Are Specific Symptoms of Depression Predictive of Alzheimer's Dementia?

Nilufar Mossaheb, MD; Sonja Zehetmayer, PhD; Susanne Jungwirth, PhD; Silvia Weissgram, MPhil; Michael Rainer, MD; Karl-Heinz Tragl, MD; and Peter Fischer, MD, PhD

ABSTRACT

Objective: To investigate whether specific symptoms of major depression are associated with later development of possible or probable Alzheimer's dementia.

Method: The analysis is part of the Vienna Transdanube Aging Study, a prospective, community-based cohort study of all 75-year-old inhabitants of 2 Viennese districts. Current depressive symptoms were captured with a *DSM-IV-TR*–based questionnaire. Diagnosis of possible or probable Alzheimer's dementia was performed according to criteria by the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association. The baseline sample included 437 not-demented and not previously depressed individuals. At 60-month follow-up, 65 of the remaining 296 subjects had possible or probable Alzheimer's dementia. The primary outcome measure was the probability of diagnosis of Alzheimer's dementia related to baseline depressive symptoms. Baseline data were collected between May 2000 and December 2002; 60-month follow-up data were collected between June 2005 and February 2008.

Results: 10.8% of those who were diagnosed with possible or probable Alzheimer's dementia at 60-month follow-up had shown loss of interest versus 2.2% in the nondemented group. The analysis showed a significant association of loss of interest only with the later occurrence of possible or probable Alzheimer's dementia (adjusted *P* value <.05, OR = 5.27 [95% CI, 1.62–17.2], area under the receiver operating characteristic curve = 0.541). The specificity of this symptom in predicting Alzheimer's dementia was 97.8, and the sensitivity was 10.4.

Conclusions: Of 9 symptoms of depression, only loss of interest was associated with the development of Alzheimer's dementia over a period of 5 years in a sample of 75-year-old not-demented, never-depressed subjects, suggesting that depressive symptoms in the elderly are mostly symptoms of genuine depression.

J Clin Psychiatry 2012;73(7):1009–1015

Submitted: *February 24, 2011; accepted November 10, 2011.*
Online ahead of print: *May 29, 2012 (doi:10.4088/JCP.11m06962).*
Corresponding author: *Nilufar Mossaheb, MD, Medical University of Vienna, Department of Child and Adolescent Psychiatry, Waehringer Guertel 18-20, 1090 Vienna, Austria (nilufar.mossaheb@meduniwien.ac.at).*

The co-occurrence of depressive symptoms in Alzheimer's dementia has been widely acknowledged.[1] Alongside other risk factors, a history of past depression has been found to be a risk factor for the development of dementia.[2–5] The timely co-occurrence of depression and dementia has led to speculations and research into the question of whether depression is a risk factor for or a prodromal feature of dementia. The debate is ongoing,[1] some authors postulating depressive symptoms as being risk factors for the subsequent development of Alzheimer's dementia,[6–9] others reinforcing the reverse causality hypothesis, ie, depressive symptoms being a consequence of the incident disease, a prodromal feature.[10–12]

Few authors have proceeded in the analysis of the association of specific depressive symptoms with Alzheimer's dementia. They frequently have found apathy to be more often associated with Alzheimer's dementia.[13,14] However, even fewer studies have looked into the predictive effect of specific symptoms of depression regarding the later development of Alzheimer's dementia in nondemented populations.

The Kungsholmen Project in Sweden[10] addressed this question on the basis of a prospective population survey of subjects aged 75 years and older over a 3-year follow-up period; in this study, both lack of interest and thoughts of death were significant predictors of later incident Alzheimer's dementia, with the former's predictive power exceeding the latter's. Others have described mood-related depressive symptoms as predictors of a dementia to come.[6,15]

The main objective of our study was to investigate whether the occurrence of specific symptoms of major depression was associated with later development of dementia. We hypothesized that motivation-related symptoms, such as lack of interest, psychomotor changes, loss of energy, and concentration difficulties would occur more frequently than mood-related symptoms in those subjects with subsequent Alzheimer's dementia. The analysis is part of the Vienna Transdanube Aging Study, a prospective, community-based cohort study of all 75-year-old inhabitants of 2 Viennese districts. In order to avoid potential bias due to previous history of depression, which has been shown to be a risk factor for dementia, subjects with a history of depression were excluded from the analysis. A follow-up period of 5 years was chosen to overcome limitations of shorter observation periods in previous studies. We used a symptomatic instead of a categorical approach and assessed depressive symptoms as cited in the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text-Revision (*DSM-IV-TR*).[16]

