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Suicidal ideation is common in autosomal dominant Alzheimer's disease at-risk persons

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Abstract

Objectives: To study the frequency of suicidal ideation and its association with clinical and neurobiological correlates among cognitively intact autosomal dominant Alzheimer's disease (ADAD) at-risk individuals.

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AUTHOR CONTRIBUTIONS

Kok Pin Ng: designing the study, analysing the data, composing the figure, and writing the article. Stéphane Richard-Devantoy: designing the study, analysing the data, and writing the article. Josie-Anne Bertrand: designing the study and writing the article. Lai Jiang: statistical design of the study and analysing the data. Tharick A. Pascoal: analysing the data and writing the article. Sulantha Mathotaarachchi: analysing the data and writing the article. Joseph Therriault: analysing the data and writing the article. Chathuri Yatawara: analysing the data and writing the article. Nagaendran Kandiah: analysing the data and writing the article. Celia M.T. Greenwood: statistical design of the study and analysing the data. Pedro Rosa-Neto: analysing the data and writing the article. Serge Gauthier: designing the study, analysing the data, composing the figure, and writing the article.

CONFLICT OF INTEREST

SG is an investigator in DIAN-TU. The other authors report no disclosure.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Dominantly Inherited Alzheimer Network. Restrictions apply to the availability of these data, which were used under license for this study.

Methods/Design: In a cross-sectional study of 183 ADAD at-risk individuals (91 mutation carriers and 92 noncarriers), we compared the frequency of suicidal ideation among carriers and noncarriers. Linear mixed-effects models with family-level random effects evaluated the relationships between geriatric depression scale (GDS), neuropsychiatric inventory-questionnaire (NPI-Q), and suicidal ideation scores among all ADAD at-risk individuals. An interaction term was added to the regression models to evaluate the interactions of suicidal ideation and mutation status on neuropsychiatric symptoms.

Results: Twenty-six (14.20%) ADAD at-risk individuals (13 [14.28%] carriers and 13 [14.13%] noncarriers) had suicidal ideation. The frequency of suicidal ideation did not differ between carriers and noncarriers. Suicidal ideation was associated with higher GDS among all ADAD at-risk individuals. When stratified into mutation carrier status, noncarriers with suicidal ideation had higher GDS than carriers. There was no statistically significant association between suicidal ideation and NPI-Q among ADAD at-risk individuals. Awareness of mutation status, neuropsychological performances, and cerebrospinal fluid AD biomarkers were not associated with suicidal ideation among carriers and noncarriers.

Conclusions: Suicidal ideation is common among cognitively intact ADAD at-risk individuals. While ADAD at-risk individuals with suicidal ideation have greater depressive symptoms, noncarriers with suicidal ideation have higher GDS scores than carriers. Interestingly, awareness of the mutation status was not associated with suicidal ideation in our study. Early identification of suicidal thoughts can facilitate timely interventions to prevent suicidal behaviours.

Keywords

autosomal dominant Alzheimer's disease; dominantly inherited Alzheimer' network; neuropsychiatric symptoms; suicidal ideation

1 | INTRODUCTION

Autosomal dominant Alzheimer's disease (ADAD) represents less than 1% of all cases of Alzheimer's disease. As several mutations associated with ADAD are known, ADAD is considered an important model to investigate and potentially better understand other more common forms of Alzheimer's disease.[1] Mutations associated with ADAD include mutations in presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), or mutations/duplication of amyloid precursor protein (*APP*). Mutation carriers typically develop dementia at an early age (~30–50 years), and their offspring have a 50/50 chance to inherit the mutation. Thereby having a parent with ADAD renders the offspring at risk for ADAD.

Individuals at risk of inheriting the genetic mutation are facing the anxiety of possibly being a mutation carrier.[2] Moreover, they may witness their loved ones suffer from ADAD.[3] Hence, these individuals may be vulnerable to harbouring suicidal thoughts. According to the studies surveying individuals who were likely to seek presymptomatic testing for *APOE* genotype (associated with most prevalent sporadic form of AD), 6.6% to 11.6% of participants endorsed that they would seriously consider suicide if found to be at high risk for AD.[4] Studies in individuals at risk for Huntington's disease (HD), an autosomal dominant neurodegenerative disease, indicate an increased prevalence of suicidal ideation.[5,6]

However, the frequency of suicidal ideation among ADAD at-risk individuals is unclear. Elucidating the frequency and neurobiological characteristics of suicidal ideation among individuals at risk for ADAD is of paramount importance, as an early identification of suicidal thoughts may facilitate a timely intervention to prevent suicidal behaviours.

