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Autism Characteristics in Older Adults with Depressive Disorders

Hilde M. Geurts, Ph.D., Max Stek, M.D., Ph.D., Hannie Comijs, Ph.D.

Objective: To study the prevalence of autism spectrum disorder (ASD) characteristics in older adults with and without depressive disorders and the social network and past negative life events in those with a high number of ASD characteristics and those without a large number of these characteristics. **Methods:** This large, multisite, naturalistic, prospective cohort study used data from the Netherlands Study of Depression in Older persons (aged 60–90 years) with ($N = 259$) and without ($N = 114$) a depressive disorder according to DSM-IV criteria. ASD characteristics were measured with the abbreviated Autism Spectrum Quotient with a cutoff score of 70. Additional measures were the Composite International Diagnostic Interview, the Inventory of Depressive Symptomatology, the Becks Anxiety Inventory, the Close Person Inventory, and the life events questionnaire. **Results:** Of the older adults with a depressive disorder, 31% showed elevated ASD characteristics, which is much higher than the observed 6% in the comparison group. High ASD characteristics were associated with elevated depression and anxiety symptoms and more comorbid anxiety disorders. Those with a high number of ASD characteristics did not differ in the size of their social network or the number of negative life events as compared with those with less ASD characteristics. **Conclusion:** ASD might be overlooked in older adults, especially within geriatric psychiatry. When diagnosing and treating depression and anxiety in older patients, one should be attentive to ASD. (Am J Geriatr Psychiatry 2016; 24:161–169)

Key Words: Depression, autism traits, older adults

INTRODUCTION

Approximately 1 in 100 persons across the world¹ meets the criteria for autism spectrum disorder (ASD),² a psychiatric neurodevelopmental disorder.

ASD is a debilitating disorder, and difficulties in social interaction and communication and stereotyped or repetitive behaviors and interests are at the core of this diagnosis. Although ASD was originally perceived as a childhood disorder, today we know

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the prevalence of ASD is similar across the life span³ and that ASD is a lifelong disorder. Only relatively recently it has been recognized that ASD can also be diagnosed in (late) adulthood.^{4,5,6} When the current older adults were children, ASD was not yet broadly known. Moreover, ASD was thought to be mainly prevalent in people with low intellectual functioning, whereas currently we know that ASD can be present among all possible intelligence levels. Therefore, many older (intellectually able) adults with ASD have probably remained unrecognized and undiagnosed.^{7,8} These adults with unrecognized ASD are often diagnosed with a secondary psychiatric condition, because ASD diagnoses were often missed in standard diagnostic assessments.^{7,9,10} The most common secondary psychiatric diagnoses are mood (primarily depression) and anxiety disorders.⁹ Hence, we expect that especially among older adults with depression there will be undiagnosed cases of ASD. If this is indeed the case, one would expect that the prevalence of ASD characteristics will be higher in a group of older adults with depression as compared with control subjects without depression within a similar age range. This hypothesis will be tested in the current study.

Another reason we expect a relatively high prevalence of ASD characteristics in (older) adults with a mood disorder stems from the literature on the relationships between ASD and depression. Both mood (especially depression) and anxiety disorders are highly prevalent comorbid diagnoses in those with an ASD diagnosis,^{11–14} Moreover, in nonclinical adult samples a positive relationship between ASD characteristics and depressive and anxiety symptoms^{15,16} has been observed. In line with these findings, high rates of ASD characteristics have been reported in clinical samples of children with a mood and/or anxiety disorder but without ASD.¹⁷ It is therefore highly likely that a similar pattern emerges when focusing on adults with depression. Indeed, recently it was shown that 37% of adults with a major depressive disorder (25–59 years) showed high ASD-like traits.¹⁸ However, to our knowledge it has yet not been tested whether this is also the case in older adults (60+) with a depressive disorder. Given the earlier findings, our second hypothesis is that reporting more ASD characteristics is associated with more depressive and anxiety symptoms.

