

Research report

The comorbidity of anxiety and depressive symptoms in older adults with attention-deficit/hyperactivity disorder: A longitudinal study



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ABSTRACT

Background: Comorbidity between Attention-Deficit/Hyperactivity Disorder (ADHD) and depression and anxiety disorders in children and young to middle-aged adults has been well documented in the literature. Yet, it is still unknown whether this comorbidity persists into later life. The aim of this study is therefore to examine the comorbidity of anxiety and depressive symptoms among older adults with ADHD. This is examined both using cross-sectional and longitudinal data.

Methods: Data were used from the Longitudinal Aging Study Amsterdam (LASA). Participants were examined in three measurement cycles, covering six years. They were asked about depressive and anxiety symptoms. To diagnose ADHD, the DIVA 2.0, a diagnostic interview was administered among a subsample ($N=231$, age 60–94). In addition to the ADHD diagnosis, the association between the sum score of ADHD symptoms and anxiety and depressive symptoms was examined. Data were analyzed by means of linear regression analyses and linear mixed models.

Results: Both ADHD diagnosis and more ADHD symptoms were associated with more anxiety and depressive symptoms cross-sectionally as well as longitudinally. The longitudinal analyses showed that respondents with higher scores of ADHD symptoms reported an increase of depressive symptoms over six years whereas respondents with fewer ADHD symptoms remained stable.

Limitations: The ADHD diagnosis is based on the DSM-IV criteria, which were developed for children, and have not yet been validated in (older) adults.

Conclusions: It appears that the association between ADHD and anxiety/depression remains in place with aging. This suggests that, in clinical practice, directing attention to both in concert may be fruitful.

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1. Introduction

Comorbidity between Attention-Deficit/Hyperactivity Disorder (ADHD) and depression and anxiety disorders in children, young to middle-aged adults has been well documented in the literature. The comorbidity with depression has been found to affect 20–70% of patients with ADHD, and the comorbidity with anxiety disorders has been found to affect 28–50% of children and adolescents with ADHD (Wilens et al., 2002; Angold et al., 1999; Spencer et al., 1999). Among adults with ADHD, 35–50% also reported depressive symptoms, recurrent brief depression or fully developed depressive episodes (Sobanski, 2006; Kooij, 2012), and odds ratios of 2.7–7.5 for mood disorders were found (Tuithof et al., 2010; Kessler et al., 2005).

Odds ratios of 1.5–5.9 for anxiety disorders were found among adults with ADHD (Kessler et al., 2006; Tuithof et al., 2010).

Longitudinal studies show contradictory results in prevalence rates of mood disorders among children with ADHD. Some studies did not find that children with ADHD develop more mood disorders in young adulthood (Mannuzza et al., 1998; Rasmussen and Gillberg, 2000), while other studies did (Fischer et al., 2002; Biederman et al., 2008, 1996). Moreover, a longer duration of major depression was found in females with ADHD (Biederman et al., 2008). Additionally, several longitudinal studies indicated that children with ADHD do not appear to develop increased anxiety disorders in adulthood (Mannuzza et al., 1998; Rasmussen and Gillberg, 2000; Fischer et al., 2002), but one study found that mid-adolescent children with ADHD had markedly elevated rates of anxiety disorders after 4 year-follow up (Biederman et al., 1996).

ADHD is a chronic disorder, which may persist into late life (Michielsen et al., 2012). Few studies have focused on ADHD among older adults and, to our knowledge, no previous study has

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tested whether comorbidity among anxiety, depression and ADHD persists into later life. It is clinically important to know whether anxiety and depression co-occur, since comorbidity between ADHD and major depressive disorder is associated with a worse outcome of depression (Biederman et al., 2008). In addition, ADHD often goes unrecognized among older adults and clinical overlap with depression may render recognition of ADHD even more difficult.

Since the DSM-IV criteria for ADHD were developed to diagnose children, the appropriateness of the DSM-IV criteria for ADHD in adults has been questioned in recent years (Barkley et al., 2007; Kooij et al., 2005). Clinical observations have shown that symptoms of ADHD in adults are different from those in children, and new suggestions for the adjustment of the adult ADHD diagnosis have been proposed, such as a reduction in the cut-off for the diagnosis using DSM-IV; at least four instead of six current symptoms have to be present (Kooij et al., 2005, Barkley et al., 2007). Although the diagnostic criteria for ADHD among adults are under development, this should not hold up studying ADHD among older adults. A way to achieve this is by studying older people with ADHD using both diagnostic and symptom rating scales for ADHD. Since comorbidity between ADHD and depression and anxiety was found in several cross-sectional studies among children and younger adults, we hypothesize that older adults with an ADHD diagnosis or with higher levels of ADHD symptoms report more anxiety and depressive symptoms than older adults without ADHD. With ageing, one has to cope with losses and deterioration in health which may be more difficult for older adults with ADHD, possibly leading to increasing level of depressive symptoms when getting older. Therefore we hypothesized that ADHD (symptoms) are also associated with an increase of depressive and anxiety symptoms over time.

