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Associations between life stress and subclinical cardiovascular disease are partly mediated by depressive and anxiety symptoms

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ABSTRACT

Background: Stress experienced during childhood or adulthood has been associated with cardiovascular disease (CVD), but it is not clear whether associations are already prevalent on a subclinical cardiovascular level. This study investigates associations between indicators of life stress and subclinical CVD, and whether these are mediated by depression and anxiety.
Methods: Subjects were 650 participants of the Netherlands Study of Depression and Anxiety, aged 20–66 years, with or without (27.5%) depressive and anxiety disorders. Life stress included childhood trauma, negative life events and recently experienced daily hassles or job strain. Subclinical CVD was measured as 1) carotid atherosclerosis (intima–media thickness and the presence of plaques) using B-mode ultrasonography, and 2) central arterial stiffness (heart rate normalized augmentation index) using calibrated radial applanation tonometry.
Results: Increased central arterial stiffness was shown in subjects who had experienced childhood trauma (per SD increase: $\beta = .07$; $p = .01$), or reported recently experienced daily hassles (per SD increase: $\beta = .06$; $p = .02$), negative life events (per SD increase: $\beta = .05$; $p = .03$), or job strain (high versus low: $\beta = .09$; $p = .01$). Associations between life stress and arterial stiffness appeared to be partly mediated by severity of depressive and anxiety symptoms. No significant associations were found for childhood life events, nor between indicators of life stress and carotid atherosclerosis.
Conclusions: Childhood trauma and recent life stress were associated with increased central arterial stiffness. This suggests that life stress – partly via depression and anxiety – might enhance the development and progression of CVD.

Introduction

Atherosclerosis and arterial stiffening are among the primary processes leading to cardiovascular disease (CVD) [1–3]. The development of these abnormalities already starts during childhood [4–6]. Many risk factors are known to be associated with the development of CVD, such as smoking and sedentary lifestyle. Stressful circumstances during childhood and adulthood may also play a role, although their precise contribution is unknown.

Previous studies have shown that childhood adversities (e.g., abuse, neglect, life events and household dysfunction) are associated with CVD in adulthood [7–12]. Childhood adversities were associated with self-reported ischemic heart disease in members of a health appraisal center [7,8]. Another study has found that coronary heart disease (CHD) patients more often reported severe illness of a family member and

Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease; NESDA, Netherlands Study of Depression and Anxiety disorders; LDL, low density lipoprotein; CIMT, carotid intima–media thickness; CIMTbif, bifurcation carotid intima–media thickness; AIx, augmentation index; AIx75, central augmentation index normalized for a heart rate of 75 beats per minute; MAP, mean arterial pressure; ATC, Anatomical Therapeutic Chemical; BMI, body mass index; MET, metabolic equivalent; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; CIDI, Composite International Diagnostic Interview; IDS, Inventory of Depressive Symptomatology; BAI, Beck Anxiety Inventory

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serious conflicts during their childhood as compared with controls [9]. Others found longitudinal evidence that subjects who had experienced adversities or traumas during childhood had increased risk of subsequent CVD [10,11]. Furthermore, evidence was found that women who experienced severe physical or sexual abuse as a child had higher risks of cardiovascular events in early adulthood; both retrospective and prospective cases were included [12].

Stressful circumstances during adulthood have also been associated with increased CVD risk [13,14]. Acute stressors can lead to sudden cardiac death [15] and feelings of tension and frustration have shown to induce myocardial infarction [16]. Furthermore, perceived mental stress [17] and posttraumatic stress disorder [18] are associated with risk of CHD. With respect to adulthood stress, job stress (i.e., strain: high demand, low control) in particular has been thoroughly investigated [19–26]. Chronic job strain after myocardial infarction is associated with increased risk of recurrent cardiovascular events [19]. Demanding work has been associated with the development of subclinical CVD, measured as carotid atherosclerosis [22] or arterial stiffness [23] in working-populations. However, the evidence is contradictory, since other studies found no associations in women while they did in man [21,24] and even negative associations in healthy male employees [20,25] between job stress and carotid atherosclerosis or arterial stiffness. Recently, a meta-analysis of published and unpublished data in over 197,000 participants has shown that job strain is associated with a small, but consistent, increased risk of CHD [26].

