0.001**	−0.209	−0.535	0.096	**<0.001**	−0.229	−0.516	0.097	**<0.001**	−0.218
Time	0.029	0.003	**<0.001**	0.365	0.033	0.003	**<0.001**	0.326	0.030	0.004	**<0.001**	0.304	0.030	0.004	**<0.001**	0.307	0.030	0.004	**<0.001**	0.299
DM	0.061	0.334	0.856	0.007	0.577	0.449	0.199	0.044	0.772	0.501	0.124	0.062	1.208	0.500	**0.016**	0.098	1.118	0.507	**0.028**	0.089
AD risk	0.870	0.188	**<0.001**	0.175	0.953	0.263	**<0.001**	0.125	1.502	0.281	**<0.001**	0.212	1.356	0.283	**<0.001**	0.193	0.872	0.285	**0.002**	0.124
DM×Time	0.007	0.011	0.540	0.024	0.021	0.013	0.107	0.057	0.011	0.014	0.446	0.032	0.021	0.014	0.141	0.063	0.018	0.015	0.222	0.052
AD risk×Time	0.034	0.006	**<0.001**	0.210	0.038	0.007	**<0.001**	0.179	0.042	0.008	**<0.001**	0.221	0.034	0.008	**<0.001**	0.177	0.025	0.008	**0.002**	0.129
DM×AD risk	1.036	0.664	0.119	0.059	2.960	0.906	**0.001**	0.116	0.310	1.004	0.758	0.013	4.274	1.038	**<0.001**	0.165	3.450	0.997	**0.001**	0.139
DM×AD risk×Time	0.045	0.022	**0.047**	0.077	0.091	0.026	**<0.001**	0.126	0.017	0.029	0.555	0.025	0.076	0.030	**0.012**	0.108	0.059	0.029	**0.042**	0.086

Bold values indicate statically significant ($P < 0.05$).
Effect size (*r*-values) interpretation: small = 0.10, medium = 0.30, large = 0.50.
AD indicates Alzheimer disease; APOE ε4, apolipoprotein E ε4; Aβ, β-amyloid; DM, type 2 diabetes mellitus; FAQ, Functional Activities Questionnaire; GDS, Geriatric Depression Scale; HIS, Hachinski Ischemia Scale; MMSE, Mini-Mental State Examination; Obj-SCD, objectively-defined subtle cognitive decline; p-tau, hyperphosphorylated tau; tau, total tau.

specific mechanism that may be responsible for the relationship between DM and p-tau involves glycogen synthase kinase-3β (GSK3β), which is both activated by insulin resistance and may also lead to insulin resistance. Briefly, insulin resistance activates GSK3β via dephosphorylation, which then activates the phosphorylation of tau.[43,44] One study has shown that when intranasal insulin was administered for 4 weeks in a rat model of DM and compared with subcutaneous insulin treatment, the intranasal insulin normalized GSK3β activation and reduced hyperphosphorylation of tau.[45] This is only 1 possible mechanism and continued translation of pathologic interactions from animal models to clinical research is needed.

There is a consistent body of literature showing that DM in combination with an APOE ε4 allele puts one at higher risk for worse cognition[12,46] and faster progression to dementia[40] than either risk factor alone. Similarly, individuals with both DM and an APOE ε4 allele have been shown to have elevated AD pathology,[14,47] despite consistent evidence showing that a DM diagnosis alone does not result in increased risk for AD neuropathology.[4] Our current findings fit well within this existing research and extend the literature to demonstrate that DM moderates the effect of APOE ε4 allele on the rate of functional decline; the interaction of DM and APOE had the largest effect relative to the other AD risk factors.

Although the differentiation of MCI and dementia is often informed by whether someone's cognitive impairments are causing functional impairment or not, this is an arbitrary categorization. More likely, functional changes are on a continuum and the determination of functional impairment may vary based on the complexity and nature of the activities that are being attempted. Determining predictors of declining everyday functioning trajectories is critical for several reasons. One key reason is for the individual's quality of life in that it would be ideal to intervene or develop a scaffolding for maintaining optimal functioning before observable everyday impairments and potentially costly errors (eg, mismanaging finances or medications). Secondly, from a health care cost perspective, early interventions (eg, improving diabetes management or teaching compensatory strategies) may allow individuals to remain independent for longer. One estimation has indicated that a treatment that slows the rate of functional decline by only 10% would reduce the average lifetime costs for an individual by $3880 in 2015 dollars ($4122 in 2018 dollars).[5,48]