2. Methods

2.1. Study sample

Data for the present study were collected amongst participants of the Longitudinal Aging Study Amsterdam (LASA), an ongoing study of changes in autonomy and well-being with aging in The Netherlands. Full details on sampling are described elsewhere (Huisman et al., 2011). In summary, a random sample of older men and women (55–85 years), stratified by age and sex, was drawn from the population registries of eleven municipalities in three geographic areas of the Netherlands. Data collection started in 1992–1993 ($N=3,107$, T1) with respondents born in 1908–1937. Further follow-ups were carried out every three years since then. In 2002–2003 a new cohort was sampled (birth years 1938–1947, $N=1,002$) from the same sampling frame as the earlier cohort. Both samples were combined and follow-up was carried out every three years. The most recent follow-up was conducted in 2008–2009 ($N=1,601$, T6). Interviews consisted of a main interview, after about four weeks followed by a medical interview in which tests were performed and structured questionnaires completed. Informed consent was obtained from all participants, and the study was approved by the Ethical Review Board of the VU University Medical Center (VUmc).

Data on ADHD were collected in 2008/2009. In order to limit the number of diagnostic interviews, a two-phase non-proportional stratified random sampling procedure was used. In the 2008/2009 wave of LASA, an ADHD screening list developed by Barkley and colleagues was part of the medical interview ($N=1,494$) (Barkley et al., 2007). The questionnaire was found to have acceptable qualities among older adults, with an internal

consistency (Cronbach's α) of 0.71 and an area under the curve (AUC) of 0.82 (Semeijn et al., *in press*).

On the basis of the results of a screening list (phase one) the sample was divided into tertiles with low, intermediate and a high priori likelihood of ADHD. These tertiles were randomly, but non-proportionally sampled for respondents who were approached for the diagnostic interview (phase two). Before phase two started, three exclusion criteria were implemented: First, low cognitive functioning, as measured with the Mini-Mental State Examination (MMSE) (Folstein et al., 1965), a frequently used screening instrument for global cognitive dysfunction. The scale consists of 23 items and scores range from 0 to 30, with higher scores indicating better cognitive functioning. Respondents with an MMSE score ≤ 18 were excluded. Second, those who experienced cognitive decline, which was defined as a difference in score of more than one standard deviation on the MMSE (≥ 3 points) over a period of six years, were excluded. Finally, respondents with a history of cerebrovascular accident were excluded. In phase two, all of the participants in the high scoring group, and random samples of the participants in the low and intermediate group (in total $N=271$) were approached for a diagnostic interview. In total 85 respondents of the low scoring group (90%), 80 of the moderate scoring group (86%) and 69 of the high scoring group (82.3%) consented to be interviewed. Three respondents were excluded from statistical analysis due to too many missing values; the first respondent refused to answer questions about childhood because of experienced traumas in that period; the second respondent had a cerebral vascular accident and was not able to answer the questions; the third respondent was not able to recollect childhood memories, see Fig. 1. Thus, the study sample consisted in total of $N=231$ and was used for both the cross-sectional and longitudinal analysis. Full details on sampling, measurements and non-response are described elsewhere (Michielsen et al., 2012). Depressive and anxiety symptoms were assessed at three measurement cycles between 2001 and 2009. All interviews were conducted in the homes of respondents by specially trained and closely supervised interviewers. All interviews were tape-recorded in order to check the quality of the data.

Depressive and anxiety symptoms were assessed at three measurement cycles between 2001 and 2009. Depressive symptoms were measured at cycle T4 (2001–2003), T5 (2005/2006) and T6 (2008/2009). Anxiety symptoms were measured at T5 (2005/2006) and T6 (2008/2009). Of two respondents, data of depressive symptoms were missing at 2001–2003 and 2005–2006. Of two respondents data on the anxiety symptoms were missing at 2005–2006.

All ADHD diagnostic interviews were conducted between May and September 2010. Since ADHD is a chronic disorder with childhood onset, it was expected that the disorder was present at previous measurement waves in older adults diagnosed with ADHD in 2010; therefore ADHD was treated as if measured at baseline. All interviews were conducted in the homes of respondents by specially trained and closely supervised interviewers. All interviews were tape-recorded in order to check the quality of the data.

