Carotid atherosclerosis in depression & anxiety: associations for age of depression onset

3.

ABSTRACT

Background | Mental health and cardiovascular disease have been associated, whereas the temporal course and underlying mechanisms are still incompletely understood. Our aims were to examine the presence of subclinical atherosclerosis in subjects with depressive or anxiety disorder, also taking into account disorder characteristics (subtype, severity, duration, age of onset, medication).

Methods | The sample included 470 depression or anxiety cases and 179 controls, aged 20-66 years, participating in the Netherlands Study of Depression and Anxiety (NESDA). Diagnoses were assigned using the DSM-IV based Composite International Diagnostic Interview. Carotid intima-media thickness (CIMT) and plaque information were obtained using B-mode ultrasound imaging.

Results | Overall, depressive and anxiety disorders were not associated with carotid atherosclerosis. However, age of depression onset was associated with CIMT (total: 0.01mm per 10 yrs, p=.01; bifurcation: 0.02mm per 10 yrs, p=.003) and plaque presence (OR=1.35 per 10 yrs, 95%CI=1.02-1.80, p=.04). When compared with controls, late-onset (≥40 yrs) depressed had an increased CIMT in the atherosclerosis progression-prone bifurcation segment (0.75 versus 0.81mm, p=.004).

Conclusion | These findings suggest a distinct pathophysiology of late-onset as compared with early-onset depression, including a vascular component.

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INTRODUCTION

Both depressive and anxiety disorders have been associated with cardiovascular disease (CVD) [1-3], but the temporal course of this relationship and the underlying pathophysiological mechanisms are still incompletely understood. To this end, investigations using early atherosclerosis markers together with mental health measures have gained great interest. Examples of such markers of systemic atherosclerosis are carotid intima-media thickness (CIMT) and plaque presence [4, 5].

One decade of research in this field has yielded mixed results. Some studies found depression to be associated with higher CIMT [6-10] and plaques [11-13], whereas others found no significant association for CIMT [11, 13, 14] or plaque [9]. With the exception of one study [12], anxiety has not been associated with increased carotid atherosclerosis [8, 11, 15, 16]. Investigation of atherosclerosis markers together with depression and anxiety characteristics can provide insightful information, also with respect to causality. More sustained exposure to psychological stress may result in a dose-response effect on the mechanisms that contribute to atherosclerosis. Of the few studies that collected information on disorder characteristics, some indeed found evidence for this exposure-hypothesis, showing that more chronic depression was most strongly associated with atherosclerosis [11, 17]. Alternatively, when anxiety or depression would be a reactive manifestation of atherosclerosis (consistent with the concept of 'vascular depression' [18]), especially a late age of onset should be associated with atherosclerosis. Until now, two studies investigated and confirmed the association between late-onset depression and increased CIMT [6, 19].

Previous studies were mainly performed in older populations, often measured CIMT in the common carotid artery only, used self-reported measures for depression or anxiety symptoms, hardly examined depression and anxiety together despite their high comorbidity, and sparsely examined psychiatric disorder characteristics. The present study has met those restrictions by carefully detailing atherosclerosis markers as well as depression and anxiety outcomes in quite a large population with a broad age range.

Our aims were to examine whether carotid atherosclerosis was associated with 1) the presence of a psychiatric diagnosis of depressive or anxiety disorders, and 2) specific disorder characteristics (recency, subtype, severity, duration, age of onset, medication).

METHODS

Sample

The present study was conducted as an extension of the 2-year assessment of the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal cohort study to examine the course of depressive and anxiety disorders. In order to represent various health care settings and stages of psychopathology, participants were recruited from community, primary care and outpatient psychiatric clinics. The NESDA baseline sample (2004-2007) included 2329 persons with a lifetime depressive and/or anxiety disorder, and 652 controls, aged 18 through 65 years and of predominantly North European origin. Details of the study rationale, recruitment strategy and methods have been

described elsewhere [20]. The research protocol was approved by the Ethical Committee of participating universities and all respondents provided written informed consent.

