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Accumulation of Depressive Symptoms and Carotid Intima-Media Thickness: the Cardiovascular Risk in Young Finns Study

Background: The association between depressive symptoms and subclinical atherosclerosis has been inconsistent. **Purpose:** We sought to replicate our previous study, which demonstrated positive relation between depressive symptoms and subclinical atherosclerosis assessed with carotid intima-media thickness (IMT) in men, using newer measurement of carotid IMT and a cumulative loading of depressive symptoms over three follow-ups.

Methods: The sample comprised 996 adults (352 men) aged 30 to 45 years in 2007 from a prospective population-based Finnish sample. The participants completed a modified version of Beck Depression Inventory in 1992, 1997, and 2001. Carotid IMT was assessed with ultrasound in 2001 and 2007. Cardiovascular risk factors (i.e., body mass index, systolic blood pressure, low-density lipoprotein cholesterol, and smoking) were measured in childhood (1980) and in adulthood (2007). **Results:** We found no association between accumulative depression index and carotid IMT before or after controlling for the traditional risk factors (all $ps \geq 0.67$). Depressive symptoms did not predict IMT progression over two time points and the highest level of carotid wall thickening. Imputed and non-imputed datasets provided similar results. Results remained the same when men and women were analyzed separately. Additional analyses revealed no significant interactions between depressive symptoms and cardiovascular risk factors (i.e., body mass index and systolic blood pressure) on carotid IMT (all $ps > 0.15$). **Conclusions:** The findings of this population-based study did not indicate any direct association between depressive symptoms and carotid IMT in asymptomatic, young adults.

Key words: atherosclerosis, carotid intima-media thickness, depression, psychosomatic.

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Since the mid-1980s, depression has been seen to play an important role in a behavioral pathogenesis of coronary heart disease (CHD) (1), even so that in 1999 Hemingway and Marmot named depression one of the four most evident behavioral risk factors of CHD (2). They concluded that in an aetiology and prognosis of CHD, from several behavioral risk factors depression and anxiety, hostility, work stress, and social support have been given the most stable and established roles by previous prospective studies (2). Since then, conflicting findings have increased (1,3,4) questioning at least a general pathogenic role of depression, i.e., a suggestion that depression plays an equal role in clinical and in healthy populations, as well as in different stages of CHD process being correlated both with preclinical stages like atherosclerosis and a progression and development of a diagnosed CHD.

Considerable evidence suggests that depression is highly prevalent in cardiac patients (5,6). One in five patients with CHD is depressed, which is at least 3 times greater than in the general population (6). However, a role of depression in subclinical stages of CHD in asymptomatic, healthy samples is less clear. Findings have been especially inconsistent regarding the thickness of the common carotid artery intima-media complex (IMT), which is widely used as a surrogate marker of carotid atherosclerosis (7,8). Both positive relationships (9–12) and null findings (13–17) have been documented. With few exceptions (18), the general pattern of findings has been that depressive symptoms are positively associated with increased IMT in people over the age of 50 (9,10,19–21); whereas no association was found for younger participants (22,23) or a combination of younger and older people (13,14). Moreover, the majority of positive findings have exclusively relied on an assessment of depressive symptoms at a single time point. Given that the relationship between depression and carotid IMT is not static (14), examining the chronic or recurrent depression in relation to IMT might help to reduce inconsistencies in the literature. In addition, in those studies, variations of study design, ultrasound protocols, definition of depression, and age of

participants may account for discrepancies in findings. Therefore, following the same participants in the same frame of reference would be needed to decrease the abovementioned potential sources for inconsistent findings in the existing literature. This study was taken with that purpose.