This study is the first to examine Obj-SCD in the context of DM and suggests that the use of Obj-SCD may be a useful method for identifying those at risk for future decline, before the development of frank cognitive impairment associated with MCI.[15] This Obj-SCD classification is a cost-effective and noninvasive method of early detection that may be particularly beneficial for those with DM given the current finding of accelerated functional decline in individuals with both DM and Obj-SCD, even after adjusting for global cognition. The Obj-SCD criteria likely err on the side of over-classification such that not everyone identified as Obj-SCD will have accelerated the functional decline. Therefore, more work is needed to determine the utility of the Obj-SCD construct in the context of DM, as it will be important not to over-pathologize this classification to the individual. However, identification of Obj-SCD in individuals with DM may have direct clinical importance in that it may be possible to intervene early and develop effective medication management strategies and tools to

manage DM before future cognitive decline. The Alzheimer's Association recently showed that if everyone who progresses to Alzheimer's dementia was diagnosed in the MCI stage rather than in the dementia phase or not at all, ~$7.9 trillion could be saved in medical or long-term care costs.[5] Cognitive impairment is a risk factor for poorer DM control, reduced exercise and diet adherence, and greater risk of hypoglycemic events.[49,50] In turn, major hypoglycemic episodes are then a risk factor for dementia in older adults with DM.[51] Thus, early detection of subtle cognitive changes may be very useful for sustaining everyday functioning in older adults with DM.

Everyday functioning, including the more complex IADLs that are measured using the FAQ, is associated with a number of cognitive functions, including memory and executive functioning.[19] Our previous work examining predictors of functional decline in MCI has shown that individuals with both memory and attention/executive function impairments demonstrated faster everyday functioning decline than those with only a memory or memory plus language impairment.[32] In this context, it is possible that the combination of early AD-related changes that may cause subtle memory changes, *plus* vascular-related changes in the context of DM that may cause early executive functioning changes, are jointly responsible for the accelerated decline in everyday functioning in those with DM plus Obj-SCD, APOE ε4, tau+, or p-tau+.

Although ADNI data has a number of advantages, including the CSF biomarkers and longitudinal data, the current study is limited by the low proportions of those with DM as well as other cerebrovascular risk factors. This resulted in a small sample size of participants with DM compared with those without DM. Given the interest in the combination of DM and positivity for an AD risk factor in predicting functional decline, the current data are limited as there are some combinations of those with both DM and an AD risk factor that yield very few participants. Therefore, the current findings should be considered preliminary evidence of these relationships but will need replication in future studies, particularly given the small effect sizes of the 3-way interactions. In addition, more detailed DM-related information such as 8-hour fasting blood glucose levels, hemoglobin A1c values, and age of onset/duration of DM diagnosis were not available, as the primary aims of ADNI are not DM-related. It will be critical for future work to extend these findings in a more representative and diverse population of older adults. Further, there is need to examine the time-course of the transition from pre-DM to DM in the context of AD biomarker changes to further determine if these processes share underlying mechanisms or are unique risk factors for cognitive and functional decline.

Exploratory sensitivity analyses showed that the pattern of results remains largely the same when those individuals who progress to dementia were excluded from the sample; however, the effects of DM plus Obj-SCD and DM plus p-tau on rate of functional change no longer reach statistical significance. It is possible that the participants who progress to dementia were predominately driving the effects for the Obj-SCD and p-tau models. Conversely, given the already small sample size for those with DM, excluding those with incident dementia may have reduced the power to detect the already small effects. The sensitivity analyses, however, also confirm that the significant APOE and tau interactions with DM to predict faster decline are not solely driven by those who progress to dementia. This supports the idea that everyday functioning difficulty is on a spectrum and does not only exist as a dichotomous distinction of those with and without functional dependence; it appears to be important independent of its application to differentiate those with and without dementia. The FAQ had a restricted range, with the majority of participants having little-to-no functional difficulty at baseline. Although this is not unexpected in a group of CN individuals, future studies may consider more sensitive measures or performance-based measures of functioning for use in older adults without notable cognitive impairment.

This longitudinal study offers initial evidence that DM moderates the association between several AD risk factors (except for Aβ+) and rate of everyday functioning decline across a 5-year period. It extends prior work that has primarily focused on individuals with existing cognitive impairment and demonstrates that CN older adults can progress from functionally independent to having functional difficulty consistent with mild dementia (eg, FAQ > 5)[34] within 5 years in the context of having both DM and a positive AD risk factor.

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