METHOD

Sample Selection

The data stem from the Vienna Transdanube Aging Study, a community-based cohort study of all 75-year-old inhabitants of Vienna's 21st (Floridsdorf) and 22nd (Donaustadt) districts (Austria). The Vienna Transdanube Aging Study was approved by the local ethics committee and all participants gave written informed consent after details of the

Clinical Points

- The timely co-occurrence of depression and dementia has raised the question of whether depression is a risk factor for or a prodromal feature of dementia.
- Loss of interest is associated with later development of Alzheimer's dementia in not-demented, not previously depressed elderly subjects.
- Most depressive symptoms in the elderly seem to be symptoms of depression and not of prodromal Alzheimer's dementia.

study were thoroughly explained. Detailed information on the study design, recruitment strategies, and participation levels have been published elsewhere.[17] Baseline data were collected between May 2000 and December 2002; 60-month follow-up data were collected between June 2005 and February 2008. The nondemented cohort at baseline consisted of 585 subjects (344 female, 241 male). Of these, 127 subjects had a positive history of depression, regardless of current depressive symptoms, and were excluded from the analysis in order to avoid potential bias due to a history of depression as a risk factor for dementia.[18] Hence, the nondemented and not previously depressed cohort at baseline consisted of 437 individuals (239 female, 198 male). At 30 months, follow-up was possible in 355 individuals, 56 of whom had possible or probable Alzheimer's dementia and 299 were not demented. At 60-month follow-up, 32 of the latter group received a diagnosis of possible or probable Alzheimer's dementia and 51 refused participation. Among the group that was diagnosed with dementia at 30-month follow-up, the diagnosis was revised in 10 cases, 14 refused further participation, leaving 32 with a stable diagnosis of dementia. Six individuals that had not participated in the 30-month follow-up could be examined at 60-month follow-up, 1 of whom was diagnosed with dementia. Hence, at 60-month follow-up a total of 65 individuals had a diagnosis of possible or probable Alzheimer's dementia, and 231 did not (Figure 1).

Clinical Evaluation

Within the Vienna Transdanube Aging Study, an in-depth neurologic, psychiatric, and neuropsychological battery is administered by experienced raters in face-to-face interviews lasting about 9 hours per subject divided into 2 days at baseline and at the follow-up assessments. Further to the above, thorough information on demographic and psychosocial data and somatic history was recorded using a structured interview. Routine laboratory measures were carried out including, among others, folic acid, vitamin B_{12} and thyroid levels. Details on apolipoprotein E (APOE) genotyping have been previously described.[19] A cerebral magnetic resonance imaging (MRI) assessment using a 1.0 Tesla unit (Siemens Impact Expert, Siemens Corp, Munich, Germany) was recorded in 532 participants at baseline and repeated at every follow-up, when possible. The obtained sequences have been described elsewhere.[20]