To date, most studies have focused on clinical CVD in association with a particular source of life stress (either during childhood or recent) [7–19]. Apart from a remarkable amount of data regarding the link between job stress and carotid atherosclerosis [20–22,25], arterial stiffness [23,24], or CHD [26], the associations between other sources of life stress and subclinical vascular health in one population have not been studied yet. Furthermore, childhood stress [10,27,28], and recent stress [29,30] have been associated with depression and anxiety, and in turn, these conditions have been associated with cardiovascular morbidity and mortality [31–33].

Aims of the study

In light of the above, the aims of this study are 1) to investigate the associations between (childhood and recent) life stress and indicators of subclinical cardiovascular disease, i.e., carotid atherosclerosis and central arterial stiffness and 2) to determine whether these associations are independent of or mediated by depression and anxiety.

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 [34]. 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 [35]. After the 2-year assessment, participants were asked for permission to be approached for additional cardiovascular measurements. Six hundred and fifty participants (response rate 66.9%) who lived in the area close to the location of measurements underwent additional cardiovascular measurements, see flow chart in Fig. 1. Median time between the NESDA 2-year assessment and cardiovascular assessment (carotid ultrasound and arterial stiffness measurements) was 68 days.

Of the eligible subjects, non-participants were younger (mean: 43.9 versus 46.5 years, $p = .001$), more likely to be female (71.8% versus 64.7%, $p = .03$) and more often had lifetime depressive and/or anxiety disorder (81.9% versus 72.7%, $p = .001$), as compared with participants. Participants and non-participants did not differ with respect to a history of CVD, smoking status, blood pressure and use of lipid-modifying or antihypertensive medication.

Life stress measures

Childhood stress

At the NESDA baseline assessment, a Dutch semi-structured interview was conducted in order to gather information on childhood life events and trauma, as was done previously [36]. Participants were asked if any of the following *negative life events* had happened before the age of 16 years: death of biological father or mother, divorce of parents, placement in care (children's home/juvenile prison/foster family). Since only 29 participants had experienced more than one life event, a dichotomous index was constructed.

Participants were also asked whether or not they had experienced any kind of *trauma* before the age of 16 years. Emotional neglect included lack of parental attention and support, or ignoring of one's problems and experiences. Psychological abuse was defined as verbal abuse, undeserved punishment, subordination to siblings and blackmailing. Physical abuse included being kicked, hit, beaten up, or otherwise. Sexual abuse was defined as being sexually approached against one's will, i.e., being touched or forced to touch someone in a sexual way. Participants were then asked whether the reported trauma had occurred once, sometimes, regularly, often or very often. Answers were categorized into 0 = absent,

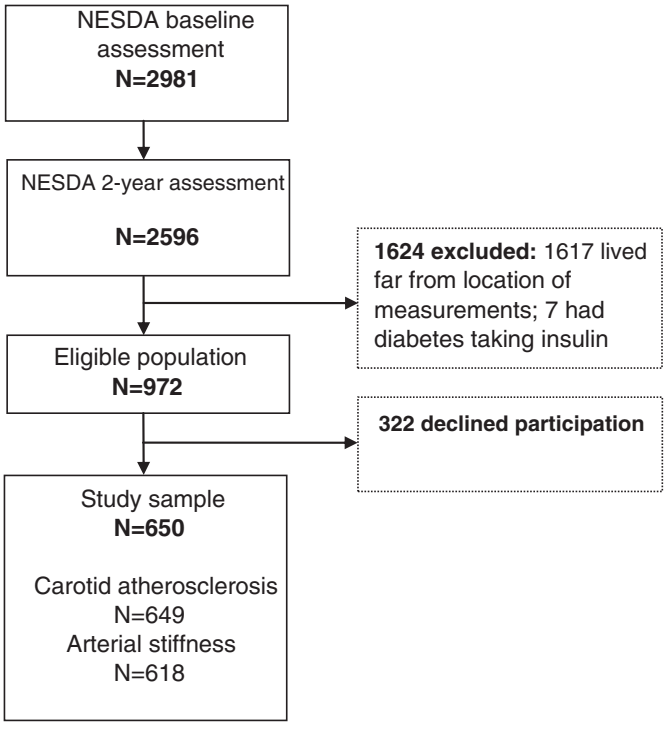

Fig. 1. Flow chart of study population. NESDA = Netherlands Study of Depression and Anxiety.

1 = once/sometimes and 2 = regular/often/very often. A childhood trauma index was constructed as the sum of the experienced number × the categorized frequency of childhood trauma (range: 0–8) [28].