3. Measures

3.1. Assessment of ADHD

To diagnose ADHD, the Diagnostic Interview for ADHD in Adults, second edition, (Diagnostisch Interview Voor ADHD bij volwassenen, DIVA 2.0) was used (Kooij and Francken, 2010). The DIVA 2.0, is a semi-structured diagnostic interview for ADHD in adults and is

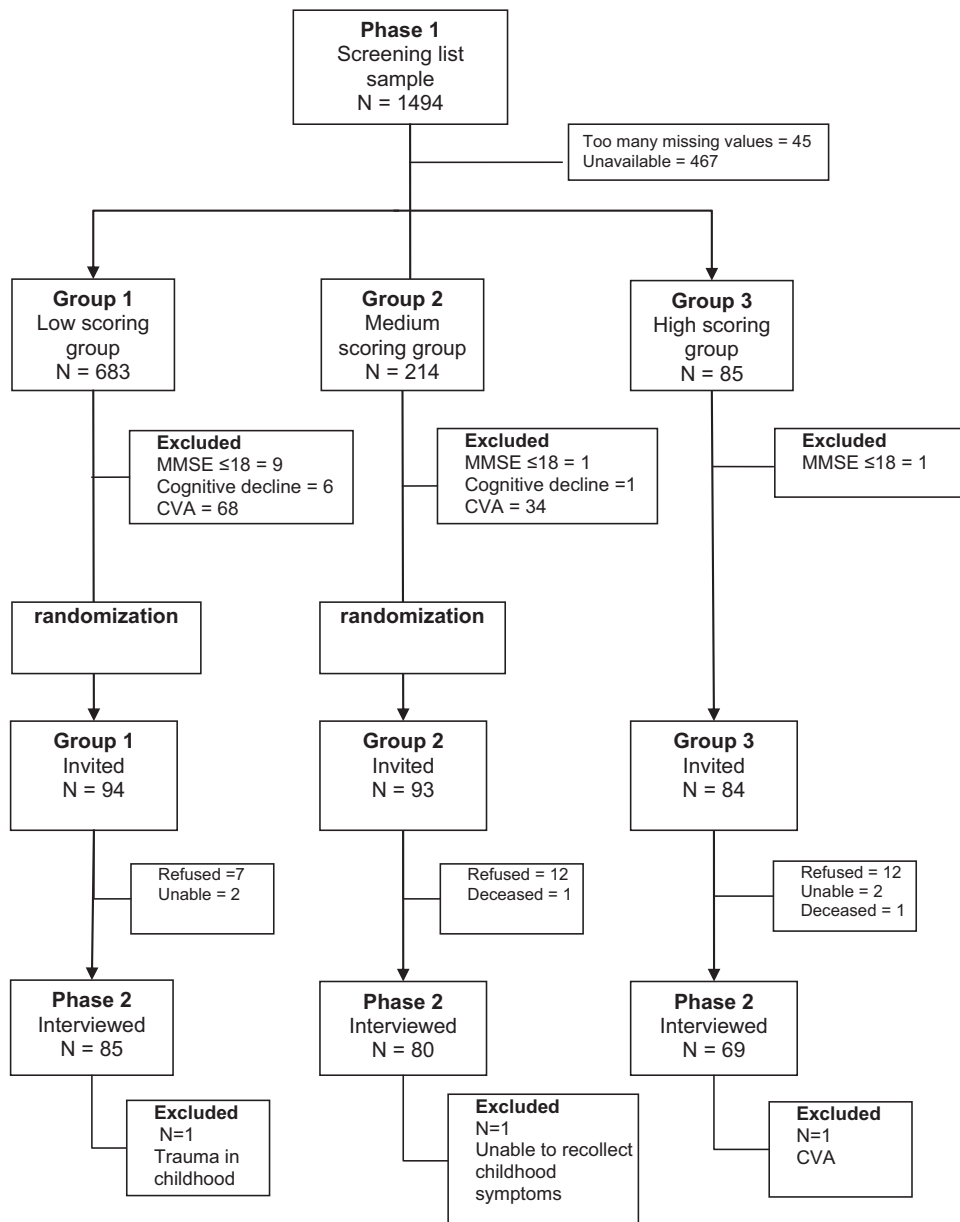


Fig. 1. Flowchart of screening and diagnostic interview phases.

based on the DSM-IV-TR criteria (American Psychiatric Association, 2000). The interview consists of two parts: the first part assesses the presence of all 18 DSM-IV TR criteria in childhood (primary school, age 6–12) and at present; the second part assesses impairment in five areas of functioning (work, education, family, social/relationships and self-confidence) in childhood and at present. For the present study, the DIVA 2.0 was modified into a structured diagnostic interview in order to facilitate a uniform assessment by lay interviewers that work for LASA. Examples of behavior often reported by adults with ADHD were added with each symptom. When participants endorsed a symptom, either at present time or in childhood, further questions were asked about the duration (“longer than six months? no/yes”), frequency (“more than once a week?(no/yes)”), and whether the symptom persisted throughout their life. In part two it was asked if the symptoms led to impairment in different areas of functioning, both in adulthood and during childhood. A question about impairment in one area was first asked and, when given a negative answer, several more specific examples of impairment were given.