While several risk factors for suicide have been identified,[7] major mental illness such as depression and low scores on tests of intelligence is among most strongly replicated risk factors for suicide.[8,9] Depression has separately been found to increase suicide risk in patients with dementia.[10] HD mutation carriers with suicidal ideation are often more depressed, anxious, and aggressive and have more frequent past attempts of suicide than mutation carriers without suicidal ideation.[6] Surprisingly, a recent study reported that depressive symptoms were less common in cognitively intact ADAD mutation carriers than in noncarriers, whereas mildly symptomatic mutation carriers had more depression-related symptoms than noncarriers.[11] The latter was in line with an earlier study in 33 women who did not know their Alzheimer's disease–related *PSEN1* genotype. Despite not demented, *PSEN1* mutation carriers in this study scored worse than noncarriers in cognitive tests (mini-mental state examination [MMSE] and trail making test), thereby indicating mild symptomatology. *PSEN1* mutation carriers in this study scored higher in the Beck depression inventory and thereby had higher levels of depression than *PSEN1* mutation noncarriers.[12] However, an investigation of individuals who endorsed that they would consider suicide when found to have "high risk" *APOE* allele did not demonstrate any specific characteristics in suicide endorsers compared with nonendorsers, with the exception of feelings of nonsupport. Thereby, further investigations are required to determine if depression or other neurobiological characteristics are associated with suicidal ideation among individuals at risk for ADAD.

Accumulating evidence has yielded support to the concept of neurobiological vulnerability to suicidal behaviour.[13,14] The involvement of genetic factors has been demonstrated by family, twin, and adoption studies.[15,16] When compared with nonsuicidal patients with similar mental disorders, individuals with a history of suicidal acts have been found to have altered functioning of the serotonergic system and hypothalamic-pituitary-adrenal axis[17] with potential dysregulations in dopamine and norepinephrine systems.[18–20] Several neuropsychological deficits have been demonstrated in patients with suicidal behaviour[21,22] including higher attention to specific negative emotional stimuli, impaired decision-making, reduced verbal fluency, and decreased problem-solving abilities. In this study, we investigate whether and which clinical and biological factors contribute to suicidal behaviours and suicide ideation in individuals at risk for ADAD.

Here, in a cross-sectional observation of cognitively intact individuals with a positive family history of ADAD from the dominantly inherited Alzheimer's network (DIAN) cohort, we investigate the frequency and the clinical and neurobiological correlates of suicidal ideation among cognitively intact ADAD at-risk individuals. We also stratify the individuals based on their mutation carrier status to test our hypothesis that the neuropsychiatric factors linked to suicide ideation are different between ADAD mutation carriers and noncarriers.

2 | METHODS

2.1 | Study participants

Data analysed in this study were obtained from the DIAN (DIAN Data Freeze 11, February 2017). DIAN is an international registry of individuals at risk for developing ADAD. It contains over 330 individuals—both symptomatic and asymptomatic ADAD mutation carriers and their noncarrier siblings (who serve as a genetically similar control sample) are included. The participants are not required to know their mutation status.[23]

We selected cognitively intact ADAD at-risk individuals, defined by clinical dementia rating 0[24] and MMSE ≥24.[25] Data from each individual's first visit with the following assessments were analysed: (a) suicide question from the Uniform Data Set (UDS) B6, (b) 15-item geriatric depression scale (GDS), (c) informant-based neuropsychiatric inventory-questionnaire (NPI-Q), (d) awareness of mutation status, (e) neuropsychological assessments, and (f) biological factors (genetic and cerebrospinal fluid [CSF]). The history of previous suicide attempts and family history of completed suicides were not available.

2.2 | Ethical approvals and patient consents

The DIAN study was approved by the Institutional Review Boards of all of the participating institutions. Informed written consent was obtained from all participants at each site.