Recent stress

At the NESDA 2-year assessment, the occurrence of *negative life events* since the baseline interview was assessed using the List of Threatening Events Questionnaire [37,38]. The 12 items ask whether over the last two years one had experienced events, such as serious illness and injury, death of a close friend or relative, unemployment, major financial loss or loss of important relationships (range: 0–12).

The experience of *daily hassles* was assessed using the 20-item Daily Hassles Questionnaire [39] (range: 0–60; with increasing number indicative of more hassles). This questionnaire includes minor events, such as lack of privacy, financial conflicts with friends or colleagues, not having enough leisure time, etc. The averaged total scores of the NESDA baseline and 2-year assessments were used in the analyses.

The presence of job strain was measured at the NESDA baseline interview, using a Dutch questionnaire [34] based on the Job Content Questionnaire. This questionnaire consists of 29 dichotomous items assessing among others job demands and decision latitude or job control. *Job strain* is based on the median split of job demands and decision latitude and is most widely used in research examining cardiovascular accompany of stress [19,21,23]. Participants perceiving high job strain (high demands combined with low decision latitude) were distinguished from the others, forming a dichotomous variable as done before [21,23,40].

Indicators of subclinical cardiovascular disease

Carotid atherosclerosis

Carotid measurements were performed by one single skilled and certified observer (AS), using an Acuson Aspen ultrasound instrument equipped with a near-field L7 linear array 5–10 MHz broadband transducer (Siemens, Erlangen, Germany), according to a previously described standardized and validated protocol [41]. High resolution B-mode images of the bilateral carotid artery were scanned with the subject in supine position, as described elsewhere [42]. In short, the distance between the leading edges of the far wall lumen–intima and media–adventitia interfaces was measured for all available segments. Bifurcation carotid intima–media thickness (CIMTbif) was used as outcome, since bifurcations in particular have been recognized as atherosclerosis progression-prone segments [43] and considering the relatively young age of this sample. Total CIMT might be not sensitive enough to detect differences, as we reported previously [42]. When data on one segment was missing, averaged thickness of the other site was used. Near and far walls of the left and right common carotid artery, carotid bifurcation and internal carotid artery were also evaluated for plaque presence (yes/no), defined as widening of the intimal and medial layers relative to adjacent segments, with the area of focal increased thickness ≥ 1.10 mm.

Central arterial stiffness

We determined the central pulse waveform and calculated the *central augmentation index* (late systolic pressure augmentation/central pulse pressure; in percentage) as a measure of arterial stiffness. Ascending aortic blood pressure waveform was generated, based on radial pressure waveforms including a generalized transfer function (2000 version 7, AtCor Medical, Sydney, Australia) and oscillometrically determined brachial pressures (Dinamap®PRO100, GE Medical Systems, Tampa, FL), as described elsewhere [44]. Because the central augmentation index (AIx) is inversely related to acute changes in heart rate [45], we here report the central augmentation index normalized for a heart rate of 75 beats per minute (AIx75).

Covariates

Analyses were adjusted for several covariates that have been linked with stress and/or cardiovascular risk and might confound associations. Socio-demographics included age, sex and education (years). 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 measurements was taken as systolic blood pressure. Mean arterial pressure (MAP) was calculated as (2 * diastolic pressure + systolic pressure) / 3, using all available brachial blood pressure readings. Use of antihypertensive medication was based on drug-container inspection and subsequent ATC coding [codes C02, C03, C07, C08 and C09]. Use of lipid-modifying medication was based on ATC code C10. LDL cholesterol (mmol/l) and glucose (mmol/l) were determined in blood samples that were taken after an overnight fasting period, transported to a laboratory within one hour and analyzed using standard laboratory techniques. 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). 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.

Lifestyle factors included body mass index (BMI), alcohol intake, smoking and physical activity. BMI was calculated as weight in kilograms divided by height in meters squared. Alcohol intake was based on number of alcoholic consumptions a week and categorized into less than 1, 1–14, and more than 14 drinks a week. Smoking status was reported as never, former, and current smoker. Physical activity was determined with the International Physical Activity Questionnaire [46] and expressed in MET-minutes (ratio of energy expenditure during activity compared to rest times the number of minutes performing the activity) per week. Height, weight and blood pressure were measured during the cardiovascular assessment, whereas other measures were taken at the NESDA 2-year assessment.