This study has several aims. First, we examine whether depressive symptoms from several follow-up studies are recurrently associated with carotid IMT in initially healthy and asymptomatic individuals. We have previously found a cross-sectional association between depressive symptoms and carotid IMT but only in men (18). Now we ask whether these results can be repeated in the same participants six years later. If our previous findings maintain, an association should become stronger along with the aging of the sample. Second, we investigate whether a cumulative loading of depressive symptoms from three measurement points (i.e., an accumulative depression index) is linked to carotid IMT. Finally, we explore whether a role of depressive symptoms varies at different risk levels of carotid IMT and in IMT progression over two time points. Those issues were neither examined in our previous study nor taken into account systematically in any previous studies.

Methods

Study population

The participants came from the Cardiovascular Risk in Young Finns Study (CRYFS), a population-based follow-up study assessing cardiovascular risks from childhood into adulthood. The original sample ($N = 3,596$, collected in 1980) included randomly selected Finnish children and adolescents from six different age cohorts from 3 to 18 years. The design of the study and the sample selection have been described in detail elsewhere (24). Participants twelve years of age and older gave informed consent, and the parents gave consent for younger participants. The study was approved by local ethics committees and conducted in accordance with the Helsinki declaration.

Procedure

The current study comprised the baseline examination in 1980 and follow-up examinations in 1992, 1997, 2001 and 2007. At baseline, clinical measurements of children/adolescent were conducted by trained staff who obtained measures of blood pressure, weight and height, and also drew venous blood samples. In the 1992, 1997, and 2001 follow-up studies, participants self-reported their depressive symptoms. In the 2001 and 2007 follow-up studies, participants' (30-45 years old in 2007) carotid IMT and cardiovascular risk factors were assessed (along with other biomedical measures not relevant for the current study). Participants with a diagnosed or self-reported diabetes or self-reported CHD ($n = 48$) were excluded from the sample. Participants were also excluded if they had not answered at least 70% of the depression items each year. There were 2303, 2079, and 2072 participants who had data for depressive symptoms in 1992, 1997, or 2001, respectively. There were 1302 participants who had data for depressive symptoms in all three measurements and 996 of these had also complete data on carotid IMT and risk factors in 2007, which formed the analytic sample of the current study. Compared with the eligible sample at the baseline of the CRYFS, the participants in the present study were more often female (64.7% vs. 45.7%, $\chi^2(1) = 103.15, p < 0.001$). Differences in other childhood/adolescence baseline characteristics were minimal and statistically nonsignificant (all $ps > 0.30$).

Measures

Depressive symptoms. Depressive symptoms were assessed using a modified version of the Beck Depression Inventory (mBDI). The original version of the BDI (25) offers 4 alternative statements of 21 items ranging from minimal to severe symptoms of depression (e.g., (0) "I do not feel sad", (1) "I feel sad", (2) "I am sad all the time and I cannot snap out of it", (3) "I am so sad or unhappy that I cannot stand it"). In the present study, the participants were asked to rate the second mildest descriptions of the original 21 items (e.g.,

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“I often feel sad”) on a five-point scale ranging from totally disagree (1) to totally agree (5). Originally, these second mildest items were selected because they were suggested to measure depressive symptoms more accurately among the normal population than corresponding clinical scales (26). Previous research supports this assumption (27,28). It has been reported that the modified version of BDI is highly correlated with original BDI-II ($r = .77$) (27). Scale reliability of the mBDI was 0.89 in 1992, 0.91 in 1997, and 0.92 in 2001. The mean score of all the 21 items formed the general depression index each year. To capture the accumulative effect of depressive symptoms in the general population, these three depressive indexes were summed together. The accumulative depression index was used as a continuous variable in all main analyses (ranged 3.10-11.46) in order not to lose any information by categorization. The sensitivity analyses were conducted using accumulative depression index as a dichotomous variable (i.e., a multiple depressive symptoms group and a fewer depressive symptoms group). Three cutoff points were applied for accumulative depression index: participants in highest 10% of the sample distribution, in highest 20%, and using median split.