In addition, risk factors for developing late-life depression are thought to be common in (young) adults with ASD, which strengthens the hypothesis that ASD characteristics will be more prevalent in adults with a known depressive disorder as compared with those without such a disorder. For example, low perceived social support, inadequacy of social activity, actual low social participation status, loneliness, high number of negative life events, and multiple morbidity (i.e., having more than one psychiatric diagnosis) are known vulnerability factors for developing late-life depressive symptoms.^{19,20} Similar psychosocial factors are thought to be common in individuals with ASD.^{21,22} For example, given the day-to-day struggles people with ASD experience with respect to relationships, education, work, and housing, they might encounter more negative life events as compared with those without ASD. However, although to our knowledge no systematic ASD studies focus on negative life events across the life span, several studies did focus on the social network of individuals with ASD. In children with ASD only 34% has at least one good friend,²³ and in adulthood 40% reported not to have any close friends at all.²⁴ This suggests that their social network is relatively small. Our third hypothesis is that those with many ASD characteristics will have a smaller social network. Moreover, we explore whether this specific subgroup will also experience more negative life events.

Therefore, the purpose of the current study is to examine the presence and role of ASD symptoms in older adults (60+ years) with and without depressive disorders. First, we determine how many persons score above the clinical cutoff on a short version of a widely used ASD screening instrument, the Autism Spectrum Quotient (AQ-28).²⁵ We hypothesize that although in healthy older adults approximately 1% will score above the ASD cutoff, this percentage will be much higher in older adults with a depressive disorder diagnosis. Second, we predict there is a positive relation between the number of ASD characteristics and the number of depression and anxiety symptoms. Third, we predict that those with a score above the AQ-28 cutoff will not just have more depressive and anxiety symptoms but will also have more actual mood and anxiety disorders, have a smaller social network, and have experienced more negative life events than those with a score below the AQ-28 cutoff.

TABLE 1. Characteristics of the Group with Depressive Disorders and the Control Group

	Group		Statistics
	Depression (N = 258)	Comparison (N = 114)	
Gender: M/F	83/175	44/70	$\chi^2(1, N = 372) = 1.45, p = 0.23$
Mean age, y (SD) ^a	70.1 (7.2) 95% CI (69.2–70.9)	69.2 (6.5) 95% CI (68.0–70.5)	$F(1,371) = 1.12, p = 0.29, p\eta^2 < 0.01$
Mean MMSE ^b (SD)	28.0 (1.8) 95% CI (27.7–28.2)	28.5 (1.4) 95% CI (28.2–28.8)	$F(1,370) = 8.55, p < 0.005, p\eta^2 = 0.02$
Mean IDS-SR total score ^c (SD)	29.6 (12.8) 95% CI (28.2–30.9)	6.6 (4.2) 95% CI (4.6–8.7)	$F(1,366) = 342.5, p < 0.001, p\eta^2 = 0.48$
Mean BAI total score ^d (SD)	17.0 (10.7) 95% CI (15.9–18.2)	3.4 (3.6) 95% CI (1.7–5.1)	$F(1,351) = 170.1, p < 0.001, p\eta^2 = 0.33$
Mean AQ-28 total score (SD)	63.8 (10.4) 95% CI (62.6–65.0)	53.0 (8.0) 95% CI (51.2–54.8)	$F(1,371) = 97.6, p < 0.001, p\eta^2 = 0.21$

Notes: CI: confidence interval; SD: standard deviation.

^aDepression group: <70 N = 157, 70–80 N = 73, >80 N = 28; comparison group: <70 N = 157, 70–80 N = 73, >80 N = 28.

^bDepression group: MMSE score ≤ 24 N = 10, >24 N = 248; comparison group: MMSE score ≤ 24 N = 0, >24 N = 117.

^cBecause not all participants filled out the IDS-SR, the descriptive of this total score is based on 255 participants in the depression group and 112 in the control group.

^dBecause not all participants filled out the BAI, the descriptive of this total score is based on 242 participants in the depression group and 110 in the control group.

METHODS

Participants

Five hundred ten older adults (> 60 years) took part in a large, multisite, naturalistic, longitudinal cohort study (2007–2010), the Netherlands Study of Depression in Older persons (NESDO). The aim of NESDO is to study the course and consequences of depressive disorders in older adults, and therefore participants (378 depressed older adults and 132 control subjects) in this prospective cohort were extensively tested. Please note that the study design of NESDO has been described elsewhere.²⁶ In short, only individuals that had a good command of the Dutch language, scored 18 or higher on the Mini-Mental State Exam (MMSE),²⁷ and were not suspected of having dementia according to clinicians were included. Persons with a bipolar or psychotic disorder were excluded.