2.3 | Neuropsychiatric assessments

In the section of the suicide question from the UDS B6, each participant was asked if he or she feels that life is not worth living, has expressed a wish to die, or has talked about committing suicide in the past or currently. The individual was classified as having current or past suicide ideation if all answers were yes. The GDS assesses the recent mood of the participants.[26] Higher GDS scores suggest greater depressive symptoms. The NPI-Q measures the presence and severity of behavioural disturbances, and higher NPI-Q scores suggest greater neuropsychiatric symptoms (NPS).[27] The 12 domains (NPS) of NPI-Q include agitation, anxiety, apathy, appetite changes, delusions, depression, disinhibition, abnormal elevated mood, hallucinations, irritability, repetitive motor behaviours, and sleep behaviour changes. The data of the awareness of mutation status and neuropsychiatric assessments were collected during the same study visit.

2.4 | Neuropsychological assessments

The UDS Neuropsychological Test Battery was administered in the DIAN study as previously described.[28] Scores from the following cognitive assessments were analysed in this study: Wechsler memory scale—revised logical memory (story A only) and digit span (forward and backward); category fluency (animals and vegetables); trail making test, parts A and B; digit symbol from the Wechsler adult intelligence scale–revised;

2.5 | Genetic assessments

DNA sequencing of *APP*, *PSEN1*, and *PSEN2* genes was performed by the DIAN Genetics Core investigators to determine the presence of family-specific disease-causing mutation as previously described.[11]

2.6 | CSF assessments

CSF $A\beta_{1–42}$, total tau, and $ptau_{181}$ were analysed by the DIAN Bio-marker Core at the Washington University. The CSF levels of $A\beta_{1–42}$, total tau, and $ptau_{181}$ were measured by immunoassay using the Luminex bead-based multiplexed xMAP technology (INNO-BIA AlzBio3™, Innogenetics, Ghent, Belgium) as previously described.[29]

2.7 | Statistical analysis

Statistical analyses were performed with the statistical software R, version 3.3.2 (R Development Core Team 2015). Descriptive statistics and frequency distributions of baseline demographics, clinical, and genetic characteristics were summarized for all ADAD at-risk individuals with and without suicidal ideation, using family-level random-effects models for both continuous and categorical measurements. The study population was then stratified into mutation carriers and noncarriers, and the baseline characteristics were summarized for each group using similar family-level random-effects models.

The frequency of suicidal ideation among all ADAD at-risk individuals was calculated. Logistic mixed-effects models compared the frequency of suicidal ideation among mutation carriers and noncarriers while accounting for clustering with families through a family-level random effect. An interaction term was then added to the model to evaluate the interactions of mutation status and awareness of mutation status on the frequency of suicide ideation.

Linear mixed-effects models with family-level random effects evaluated the differences in GDS and NPI-Q scores between suicidal and nonsuicidal individuals among all cognitively intact ADAD at-risk individuals. If a significant interaction was identified between mutation status and suicidal ideation, we then evaluated the mutation carrier and noncarrier groups separately using the same model. We modelled GDS/NPI-Q as a function of suicidal ideation and covariates. Below, the model is written in pseudo-R format (R Development CoreTeam 2015), where GDS_{ij}/$NPI\text{-}Q_{ij}$ denotes the GDS or the NPI-Q score for the jth person from the ith family, $Suicide_{ij}$ indicates if this person demonstrates suicidal ideation, and X_{ij} represents fixed-effect covariates for age, gender, education, *APOE* ε4 status, and family mutation type (*APP*, *PSEN1*, and *PSEN2*):

$$\mathrm{GDS}_{ij}/\mathrm{NPI}-\mathrm{Q}_{ij} = \beta_0 + \beta_1\left(\mathrm{Suicide}_{ij}\right) + \beta_2\left(X_{ij}\right) + F_i + \varepsilon_{ij},$$

where F_i represents a random effect for all individuals from family i and ε_{ij} is the residual error assumed independent and normally distributed for all individuals.

The family-level random-effect term accounts for the correlations between individuals within the same family. Although correlations between family members might vary with the relationship type, because of the fairly small sizes of the families, this was modelled with a single random effect.

An interaction term was added to the regression models to evaluate the interaction between suicidal ideation and mutation status on GDS/NPI-Q:

$$\mathrm{GDS}_{ij}/\mathrm{NPI}-\mathrm{Q}_{ij}=\beta_0+\beta_1\left(\mathrm{Suicide}_{ij}\right)+\beta_2\left(\mathrm{Mutation\ Status}_{ij}\right)+\beta_3\left(\mathrm{Suicide}_{ij}\times\mathrm{Mutation\ Status}_{ij}\right)+\beta_4\left(X_{ij}\right)+F_i+\varepsilon_{ij}.$$

We compared the Akaike's information criterion (AIC) of the model with the interaction term with a reduced model without the interaction term to infer whether the interaction model demonstrates a better fit to the data. We further evaluated the associations of suicidal ideation with individual subcomponents of the NPI-Q using similar linear mixed-effects models.