Carotid IMT. Ultrasound studies in the present study were performed in 2001 and 2007 using Sequoia 512 ultrasound mainframes with 13.0-MHz linear array transducers. The left carotid artery was scanned by ultrasound technicians following a standardized protocol (29). In brief, a magnified image was recorded of the angle showing the greatest distance between the lumen-intima interface and the media-adventitia interface. A moving scan (duration 5 seconds) that included the beginning of the carotid bifurcation and the common carotid artery was recorded and stored in digital format on optical discs for subsequent off-line analysis. The digitally stored scans were manually analyzed by a single reader who was blinded to subjects' details. The analyses were performed using ultrasound calipers. From the 5-second clip image, the best quality end-diastolic frame was selected (incident with the R-wave on a continuously recorded electrocardiogram). From this image, at least four

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measurements of the common carotid wall were taken approximately 10 mm proximal to the bifurcation in order to derive mean carotid IMT. A 6.4% between-visit coefficient and a 5.2% between-observer coefficient of variation in the IMT measurements have been reported (29). Six-year change in carotid IMT was calculated as mean carotid IMT from 2007 minus mean carotid IMT from 2001. In agreement with prior research (30), we controlled for baseline carotid IMT (from 2001) in all analyses where the outcome variable was carotid IMT progression. To capture the severe thickening of a carotid wall, carotid IMT was divided into quartiles based on the population distribution (31). High level of carotid wall thickening was defined by assigning a point to the top 25% of the participants and 0 to all other participants.

Cardiovascular risk factors. The risk variables measured in childhood (in 1980) included low-density lipoprotein (LDL) cholesterol, body mass index (BMI), and systolic blood pressure. The risk factors measured in adulthood (2007) were LDL cholesterol, BMI, systolic blood pressure, and smoking. These risk factors have been previously shown to predict adult common carotid artery IMT in the same data set (29). Smoking status was assessed by a questionnaire, and those smoking on a daily basis were classified as smokers. BMI was calculated as weight in kilograms divided by the square of their height in meters. Height was measured with a wall-stationed stadiometer and weight with digital scales. All measurements of lipid levels were performed in duplicate in the same laboratory. Standardized enzymatic methods were used for measuring levels of serum total cholesterol, triglycerides, and high-density lipoprotein cholesterol. The LDL cholesterol concentration was calculated by the Friedewald formula (32). Blood pressure was measured with a standard mercury sphygmomanometer in 1980 and with a random zero sphygmomanometer in 2007. Details of the methods have been reported elsewhere (29).

Statistical analyses

Main analyses. Linear regression analyses were used to examine the relationships between accumulative depression index and carotid IMT. Interactions between sex and depressive symptoms, as well as age and depressive symptoms on carotid IMT were analyzed, but both appeared nonsignificant. Thus, these interactions were dropped from further analyses. Two models were constructed: in Model 1, only sex and age were controlled for; in Model 2, sex, age, and the cardiovascular risk factors from childhood and adulthood were adjusted for. All analyses were first performed with carotid IMT in 2007 as the dependent variable and then with IMT progression over 6 years. In addition, logistic regression analyses were used to test the relationship between the accumulative depression index and the severe thickening of a carotid wall. All analyses were also repeated separately for men and women, as well as for older (aged 39-45 years in 2007) and younger (30-36 years old in 2007) age groups. Finally, sensitivity analyses were conducted to examine whether high levels of depressive symptoms (as indicated using three different cutoff points, such as participants in top 10%, top 20%, and based on median split) contributed to the progression of atherosclerosis.

We also examined whether depressive symptoms from the 1992, 1997, 2001, and 2007 follow-ups were associated with carotid IMT from 2007 separately for men and women. Following the same procedure as previously applied (18), several regression models were tested. First, carotid IMT was regressed on age and depressive symptoms from 1992, 1997, 2001, and 2007 in separate models. Second, age and depressive symptoms from 1992, 1997, 2001, and 2007 were entered as independent variables into the model simultaneously. Finally, the cardiovascular risk factors from 1980 and 2007 along with depressive symptoms from four time points were entered into the fully-adjusted regression model. We also repeated the analyses using the dichotomous depression variables from each year. In order to be consistent with our previous findings (18), we classified participants with the mean depression score in

the highest 10% into the multiple depression group and others into a fewer depression group in those analyses.