Potential mediators

We previously found that depression and anxiety were associated with higher central arterial stiffness [44]. In order to be able to examine whether associations for life stress are driven by or independent of psychopathology, severity of symptoms was considered in additional mediation analyses. Severity of symptoms was measured using the 30-item Inventory of Depressive Symptomatology (IDS) self-report version [47] and the 21-item Beck Anxiety Inventory (BAI) [48]. We computed a composite score of depression and anxiety symptom severity by averaging baseline (T), 1-year (T) and 2-year (T_2) data for both BAI and IDS, and adding up their z-scores.

Causal mediation analyses are based on the untestable sequential ignorability assumption, which implies that there are no unmeasured confounders [49]. We performed sensitivity analyses in order to examine the robustness of the indirect effects to the violation of sequential ignorability due to an unobserved confounder of the mediator and the outcome.

Statistical analyses

First, linear regression analyses were used to determine the cross-sectional association between childhood (negative events, trauma) and recent (negative life events, daily hassles, job strain) life stress and indicators of subclinical CVD (CIMT and arterial stiffness). Logistic regression analyses were used to examine the cross-sectional association between life stress indicators and carotid plaque presence. Analyses for job strain were conducted in a subpopulation of working subjects (N = 488). Adjustment included socio-demographics and indicators of cardiovascular health, i.e., blood

pressure (carotid atherosclerosis: systolic blood pressure; arterial stiffness: MAP), LDL cholesterol, use of antihypertensive and lipid-modifying medication. In an additional adjustment step, lifestyle factors, i.e., BMI, alcohol intake, smoking status and physical activity were included. In order to prevent overadjustment, we have decided not to include use of antidepressants among the covariates, since we previously found no straight-forward associations between the use of antidepressant medication and subclinical CVD in this sample [42,44]. Besides, to be sure that the different kinds of trauma included in the childhood trauma index are consistently associated with subclinical CVD, the individual βs for emotional neglect, psychological abuse, physical abuse and sexual abuse were determined in separate analyses.

In order to determine whether associations were different for men vs. women [9,11] and for controls vs. lifetime psychopathology cases, interaction terms sex * life stress and lifetime psychopathology * life stress were subsequently added to analyses (including socio-demographics and indicators of cardiovascular health). To investigate whether any significant association was driven by diseased cases, sensitivity analyses were conducted in which participants with CVD and/or diabetes, were excluded.

Second, in case of significant associations between life stress and subclinical CVD, potential mediation by depression and anxiety was investigated using Preacher and Hayes models [50]. This was done by testing significance of the indirect effect of the independent variable (IV) on the dependent variable (DV) through the mediator (M), quantified as the product of the effects of IV on M, *a*, and of M on DV, *b* (see Fig. 2). A bootstrapping approach was used in which a point estimate of the indirect effect was derived from the mean of 5000 estimates of *ab* and 95% confidence intervals were computed. The severity of depressive and anxiety symptoms was taken as psychopathology variable. Mediation analyses were adjusted for socio-demographics and indicators of cardiovascular health.

Mediation analyses were replicated using R version 3.1.2 with the R package mediation (4.4.3) for causal mediation analysis [49]. Significant indirect effects were then included in sensitivity analyses to examine their robustness to the violation of sequential ignorability. The sensitivity parameter is the correlation (ρ) between the error terms in the models for the mediator and the outcome. When the assumption of sequential ignorability is met, ρ is equal to zero; ρ being different from zero indicates departure from sequential ignorability. The results of the sensitivity analyses show how much the value of the indirect effect varies as a function of ρ.

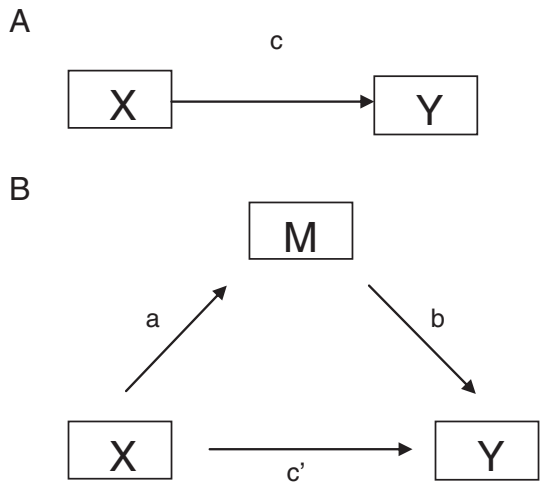

Fig. 2. Preacher and Hayes mediation model. Panel A: Illustration of a direct effect. *X* affects *Y*. Panel B: Illustration of a mediation design. *X* indirectly affects *Y* through *M*.