In a secondary analysis, we used similar linear mixed-effects models with family-level random effects to evaluate the differences in cognitive scores between suicidal and nonsuicidal individuals among all cognitively intact ADAD at-risk individuals.

Results are reported as (β,SE), which refer to the slope estimates from the regression models and their standard errors. Bonferroni corrections were performed to correct the aforementioned analyses for multiple comparisons for all neuropsychiatric and neuropsychological outcomes.

3 | RESULTS

3.1 | Baseline demographics and sample characteristics

One hundred eighty-three (n = 183) cognitively intact ADAD at-risk individuals were included in the study. Ninety-one (49.73%) were mutation carriers and 92 (50.27%) were noncarriers. There was no statistically significant difference in the age, gender, education, *APOE* ε4 status, parental age of onset, estimated age of onset, and mutation type among all cognitively intact ADAD at-risk individuals with or without suicidal ideation (Table 1).

Mutation carriers with suicidal ideation had significantly lower education compared with those without suicidal ideation (12.92 vs 14.97 years; slope = −2.00, SE = 0.77, P = .011) (Table 1). There is no statistically significant difference in age, gender, *APOE* ε4 status, parental age of onset, estimated age of onset, and mutation type among mutation carriers with or without suicidal ideation. Among mutation noncarriers, those with suicidal ideation compared with those without suicidal ideation did not differ significantly in age, gender, education and *APOE* ε4 status, parental age of onset, estimated age of onset, or mutation type (Table 1).

3.2 | Frequency of suicide ideation

Among the total cognitively intact ADAD at-risk individuals, 26 (14.20%) had suicidal ideation. When stratified into mutation carrier status, 13 (14.28%) mutation carriers and 13 (14.13%) noncarriers had suicidal ideation (Table 1). There was no statistically significant difference in the frequency of suicidal ideation between mutation carriers and noncarriers (slope = 0.05, SE = 0.45, P = 0.91).

3.3 | Awareness of mutation status

The frequency of awareness of mutation status did not differ significantly among all cognitively intact ADAD at-risk individuals with or without suicidal ideation (7 [26.92%] vs 40 [25.47%]; slope = 0.03, SE = 0.58, $P = .95$). There was no significant interaction between mutation status and awareness of mutation status on the frequency of suicidal ideation (slope = 0.54, SE = 0.71, $P = .44$), suggesting no significant difference in the association between suicidal ideation and awareness of mutation status among mutation carriers and noncarriers.

3.4 | Neuropsychiatric symptoms

Using linear mixed-effects models, suicide ideation was associated with higher GDS scores among all cognitively intact ADAD at-risk individuals (slope = 2.54, SE = 0.36, $P \leq .001$, 95% CI, 1.79–3.17) (Table 2). A significant interaction between the variables of suicidal ideation and mutation status on GDS indicated that GDS was higher among mutation noncarriers with suicidal ideation compared with mutation carriers (slope = −2.78, SE = 0.69, $P \leq .001$). By calculating AIC, the model with the interaction term fitted better than the model without the interaction (AIC was 706.89 with the interaction vs 721.42 without, $P \leq .001$). When stratified into mutation carrier status, mutation carriers with suicidal ideation had higher GDS scores than those who were not suicidal (slope = 1.13, SE = 0.50, $P = .026$, 95% CI, 0.183–2.096). Among noncarriers, those who were suicidal had higher GDS scores (slope = 3.95, SE = 0.49, adjusted $P \leq .001$, 95% CI, 2.91–4.86).

While we found that suicidal ideation was associated with higher NPI-Q scores among all cognitively intact ADAD at-risk individuals (slope = 0.64, SE = 0.31, $P = .042$, 95% CI, 0.04–1.26) (Table 2), this result was not statistically significant after Bonferroni correction for multiple comparisons. Exploratory analysis of the NPI-Q subcomponent suggested that suicidal ideation is associated with severity of depressive symptoms among all cognitively intact ADAD at-risk individuals (slope = 0.29, SE = 0.11, $P = .016$, 95% CI, 0.08–0.50) (Figure 1). There was no significant interaction between suicidal ideation and mutation status on NPI-Q scores, suggesting no significant difference in NPI-Q between mutation carriers and noncarriers with or without suicidal ideation.