For the ADHD diagnosis, it was required to have at least four symptoms of either inattention and/or hyperactivity-impulsivity during the 6 months or longer prior to the interview (Kooij et al., 2005), and to have at least six symptoms of either inattention and/or hyperactivity-impulsivity in childhood (DSM-IV criterion A). It was also required to have clinically significant impairment in at least two areas of daily life during the past 6 months or longer prior to the interview and in childhood (criterion C and D). For the continuous ADHD variable, the sum score of all the ADHD symptoms in present time and in childhood was calculated (range 0–36).

3.2. Depression and anxiety

Depressive symptoms were measured with the Center for Epidemiologic Studies Depressive Scale (CES-D) (Radloff, 1977). The CES-D is a self-report scale and consists of 20 items covering depressive symptomatology experienced in the past week. Each answer is rated on a 4-point scale ranging from 0 ‘rarely

or never” to 3 ‘mostly or always’. The total score of the 20 items ranges from 0 to 60, higher scores indicating more depressive symptoms. A score of 16 and higher suggests a clinical relevant level of depressive symptoms. Criterion validity of the CES-D for the 1-month prevalence of major depressive was excellent (sensitivity 100%, specificity 88%, Beekman et al., 1997).

Anxiety symptoms were measured with the Hospital Anxiety and Depression Scale-Anxiety subscale (HADS-A, Zigmond and Snaith, 1983). It consists of 7 Likert type items ranging from 0 (rarely or never) to 3 (mostly or always). The anxiety score is the sum of the scores and ranges from 0 to 21, higher scores indicating more anxiety symptoms. A score of 8–10 on the HADS-A suggests a clinical relevant level of anxiety symptoms (Snaith, 2003).

A score of eight and higher on the HADS was interpreted as a clinical relevant level of anxiety symptoms and a score of sixteen and higher on the CES-D was interpreted as a clinical relevant level of depressive symptoms. Respondents with scores of eight or higher on the HADS were labeled as having anxiety, and respondents with a score of 16 or higher on the CES-D were labeled as having depression. A ‘comorbidity’ variable was computed that divides the respondents in four categories: (1) respondents without depression and anxiety; (2) depression only; (3) anxiety only and (4) anxiety and depression. The ‘comorbidity’ variable was computed with data from 2005–2006 and from 2008–2009.

3.3. Confounders

The following variables were examined as potential confounders: gender, age at baseline, level of education, health status, cognitive functioning and alcohol use. Level of education included the number of years of education. Health status variables included total amount of self-reported chronic diseases (cardiac disease, peripheral atherosclerosis, stroke, diabetes mellitus, asthma, chronic bronchitis or pulmonary emphysema, arthritis or cancer). Cognitive status was assessed with the Mini Mental State Examination (Folstein et al., 1975), a screening test of cognitive functioning in the routine clinical examination of older patients. The MMSE consists of 20 items and scores range from 0 to 30, higher scores indicating better cognitive functioning. The number of alcoholic drinks per week reflected alcohol use.

4. Statistical analysis

T-tests were used to examine the cross-sectional differences on depressive and anxiety symptoms in 2008/2009 between respondents with and without ADHD. Linear regression analyses were performed to assess the association between ADHD diagnosis and the ADHD symptoms and depressive and anxiety symptoms at 2008/09 as outcome variables. The CES-D and the HADS score were transformed ($\ln(1 + \text{CES-D score})$) and ($\ln(1 + \text{HADS-score})$) to obtain a near-normal distribution. Potential confounders were determined by computing correlations between ADHD, CES-D and the HADS with a $P \leq 0.20$ in 2008–2009 (Maldonado and Greenland, 1993). Possible confounders associated with ADHD and the outcome variable were added one by one to the models to investigate whether they were confounding the association between ADHD and depressive and anxiety symptoms. Potential confounders that showed a confounding effect on the studied associations, i.e. $\geq 10\%$ change in the unstandardized regression coefficient (B) of the main predictor, were retained in the models.

Effect size measures (Cohen’s d) relating to the difference between older adults with and without ADHD on the transformed CES-D and HADS in 2008/2009 were determined. Effect sizes of

$d=0.2$ denotes a “small” effect, a value of $d=0.5$ denotes a “medium” effect, and a value of $d=0.8$ denotes a “large” effect (Cohen, 1988).

Linear mixed models were used to analyze the association between ADHD diagnosis and symptoms and transformed depressive symptoms over six years, and between ADHD diagnosis and symptoms and transformed anxiety symptoms over three years. In the first models ADHD and time were independent variables and the CES-D/HADS symptoms were dependent variables. The potential confounders associated with ADHD and the outcome variables were added one by one, to investigate whether they were confounding the association between ADHD and depressive and anxiety symptoms. Next, an interaction term between ADHD and time was added to models. The interaction was evaluated at the significance level of $p=0.10$. Since depressive symptoms were measured at three time points, it was possible to evaluate if the model could be better described by a quadratic growth trend than a linear trend. Therefore time² was added in the model and compared with the linear model. Data were analyzed using PASW Statistics 18, Release Version 18.0.0 (SPSS, Inc., 2009, Chicago, IL).