Supplementary analyses. We also conducted additional analyses to test whether the absence of the association between depressive symptoms and IMT may be explained by moderating effect of cardiovascular risk factors, which were associated with higher IMT. Three separate linear regression models were applied first to test the interactions between accumulative depression index and adult BMI, as well as between accumulative depression index and systolic blood pressure from childhood and adulthood on carotid IMT without any adjustments; next adjusted for age and sex; and finally conducted separately for men and women.

Multiple imputation by chained equations was done in STATA 13.1 (33) to estimate missing values for participants with missing data in depressive symptoms and cardiovascular risk factors. We calculated the main statistical analyses using the pooled estimates of 50 imputed data sets ($n = 2,160$).

All statistical analyses were calculated in STATA version 13.1.

Results

Table 1 shows the characteristics of the study participants. There were statistically significant sex differences in adults' low-density lipoprotein cholesterol, BMI, systolic blood pressure, depressive symptoms, and carotid IMT (all $ps < 0.001$). Women were more depressed on average compared to men (6.42 vs. 5.94, $p < 0.001$). In contrast, the LDL cholesterol, BMI, and systolic blood pressure were significantly higher in men. To continue, men also had higher carotid IMT than women in 2007 (0.63 vs. 0.61, $p < 0.001$). The data about IMT progression was available for 915 participants. The bivariate correlation between two measurements of carotid IMT (from 2001 and 2007) was $r = 0.61$, $p < 0.001$. The IMT progression variable was normally distributed for both men and women with average scores

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0.05 mm ($SD = 0.09$) and 0.04 mm ($SD = 0.08$), respectively. The measurement error in the IMT assessments was at least of similar size or even larger than the standard deviation of IMT progression. Thus, the IMT progression assessment was diluted by measurement error which makes finding significant associations quite unlikely. Despite this, IMT progression was analyzed to examine all possible associations.

Table 2 presents the bivariate correlations between depressive symptoms and cardiovascular risk factors. In men, only higher BMI in adulthood was related to accumulation of depressive symptoms. In women, both higher BMI and smoking in adulthood were associated with higher depressive symptoms. Neither carotid IMT nor IMT progression was directly related to accumulative depressive symptoms in men or women.

No statistically significant associations were found between the accumulative depression index and either carotid IMT or progression of carotid IMT over six years (Table 3). Correspondingly, the logistic regression analyses revealed no significant associations between accumulative depression index and the higher level of carotid IMT (findings not shown). The association was not significant before or after controlling for various cardiovascular risk factors (BMI, systolic blood pressure, LDL-cholesterol, and smoking in childhood and adulthood). Older age and male sex were robustly associated with higher carotid IMT in all models (all $ps < 0.001$). Higher childhood systolic blood pressure and increased BMI in adulthood were also related to higher level of carotid IMT (all $ps < 0.01$). The results were the same when we additionally controlled for adult waist circumference in order to take into account the participants' gaining body fat. The findings also remained intact when accumulative depression index was used in the sensitivity analyses as a dichotomous variable (multiple symptoms depressive group was coded as highest 10%, 20%, and 50% of the sample). All variations of these primary analyses also failed to yield meaningful associations. No significant results were found when the analyses were conducted separately

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for men and women (Supplementary Table 1) or for older and younger age groups (Supplementary Table 2). Moreover, when the initially excluded participants ($n = 48$) who had a diagnosed or self-reported diabetes or self-reported CHD were included in the sample, no significant differences were observed. Finally, the analyses with the imputed data also failed to provide significant associations between depressive symptoms and carotid IMT, as well as IMT progression (Supplementary Table 3) and the higher level of carotid IMT (data not shown).