For the current study participants (N = 376) were included when they filled out the shortened version of the AQ-28,²⁵ which was included in a 6-month follow-up measurement between 2011 and 2012. These participants also filled out the Dutch versions of the Inventory of Depressive Symptomatology Self Report (IDS-SR)²⁸ and the Becks Anxiety Inventory (BAI).²⁹ Informed consent was obtained from all

participants before they participated in NESDO; none of the participants had an MMSE score below 21 and so were able to give both oral and written informed consent.²⁶ The study was approved by the medical ethical committee of the VU University Medical Center and all participating institutes.

Depression Group. Two hundred fifty-nine older adults with a depressive disorder in the past 6 months participated at baseline in the study. Table 1 presents the characteristics for 258 participants (mean age: 70 years [range: 60–90]; 83 men and 175 women); one participant's AQ score was three standard errors above the group mean and was therefore excluded. Older adults with late-life depression in various developmental and severity stages were recruited for inclusion in NESDO via mental health care institutes and general practitioners. Those with a primary diagnosis of major or minor depression or dysthymia or after a positive screening with the Geriatric Depression Scale³⁰ who could give written informed consent were interviewed to determine whether they indeed met depression criteria. The Composite International Diagnostic Interview (CIDI)³¹ was used to assess the presence of a depression disorder (major depression, dysthymia, and minor depression) and/or comorbid anxiety disorder (generalized anxiety disorder [GAD], social phobia, panic disorder, and agoraphobia) according to the *Diagnostic and Statistical*

Manual of Mental Disorders, Fourth Edition, criteria in the last 6 months before the measurement day. The CIDI revealed that at baseline 26% (N = 67) met criteria for dysthymia, 94% (N = 243) for major depression, and 3.9% (N = 10) for minor depression. With respect to the comorbidity with anxiety, the CIDI showed that 17.3% (N = 25) met the diagnostic criteria for GAD, 33.3% (N = 48) for social phobia, 12.5% (N = 18) with agoraphobia, 9.7% (N = 14) for panic disorder without agoraphobia, and 13.9% (N = 20) for agoraphobia.

Comparison Group. One hundred seventeen older adults who had no lifetime depression participated and were recruited via general practices. [Table 1](#) presents the characteristics for 114 participants (mean age: 9.2 years [range: 60–85]; 44 men and 70 women) because 3 participants had an IDS-SR score during follow-up three standard errors above the group mean and 2 of these participants also had a BAI score of three standard errors above the group mean.

Measures

The IDS-SR²⁸ consists of 30 items related to key symptoms of depression, such as items related to mood, motivation, and somatic symptoms. All items were answered on a four-point scale (0–3). A higher score on the IDS-SR indicates more serious depression ([Table 1](#), potential score range is 0–84 as 28 of 30 items are scored). The psychometric properties of this self-report scale are sound.²⁸

The BAI²⁹ consists of 21 items, which measures the emotional, physiological, and cognitive symptoms of anxiety. All items were answered on a four-point-scale (0–3). A higher score on the BAI indicates the presence of more severe anxiety symptoms ([Table 1](#), potential score range is 0–63). The BAI was found to have sound psychometric properties.²⁹

The AQ²⁸²⁵ consists of 28 items related to ASD characteristics such as impaired social relationships, impaired communication, and the need for a structured environment. All items were answered on a four-point scale (1–4). For the current study we used the AQ-28 total score. A higher score on the AQ means that more severe ASD characteristics are present ([Table 1](#), potential score range is 28–112). The AQ-28 is based on the 50-item AQ,³² and this abridged version of the AQ is recommended to be used in large-scale studies when filling out the full