3.5 | Neuropsychological performances

There was no statistically significant difference in cognitive scores among all cognitively intact ADAD at-risk individuals, with or without suicidal ideation (Table 3). There was no significant interaction between suicidal ideation and mutation status on cognitive scores, suggesting no significant difference in cognitive scores between mutation carriers and noncarriers with or without suicidal ideation.

3.6 | CSF AD biomarkers

There was no statistically significant difference in the CSF AD biomarkers ($A\beta_{1–42}$, p-tau_{181}, and t-tau) among all cognitively intact at-risk individuals, mutation carriers, or noncarriers with or without suicidal ideation (Table 1).

4 | DISCUSSION

Our study showed that 14.2% of cognitively intact ADAD at-risk individuals harbored suicidal thoughts regardless of their genetic mutation status. While suicidal ideation was associated with greater depressive symptoms in all cognitively intact ADAD at-risk individuals, mutation noncarriers with suicidal ideation had higher GDS than mutation carriers with suicidal ideation. Awareness of mutation status, neuropsychological performances, and levels of CSF AD biomarkers were not associated with suicidal ideation among mutation carriers and noncarriers.

The frequency of suicidal ideation among cognitively intact ADAD at-risk individuals is clinically significant, given that the prevalence of suicidal ideation in the general population is 9.2% according to a cross-national study[30] and has been shown to be much lower in certain populations.[31] We further found that suicidal ideation is equally common among mutation carriers and noncarriers. With the availability of genetic counselling, individuals within ADAD families may undergo genetic testing, especially if clinical trials are available.[32] While the knowledge of genetic mutation carrier status may alleviate the uncertainty and anxiety of developing AD and allow planning for the future,[33] some individuals may react adversely to having a genetic mutation as they are destined to develop AD years later, hence possibly leading to suicidal thoughts.[34,35] We also hypothesized that noncarriers may develop suicidal ideation because of a variety of reasons: anxiety of potentially being a carrier, burden of being a caregiver for their loved ones, seeing their loved ones suffer, and losing them because of AD. Our results suggest that suicidal thoughts may not be related to AD pathophysiology, given a lack of association between suicidal ideation and CSF AD biomarkers. Hence, our findings indicate that being an individual at risk for ADAD, independent of the mutation carrier status, is a vulnerability factor for suicide ideation.

In our study, ADAD mutation carriers and noncarriers with suicidal ideation have significantly higher GDS scores than those without suicidal ideation. Although our findings are consistent with the literature whereby depression is a well-known risk factor for suicidal ideation,[36] we found that ADAD mutation noncarriers with suicidal ideation have greater depressive symptoms than mutation carriers with suicidal ideation. This finding is important for clinicians as noncarriers might not undergo neuropsychiatric assessments or screening for suicidal thoughts during routine clinic consults.[6] Greater depressive symptoms in noncarriers with suicidal ideation may be partly due to guilt and partly due to the burden of being in the family with ADAD having the insight into what their family members with the genetic mutation will go through.[37] Hence, during the evaluation of ADAD at-risk individuals, both mutation carriers and noncarriers, especially those with greater depressive symptoms, should be monitored closely for suicidal ideation.

Importantly, being aware of the mutation status did not influence the frequency of suicidal ideation regardless of the mutation carrier/noncarrier status. One might assume that the knowledge of not having inherited the mutation would alleviate the anxiety of possibly developing AD, hence decreasing suicidal thoughts, while the confirmation of having inherited genetic mutation would increase the vulnerability to suicidal thoughts.[37] However, our findings suggest that the knowledge of mutation status may not influence the risk for

suicidal ideation. That may indicate the presence of additional yet unclear risk factors for suicidal ideation in the ADAD at-risk families, warranting further investigations.