5. Results

Descriptive statistics of the respondents are presented in Table 1. Of the 231 respondents, 137 were female (59%). The average age was 71 years ($SD=7.7$, range 60–94, not tabulated). The respondents with ADHD were significantly younger ($M=68$ years, $SD=4.87$) than the respondents without ADHD ($M=72$ years, $SD=7.85$), $t(36.1)=3.49$, $p < 0.01$. Older adults with an ADHD diagnosis reported significantly more depressive symptoms at 2001–2003, 2005–2006 and 2008–2009, and more anxiety symptoms at 2005–2006 and 2008–2009 compared to older adults without ADHD (see Table 1). In addition, Table 1 shows that older adults with ADHD reported significantly more often clinical relevant levels of depressive symptoms in 2005–2006 and 2008–2009 and of anxiety symptoms in 2008–2009 compared to older adults without ADHD. Of the older adults with ADHD, 26.1% met the criteria of both clinical levels of anxiety disorder and depression, versus 8.2% of the older adults without ADHD in 2008–2009, See Table 1. This pattern was also found in 2005–2006, 22.7% of the older adults with ADHD compared to 8.7% of older adults without ADHD reported clinical relevant levels of anxiety and depression. Due to the low numbers in the cells, the significant difference between older adults with and without ADHD could not be calculated. Table 2 shows the ADHD characteristics of the sample. The combined subtype was the most prevalent subtype in the sample.

5.1. Cross-sectional results

The effect size of differences in reporting depressive symptoms between older adults with and without ADHD was $d=0.68$ and the effect size of the difference in reporting anxiety symptoms was $d=0.60$. Both effect-sizes can be interpreted as clinically relevant, medium effects.

Only age at baseline and cognitive functioning were associated with ADHD and depressive and anxiety symptoms at $P < 0.20$, therefore they were retained as putative confounders. Table 3 shows the unadjusted and adjusted regression estimates (B) from the regression analyses for the cross-sectional association between ADHD diagnosis and ADHD symptoms and the \ln -transformed depressive and anxiety symptoms scores in 2008–2009. The results show that ADHD diagnosis was significantly associated with depressive symptoms, also after adjusting for the confounding variables age and MMSE-score, and with

Table 1
Demographic characteristics of older adults with and without ADHD in 2008–2009.

	Without ADHD		ADHD		P
Sex, N (%)					0.51
Male	83	(39.9)	11	(47.8)	
Female	125	(60.1)	12	(52.2)	
Age, M (SD)	72.04	(7.85)	68.02	(4.87)	< 0.01
Years of education, M (SD)	9.69	(3.30)	8.83	(3.11)	0.22
MMSE total score, M (SD)	27.99	(1.75)	27.39	(2.29)	0.14
Total chronic diseases, M (SD)	2.11	(1.31)	2.04	(1.30)	0.82
Depression symptoms					
in 2008–2009, M (SD)	8.67	(7.46)	16.78	(12.54)	< 0.01
in 2005–2006, M (SD)	8.32	(7.15)	15.64	(11.01)	< 0.01
in 2001–2003, M (SD)	8.59	(6.90)	12.83	(8.79)	< 0.03
Anxiety symptoms					
at 2008–2009, M (SD)	3.39	(3.51)	5.52	(3.87)	< 0.01
in 2005–2006, M (SD)	3.42	(3.17)	6.05	(3.91)	< 0.01
Depression 2008–2009^a Yes (N, %)	35	(16.8)	10	(43.5)	< 0.01
Depression 2005–2006^a Yes (N, %)	12	(17.4)	10	(45.5)	< 0.01
Depression 2001–2003^a Yes (N, %)	30	(14.6)	5	(21.7)	0.36
Anxiety 2008–2009^a Yes (N, %)	24	(11.5)	8	(34.8)	< 0.01
Anxiety 2005–2006^a Yes (N, %)	25	(12.1)	6	(27.3)	0.09
Depression and anxiety in 2008–2009^a					
No comorbidity, N (%)	166	(79.8)	11	(47.8)	
Only depression, N (%)	18	(8.7)	4	(17.4)	
Only anxiety, N (%)	7	(3.4)	2	(8.7)	
Depression and anxiety, N (%)	17	(8.2)	6	(26.1)	
Depression and anxiety in 2005–2006^a					
No comorbidity, N (%)	164	(79.2)	11	(50.0)	
Only depression, N (%)	18	(8.7)	5	(22.7)	
Only anxiety, N (%)	7	(3.4)	1	(4.5)	
Depression and anxiety, N (%)	18	(8.7)	5	(22.7)	

^a Scores on the HADS of ≥ 8 were labeled as a clinically relevant level of anxiety, and scores on the CES-D of ≥ 16 were labeled as a clinically relevant level of depression.