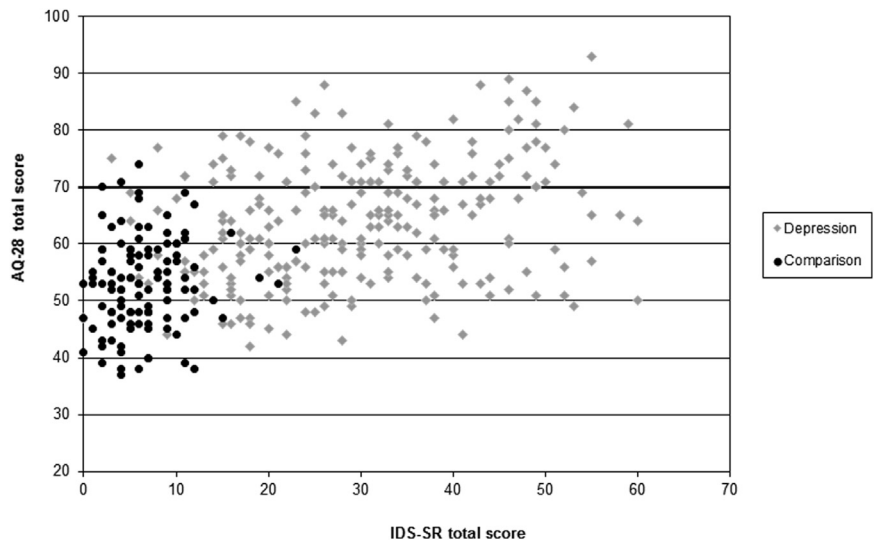
AQ version is too demanding. Other validated adult ASD questionnaires consist of a larger number of items as compared with the AQ-28, and therefore we chose to use the AQ-28 to ensure the additional time investment of the participants was kept to a minimum. The test–retest and inter-rater reliability and validity of the AQ-28 are acceptable to good.²⁵ We used a cutoff of 70 to determine the percentage of individuals that have relatively severe ASD characteristics. This stringent cutoff has a sensitivity of 0.94 and a specificity of 0.91 when distinguishing between ASD and healthy control adult samples (mean age between 21 and 45 years).²⁵

In addition, we used information from two other questionnaires filled out by the participants: the Close Person Inventory³³ and the life events questionnaire.³⁴ The Close Person Inventory consists a series of questions related to details about present social support from the four most intimate persons of the participant. For the current study we used the reported number of persons in the network of the participant with who the participant has regular and important contact and is older than 18 years of age. The life events questionnaire consists of a series of questions related to different types of life events that are experienced as negative by most people (such as illness, death of a family member, financial problems). For the current study we used the number of negative life events across the last 5 years.

Statistical Analyses

To determine whether in the depression group more participants score ASD positive on an ASD screener, percentages were calculated of those scoring above the 70 point cutoff on the AQ-28 per group. A χ^2 test was conducted to compare these percentages. Second, we ran Pearson correlation analyses to explore the relationship between AQ-28 and the depression and anxiety questionnaire scores in each of the two groups. Third, we compared those individuals with a score above the AQ-28 cutoff with those with a score below the AQ-28 cutoff. The inclusion in these two groups was independent of whether or not they had a depression diagnoses when the study started. We conducted a MANOVA with group as the between-subject factor and the total scores of the questionnaires (except for the AQ-28) as dependent measures. We also conducted χ^2 tests and

FIGURE 1. The relationship between the ASD characteristics (AQ-28 total score) and depression symptoms (IDS-SR total score) for depressed older adults (gray diamonds) and comparison group (black circles). The cutoff of the AQ-28 is 70, represented by the bold line.



ANOVAs to test whether these two groups differed in gender distribution, CIDI scores, social support, and negative life events.

All analyses were conducted with SPSS version 21, IBM, Inc., Armonk, NY. Confidence intervals for the percentages were calculated via <http://vassarstats.net/prop1.html> (i.e., we used the so-called Wilson procedure without correction for continuity, see Newcombe³⁵) and confidence intervals for correlations via http://onlinestatbook.com/lms/estimation/correlation_ci.html.³⁶ Partial η^2 was reported as effect size.