We also examined the link between depressive symptoms from 1992, 1997, 2001, and 2007 with carotid IMT separately for men and women. The relation between continuous depressive symptoms scores from these years and carotid IMT were not statistically significant in all models either for men or women. The high level of depressive symptoms (highest 10%) in 1997 and 2001 were associated with carotid IMT only in men when depressive symptoms from four follow-ups were entered into the model simultaneously (depressive symptoms in 1997: unstandardized $B = -0.07$, $p = 0.016$; depressive symptoms in 2001: unstandardized $B = 0.08$, $p = 0.003$). The adjustment for additional cardiovascular risk variables did not substantially alter this association (see Supplementary Table 4). The analyses with the imputed data, however, revealed no statistically significant associations between both continuous and dichotomous depressive symptoms scores and carotid IMT in any models either for men or women (Supplementary Table 5).

Finally, no significant interactions between depressive symptoms and cardiovascular risk factors (i.e., BMI and systolic blood pressure) on carotid IMT were found (all $ps > 0.15$). The findings with the imputed data were similar to those in the complete data.

Discussion

Findings from this population-based cohort study do not provide an evidence for an association between depressive symptoms and carotid IMT in healthy, asymptomatic

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individuals. Associations were nonsignificant before and after adjusting for traditional CHD risk factors in childhood and adulthood. Neither linear relationships nor the relationships between extremely high levels of accumulative depressive index and carotid IMT were found. Cumulative score of depressive symptoms also failed to explain IMT progression over a follow-up of 6 years. Several variations of the analyses (i.e., separation of men and women, multiple imputation, and covariate removal) were not able to identify a reason for the lack of expected results. This indicates that among healthy people under the age of fifty depressive symptoms may not play any significant role in a pathogenesis of CHD.

Prior population-based studies have investigated the association between depression and atherosclerosis, although evidence is controversial: some studies found the relationship significant (10,19,34), while others did not (13,16,35). Overall, the systematic methodological differences, such as different sample size, prospective or cross-sectional study designs, and the way depression and carotid IMT were measured do not seem to account for the absence or presence of a significant relationship between depression and atherosclerosis. In addition, we were not able to replicate our previous findings (18) in older age cohorts and in other study waves. Thus, we have to include our own positive result to the list of “random findings” as well.

To the best of our knowledge, no previous study has systematically examined all possible variants of an association between depressive symptoms and atherosclerosis, i.e., linear associations, associations in the extremes and in different sex groups, using the IMT progression variable over 6 years, and cumulative score for depressive symptoms over a follow-up period of 9 years. Although no evidence was found in our study, the findings cannot falsify the role of depression in a pathogenesis of CHD. A recent review suggests that depression is a non-causal risk marker for CHD, and that causality cannot be established (36). According to this view, depression co-varies with some mechanisms leading to CHD but is

not causally related to it. Therefore, it is possible that depression plays a role in the pathogenesis of CHD through other parameters (e.g., behavioral or biological factors) by making depressed patients more vulnerable to other cardiac risks (1). For example, depression is associated with higher rates of harmful lifestyle habits, including unhealthy diet, reduced exercise, and smoking (6). With respect to biological mechanisms, some evidence suggests that depression is linked to inflammatory process (37), altered hypothalamic pituitary adrenal hormones (38), autonomic nervous system dysregulations (39), and platelet dysfunction (40), all of which are implicated in the pathogenesis of CHD. Moreover, time dynamics should be also taken into account. Those individuals who were depressed early in life may be a selected group who would have developed especially unhealthy lifestyles, which in turn would increase their IMT. However, in this case the association between depression and IMT should be attenuated if health behaviors were taken into account. This was not the case in our previous study that found association between depression and IMT in men even though the health behaviors were adjusted for (18). It should be noted that lifestyle may also have a stronger impact with increasing age (41), whereas depression may play less important role (42).