Of the 2981 baseline participants invited, 2596 participated in the 2-year assessment. Predictors of non-response included younger age, lower education and major depressive disorder at baseline [21]. After the 2-year assessment, participants were asked for permission to be approached for additional cardiovascular measurements (see flow chart, **Figure 1**). Because of logistical reasons, 1617 subjects living far from the location of measurements and 7 subjects with diabetes taking insulin were excluded, leaving 972 eligible subjects. When asked and when contacted by telephone, 165 and 157 persons declined, respectively. Those willing to participate were scheduled to visit the Amstelland Hospital, Amstelveen, where the measurements took place (June 2007- July 2009).

We obtained carotid ultrasound data from 649 subjects (response rate 66.8%). Non-participants of the current study (both non-eligible and eligible; n=1947) were younger (mean: 43.2 versus 46.4 years, p<.001) and more often had lifetime depressive or anxiety disorders (81.3% versus 72.5%, p<.001), as compared with participants. No significant differences between participants and non-participants were found with respect to indicators of suspected cardiovascular health (i.e. history of CVD, diabetes, use of statins or antihypertensive agents; all p-values >.10).

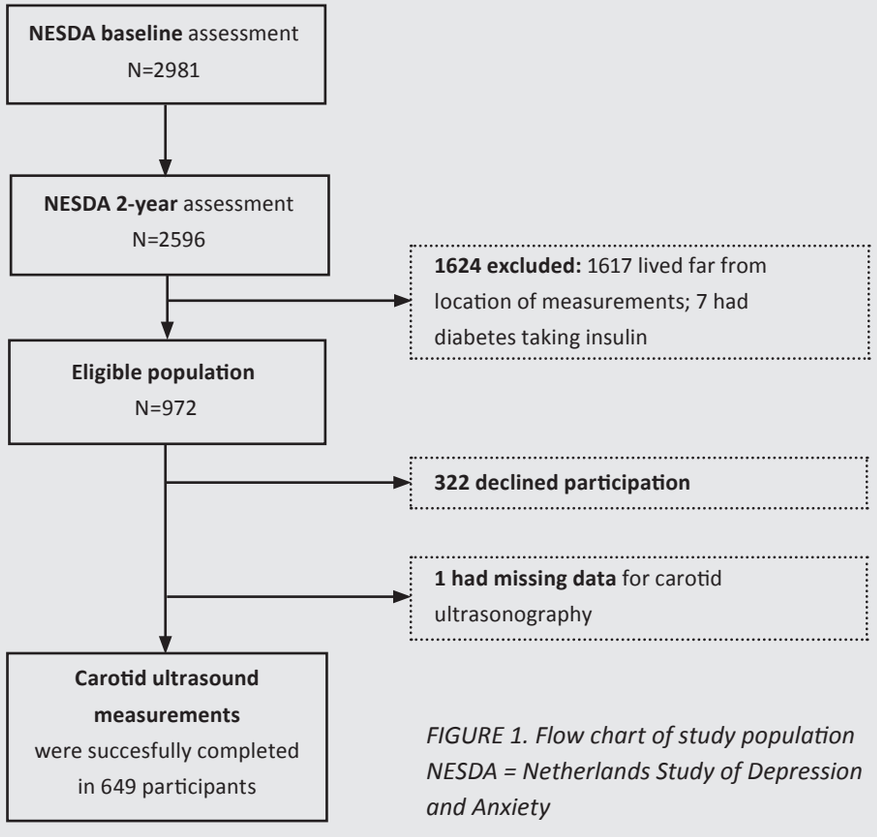

FIGURE 1. Flow chart of study population
NESDA = Netherlands Study of Depression and Anxiety

Psychopathology & disorder characteristics

Diagnoses of depressive (major depression, dysthymia) and anxiety (generalized anxiety disorder, social phobia, panic disorder and/or agoraphobia) disorders were established according to the DSM-IV based Composite International Diagnostic Interview (CIDI; WHO version 2.1) [22]. Participants were classified as having no (n=179) or having a lifetime (n=470) diagnosis of depressive or anxiety disorder.