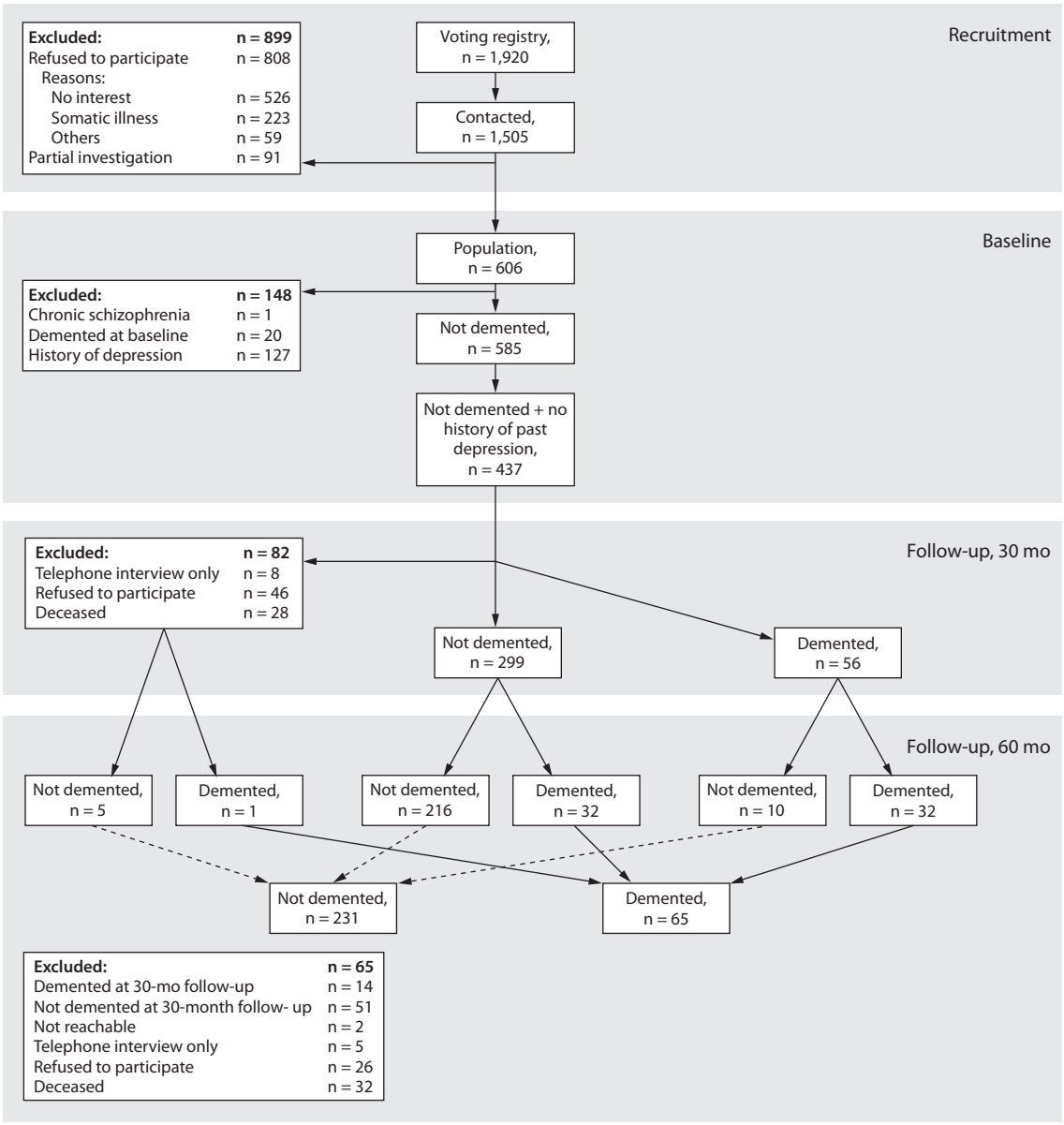
Current depressive symptoms were captured by an experienced geriatric psychologist at each time-point with a questionnaire based on *DSM-IV-TR* criteria for depressive episode (for detailed questionnaire, see Mossaheb et al[21]). Each symptom category from A1 to A9 was assessed separately (see Table 1) in order to gather information not only on a potential diagnosis of depression but also on the occurrence of specific symptoms of depression regardless of clinical diagnosis of depression. Depression was further assessed with the Hamilton Depression Rating Scale (HDRS)[22] and the Short Geriatric Depression Scale.[23] Details on the neuropsychological investigations have been described elsewhere.[24,25] The following subtests of the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery were used: animal fluency, Boston naming test, word list-learning, word list-delayed recall, word list learning-intrusions, word list delayed recall-intrusions, figures-copy, and figures delayed recall.[26,27] Furthermore, the German translation of the Mini-Mental State Examination (MMSE) was applied.[26,27] Diagnosis of possible or probable Alzheimer's dementia was performed by an expert panel through consensus diagnosis according to criteria by the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association,[28] using clinical investigations, clinical dementia rating,[29] results of psychometric tests, the MMSE and the Instrumental Activities of Daily Living Scale[30] as well as the cerebral MRI, when available.[25] The final diagnosis was reviewed by an experienced geriatric psychiatrist (P.F.).

Statistical Analysis

Two hundred ninety-six of the 437 nondemented and not previously depressed subjects from the baseline investigation were investigated at 60-month follow-up. Sixty-five of those had a diagnosis of possible or probable Alzheimer's dementia. The primary outcome measure was the probability of diagnosis of Alzheimer's dementia related to baseline depressive symptoms. We dealt with the missing information in 3 different ways. (1) For the main analysis, we used the observations from the investigation at the second follow-up. Three patients diagnosed with probable Alzheimer's dementia at the first and missing at the second follow-up were also included. All other missing subjects at the second follow-up were not considered. (2) The last observed diagnosis of each patient (first or second follow-up) was considered (last observation carried forward). (3) If subjects were missing at the second follow-up, their diagnosis was set to Alzheimer's dementia (worst case).

Univariate logistic regression analyses for the 9 *DSM-IV-TR* depression items A1–A9 on the diagnosis healthy versus possible/probable Alzheimer's dementia were calculated. *P* values, odds ratios (ORs), the corresponding 95% confidence intervals (CIs), and the area under the receiver operating characteristic curve (aROC) were calculated. The *P* values were adjusted for multiplicity according to Bonferroni correction. All adjusted *P* values $< .05$ were further considered in a multiple logistic regression

Figure 1. Flowchart of Study Population



model when the known risk factors APOE ε4, folic acid, and education additionally were included. These computations were done using the statistical computing environment R version 2.10 (R Foundation for Statistical Computing, Vienna, Austria).