To continue, we should not exclude a role of depression for atherosclerosis in the certain context (i.e., the effect of age). The considerable amount of studies have found an association between depression and atherosclerosis in older populations (50 years of age and older) (9,10,12,19–21,43). Although there was no relation between depressive symptoms and carotid IMT in older participants (aged 39-45 years) in this study, it is possible that atherosclerosis may be detectable relatively late in life. This may be a reason why studies with younger participants (age 24-52) have not found an association (22,23). Finally, different measurements of atherosclerosis may partly account for inconsistent findings in the literature. Although carotid IMT is often considered as a surrogate marker of atherosclerosis, some

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evidence has suggested that carotid IMT reflects an adaptive response of the vessel wall to changes in shear stress, lumen diameter, tensile stress, and pressure instead of an atherosclerotic thickening (44). Some studies have shown that depression is related to plaque (11,23) or coronary artery calcification (12), which are considered as more reliable predictors of the atherosclerotic process than IMT (23,45).

Strengths and Limitations

Strengths of this study involve its populations-based sample, long follow-up period over 27 years, longitudinal design with several measurements of depressive symptoms and IMT, and the possibility to adjust for childhood cardiovascular risk factors, thereby eliminating the confounding influence of baseline health. The accumulative depression index based on three time points over 10 years ascertained to capture chronic or recurrent depressive symptoms better than a measurement from a single point in time.

In interpreting these results, several limitations should be taken into account. As with most longstanding studies, attrition in this follow-up study was considerable. To deal with the possibility that selective drop-out would have biased our findings, we conducted analyses using multiply imputed data, and the results were similar in most cases to those in the original data. Furthermore, we were not able to define a clinically significant cutoff point for the high level of depressive symptoms; therefore, we conducted several sensitivity analyses using different cutoff points to detect any differences in the findings. Moreover, carotid IMT was not measured at the baseline, therefore it is possible that there are common pathophysiological processes behind the association between depressive symptoms and increased IMT. Finally, the sample was mainly White Caucasian, which limits generalizability of our findings to ethnically more diverse populations.

Conclusions

In summary, the findings of this population-based study do not indicate any direct association between depressive symptoms and atherosclerosis in asymptomatic, young adults. This study, however, do not completely question a role of depression in a pathogenesis of CHD, as it may co-vary with some mechanisms leading to CHD but is not causally related to it.

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Disclosure of potential conflicts of interests

The authors declare that they have no conflict of interest.

Research involving Human Participants and/or Animals

Ethical approval: “All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.”

Informed consent

“Informed consent was obtained from all individual participants included in the study; in addition, parents’ consent was requested for participants less than 12 years of age in 1980.”

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Table 1. Characteristics of the study participants (n = 996)

	Men (n = 352)		Women (n = 644)		p-value
	Mean (SD)	Range	Mean (SD)	Range	
Age in 1980, years	10.2 (4.98)	3-18	10.8 (5.04)	3-18	0.106
<i>Childhood risk factors</i>					
LDL-cholesterol, mmol/l	3.3 (0.71)	1.09-6	3.4 (0.76)	1.62-7.55	0.079
Body mass index, kg/m ²	17.6 (2.95)	9.2-36.02	17.8 (2.83)	12.79-28.33	0.286
Systolic blood pressure, mm Hg	112.9 (12.51)	78-164.67	111.8 (11.2)	68-140.67	0.175
<i>Adulthood risk factors</i>					
LDL-cholesterol, mmol/l	3.3 (0.83)	0.85-6.56	2.9 (0.72)	0.75-5.47	0.001
Body mass index, kg/m ²	26.3 (3.95)	17.54-45.89	25.2 (4.58)	16.56-47.33	0.001
Systolic blood pressure, mm Hg	125.2 (12.21)	97-168.67	116.4 (13.28)	88-162.67	0.001
Daily smokers (%)	16.8%		13.98%		0.239
Carotid IMT, mm	0.63 (0.11)	0.4-1.08	0.61 (0.09)	0.41-1.04	0.001
IMT progression, mm	0.05 (0.09)	-0.24-0.42	0.04 (0.08)	-0.20-0.29	0.069
Accumulative depression index	5.94 (1.57)	3.10-11.29	6.42 (1.61)	3.24-11.46	0.001