RESULTS

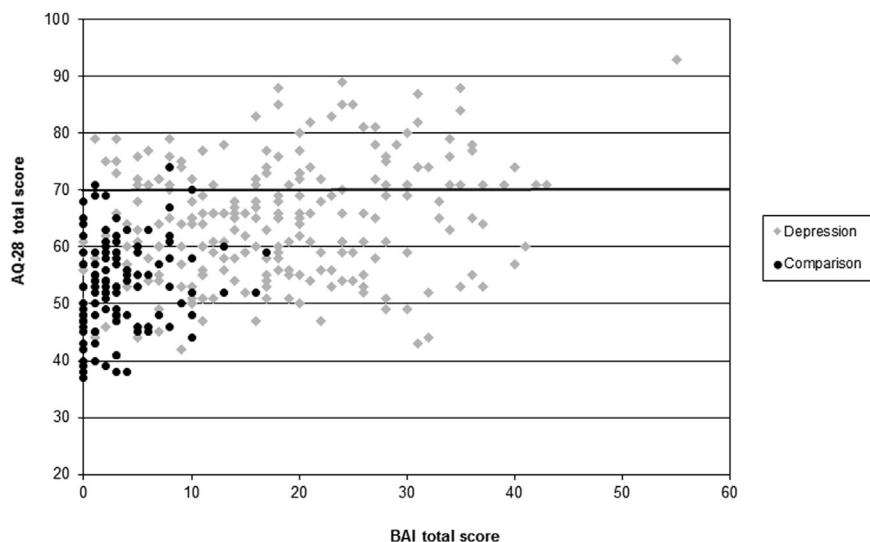
Those of the original NESDO cohort ($N = 134$) excluded from the current study because of missing AQ-28 data were slightly older ($F(2, 504) = 7.77$, $p < 0.001$, partial $\eta^2 = 0.03$) but did not differ on the IDS-SR and BAI total scores from those that did fill out the AQ-28 (respectively, $F(2, 504) = 1.55$, $p = 0.21$, partial $\eta^2 = 0.01$ and $F < 1$, $p = 0.87$, partial $\eta^2 = 0.00$). Hence, there seems to be no selection bias in the current sample that might confound our interpretation of the presented AQ-28 analyses. Moreover, the depression and the comparison group

did not differ from each other with respect to gender and age, suggesting that on a group level the two groups were well matched on gender and age. We did, as expected, find significant differences with respect to all anxiety and depression measures, Wilks $\lambda = 0.50$, $F(2,349) = 171.8$, $p < 0.001$, partial $\eta^2 = 0.70$. With respect to the MMSE the depression group had a slightly lower score, but the effect size was rather small (Table 1).

In the comparison group 2.6% ($N = 3$; 95% confidence interval: 0.9%–7.5%) had a score above the AQ-28 cutoff of 70, whereas in the depression group 31.0% ($N = 80$; 95% confidence interval: 25.7%–37.0%) scored above this cutoff, which is significantly more, $\chi^2(1, N = 372) = 36.73$, $p < 0.001$. In both groups we observed positive but small correlations between the AQ-28 total score and the IDS-SR total score (comparison group: $r(108) = 0.12$, p (two-tailed) = 0.20; depression group: $r(241) = 0.29$; p (two-tailed) < 0.001) and the BAI total score (comparison group: $r(108) = 0.17$, p (two-tailed) = 0.07; depression group: $r(241) = 0.28$, p (two-tailed) < 0.001 ; see Figs. 1 and 2 for details). These low correlations imply there is hardly any overlap between the constructs we intend to measure with the AQ-28 and the IDS-SR and BAI.

The high ASD group (i.e., group scoring above AQ-28 cutoff; $N = 83$) and low ASD group (i.e., group scoring below AQ-28 cutoff; $N = 284$) did not

FIGURE 2. The relationship between the ASD characteristics (AQ-28 total score) and anxiety symptoms (BAI total score) for depressed older adults (gray diamonds) and comparison group (black circles). The cutoff of the AQ-28 is 70, represented by the bold line. The participant in the upper right corner is not an outlier (i.e., within three standard errors from group mean), and excluding this participant did not alter the main pattern of findings.



differ from each other with respect to age, but we observed other significant differences. There were relatively more men in the high ASD group as compared with the low ASD group. Moreover, and by definition in line with the former group analyses, on the IDS-SR and BAI total scores the high ASD group showed more symptoms than the low ASD group. With respect to the diagnosis at inclusion (i.e., CIDI scores), major depression, dysthymia, GAD, social phobia, and agoraphobia were more common in the high ASD group as compared with the low ASD group (Table 2). In contrast to our hypothesis, there were no significant differences between the two groups in the size of the social network (Close Person Inventory score). The exploratory analyses revealed the number of negative life events (life events questionnaire score) also did not differ between the high and low ASD groups.