We used χ^2 tests to calculate comparisons of frequencies of Alzheimer's dementia between 2 groups of MMSE or between groups of mild cognitive impairment.

RESULTS

Possible/Probable Alzheimer's Dementia at 60-Month Follow-Up

At 60-month follow-up, 231 individuals (78%) were nondemented, whereas 65 (22%) received a diagnosis of possible or probable Alzheimer's dementia.

Sex Distribution

In the baseline sample (n = 437), the sex distribution was 45.3% (n = 198) male and 54.7% (n = 239) female. Among those subjects who had a possible or probable Alzheimer's dementia at 60-month follow-up, 47.7% were female compared to 59.3% in the nondemented group ($\chi^2_1 = 2.788$, $P = .095$ [Table 1]).

Education

There was no statistically significant difference in education between the nondemented and the Alzheimer's dementia group ($\chi^2_2 = 0.460$, $P = .8$).

Mild Cognitive Impairment

When comparing those individuals that were diagnosed with possible or probable Alzheimer's dementia at 60-month

© Copyright 2012 Physicians Postgraduate Press, Inc.

Table 1. Characteristics at Baseline of Population at 60-Month Follow-Up (possible/probable Alzheimer's dementia versus not demented)

Characteristic	No Alzheimer's Dementia (n = 231)	Possible/Probable Alzheimer's Dementia (n = 65)
Female sex, %	59.3	47.7
Age, mean (SD), y	75.7 (0.45)	75.7 (0.4)
Education, %		
Illiterate/elementary/maximum 8 years of schooling	22.1	20
Vocational school	58.4	63.1
Secondary school/university	19.5	16.9
MMSE score, mean (SD)	28.3 (1.4)	27.6 (1.5)
Folic acid level, mean (SD), nmol/L	9.9 (5.1)	8.5 (3.7)
APOE ε4 (no. of alleles), %		
0	77.1	69.2
1	19.5	27.7
2	1.3	1.5
Missing data	2.2	1.5
DSM-IV-TR classification, %		
A1 (depressed mood)	6.1	7.7
A2 (loss of interest)	2.2	10.8
A3 (change of appetite)	0.4	0
A4 (sleep disturbance)	21.6	27.7
A5 (psychomotor change)	3.5	7.7
A6 (loss of energy)	4.8	7.7
A7 (worthlessness)	1.3	1.5
A8 (concentration difficulty)	3.9	4.6
A9 (suicidal ideation)	0	0
MCI classification, %		
Cognitively healthy	88.3	67.7
Amnestic single	1.3	9.2
Amnestic multiple	0.9	9.2
Nonamnestic single	6.5	12.3
Nonamnestic multiple	2.6	1.5
Not classifiable	0.4	0

Abbreviations: APOE = apolipoprotein E, MCI = mild cognitive impairment, MMSE = Mini-Mental State Examination.

follow-up with those that did not with respect to mild cognitive impairment classification at baseline, there was a significantly lower percentage of subjects without mild cognitive impairment in those who ended up having a diagnosis of possible or probable Alzheimer's dementia (67.7% versus 88.3% in the nondemented group, $\chi^2_5 = 28.933$, $P < .0001$ [see Table 1]). Loss of interest was present in 2.8% (n = 7) of subjects without mild cognitive impairment, in 50% (n = 4) of subjects with amnestic multiple mild cognitive impairment, and 4.3% (n = 1) of those with nonamnestic single mild cognitive impairment ($\chi^2_5 = 45.108$, $P < .0001$).

MMSE

Of the nondemented subjects, 89.6% had an MMSE score between 27 and 30 at baseline versus 80% in the possible/probable–Alzheimer's dementia group. This difference was not significant ($\chi^2_1 = 4.283$, $P = .38$).

Depressive Symptoms

Among the 65 individuals with possible or probable Alzheimer's dementia at 60-month follow-up, 57 (87.7%) had no diagnosis of *DSM-IV-TR* depression at baseline, 2 (3.1%) were diagnosed with subsyndromal depression, and 4 (6.2%) with minor and 2 (3.1%) with major depression.