Results

Sample characteristics

Characteristics of the study sample (N = 650) are shown in Table 1. Sixty-five percent of the sample consisted of women and the mean age was 46.5 ± 12.1 years. Of all participants, 21.5% reported negative life events and 47.5% reported trauma during childhood. Mean scores for recent stress were 10.2 ± 7.0 for daily hassles and 1.7 ± 1.3 for negative life events; 24.6% of the working population experienced job strain. Twenty-seven and a half percent of the participants had no lifetime diagnosis of depressive or anxiety disorder, 43.9% had a remitted and 28.6% a last month diagnosis.

Table 1
Sample characteristics (n = 650)

	Mean (SD) or %
Demographics	
Sex, female	65.2
Age, years	46.5 (12.1)
Education, years	13.2 (3.3)
Health	
Systolic blood pressure, mm Hg	114 (15)
Mean arterial pressure, mm Hg	83 (11)
LDL cholesterol, mmol/l	2.9 (.9)
Use of antihypertensive medication	17.5
Use of lipid-modifying medication	7.4
Diabetes mellitus	4.2
Cardiovascular disease	6.2
Lifestyle	
Body mass index, kg/m^2	25.4 (4.6)
Physical activity, MET minutes/week	3838.1 (3121.5)
Smoking status	
Never	31.4
Former	38.1
Current	30.5
Alcohol intake, drinks/week	
<1	27.2
1–14	54.6
>14	18.2
Psychopathology	
Depressive and/or anxiety disorder	
Healthy controls	27.5
Remitted depression or anxiety	43.9
Last month depression or anxiety	28.6
IDS	16.7 (11.6)
BAI	9.2 (8.3)
IDS + BAI[a]	−.005 (1.9)
Life stress variables	
Childhood stress	
Negative life events	21.5
Trauma index	1.5 (2.0)
Trauma categories	
0	52.5
1–3	27.0
4–8	20.5
Recent stress	
Negative life events	1.7 (1.3)
Daily hassles	10.2 (7.0)
Job strain	24.6
Subclinical cardiovascular disease	
Bifurcation CIMT, mm	.75 (.21)
Plaque presence	14.6
AIx75, percentage	14.0 (14.8)

LDL = low density lipoprotein; MET = metabolic equivalent; IDS = Inventory of Depressive Symptomatology, mean over baseline (T), 1-year (T) and 2-year (T_2); BAI = Beck Anxiety Inventory, mean over baseline (T), 1-year (T) and 2-year (T_2); CIMT = carotid intima–media thickness; AIx75 = central augmentation index at heart rate 75; SD = standard deviation.

[a] Composite score of IDS and BAI z-scores.

Table 2
Associations between life stress and carotid atherosclerosis[a]

	Bifurcation CIMT (mm) N = 644			Plaque presence (yes/no) N = 649		
	β	p	SE	OR	95% CI	SE
Childhood stress						
Negative life events						
No	REF			REF		
Yes	−.02	.52	.01	.62	.33–1.19	.33
Trauma index, per SD increase						
	.01	.68	.01	1.07	.84–1.36	.13
Trauma, categories						
0	REF			REF		
1–3	−.01	.82	.01	.86	.46–1.60	.32
4–8	.01	.81	.02	1.14	.61–2.12	.32
Emotional neglect						
	−.01	.75	.01	.99	.76–1.29	.14
Psychological neglect						
	.01	.63	.01	1.05	.78–1.42	.15
Physical abuse						
	.03	.23	.01	1.45	.92–2.29	.23
Sexual abuse						
	.01	.64	.01	1.10	.68–1.77	.25
Recent stress						
Negative life events, per SD increase						
	.002	.96	.01	1.01	.79–1.29	.12
Daily hassles, per SD increase						
	.01	.68	.01	1.14	.90–1.44	.12
Job strain						
No	REF			REF		
Yes	.004	.92	.02	1.30	.58–2.90	.41

[a] Based on linear (CIMT) and logistic (plaque) regression analyses. CIMT = carotid intima–media thickness; SD = standard deviation; SE = standard error. SD trauma = 2.0; SD recent negative life events = 1.3; SD daily hassles = 7.0. Adjusted for age, sex, education, systolic blood pressure, LDL cholesterol, use of antihypertensive medication and use of lipid-modifying medication.