The psychopathology group is heterogeneous, including subjects with a remitted or current disorder and varying severity and duration of symptoms. We therefore distinguished several characteristics to explore whether specific aspects of depressive or anxiety disorders were associated with carotid atherosclerosis. Based on disorder recency, we categorized subjects as having a remitted (lifetime, not current; n=221) or current (past year; n=249) disorder. Remitted diagnoses may be less reliable being retrospective [23] and probably indicate increasingly less severe depression or anxiety exposure over time. We also classified participants as having lifetime pure depression (n=94), pure anxiety (n=75), or comorbid depression and anxiety (n=301), in order to assess the possible influence of type of disorder. Because more severe and chronic depressive or anxiety disorders may be more strongly associated with atherosclerosis [11, 17], detailed information on the severity and duration of symptoms was collected. Severity was measured with the 30-item Inventory of Depressive Symptomatology (IDS) self-report version [24] and the 21-item Beck Anxiety Inventory (BAI) [25]. Symptom severity over the last two years was calculated as the average of the baseline (T0), 1-year (T1), and 2-year (T2) total scores. Duration was assessed using the Life Chart method among subjects with a depressive or anxiety disorder [26]. The percent of time with symptoms during the past six years was computed using T0 (covering 4 years) and T2 (covering 2 years) data. Further, age of onset of depressive and anxiety disorders was based on the CIDI data. Dependent on the type of disorder diagnosed in the CIDI, the participant was asked "When was the first time you (had a period of two weeks when you felt sad, empty, or depressed / lost interest / lacked energy …etc) or (were worrying for 6 months or more / were afraid of… / avoided…)?" Age of onset was used in a continuous and dichotomized (early-onset <40 years / late-onset ≥ 40 years) way. Since antidepressant medication has shown several effects on cardiovascular physiology [27], we assessed current medication use based on drug container inspection of all drugs used in the past month and classified according to the World Health Organization Anatomical Therapeutic Chemical (ATC) classification. Use of psychotropic medication (tricyclic antidepressants, N06AA; selective serotonin reuptake inhibitors, N06AB; other antidepressants, N06AF/N06AX) was considered present when taken at least 50% of days and for at least one year.

Atherosclerosis indicators

Carotid measurements were performed using an Acuson Aspen ultrasound instrument equipped with a near-field L7 linear array 5-10MHz broadband transducer (Siemens, Erlangen, Germany) according to a previously described standardized and validated protocol [28]. High resolution B-mode images of the bilateral common carotid artery (CCA; 10mm proximal to carotid dilatation), carotid bifurcation (CB; between dilatation and flow divider) and internal carotid artery (ICA; 10mm distal to tip of flow divider) were scanned

	Healthy controls N = 179	Depressive and/or anxiety disorder N = 470	p*
Demographics			
Age (years), mean ± sd	47.7 ± 12.5	45.9 ± 11.9	.10
Sex, % female	63.1	66.2	.47
Education level (years), mean ± sd	13.3 ± 3.2	12.6 ± 3.2	.02
Lifestyle			
Smoking status, %			
Never	38.5	26.4	<.001
Former	45.3	43.8	
Current	16.2	29.8	
Alcohol intake, %			.40
< 1 drink/week	23.5	28.7	
1-14 drinks/week	57.0	53.6	
> 14 drinks/week	19.6	17.7	
Physical activity level, %			.32
Low	15.1	19.4	
Moderate	46.4	47.2	
High	38.5	33.4	
Body mass index, mean ± sd	25.3 ± 4.6	25.4 ± 4.6	.81
Health			
Systolic pressure (mmHg), mean ± sd	116 ± 15	113 ± 15	.02
Use of antihypertensive medication, %	19.0	16.8	.51
LDL (mmol/l), mean ± sd	3.1± 0.8	2.9 ± 0.9	.03
Use of statins, %	3.4	7.9	.04
Diabetes Mellitus, %	1.7	5.1	.05
Cardiovascular Disease, %	6.1	8.3	.36
Psychopathology			
Depressive disorder, %			
No	100	16.0	
Remitted	0	49.8	
Current (1-year)	0	34.3	
Anxiety disorder, %			
No	100	20.0	
Remitted	0	37.9	
Current (1-year)	0	42.1	
IDS total score mean ± sd	6.3 ± 5.4	20.7 ± 10.9	<.001
BAI total score mean ± sd	6.0 ± 4.3	15.5 ± 8.6	<.001
Percent of time affected in last 6 years, median (IQR)	n.a.	41 (53)	
Age of onset depression, median (IQR)	n.a.	26 (20)	
Age of onset anxiety, median (IQR)	n.a.	17 (17)	
Use of antidepressant medication, %	n.a.	18.9	