Table 2. Logistic Regression Analysis of Occurrence of *DSM-IV-TR* Major Depressive Disorder Symptoms at Baseline: Complete Case Data[a]

DSM-IV-TR Symptom	*P* Value	Adjusted *P* Value	Odds Ratio (95% CI)	Area Under the Curve
A1 (depressed mood)	.68	1	1.25 (0.43–3.61)	0.507
A2 (loss of interest)	.00585	.047	5.27 (1.62–17.2)	0.541
A3 (change of appetite)	.99	1	0 (0–Inf)	0.502
A4 (sleep disturbance)	.25	1	1.43 (0.77–2.65)	0.534
A5 (psychomotor change)	.168	1	2.25 (0.71–7.12)	0.520
A6 (loss of energy)	.392	1	1.61 (0.54–4.82)	0.514
A7 (worthlessness)	.9	1	1.15 (0.12–11.25)	0.501
A8 (concentration difficulty)	.83132	1	1.16 (0.3–4.4)	0.503

[a]Only 1 subject had symptom A9, and therefore the symptom is not included in the analysis.

The respective numbers for those who were not demented at 60-month follow-up were 208 (90%) no depression, 8 (3.5%) subsyndromal depression, 15 (6.5%) minor depression, and none with a major depression. Distribution of diagnoses of *DSM-IV-TR* depression at baseline did not differ significantly between the 2 groups ($\chi^2_3 = 7.171$, $P = .067$).

The analysis of the complete case data resulted in a significant association of *DSM-IV-TR* symptom A2—loss of interest or pleasure in activities—with the later occurrence of possible or probable Alzheimer's dementia (Table 2). None of the other 8 analyzed symptoms yielded significant effects. The presence of the symptom *loss of interest* was associated with a higher risk of developing Alzheimer's dementia. The aROC was only 0.541. Note, however, that only 12 patients had a positive value for the symptom *loss of interest* (5 of the 231 nondemented, not previously depressed individuals, and 7 of the Alzheimer's dementia subjects). The specificity of symptom A2 in predicting Alzheimer's dementia was 97.8; the sensitivity, 10.4; however, this finding is most probably due to the low number of individuals positive for that symptom. No significant results were found for the last observation carried forward and the worst-case calculations after adjusting for multiplicity (Tables 3 and 4). Only in the unadjusted analyses can a borderline significance of symptom A2 be found.

When 3 of the known risk factors, APOE ε4, folic acid, and education were inserted in the model, in addition to *DSM-IV-TR* A2 ($P = .036$), folic acid was significantly associated with the development of Alzheimer's dementia ($P = .02$). Subjects with a higher folic acid level had a lower risk of developing Alzheimer's dementia (OR = 0.92, 95% CI, 0.85–0.99). Apolipoprotein E ε4 allele numbers ($P = .08$) and education ($P = .89$) were not significant. The aROC was 0.626.

DISCUSSION

The main question of this analysis was whether specific symptoms of depression in not-demented, never depressed individuals might be indicative of a dementia to come. Our principal finding was that only baseline loss of interest, 1 of 9 symptoms of *DSM-IV-TR* depression, showed a significant

Table 3. Logistic Regression Analysis of Occurrence of *DSM-IV-TR* Major Depressive Disorder Symptoms at Baseline: Last Observation Carried Forward Data[a]

DSM-IV-TR Symptom	*P* Value	Adjusted *P* Value	Odds Ratio (95% CI)	Area Under the Curve
A1 (depressed mood)	.95	1	0.97 (0.38–2.48)	0.501
A2 (loss of interest)	.02434	.19	3.33 (1.17–9.49)	0.530
A3 (change of appetite)	.98	1	0 (0–Inf)	0.504
A4 (sleep disturbance)	.39	1	1.28 (0.72–2.28)	0.523
A5 (psychomotor change)	.061	.49	2.29 (0.96–5.45)	0.530
A6 (loss of energy)	.375	1	1.52 (0.61–3.8)	0.514
A7 (worthlessness)	.92	1	0.89 (0.1–9.09)	0.501
A8 (concentration difficulty)	.30926	1	1.62 (0.64–4.08)	0.516

[a]Only 1 subject had symptom A9, and therefore the symptom is not included in the analysis.

Table 4. Logistic Regression Analysis of Occurrence of *DSM-IV-TR* Major Depressive Disorder Symptoms at Baseline: Worst Case Data[a,b]

DSM-IV-TR Symptom	*P* Value	Adjusted *P* Value	Odds Ratio (95% CI)	Area Under the Curve
A1 (depressed mood)	.21	1	1.57 (0.77–3.23)	0.516
A2 (loss of interest)	.05747	.46	2.80 (0.97–8.08)	0.518
A3 (change of appetite)	.29	1	3.40 (0.35–32.94)	0.505
A4 (sleep disturbance)	.18	1	1.35 (0.87–2.1)	0.528
A5 (psychomotor change)	.024	.19	2.67 (1.13–6.28)	0.526
A6 (loss of energy)	.049	.39	2.15 (1–4.6)	0.525
A7 (worthlessness)	.89	1	1.12 (0.22–5.63)	0.501
A8 (concentration difficulty)	.06014	.48	2.22 (0.97–5.09)	0.522