We could not identify any specific impairment in the psychometric performances comparing suicidal and nonsuicidal individuals. This is partly in line with the literature. Indeed, it has been found that deficits in decision-making, category verbal fluency, and interference Stroop test are associated with suicidal behaviours but only in patients with mood disorders.[22,38] However, differences in cognitive control have been found in suicide attempters compared with suicide ideators in young[39] and elderly[40] populations. Neurocognitive alterations represent relevant vulnerability factors and potential endophenotypes of suicidal behaviour and should thus be further investigated in nonsymptomatic AD and demented populations.

There are limitations in our study. First, the single suicide question encompasses three components, which assess different levels of suicidal ideation. This may reduce the specificity in detecting the specific suicidal thought that may lead to an attempt. Second, the suicide question includes both present and previous suicide ideation. Having had suicidal ideation in the past may not relate to current NPS. Third, GDS is originally designed to detect depressive symptoms among elderly individuals and may thus not be suitable for the younger participants in the DIAN cohort. Fourth, as our study is cross sectional and the data of suicide attempts are not available, the nature of the suicidal thoughts and whether they lead to a suicide attempt cannot be concluded from our study. Fifth, while the inclusion of a comparator group, ideally of family members of individuals with sporadic AD, will be ideal to control for stress and caregiver burden, these data are unavailable for this study. Hence, this may confound the interpretation of our results. However, in addition to ADAD mutation carriers, we have included their noncarrier siblings as a comparator group. The noncarrier siblings, who also serve as a genetically similar control sample, may enable the control for stress and caregiver burden. Lastly, it may be considered more logical to model suicidal ideation as the outcome and GDS or NPI-Q as predictor variables, rather than the reverse as we have done here. Our choice is made for practical reasons: The data set is of modest size, and linear mixed-effects models are far more stable than logistic mixed-effects models. We are unable to obtain estimates for all our models of interest when using logistic models. All our results should be interpreted as associative, and inference of cause-effect must be explored in studies explicitly designed for such a goal.

Suicide prevention requires a multifaceted approach, especially focusing on mental health conditions. A review of suicide prevention strategies suggests that educating the clinician in identifying and treating depression and restricting access to lethal methods can reduce suicide rates.[41] Furthermore, a qualitative study in HD shows that partners, relatives, and health care professionals play an important role in supporting HD patients with suicidal ideation in their coping strategies.[42] Therefore, identification and intervention to address the complex issues of neurobiological markers and dementia will help clinicians mitigate the risk of suicide in patients with AD. We suggest that, in future studies, a more comprehensive suicide questionnaire, such as the Columbia suicide severity rating scale[43] that measures a broader spectrum and levels of suicidal thoughts, should be used. In addition, a prospective study will be important to better understand the trajectory of suicidal thoughts in cognitively

intact ADAD at-risk individuals, so as to determine which risk factors are more associated with suicide attempts.

5 | CONCLUSION

Our findings suggest that suicidal ideation is common among both mutation carriers and noncarriers in ADAD at-risk families. Both ADAD mutation carriers and noncarriers should be monitored closely so that timely interventions can be offered to alleviate any suicidal ideation to prevent a suicide attempt.

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Key points

- 14.2% of ADAD at-risk persons have suicidal thoughts regardless of their mutation status.
- Suicidal ideation is associated with greater depressive symptoms in all asymptomatic ADAD at-risk individuals.
- Nonmutation carriers with suicidal thoughts have greater GDS than mutation carriers with suicidal thoughts.
- No neurobiological correlates of suicidal ideation among cognitively intact ADAD at-risk individuals.