DISCUSSION

As predicted, a larger proportion of older adults with a current depressive disorder showed a relatively high number ASD characteristics as compared with those without depressive disorders. Moreover,

an increase in the severity of the ASD characteristics was related to an increase in self-reported anxiety and depressive symptoms, but given the low to medium correlations between ASD and depression and anxiety symptoms, the elevated prevalence of ASD characteristics in older adults with a depressive disorder does not seem to be due to item overlap of the questionnaires. Those with high ASD characteristics did have more comorbid disorders, but, in contrast with our expectations, neither had a smaller social network or experienced more negative life events as compared with those with a low number of ASD characteristics.

Approximately 31% of the older adults scored above the ASD cutoff, which is slightly lower than the percentage (36%) of those with high ASD traits in much younger adult population with depressive disorders.¹⁸ In the relatively small Matsuo et al.¹⁸ study, however, another ASD questionnaire was used and the cutoff was far more liberal. If we used a similarly liberal cutoff (i.e., 65), 43% of the older adults show elevated ASD characteristics. This more liberal cutoff of 65 is recommended in the clinical setting when one suspects ASD,²⁵ and when using this cutoff approximately 6.1% of older adults without a history of mood or anxiety disorders did

TABLE 2. Characteristics of Those Scoring Above the AQ-28 Cutoff and Scoring Below This Cutoff

	Group		Statistics
	High ASD (N = 83)	Low ASD (N = 289)	
Gender: M/F	37/46	90/199	$\chi^2(1, N = 372) = 5.18, p = 0.02$
Mean age, y (SD)	68.6 (6.6)	70.2 (7.1)	$F(1,371) = 3.42, p = 0.07, \eta^2 = 0.01$
	95% CI (67.1–70.1)	95% CI (69.4–71.0)	
CIDI at baseline (%)			
Mood disorders			
MDD	76 (91.6)	167 (57.8)	$\chi^2(1, N = 372) = 32.5, p < 0.001$
Dysthymia	29 (34.9)	38 (13.1)	$\chi^2(1, N = 372) = 20.7, p < 0.001$
Minor depression	4 (4.8)	12 (4.2)	$\chi^2(1, N = 372) = 0.07, p = 0.79$
Comorbid anxiety			
GAD	10 (12.0)	15 (5.2)	$\chi^2(1, N = 372) = 4.8, p = 0.028$
Social phobia	25 (30.1)	23 (8.0)	$\chi^2(1, N = 372) = 28.2, p < 0.001$
Panic w. agoraphobia	7 (8.4)	11 (3.8)	$\chi^2(1, N = 372) = 3.0, p = 0.083$
Panic w/o agoraphobia	3 (3.6)	11 (3.8)	$\chi^2(1, N = 372) = 0.01, p = 0.94$
Agoraphobia	10 (12.0)	10 (3.5)	$\chi^2(1, N = 372) = 9.35, p = 0.002$
Mean IDS-SR total score ^a (SD)	32.9 (13.6)	19.6 (14.3)	$F(1,366) = 57.2, p < 0.001, \eta^2 = 0.14$
	95% CI (29.8–35.9)	95% CI (17.9–21.2)	
Mean BAI total score ^b (SD)	20.3 (12.1)	10.5 (9.8)	$F(1,351) = 55.7, p < 0.001, \eta^2 = 0.14$
	95% CI (18.1–22.6)	95% CI (9.3–11.8)	
No. of negative life events in past 5 y ^c	1.7 (1.3)	1.6 (1.3)	$F(1,368) = 0.56, p = 0.46, \eta^2 = 0.00$
	95% CI (1.4–2)	95% CI (1.4–1.7)	
Network of persons (%) ^d			
0–5	49 (59.1)	129 (45.4)	$\chi^2(1, N = 367) = 5.39, p = 0.145$
6–10	22 (26.5)	88 (31.0)	
11–15	6 (7.2)	32 (11.3)	
>16	6 (7.2)	35 (12.3)	

Notes: CI: confidence interval; MDD: major depressive disorder; SD: standard deviation.