TABLE 1. Sample characteristics based on psychopathology status (N=649)

**p-value based on χ^2-statistics (categorical variables) and t-statistics (continuous variables)*
remitted = lifetime, not current; current= last year at T2.
BAI= Beck Anxiety Inventory, averaged over T0, T1 and T2 ; LDL= low density lipoprotein;
IDS= Inventory of Depressive Symptomatology, averaged over T0, T1 and T2; n.a.= not applicable.

with the subject in supine position. For all available segments the distance between the leading edges of the far wall lumen-intima and media-adventitia interfaces was measured. Total CIMT ($CIMT_{tot}$) was calculated as the average of the bilateral CCA, CB and ICA. We additionally used bifurcation CIMT ($CIMT_{bif}$) as the outcome, since bifurcations particularly have been recognized as atherosclerosis progression-prone segments [29, 30] and considering the relatively young age of our sample. If data on one segment was missing, averaged thickness of available segments was used. Near and far walls of the CCA, CB and ICA were also evaluated for the presence of plaques (yes/no), defined as widening of the intimal and medial layers relative to adjacent segments, with the area of focal increased thickness ≥ 1.10mm.

All scans were performed and analyzed by one sonographer [AS], who was trained at the Department of Vascular Medicine, Academic Medical Centre, Amsterdam, The Netherlands. Pearson's correlation of ρ= 0.98 and a mean $CIMT_{tot}$ absolute difference of <.02mm were achieved for within-sonographer reproducibility. Regarding reproducibility of CIMT analysis, Pearson's correlations of ρ= .99 and ρ= .93 were achieved for within-reader and between-reader (when compared with an experienced reader) comparisons, respectively.

Covariates

Sociodemographics included age, sex and education (years). Various lifestyle and health indicators were considered as covariates since these have been linked with both depression/anxiety and atherosclerosis and might confound an association. Smoking status was defined as non-smoker, former smoker or current smoker. Alcohol intake was measured as number of alcoholic consumptions a week. Physical activity was measured with the International Physical Activity Questionnaire (Craig et al. 2003) in MET-minutes per week [ratio of energy expenditure during activity compared to rest times the number of minutes performing the activity] and categorized as low, medium or high. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Systolic blood pressure was measured on the right arm during supine rest, using a Dinamap®PRO100 monitor (GE Medical Systems, Tampa, Florida, USA). The average of three series of two readings was taken as systolic blood pressure. Use of antihypertensive medication was based on drug-container inspection and ATC coding [codes C02, C03, C07, C08 and C09].

	Total CIMT (mm)				Bifurcation CIMT (mm)			Carotid plaque presence (N=95)			
	N	Mean	95%CI	*p*	Mean	95%CI	*p*	%	OR	95%CI	*p*
Demographics adjusted				.27			.77				
Controls	179	0.67	0.65 – 0.68		0.75	0.73 – 0.78		12.8		*reference*	
Depressive or anxiety disorder	470	0.66	0.65 – 0.66		0.75	0.74 – 0.76		15.1	1.53	0.88 – 2.66	.13
Fully adjusted				.63			.79				
Controls	179	0.66	0.65 - 0.68		0.75	0.73 – 0.77		12.8		*reference*	
Depressive or anxiety disorder	470	0.66	0.65 – 0.67		0.75	0.74 – 0.77		15.6	1.57	0.87 – 2.83	.14

*TABLE 2. Association between carotid atherosclerosis and psychopathology status (N=649)**

** Based on analyses of covariance (ANCOVA; estimated marginal means) and logistic regression analyses, adjusted for sociodemographics (age, sex, education) and other covariates (fully; demographics plus BMI, smoking status, alcohol intake, physical activity, systolic blood pressure, use of antihypertensive medication, LDL-cholesterol, use of statins, diabetes mellitus, cardiovascular disease).*

Blood samples were taken after an overnight fasting period, transported to a laboratory within one hour and analyzed using standard laboratory techniques. Low density lipoprotein (LDL) cholesterol (mmol/l) and glucose (mmol/l) were determined. The presence of type 2 Diabetes Mellitus was based on glucose levels ≥7 mmol/l or use of blood-glucose lowering medication (ATC code A10).