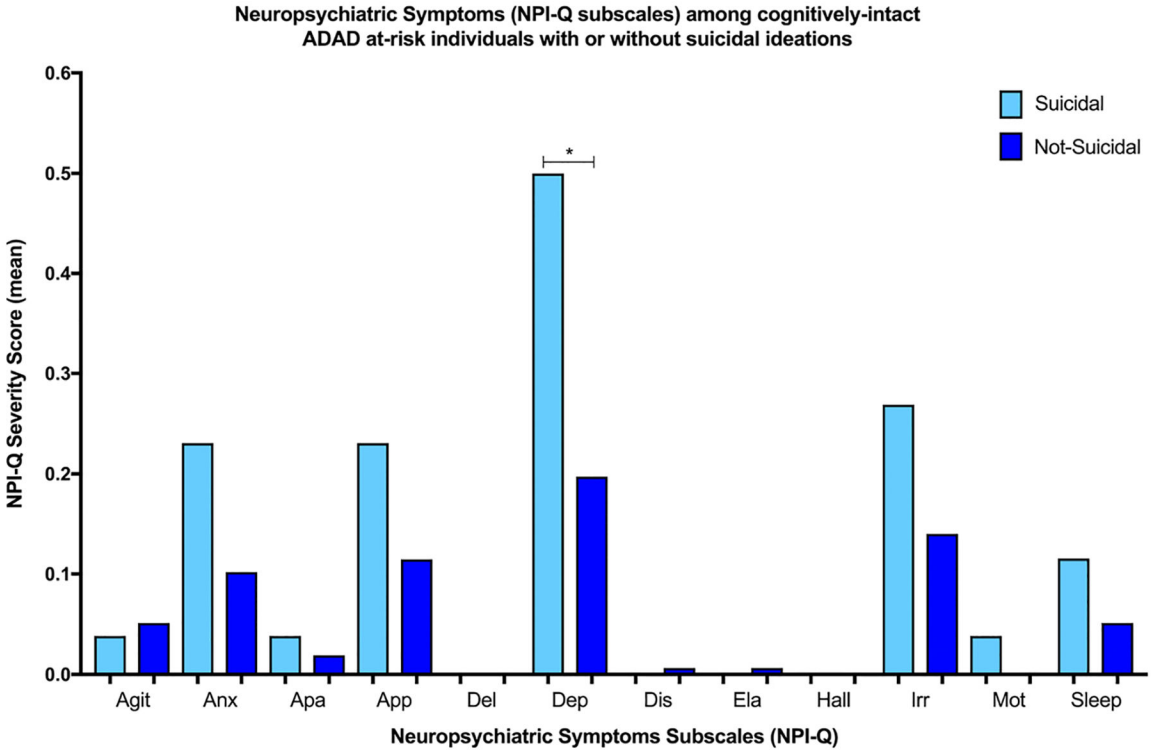

FIGURE 1.

Neuropsychiatric symptoms (NPI-Q subscales) among cognitively intact ADAD at-risk individuals with or without suicidal ideations.The figure shows the differences in NPI-Q subscale mean severity scores among cognitively intact ADAD at-risk individuals, with and without suicidal ideations.*$P < .05$.Agit, agitation; Anx, anxiety; Apa, apathy; App, appetite changes; Del, delusions; Dep, depression; Dis, disinhibition; Ela, abnormal elevated mood; Hall, hallucinations; Irr, irritability; Mot, repetitive motor behaviours; Sleep, sleep behaviour changes

TABLE 1

Baseline demographics and sample characteristics of cognitive-intact ADAD mutation and nonmutation carriers with and without suicidal ideation

	Total ADAD at-Risk Individuals (n = 183)		ADAD Mutation Carriers (n = 91)		ADAD Nonmutation Carriers (n = 92)	
	Suicide Ideation (n = 26)	**No Suicide Ideation (n = 157)**	**Suicide Ideation (n = 13)**	**No Suicide Ideation (n = 78)**	**Suicide Ideation (n = 13)**	**No Suicide Ideation (n = 79)**
Age in years, mean, (SD)	41.48 (8.68)	39.76 (10.32)	41.54 (8.05)	37.00 (9.36)	41.62 (9.59)	42.48 (10.55)
Male, n (%)	11 (42.30)	60 (38.21)	6 (46.15)	30 (38.46)	5 (38.46)	30 (37.97)
Education in years, mean, (SD)	13.77 (2.48)	14.96 (2.54)	12.92 (2.32)	14.97 (2.62) *	14.62 (2.43)	14.94 (2.48)
APOE ε4 carriers, n (%)	7 (26.92)	42 (26.75)	3 (23.07)	21 (26.92)	4 (30.76)	21 (26.58)
Parental age of onset in years, mean (SD)	47.69 (6.19)	46.39 (6.55)	48.92 (4.82)	46.63 (6.62)	46.46 (7.31)	46.15 (6.52)
EYO, years, mean (SD)	−7.86 (9.45)	−7.73 (9.65)	−9.35 (8.59)	−10.02 (8.17)	−6.37 (10.36)	−5.46 (10.48)
Mutation Type						
APP, n (%)	8 (30.76)	41 (26.11)	4 (30.76)	16 (20.51)	4 (30.76)	25 (31.64)
PS1, n (%)	18 (69.23)	101 (64.33)	9 (69.23)	55 (70.51)	9 (69.23)	46 (58.22)
PS2, n (%)	0 (0.00)	15 (9.55)	0 (0.00)	7 (8.97)	0 (0.00)	8 (10.12)
Aware of mutation status, n (%)	7 (26.92)	40 (25.47)	3 (23.07)	23 (29.48)	4 (30.76)	17 (21.51)
CSF $A\beta_{1–42}$, pg/mL, mean (SD)[a]	394.66 (105.75)	416.54 (138.46)	378.92 (116.97)	360.33 (143.66)	423.52 (82.92)	466.18 (113.40)
CSF p-tau_{181p}, pg/mL, mean, (SD)[a]	42.26 (30.31)	39.73 (24.63)	50.28 (34.93)	49.45 (29.82)	27.57 (9.96)	31.01 (14.13)
CSF t-tau, pg/mL, mean (SD)[a]	67.36 (28.79)	73.66 (56.19)	71.77 (34.11)	91.21 (73.37)	59.28 (14.32)	58.16 (27.00)