^aBecause not all participants filled out the IDS-SR, the descriptive of this total score is based on 367 participants.

^bBecause not all participants filled out the BAI, the descriptive of this total score is based on 352 participants.

^cBecause not all participants filled out the life events questionnaire and there were two outliers, the descriptive of this total score is based on 369 participants.

^dBecause not all participants filled out the Close Person Inventory and there were two outliers, the descriptive of this total score is based on 367 participants.

show elevated ASD characteristics. This is much higher than the expected 1% prevalence of ASD across the lifespan, which might suggest that the AQ-28 may overestimate ASD characteristics in older adults. Nonetheless, in the aforementioned adult study,¹⁸ the social responsiveness scale for adults was used and with this ASD measure even 14% of the young and middle aged healthy control subjects did show elevated ASD traits. Because with increasing age (societal) withdrawal is considered adaptive and the mean age of the validation sample of the AQ-28 is much lower as compared with the current study, the question that remains is how many of these individuals with elevated ASD characteristics or traits will actually meet the ASD diagnostic criteria? The observed increased prevalence of ASD characteristics in older adults with depressive disorders, the earlier observation that adults with unrecognized ASD are

often diagnosed with a secondary psychiatric condition such as depressive disorders and anxiety disorders,^{7,9,10} and the observation that having more traits is associated with more comorbidities and a higher risk for mental health problems³⁷ all suggest that also within geriatric psychiatry settings one should be attentive to ASD.

There are some potential caveats in the current study. First, although ASD is often more common in males than females,³⁸ depressive disorders are more common in females than males.³⁹ Most of the current sample were women, and whether a similar picture emerges in older depressed men needs to be answered in future studies. In line with the literature, however, also in the current study those with elevated ASD characteristics were relatively more often men. Second, participants were included based on a current depression, and when anxiety was the primary diagnosis people were

not included, but having a comorbid anxiety disorder was not an exclusion criteria. In the high ASD characteristics group social phobia was rather common (30%). The differential diagnosis of social phobia and ASD is not an easy endeavor, and, although speculative, it might be that some of those with social phobia are misdiagnosed cases of ASD.⁴⁰ Third, we focused on older adults with a depressive diagnosis in the past 6 months, but some might be currently in remission. The proportion of adults with high ASD traits was much lower in a remitted major depressive disorder group (22%) as compared with an unremitted group (46%).¹⁸ Exclusion of those in remission will therefore probably even enhance the prevalence of those with high ASD characteristics. One could hypothesize that those with a lifetime history of depression might have even more ASD symptoms because comorbidity of ASD with depression is already common at a young age.¹⁸ Fourth, although we excluded persons with (possible) dementia according to the clinician, we recognize that diagnosing dementia in persons who are severely depressed can be very difficult. Therefore, we cannot be sure that we did not include persons in an early-phase dementia. However, given that there is no differences between the high and the low AQ group in the number of participants with these relatively low MMSE scores, this does not seem to be a likely explanation for our pattern of findings.

To conclude, ASD symptoms are more common in older adults with a known history of depression than in a comparison group without lifetime depression, which suggest that clinicians need to be attentive to

ASD symptomatology within the geriatric psychiatry setting. Whether this also implies that ASD diagnoses are missed in this specific group of older adults needs to be determined in future studies, because for a clinical diagnosis established diagnostic assessments are essential. However, in such a study it is important to take into account the differential diagnosis with social phobia because the question remains as to whether especially those formerly diagnosed with a social phobia are missed ASD cases.

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Dr. Geurts designed the current study, analyzed the data, interpreted the data, and drafted the manuscript. Drs. Stek and Comijs were two of the major designers of the NESDO cohort study and responsible for the infrastructure of the study. All authors read and approved the final manuscript and take full responsibility for the content.

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