Use of statins and other LDL-lowering medication was based on ATC codes C10AA, C10AC and C10AX. Cardiovascular disease (CVD) included a history of myocardial infarction, stroke, angina-pectoris, percutaneous transluminal coronary angioplasty and coronary artery bypass grafting, and was adjudicated using standardized algorithms considering self-report and medication use. Height, weight and blood pressure were measured during the ultrasound measurements visit, whereas other covariates were assessed at the 2-year assessment. Median time between 2-year assessment and ultrasound measurements was 2 months.

Statistical analyses

Sample characteristics for healthy controls and subjects with lifetime psychopathology were compared using analyses of variance and χ^2-statistics. First, we determined estimated marginal means by analysis of covariance to compare CIMT between study groups, subsequently adjusting for sociodemographics and other covariates. In addition, we conducted logistic regression analyses to determine odds ratios for psychopathology in association with plaque presence, again adjusting in two steps. Second, to assess the effects of psychiatric characteristics on atherosclerosis, we conducted adjusted regression analyses examining the associations of recency, type of disorder, severity, duration, age of onset and medication use with CIMT (linear regression) and plaque (logistic regression) among subjects with lifetime depression and/or anxiety. All analyses were conducted using SPSS version 15.0 (SPSS, Chicago, IL).

RESULTS

Sample characteristics

Mean age of this sample (N=649) was 46.4 years (SD=12.1) and 65.3% was female. Of the participants with lifetime psychopathology (N=470), 47% had a remitted and 53% had a last-year depressive or anxiety disorder. **Table 1** presents characteristics for controls and subjects with lifetime depressive or anxiety disorders. Compared to controls, subjects with lifetime psychopathology, had less education, were more often current smokers, had a lower systolic blood pressure, a lower level of LDL-cholesterol, and more frequently had diabetes mellitus or used statins.

Psychopathology and carotid atherosclerosis

Mean $CIMT_{tot}$ was 0.66mm (SD=0.15), mean $CIMT_{bif}$ was 0.75mm (SD=0.21), and 14.6% of the sample had carotid plaques. Subjects with and without depressive or anxiety disorders did not differ with respect to CIMT (**Table 2**). Likewise, no significant difference was found in prevalence of plaques for affected subjects (15.3%) and controls (12.8%).

	Total CIMT				Bifurcation CIMT			
	Demographics adjusted		*Fully adjusted*		*Demographics adjusted*		*Fully adjusted*	
	β	*p*	*β*	*p*	*β*	*p*	*β*	*p*
Recency								
Current versus remitted	-.05	.17	-.04	.19	-.05	.14	-.05	.15
Type of disorder								
Pure depression (*reference)*								
Pure anxiety	.02	.55	.03	.37	-.03	.51	-.02	.59
Comorbid depression and anxiety	.003	.94	.002	.97	.02	.64	.01	.80
Severity [a]								
Depressive symptoms (IDS)	-.02	.55	-.05	.10	.02	.51	-.002	.96
Anxiety symptoms (BAI)	-.01	.84	-.03	.34	.04	.25	.01	.70
Duration								
Percent of time with symptoms in past 6 yrs	.02	.61	-.002	.95	-.02	.62	-.03	.36
Age of onset [b]								
Age of onset depressive disorder	.11	.01	.10	.01	.13	.003	.12	.003
Age of onset anxiety disorder	-.001	.99	.01	.77	.003	.95	.01	.90
Medication								
Use of antidepressant medication	.05	.14	.01	.75	.04	.29	-.01	.88

*TABLE 3. Association between various psychiatric characteristics and carotid intima-media thickness (CIMT) among depression and anxiety cases (N=470)**