Table 3
Associations between life stress and arterial central stiffness[a]

	AIx75 N = 618		
	β	p	SE
Childhood stress			
Negative life events			
No	REF		
Yes	.04	.13	.90
Trauma index, per SD increase			
	.07	.01	.38
Trauma, categories			
0	REF		
1–3	.004	.87	.87
4–8	.07	.01	.98
Emotional neglect			
	.06	.03	.40
Psychological neglect			
	.05	.04	.48
Physical abuse			
	.06	.02	.74
Sexual abuse			
	.03	.32	.73
Recent stress			
Negative life events, per SD increase			
	.05	.03	.37
Daily hassles, per SD increase			
	.06	.02	.38
Job strain			
No	REF		
Yes	.09	.01	1.05

[a] Based on linear regression analyses. AIx75 = central augmentation index at heart rate 75; SD = standard deviation; SE = standard error. SD trauma = 2.0; SD recent negative life events = 1.3; SD daily hassles = 7.0. Adjusted for age, sex, education, mean arterial pressure, LDL cholesterol, use of antihypertensive medication and use of lipid-modifying medication.

Life stress and subclinical CVD

Table 2 shows associations between life stress and carotid atherosclerosis. No significant associations were found between either childhood or recent stressors and CIMTbif or plaque presence. This did not change after further adjustment for lifestyle factors. In line with this, none of the separate traumas was significantly associated with CIMTbif or plaque presence.

Table 3 shows associations between life stress and arterial stiffness. People who had experienced childhood trauma showed significantly increased AIx75 and this effect was especially driven by those with the highest trauma score ($\beta = 0.07$; $p = 0.01$). Apart from sexual abuse, all separate childhood traumas showed significant associations with increased AIx75. No significant association was found between childhood negative life events and arterial stiffness. Recent negative life events, daily hassles and job strain all showed significant associations with AIx75, which remained significant after additional correction for lifestyle factors.

Mediation by psychopathology

Table 4 shows the results of mediation models in which life stress as well as severity of depressive and anxiety symptoms were entered with arterial stiffness as the dependent variable. The significant indirect effects indicate that severity of depressive and anxiety symptoms partly mediated the association between life stressors (i.e., childhood trauma, daily hassles, recent negative life events, job strain) and central arterial stiffness. All direct effects were non-significant, except for job strain of which the direct effect was still significant and considerably greater than the indirect effect.

Mediation analyses were replicated using R and showed the same results as the Preacher and Hayes models. Sensitivity analyses to examine the robustness of the indirect effects to the violation of sequential ignorability indicate (results not shown) that the indirect effect equals zero, when ρ becomes >.01, for childhood trauma, daily hassles and job strain. The indirect effect between recent negative life events and arterial stiffness equals zero when ρ becomes >.02, which indicates that this indirect effect is more robust than the others to the sequential ignorability violation.

Additional analyses

Interaction analyses with sex and lifetime psychopathology were performed to determine whether associations between life stress and subclinical CVD were different for men vs. women and for controls vs. lifetime psychopathology cases. Interaction terms for both sex * life stress and lifetime psychopathology * life stress that were added successively to the analyses were not significant (data not shown). Sensitivity analyses in a subsample of participants free of CVD and diabetes (N = 563) to determine whether any significant association was driven by diseased cases showed similar results. All prior significant associations between life stress and arterial stiffness remained significant. This indicates that observed associations were not driven by those with CVD or diabetes.

Discussion

Childhood trauma, daily hassles, job strain and recent negative life events were associated with increased central arterial stiffness. Significant associations between life stress and arterial stiffness were partly mediated by depression and anxiety. Furthermore, no associations were found between life stress and carotid atherosclerosis, nor between childhood life events and arterial stiffness.