[a]Only 1 subject had symptom A9, and therefore the symptom is not included in the analysis.
[b]Diagnosis was set to Alzheimer's dementia (worst case) for subjects who were missing at the second follow-up.

association with the occurrence of possible or probable Alzheimer's dementia after a follow-up period of 5 years in originally nondemented individuals without a history of previous depressive episodes. The occurrence of this symptom was associated with a higher risk of developing Alzheimer's dementia, whereas none of the remaining 8 symptoms had a predictive value. The Vienna Transdanube Aging Study, apart from being a prospective cohort study, shows additional strengths substantiating these specific findings: the sample is homogenous with respect to age, therefore excluding influences of different age groups as the incidence of dementia is known to increase with age.[31] Subjects with a history of depression were excluded from the analysis in order to avoid potential bias, since prior depression is an established risk factor for Alzheimer's dementia[2] and is most probably related to the occurrence of depressive symptoms at baseline; thus, history of depression as a single antecedent might be related to both subsequent Alzheimer's dementia and current depression, possibly leading to a spurious association between the two if not excluded. Baseline depressive symptoms were thoroughly assessed, not only by means of depression scales but also on a symptomatic level with a detailed *DSM-IV*–based questionnaire (see Mossaheb et al[21]). Finally, there was no difference in the distribution of depression diagnoses between the 2 groups.

The symptom *loss of interest* had a high specificity (97.8%) and a low sensitivity (10.4%) in predicting Alzheimer's dementia, implying that in elderly subjects presenting with symptoms of possible depression but without loss of interest later development of Alzheimer's dementia is less probable; also, only 12 individuals exhibited the symptom *loss of interest*, whereas 65 were diagnosed with Alzheimer's dementia after 5 years, 7 of whom presented that symptom. Conversely, one can argue that elderly patients with symptoms of depression should be treated for a genuine depression. Indeed, late-onset depression in the elderly increases with age with prevalence rates of up to 30%.[21]

Our findings are in line with those of the Kungsholmen Project[10] with respect to loss of interest; however, their sample additionally exhibited thoughts of death as a depressive symptom predictive of future dementia. This discrepancy may be due to the fact that the Kungsholmen sample was not homogenous with respect to age and cognitive deficits, showing significant differences between the not-demented and demented individuals in age and MMSE scores. Mood-related symptoms have also been described by at least 2 other groups.[6,15] Kim and colleagues' prospective community survey[15] of subjects aged 65 years and older with a 2-year follow-up indicated depressed mood, feelings of worthlessness, concentration difficulties, and suicidal ideations emerged as particularly strong predictors of subsequent development of Alzheimer's dementia in the context of synergistic effects of the occurrence of APOE ε4 and late-life depression. However, the 2 latter studies seem to have included subjects with a past history of depression.[6,15] In excluding previously depressed participants, we expected to eliminate potential confounding caused by the independent risk component of past depression.

Participants were not demented at baseline and did not differ significantly in their baseline MMSE scores; thus, early stages of evident cognitive decline that could have been detected with current methods were excluded. Yet, there was a higher percentage of subjects with baseline mild cognitive impairment in those that were later diagnosed with possible or probable Alzheimer's dementia. This finding is in line with the current knowledge that approximately one-third of patients with mild cognitive impairment progress to Alzheimer's dementia with an annual conversion rate of 5%–10%. However, a large majority of people with mild cognitive impairment do not develop dementia even after several years of follow-up.[32] Also, only 5 of the 12 participants who presented with loss of interest had mild cognitive impairment at baseline. Therefore, we cannot conclude that loss of interest was a symptom specific of mild cognitive impairment in our population. Moreover, some patients were diagnosed with Alzheimer's dementia at 30-month follow-up but were reassessed as not demented at the next

follow-up. Theoretically, in the same way, some of the 65 patients diagnosed with possible or probable Alzheimer's dementia at 60-month follow-up might also "convert" to being diagnosed as not demented over a longer observation period, thus somewhat limiting the liability of the results. Different factors may have led to the false-positive diagnoses, such as current depression with depressive pseudodementia, somatic illnesses leading to fatigue or transient cognitive deficits.

In order to account for established risk factors of Alzheimer's dementia, we included folic acid levels, education, and APOE ε4 allele numbers into our analysis.[18] As expected, subjects with higher folic acid levels had a slightly lower risk of developing Alzheimer's dementia. Interestingly, in our sample, APOE ε4 allele frequency did not differ between 2 groups. The APOE ε4 allele is a well-known risk factor for Alzheimer's dementia.[18] Researchers have postulated that it is associated with depression itself[33]; this hypothesis, however, has been refuted by other groups.[34] Recently, APOE ε4 has been shown to have synergistic effects with depression on incident dementia.[15] However, the authors reveal no information on whether patients with a history of depression were included or excluded from the analysis. Possibly, the lack of APOE ε4 effect in our sample can be explained by the exclusion of patients with a past history of depression and by the size of the Alzheimer's dementia sample.