Table 2
ADHD characteristics of the sample (N=231).

	N	%
ADHD^a		
No	208	90
Yes	23	10
ADHD, inattentive subtype		
No	224	97
Yes	7	3
ADHD, hyperactive/impulsive subtype		
No	227	98.3
Yes	4	1.7
ADHD, combined type		
No	219	94.8
Yes	12	5.2
	Mean	SD
Total ADHD symptoms	7.75	6.64

^a = ≥ 4 symptoms of inattention and/or hyperactivity-impulsivity at present time and ≥ 6 symptoms of inattention and/or hyperactivity impulsivity in childhood.

anxiety symptoms in 2008–2009. No confounders were found in the latter association.

ADHD symptoms were significantly associated with depressive symptoms, also after adjusting for the confounding variable age and with anxiety symptoms; for the latter association no confounders were found.

5.2. Longitudinal results

In Table 4 the results from the longitudinal analyses are shown in which the association between ADHD diagnosis and ADHD symptoms and depressive and anxiety symptoms were studied over a period of 3 and 6 years.

In the unadjusted models the results show that over six years, ADHD diagnosis was significantly associated with more In-transformed depressive symptoms. When the model was adjusted for age, ADHD remained significantly associated with depressive symptoms. This model was best described by linear trend. In addition, ADHD diagnosis was positively associated with anxiety symptoms in three years. No confounding variables were found in the association between ADHD diagnosis and anxiety symptoms. For both depressive and anxiety symptoms, the interaction between time and ADHD diagnosis was not significant; although those with ADHD report more depressive and anxiety symptoms at all measurements, the course of depressive and anxiety symptoms in older adults with ADHD was the same as in older adults without ADHD ($B=0.08$, $p=0.33$ for depression, $B=-0.05$, $p=0.32$ for anxiety).

The association between the ADHD symptoms, depressive and anxiety symptoms were studied over a period of three and six years (Table 4). In the unadjusted models the results show that over six years ADHD symptoms were significantly associated with depressive symptoms. When the model was adjusted for age, ADHD remained significantly associated with depressive symptoms. The association between ADHD symptoms and depressive symptoms was best described by a linear trend. ADHD symptoms were also significantly associated with anxiety symptoms over three years. No confounding variables were found in the association between ADHD symptoms and anxiety symptoms.

The interaction between time and the ADHD symptoms on the course of depressive symptoms was significant ($B=0.007$, $p=0.06$), meaning that a higher level of ADHD symptoms was independently related to an increase of depressive symptoms. This is shown in Fig. 2, where low, medium and high groups of ADHD symptoms (based on tertiles) are shown in relation to depressive symptoms over time. The low (0–4 symptoms) and medium (4–9 symptoms) ADHD severity groups showed a stable pattern of severity of depressive symptoms over time while the

Table 3

Cross-sectional associations between ADHD diagnosis and symptoms, and depressive and anxiety symptoms, before and after adjustments for confounders.

	ADHD diagnosis unadjusted*			ADHD diagnosis adjusted*			ADHD symptoms unadjusted*			ADHD symptoms adjusted*		
	B	95% CI	P	B	95% CI	P	B	95% CI	P	B	95% CI	P
CES-D	0.60	0.22–0.98	< 0.01	0.61 ^a	0.23–0.99	< 0.01	0.04	0.02–0.06	< 0, 01	0.05 ^b	0.03–0.07	< 0, 01
HADS	0.48	0.13–0.83	< 0.01	–	–	–	0.03	0.02–0.05	< 0.01	–	–	–

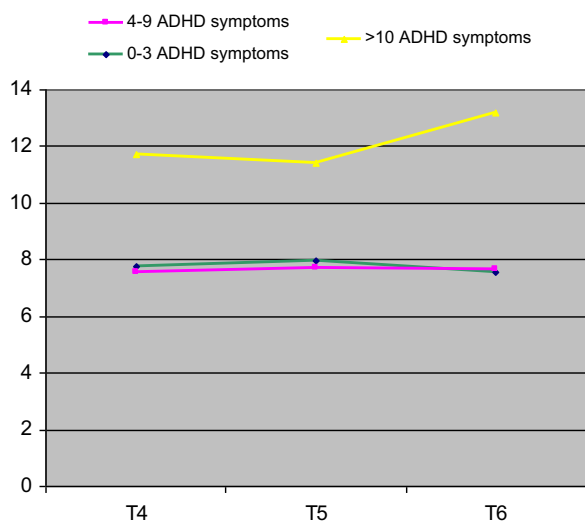
* LN transformed scores of the CES-D and HADS were used.

^a Adjusted for age and MMSE-score.^b Adjusted for age.**Table 4**

Longitudinal associations between ADHD diagnosis and symptoms, and depressive and anxiety symptoms, before and after adjustments for confounders.