** Based on linear regression analyses adjusted for sociodemographics (age, sex, education) and other covariates (fully; demographics plus smoking status, alcohol intake, physical activity, BMI, systolic blood pressure, use of antihypertensive medication, LDL-cholesterol, use of statins, diabetes mellitus, cardiovascular disease).*

Disorder characteristics and CIMT

Table 3 shows the associations between specific depression and anxiety characteristics (recency, type of disorder, severity, duration, age of onset, medication) and CIMT among subjects with lifetime psychopathology. No significant associations were found for disorder characteristics, except for age of first onset in subjects with a lifetime diagnosis of depressive disorder (N=394). Later age of depression onset was associated with increased CIMT. After full adjustment, every 10 years of later reported onset of depressive disorder was associated with 0.01mm increase of $CIMT_{tot}$ (p=.01) and 0.02mm increase of $CIMT_{bif}$ (p=.004). Early-onset nor late-onset depressed significantly differed from controls with respect to the adjusted mean $CIMT_{tot}$, but late-onset depressed had a higher $CIMT_{bif}$ (0.81 vs. 0.75mm in controls; p=.004) (**Figure 2**).

Disorder characteristics and carotid plaque

Table 4 shows the associations between disorder characteristics and plaque presence in the psychopathology sub-sample. After full adjustment, of all characteristics only age of depression onset was significantly associated with plaque presence (per 10 years: OR=1.35, 95%CI=1.02-1.79, p=.04). As compared with controls, early-onset depressed did not differ, but those with late-onset depressive disorder had an increased plaque risk (demographics-adjusted OR=1.96, 95%CI=1.00-3.84, p=.05), which turned insignificant after full adjustment (OR=1.78, 95%CI=0.86 -3.68, p=.12).

Sensitivity analyses

In order to test whether significant associations between age of depression onset and carotid atherosclerosis were driven by subjects with CVD, fully adjusted analyses were conducted without CVD cases (N=48). Results were very similar (per 10 years later onset: $\beta_{CIMTtot}$=.09, p=.03; $\beta_{CIMTbif}$=.10, p=.02; OR_{plaque}=1.39, 95%CI=1.01-1.91, p=.04) among depressed cases. The adjusted mean $CIMT_{bif}$ of late-onset depressed also remained increased as compared with controls (0.78 vs. 0.74mm in controls; p=.04).

We also repeated the analyses among participants aged ≥ 40 years to test specifically whether associations had been moderated or confounded by age. Observations were similar, showing associations between carotid atherosclerosis and age of depression onset within depressed cases (N=266; per 10 years later onset: $\beta_{CIMTtot}$= 0.13, p=.01; $\beta_{CIMTbif}$= 0.15, p=.003; OR_{plaque}= 1.35, p=.04) and an increased mean $CIMT_{bif}$ for late-onset depressed as compared with controls (N=389; 0.88. vs 0.83mm, p=.03).

DISCUSSION

In this sample of subjects with lifetime depressive or anxiety disorders and controls, we found no significant associations between diagnoses of depression or anxiety and carotid atherosclerosis. Nevertheless, a later age of onset of depressive disorder was associated with increased CIMT and plaque, and late-onset depressed had an increased $CIMT_{bif}$ as compared with controls.

The absence of a significant overall association between anxiety disorder and carotid atherosclerosis is consistent with most previous studies [8, 11, 15, 16]. One study, however, reported sustained anxiety to be associated with 4-year increase in CIMT and (in men only) with plaque occurrence [12]. A reason for this deviant observation may be that trait anxiety was used instead of a psychiatric diagnosis.

The finding that depressive disorders overall were not associated with carotid atherosclerosis is in line with some [14], but not with other studies [7-9, 11, 13]. Since studies with positive findings generally involved middle-aged or older populations, the observed associations between depression and CIMT or plaques might have been driven by subjects with late-onset depression. The observations of increased CIMT in depressed men aged below 40 years [7] and of higher plaque risk in subjects with recurrent depressive episodes who had no later onset than single episode cases [11], however, argue against this interpretation.