Note. LDL-cholesterol = low-density lipoprotein cholesterol, IMT = intima-media thickness

Table 2. Correlation coefficients between childhood and adulthood risk factors and accumulative depression index

	Accumulative depression index		
	Complete cases (<i>n</i> = 996)	Men (<i>n</i> = 352)	Women (<i>n</i> = 644)
Age in 1980, years	-0.02	-0.00	-0.04
<i>Childhood risk factors</i>			
LDL-cholesterol, mmol/l	-0.1	-0.00	-0.03
Body mass index, kg/m ²	0.00	0.04	-0.03
Systolic blood pressure, mm Hg	-0.04	-0.04	-0.04
<i>Adulthood risk factors</i>			
LDL-cholesterol, mmol/l	-0.04	-0.2	-0.01
Body mass index, kg/m ²	0.10**	0.17**	0.10*
Systolic blood pressure, mm Hg	-0.02	0.04	0.02
Daily smokers (%)	0.07**	0.05	0.09*
Carotid IMT, mm	-0.01	0.01	0.01
IMT progression, mm	0.05	0.05	0.06

Note. ****p* < .001, ***p* < .01, **p* < .05

Table 3. Unstandardized regression coefficients for accumulative depression index predicting carotid IMT and IMT progression, men and women combined

Complete cases	Carotid IMT		Carotid IMT progression†	
	B (SE)	95% CI	B (SE)	95% CI
Model 1				
Age, years	0.007 (0.001)***	0.006, 0.008	0.004 (0.001)***	0.003, 0.005
Male sex	0.028 (0.006)***	0.016, 0.039	0.002 (0.005)***	0.009, 0.029
Accumulative depression index	0.001 (0.002)	-0.002, 0.005	0.002 (0.002)	-0.001, 0.005
Model 2				
Age, years	0.005 (0.001)***	0.003, 0.007	0.003 (0.001)***	0.001, 0.004
Male sex	0.017 (0.006)**	0.005, 0.029	0.014 (0.005)*	0.003, 0.025
<i>Childhood risk factors</i>				
LDL-cholesterol, mmol/l	0.001 (0.004)	-0.008, 0.009	0.001 (0.004)	-0.007, 0.009
Body mass index, kg/m ²	0.002 (0.001)	-0.001, 0.005	0.001 (0.001)	-0.001, 0.004
Systolic blood pressure, mm Hg	0.001 (0.000)**	0.000, 0.001	0.001 (0.000)*	0.000, 0.001
<i>Adulthood risk factors</i>				

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LDL-cholesterol, mmol/l	0.003 (0.004)	-0.006, 0.011	0.005 (0.004)	-0.002, 0.013
Body mass index, kg/m ²	0.004 (0.001)***	0.002, 0.005	0.002 (0.001)***	0.001, 0.004
Systolic blood pressure, mm Hg	0.000 (0.000)	-0.000, 0.001	0.000 (0.000)	-0.000, 0.000
Daily smoking	0.005 (0.007)	-0.010, 0.020	-0.001 (0.007)	-0.014, 0.013
Accumulative depression index	-0.000 (0.002)	-0.003, 0.003	0.002 (0.002)	-0.001, 0.005

Note. *** $p < .001$, ** $p < .01$, * $p < .05$.

†Baseline carotid IMT (measured in 2001) was included into Model 1 and Model 2 as a control variable.