Note. *P* values were assessed using family-level random-effects models for the continuous variables and categorical variables, taking into account the analysis of multiple family members within the families. A logistic mixed-effect model compared the frequency of suicidal ideation among mutation and nonmutation carriers, accounting for family-level random effect.

Abbreviations: ADAD, autosomal dominant Alzheimer's disease; CSF, cerebrospinal fluid; EYO, estimated years of onset; GDS, geriatric depression scale.

[a]27 mutation carriers and 26 nonmutation carriers did not have CSF data for the visit.

*$P < .05$.

TABLE 2

Associations between neuropsychiatric symptoms and suicidal ideation, among ADAD mutation and nonmutation carriers

	Total ADAD at-Risk Individuals (n = 183)			
	Slope	**Standard Error**	**Confidence Interval**	**Unadjusted *P* value**
GDS	2.54	0.36	1.79–3.17	<.001
NPI-Q	0.64	0.31	0.04–1.26	.042
		ADAD Mutation Carriers (n = 91)		
GDS	1.13	0.50	0.183–2.096	.026
		ADAD Nonmutation Carriers (n = 92)		
GDS	3.95	0.49	2.91–4.86	<.001

Note. *P* values were assessed using linear mixed-effect models with family-level random effects, corrected for age, gender, *APOE*, education, and family mutation type, taking into account the analysis of multiple family members within the families. As no significant interaction between suicidal ideation and mutation status on NPI-Q scores was found, no further analysis was performed on the mutation and nonmutation carrier groups.

Abbreviations: ADAD, autosomal dominant Alzheimer's disease; GDS, geriatric depression scale; NPI-Q, neuropsychiatric inventory-questionnaire.

TABLE 3

Means and standard deviations of neuropsychological assessments among asymptomatic ADAD at-risk individuals, with or without suicidal ideation

	Total ADAD at-Risk Individuals (n = 183)		
	Suicide Ideation (n = 26) Mean (SD)	**No Suicide Ideation (n = 157) Mean (SD)**	***P* value**
MMSE	28.85 (1.40)	29.30 (0.98)	.148
Boston naming test	27.92 (1.80)	28.01 (1.98)	.963
WAIS-R digit symbol	58.58 (11.56)	62.66 (12.73)	.508
Digit span forward	9.04 (2.18)	9.25 (1.80)	.738
Digit span backward	7.46 (1.98)	7.65 (2.16)	.936
Trail A	21.15 (6.38)	22.47 (6.90)	.148
Trail B	56.73 (19.39)	56.45 (24.17)	.377
Letters fluency	44.88 (10.30)	43.10 (11.44)	.325
Animal	22.62 (5.44)	23.09 (5.24)	.912
Vegetable	14.96 (4.09)	15.62 (4.24)	.579
Logical memory	14.50 (4.48)	15.32 (3.82)	.606
Words immediate	5.27 (1.80)	5.71 (1.95)	.572
Words delayed	2.62 (2.08)	2.55 (2.02)	.482

Note. *P* values were assessed using linear mixed-effect models with family-level random effects, corrected for age, gender, *APOE*, education, and family mutation type, taking into account the analysis of multiple family members within the families.

Abbreviations: ADAD, autosomal dominant Alzheimer's disease; MMSE, mini-mental state examination; WAIS-R, Wechsler adult intelligence scale–revised.