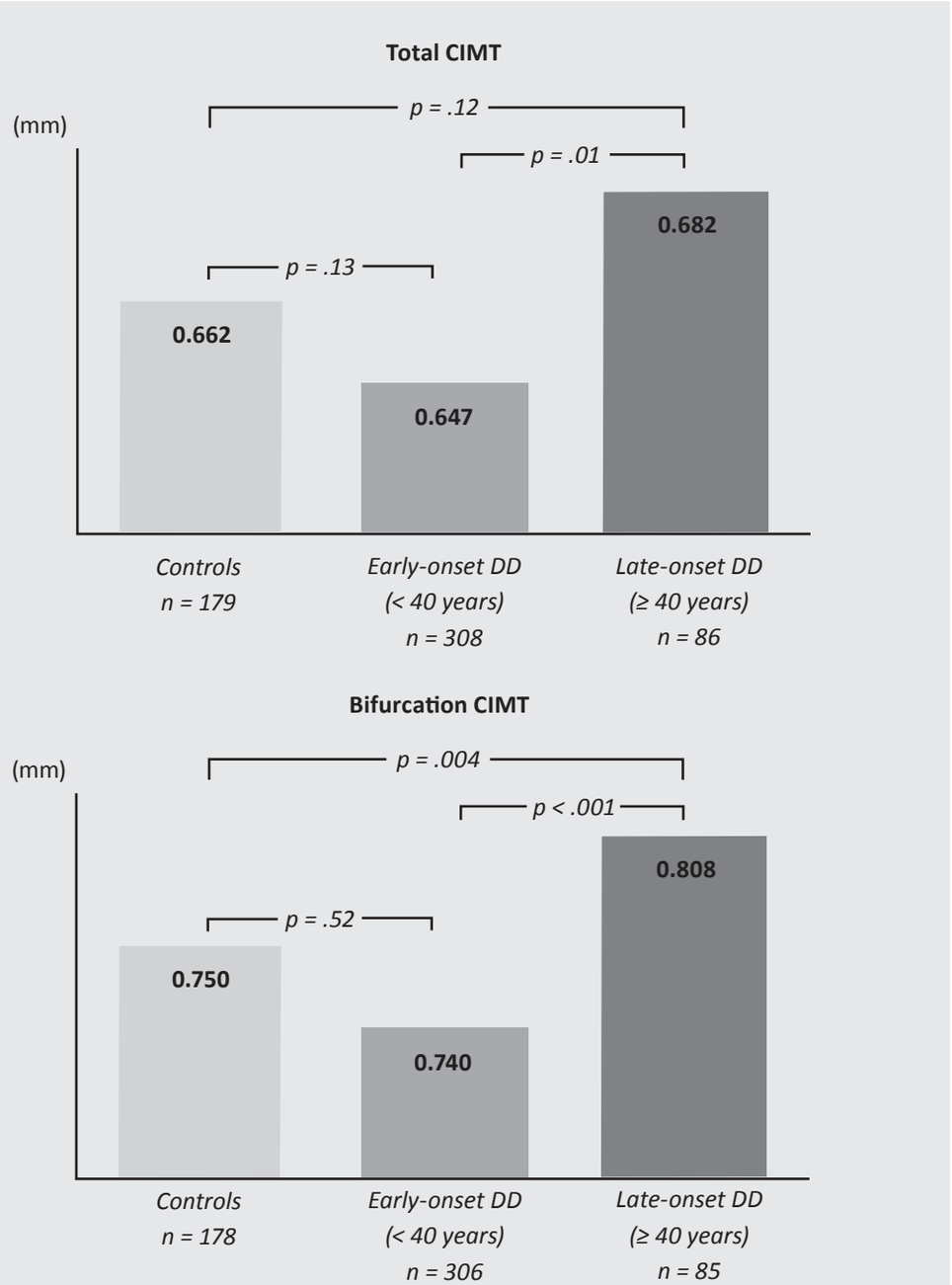

FIGURE 2. Fully adjusted means of carotid intima-media thickness (CIMT) based on age of onset depressive disorder (DD) categories.

Based on logistic regression analyses, adjusted for age, sex, education, smoking status, alcohol intake, physical activity, BMI, systolic blood pressure, use of antihypertensive medication, LDL-cholesterol, diabetes mellitus, cardiovascular disease, use of statins.