In spite of the fact that loss of interest was the only predictive symptom and that it was present in only a small number of subjects, one might ponder on the question, Why specifically is this symptom present years before the emergence of Alzheimer's dementia? It is conceivable that Aβ42-amyloid deposits in the frontal and limbic cortex occurring very early in the development of neurodegenerative and atrophying processes involved in Alzheimer's dementia [19,35] lead to the emergence of motivational symptoms, such as loss of interest, as first features of the underlying illness. This hypothesis implies the idea that the aforesaid symptom is a prodrome of Alzheimer's dementia. However, within the ongoing debate on risk versus prodrome, our results do not corroborate that reverse causality hypothesis as we could not establish an association between 8 of 9 symptoms of depression and Alzheimer's dementia. The relevance of loss of interest as a potentially prodromal feature is somewhat limited due to the small number of subjects who experienced that symptom. Furthermore, our data reflect the relationship between depressive symptoms and later diagnosis of Alzheimer's dementia in a cohort of 75-year-old individuals not previously depressed, and cannot be generalized to all elderly groups. Altogether, within the confines of this study, our results point rather toward the idea that, in most cases, depression in the elderly really is genuine depression or an independent disease.

CONCLUSION

We found that only the symptom *loss of interest* was associated with the development of Alzheimer's dementia over a period of 5 years in a sample of 75-year-old, not-demented, never-depressed subjects. No other symptom of depression showed association with Alzheimer's dementia. Our data suggest that depressive symptoms in the elderly are symptoms of genuine depression and should be treated as such.

Author affiliations: Departments of Child and Adolescent Psychiatry and Psychiatry and Psychotherapy (Dr Mossaheb), and Section of Medical Statistics (Dr Zehetmayer), Medical University Vienna; Ludwig Boltzmann Institute of Aging Research (Drs Jungwirth, Tragl, and Fischer and Ms Weissgram); and Department of Psychiatry, Danube Hospital (Drs Rainer and Fischer), Vienna, Austria.
Potential conflicts of interest: None reported.
Funding/support: The Vienna Transdanube Aging Study (VITA) is supported by a donation to the Ludwig Boltzmann Society dedicated to geriatric psychiatry research; the study is thus supported by the Ludwig Boltzmann Institute of Aging Research, Austria. The VITA is done at the Ludwig Boltzmann Institute of Aging Research within the Danube Hospital in Vienna, Austria.
Additional information: The database from the VITA is not open to the public. Information on the VITA can be obtained from Dr Tragl (http://www.lbg.ac.at/node/156) and from Dr Fischer (p.fischer@wienkav.at).

REFERENCES

1. Steffens DC, Potter GG. Geriatric depression and cognitive impairment. *Psychol Med*. 2008;38(2):163–175.
2. Brommelhoff JA, Gatz M, Johansson B, et al. Depression as a risk factor or prodromal feature for dementia? findings in a population-based sample of Swedish twins. *Psychol Aging*. 2009;24(2):373–384.
3. Steffens DC, Plassman BL, Helms MJ, et al. A twin study of late-onset depression and apolipoprotein E epsilon 4 as risk factors for Alzheimer's disease. *Biol Psychiatry*. 1997;41(8):851–856.
4. Jorm AF. History of depression as a risk factor for dementia: an updated review. *Aust N Z J Psychiatry*. 2001;35(6):776–781.
5. Jorm AF. Is depression a risk factor for dementia or cognitive decline? a review. *Gerontology*. 2000;46(4):219–227.
6. Devanand DP, Sano M, Tang MX, et al. Depressed mood and the incidence of Alzheimer's disease in the elderly living in the community. *Arch Gen Psychiatry*. 1996;53(2):175–182.
7. Saczynski JS, Beiser A, Seshadri S, et al. Depressive symptoms and risk of dementia: the Framingham Heart Study. *Neurology*. 2010;75(1):35–41.
8. Wilson RS, Arnold SE, Beck TL, et al. Change in depressive symptoms during the prodromal phase of Alzheimer disease. *Arch Gen Psychiatry*. 2008;65(4):439–445.
9. Rosenberg PB, Mielke MM, Xue QL, et al. Depressive symptoms predict incident cognitive impairment in cognitive healthy older women. *Am J Geriatr Psychiatry*. 2010;18(3):204–211.
10. Berger AK, Fratiglioni L, Forsell Y, et al. The occurrence of depressive symptoms in the preclinical phase of AD: a population-based study. *Neurology*. 1999;53(9):1998–2002.
11. Chen P, Ganguli M, Mulsant BH, et al. The temporal relationship between depressive symptoms and dementia: a community-based prospective study. *Arch Gen Psychiatry*. 1999;56(3):261–266.
12. Bartolini M, Coccia M, Luzzi S, et al. Motivational symptoms of depression mask preclinical Alzheimer's disease in elderly subjects. *Dement Geriatr Cogn Disord*. 2005;19(1):31–36.
13. Savva GM, Zaccai J, Matthews FE, et al; Medical Research Council Cognitive Function and Ageing Study. Prevalence, correlates and course of behavioural and psychological symptoms of dementia in the population. *Br J Psychiatry*. 2009;194(3):212–219.
14. Leontjevas R, van Hooren S, Waterink W, et al. Apathy and depressive mood in nursing home patients with early-onset dementia. *Am J Alzheimers Dis Other Demen*. 2009;24(4):341–348.
15. Kim JM, Stewart R, Kim SY, et al. Synergistic associations of depression and apolipoprotein E genotype with incidence of dementia. *Int J Geriatr Psychiatry*. 2011;26(9):893–898.
16. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
17. Fischer P, Jungwirth S, Krampla W, et al. Vienna Transdanube Aging "VITA": study design, recruitment strategies and level of participation. *J Neural Transm suppl*. 2002;(62):105–116.
18. Fischer P, Zehetmayer S, Jungwirth S, et al. Risk factors for Alzheimer dementia in a community-based birth cohort at the age of 75 years.