	ADHD diagnosis unadjusted*			ADHD diagnosis adjusted*			ADHD symptoms unadjusted*			ADHD symptoms adjusted*		
	B	95% CI	P	B	95% CI	P	B	95% CI	P	B	95% CI	P
CES-D ^a	0.55	0.23–0.87	< 0.01	0.62 ^c	0.31–0.94	< 0.01	0.03	0.02–0.05	< 0.01	0.02 ^c	0.002–0.004	0.03
HADS ^b	0.55	0.24–0.86	< 0.01	–	–	–	0.03	0.01–0.04	< 0.01	–	–	–

* LN transformed scores of the CES-D and HADS were used, since the scales were not normally distributed.

^a 3 and 6 year follow-up.^b 3 year follow-up.^c adjusted for age.**Fig. 2.** The scores of low, medium and high ADHD symptoms on the CES-D at three different measurement cycles.

high (> 10 symptoms) severity group of ADHD symptoms showed an increase of depressive symptoms over time. The interaction between ADHD symptoms and time on the course of anxiety symptoms was not significant ($B = -0.005$ $p = 0.48$), suggesting that changes of the anxiety symptoms over time were not different for respondents with less or more ADHD symptoms.

6. Discussion

This is the first study to test whether comorbidity between anxiety and depressive symptoms and ADHD persists into older age. The most important finding is that ADHD diagnosis and ADHD symptoms among older adults were indeed associated with comorbid anxiety and depressive symptoms. This association was found cross-sectionally and longitudinally for both depressive and anxiety symptoms.

ADHD, whether defined in terms of a diagnosis or in terms of symptoms, was clearly associated with depressive symptoms. The

effect size is comparable to the differences found between ADHD patients that are treated with amphetamines and those treated with placebo's in Randomised Controlled Trials, which illustrates the clinical relevance of this finding (Castells et al., 2011). The found comorbidity is very similar to what has been found among children and younger adults (Wilens et al., 2002; Angold et al., 1999; Spencer et al., 1999; Sobanski, 2006) suggesting that the association between ADHD and depressive disorders remains in place in older age. In addition, this study showed that older adults with ADHD diagnosis or ADHD symptoms reported more depressive symptoms during six years compared to older adults without ADHD. A surprising finding was that the interaction between time and ADHD symptoms was significant, indicating that the mood of those with ADHD deteriorates over time, when compared to those without ADHD. This interaction was not found between ADHD diagnosis and time. Since there is little literature available on longitudinal course of depressive symptoms among children adults with ADHD, it is unknown what could be the underlying mechanism behind this interaction. A possible explanation could be that older adults with chronically elevated levels of ADHD symptoms may have limited coping strategies to deal with the adverse effects of ageing compared to older adults with low levels of ADHD symptoms. Adults with ADHD are known to use maladaptive coping strategies, such as confrontation, escape-avoidance and a lack of playful problem solving (Young, 2005). With ageing, one has to cope with losses and deterioration in health and this may be more difficult for older adults with severe ADHD symptoms, possibly leading to increasing level of depressive symptoms. Another possible explanation may be that increased level of depressive symptoms may exacerbate ADHD symptoms such as inattentiveness.

Comorbidity between ADHD and depression raises questions about their etiology, which still remain to be solved (Scholiers, 2010). Two possible etiological pathways will be discussed; (1) a shared etiology, and (2) ADHD leads to depression. For comorbid depression and ADHD there is evidence for a common genetic origin. Family studies reviewed by Faraone and colleagues supported the hypothesis that ADHD and depression shared common familial risk factors (Faraone and Biederman, 1997). In a twin study among children and adolescents it was found that the contribution of heredity was greater on the co-occurrence of ADHD and depression than the contribution of environmental factors (Cole et al., 2009).

In recent years more insight is gained into the candidate genes conferring liability to both depressive and ADHD traits, such as the SNAP-25 gene (Cole et al., 2009; Kim et al., 2007). Some studies support the second pathway; ADHD leading to depression. ADHD symptoms in early life may lead to problems in social interactions (Ostrander and Herman, 2006), academic functioning (Herman et al., 2007) and parental interactions (Daviss, 2008; Ostrander and Herman, 2006) and this may lead indirectly, or directly to depressive symptoms later on in life. In contrast, a longitudinal study has found that major depressive episodes was independent of ADHD related impairment and comorbid depression should be seen as a 'true' depression, rather than ADHD-related demoralization (Biederman et al., 1998). In short, both pathways may be relevant, but more longitudinal research is needed to quantify the genetic, environmental and behavioral influences on comorbidity between ADHD and depression.