Our findings for age of onset of depressive disorder confirm earlier observations by showing a positive association with carotid atherosclerosis [19]. We have expanded those observations by carefully detailing $CIMT_{tot}$ as well as carotid lesions instead of using CCA only, and by additionally comparing depressed cases with controls. As compared with controls, we found no significant differences for $CIMT_{tot}$ or plaques, but still for $CIMT_{bif}$ in late-onset cases. One study found that late-onset depressed had a significantly increased CIMT as compared with controls [6]. The difference in significance levels can be due to the older age of their sample (mean age: over 70 years vs. 46 years in our study). Since especially bifurcations are atherosclerosis progression-prone segments, it was not surprising that we found more distinct and significant $CIMT_{bif}$ differences between groups. Predilection segments such as bifurcations therefore probably are most suitable for finding differences in atherosclerotic burden between groups in younger populations.

Various hypotheses have been generated as to the mechanisms linking psychopathology to atherosclerosis. In addition to an unhealthy lifestyle [31], inflammatory processes, dysfunction of the autonomic nervous system and hyperactivity of the hypothalamic-pituitary-adrenal axis have been suggested as pathophysiological factors [32]. With respect to the vascular depression hypothesis, frontostriatal and frontolimbic impairment has been proposed as a causal process [33]. White matter lesions, which have been associated with carotid atherosclerosis [34], could result in cerebral ischemia in those regions concerned with mood regulation [35, 36]. Regarding causality hypotheses, our data is inconsistent with the exposure-hypothesis (no associations between atherosclerosis and severity or duration of symptoms), but makes sense in the view of the vascular depression hypothesis, which assumes that atherosclerosis makes subjects vulnerable to develop depression. Hence, late-onset as compared with early-onset depression probably has a different pathophysiology. This idea has recently received support from a genetic perspective [37], as early-onset depression was found to be linked to a familial loading of depression, but late-onset depression to a familial loading of vascular disease. The meta-analysis of Nicholson and colleagues also provides indirect support for the reverse causation hypothesis by showing that depression is associated with subsequent CVD especially in studies with a shorter follow up period. Longitudinal evidence for the absence of an association between early-onset depression and incident coronary disease over 37 years of follow-up was recently found in a large study among young Swedish men from 18 to 20 years (Janszky et al. 2010 [38]).

Some limitations of this study should be mentioned. First, the cross-sectional design limits the ability to make definite causal inferences. Second, plaque prevalence was low (14.6%) in our relatively young population, which probably resulted in a lack of power in multivariate testing. Third, since information on previous use of antidepressant medication was not available in this study, no stringent conclusions can be drawn as to their (potentially harmful) effect on carotid atherosclerosis. Fourth, since nonparticipants more often had lifetime diagnoses of depressive or anxiety disorders than participants, selection bias could have occurred. However, since indicators of compromised cardiovascular health were similar between participants and non-participants, it is not likely this has led to different results. Fifth, data on age of onset were retrospective and which might have affected

reliability. Sixth, we used a cut-off at 40 years of age for 'late-onset depression', though earlier studies used higher cut-off values. However, results from the Swedish Twin Registry have shown that from an age of depression onset at 40 years co-twins had an elevated risk for vascular disease [37]. When the association found between late-onset depression and atherosclerosis reflects a relationship of low mood being a manifestation of poor vascular health, a cut-off at 40 years can be reasonable, since atherosclerotic as well as white matter lesions appear from the fourth decade of life [39, 40]. If in the late 30s compromised cardiovascular health can be observed, from then on lesions can be invoked that cause (vulnerability to) depression. Strengths of this study include the broad age range of our sample, the use of DSM-IV-based diagnoses, data on various psychiatric characteristics, and carefully detailed carotid atherosclerosis measures.

In conclusion, we found that depressive disorders with a later onset, but not anxiety or depression overall, are characterized by a higher prevalence of carotid atherosclerosis. This suggests that late-onset as compared with early-onset depression has a distinct pathophysiology involving a vascular component. Prospective studies are needed to confirm this relationship and elucidate the underlying mechanisms. If longitudinal results will support our findings, the need for preventive anti-atherosclerotic measures should be evaluated in subjects with a late first onset of depressive disorder.

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