Dement Geriatr Cogn Disord. 2008;25(6):501–507.
19. Blasko I, Kemmler G, Jungwirth S, et al. Plasma amyloid beta-42 independently predicts both late-onset depression and Alzheimer disease. *Am J Geriatr Psychiatry*. 2010;18(11):973–982.
20. Fischer P, Krampla W, Mostafaie N, et al. VITA study: white matter hyperintensities of vascular and degenerative origin in the elderly. *J Neural Transm suppl*. 2007;72:181–188.
21. Mossaheb N, Weissgram S, Zehetmayer S, et al. Late-onset depression in elderly subjects from the Vienna Transdanube Aging (VITA) study. *J Clin Psychiatry*. 2009;70(4):500–508.
22. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
23. Sheikh JI, Yesavage JA. A knowledge assessment test for geriatric psychiatry. *Hosp Community Psychiatry*. 1985;36(11):1160–1166.
24. Jungwirth S, Zehetmayer S, Weissgram S, et al. Do subjective memory complaints predict senile Alzheimer dementia? *Wien Med Wochenschr*. 2008;158(3–4):71–77.
25. Jungwirth S, Zehetmayer S, Bauer P, et al. Prediction of Alzheimer dementia with short neuropsychological instruments. *J Neural Transm*. 2009;116(11):1513–1521.
26. Morris JC, Mohs RC, Rogers H, et al. Consortium to establish a registry for Alzheimer's disease (CERAD) clinical and neuropsychological assessment of Alzheimer's disease. *Psychopharmacol Bull*. 1988; 24(4):641–652.
27. Berres M, Monsch AU, Bernasconi F, et al. Normal ranges of neuropsychological tests for the diagnosis of Alzheimer's disease. *Stud Health Technol Inform*. 2000;77:195–199.
28. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34(7):939–944.
29. Hughes CP, Berg L, Danziger WL, et al. A new clinical scale for the staging of dementia. *Br J Psychiatry*. 1982;140(6):566–572.
30. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist*. 1969;9(3): 179–186.
31. Fratiglioni L, Launer LJ, Andersen K, et al; Neurologic Diseases in the Elderly Research Group. Incidence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. *Neurology*. 2000;54(suppl 5):S10–S15.
32. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia—meta-analysis of 41 robust inception cohort studies. *Acta Psychiatr Scand*. 2009;119(4):252–265.
33. Krishnan KR, Tupler LA, Ritchie JC Jr, et al. Apolipoprotein E-epsilon 4 frequency in geriatric depression. *Biol Psychiatry*. 1996;40(1):69–71.
34. Slifer MA, Martin ER, Gilbert JR, et al. Resolving the relationship between ApolipoproteinE and depression. *Neurosci Lett*. 2009;455(2): 116–119.
35. Chételat G, Villemagne VL, Bourgeat P, et al; Australian Imaging Biomarkers and Lifestyle Research Group. Relationship between atrophy and beta-amyloid deposition in Alzheimer disease. *Ann Neurol*. 2010; 67(3):317–324.