Older adults with ADHD or more ADHD symptoms also reported higher levels of anxiety symptoms compared to older adults without ADHD or with lower levels of ADHD, which is in concordance with clinical findings among younger adults with ADHD (Young et al., 2003). The longitudinal analyses showed that older adults with ADHD diagnosis or with more ADHD symptoms reported more anxiety symptoms during three years compared to older adults without ADHD. The results of this study show that older adults with ADHD reported repeatedly high levels of depressive and anxiety symptoms over time and the anxiety symptoms fluctuate less than depressive symptoms over time. Preliminary results from our study showed that a fifth of the older adults with ADHD reported both anxiety and depressive symptoms at two measurement cycles. Although this finding could not be tested for significance due to small numbers, it is in agreement with other studies that showed that depression and anxiety often co occur in the older population (Beekman et al., 2000; Lenze, 2000). The co occurrence may lead to an additional burden in older adults with ADHD and prevention and treatment for older adults with ADHD focusing on depression and anxiety symptoms should be developed.

Comorbidity of ADHD and anxiety has received less attention than for example the comorbidity between ADHD and conduct disorders, but a few studies have focused on the etiology of the comorbidity of ADHD and anxiety. Several etiological pathways are proposed. Most of evidence of genetic influences on the co-occurrence of ADHD and anxiety comes from familial studies (Jarrett and Ollendick, 2008). These results suggest that ADHD and anxiety have independent genetic transmission (Faraone, 2000). A temperamental perspective on the comorbidity of ADHD and anxiety is given by Nigg et al. (2004). They describe two developmental pathways that may lead to both conditions. Their first pathway describes how ADHD may lead to anxiety. This pathway involves primary ADHD, with weak regulatory control in early childhood and high negative withdrawal or anxiety. Such a pathway may involve temperament risks at an early age that may result in an inability to effectively regulate anxiety (Jarrett and Ollendick, 2008; Nigg et al., 2004). In addition, according to their second pathway, anxiety interferes with normal regulatory development and may lead to cognitive dysfunction such as inattentiveness (Jarrett and Ollendick, 2008; Nigg et al., 2004). In short, the study of the co-occurrence of ADHD and anxiety is complex and it is possible that there are multiple pathways to the development of ADHD and anxiety (Nigg et al., 2004). Future longitudinal studies will be needed to examine genetic and temperamental influences on the co-occurrence and course of ADHD and anxiety.

7. Strengths and limitations

An important strength of the current study is that it is the first longitudinal study to examine the association between ADHD and

depressive and anxiety symptoms in a population-based cohort of older adults. This represents a first step in understanding the comorbidity of mood and anxiety with ADHD among older adults. Another strength is the investment to measure ADHD using both symptoms and a diagnostic interview. Validated diagnostic tools for ADHD among older adults do not exist (yet) and to overcome this problem two different ways of measuring ADHD was used. Some limitations of the present study should be mentioned. The ADHD diagnosis is based on the DSM-IV-criteria, which have been developed for children, and have not yet been validated in (older) adults. Therefore, a lower cut-off point was used in this study. This cut-off point was suggested for diagnosing ADHD in adults (Kooij et al., 2005; Barkley et al., 2007), but it has not been validated yet among older adults. It seems likely that the presentation of symptoms of ADHD may be different for older adults than for children or adults, and DSM-IV ADHD symptoms may have to be adjusted for older age groups. More research is necessary to obtain insight into the symptoms at older age and potentially age-appropriate cut-off points. In addition, in our study other psychiatric disorders were not included in the diagnostic interview. This could mean that inattention symptoms due to cognitive impairment, depression or anxiety in older persons may have led to a misdiagnosis. However, a respondent would only receive an ADHD diagnosis in our study when six out of nine ADHD symptoms were already present in childhood. This childhood onset and lifetime persistence of symptoms and impairment should filter out the false positives. Since we did not include other psychiatric disorders, the association between ADHD and depressive/anxiety disorders should be interpreted with some caution and further research on ADHD and comorbid disorders in older adults is needed. Another limitation is that ADHD was diagnosed after the three cycles in which depressive and anxiety symptoms were assessed. Causal inferences about the way ADHD and depressive and anxiety symptoms interact must be made with caution. However, ADHD is thought to be a chronic disorder and it is therefore very likely that the disorder was already present when depressive and anxiety symptoms were assessed. The final limitation is that anxiety and depression were examined separately, which is a somewhat artificial separation, since it is known that these two disorders often co occur in older adults (Beekman et al., 2000). However the power in our study was insufficient to include comorbid variables in our regression models.

8. Implications

Both the size of the associations found and their stability over time endorse the clinical relevance of the comorbidity between ADHD and depression and anxiety. A clinical implication is that when older adults report depressive and anxiety symptoms, clinicians should be alert for possible comorbid ADHD. Since this study is the first study to demonstrate that older adults with ADHD experience chronic depressive and anxiety symptoms, further (longitudinal) research is needed to confirm the development and etiology of the co-occurrence of these disorders.

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Conflict of interest

Sandra Kooij has been a speaker for Eli Lilly, Janssen and Shire and has received unrestricted research grants from Janssen and Shire for this study. Aartjan Beekman has received an unrestricted research grants for research from

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