In our sample, life stress – experienced either during childhood or recently – is associated with increased central arterial stiffness. To the best of our knowledge, the relation between childhood stress and arterial stiffness has never been reported before. Yet, our observations fit in results of previous studies that found positive associations between number of childhood adversities and self-reported ischemic heart disease [7,8], the study that found women to have higher risks of cardiovascular events as a result of severe physical and sexual abuse [12] and longitudinal evidence that subjects had increased risk of subsequent CVD [10,11]. One of those studies [11] used a measure for childhood trauma (abuse and neglect) that is comparable to our trauma sum score, while another study used physical abuse and sexual abuse separately [12] and the others combined both trauma and life events as childhood adversities in their outcome measure [7,8,11]. Increased arterial stiffness was found in people who more frequently experienced trauma during childhood. This confirms results of previous studies, that especially in case of a high sum score for childhood adversities associations with self-reported ischemic heart disease were significant [7,8]. Our finding that job stress was associated with increased arterial stiffness is in line with one study in which demanding work was

Table 4
Summary of Preacher and Hayes mediator model analyses for associations between life stress and arterial stiffness (5000 bootstraps)

Independent variable (IV)	Mediating variable (M)	Dependent variable (DV)	Effect of IV on M (a)	Effect of M on DV (b)	Direct effect (c^1)	Indirect effect (a × b)	95% CI	Total effect (c)
Childhood stress								
Negative life events	IDS + BAI[b]	AIx75	.32	.81***	1.12	.26	(−.02–.70)	1.38
Trauma index, per SD increase	IDS + BAI[b]	AIx75	.68***	.74***	.48	.50[a]	(.21–.83)	.98**
Recent stress								
Negative life events, per SD increase	IDS + BAI[b]	AIx75	.42***	.78***	.46	.32[a]	(.15–.57)	.79*
Daily hassles, per SD increase	IDS + BAI[b]	AIx75	1.35***	.98***	−.41	1.33[a]	(.60–2.06)	.92*
Job strain	IDS + BAI[b]	AIx75	.70***	.58*	2.54*	.40[a]	(.07–.93)	2.94**

AIx75 = central augmentation index at heart rate 75; SD = standard deviation. As covariates included in the mediator model: age, sex, education, mean arterial pressure. LDL cholesterol, use of antihypertensive mediation and use of lipid-modifying medication.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.
[a] Significant, based on 95% CI.
[b] Composite score of IDS and BAI z-scores.\

found to be positively associated with stiffness [23]. Also meta-analytic data have demonstrated that job strain predicts higher CHD incidence [26]. In contrast with these findings, another study has shown negative associations between job strain and arterial stiffness in young (24–39 years) Japanese men [24]. Next to an association between job stress and arterial stiffness, our study gave information on the relation between other forms of recent stress and arterial stiffness. Whereas previous research on subclinical CVD was focused on job-related stress, we also found recent negative life events and daily hassles to be associated with arterial stiffness. These observations are concordant with a study showing that perceived mental stress is associated with CVD mortality [17]. The observed associations between life stress and arterial stiffness were not driven by those with current or previous CVD or diabetes, since associations remained significant after exclusion of these participants.

Unlike childhood trauma, the experience of childhood life events was not associated with any arterial stiffening. More than half of the experienced childhood life events was determined by parental divorce, which is in line with previous studies reporting no association between parental divorce [9,11] or marital discord [8] and CVD. Within the NESDA population, divergent findings between life events and trauma during childhood have been found earlier, as childhood trauma but not life events was associated with depressive and anxiety disorders [28].

A novel finding in our study is the observed significant association between life stress and arterial stiffness that appeared to be partly mediated by depression and anxiety. Our observation, indicating that severity of depressive and anxiety symptoms accounted for the association between childhood trauma and increased arterial stiffness is partly in line with previous evidence. One study has shown that correction for depressed affect reduced the strength of the relation between trauma and ischemic heart disease, but the association remained significant [8]. In another study, adjustment for depression along with other CVD risk factors weakened some of the associations between childhood adversities and CVD, although several associations remained significant [11]. Furthermore, adult risk factors known to be associated with early abuse, including depression, accounted for as much as 60% to 80% of the associations of severe abuse in childhood with CVD risk [12]. Our study underlines the important role severity of depressive and anxiety symptoms could play in the relation between life stress and cardiovascular damage (i.e., arterial stiffness).

Several mechanisms could play a role in the positive associations between life stress and arterial stiffness. Unhealthy lifestyle is one possibility, since life stress leads to unhealthy behaviors [51] that are known for their stiffness-enhancing effects [52]. However, after correction for lifestyle, significant associations between life stress indicators and arterial stiffness somewhat weakened, but remained significant. This is indicative of a role for lifestyle in the path between life stress and arterial stiffness, but it does not fully explain the associations. Most importantly, the role of depression and anxiety as potential mediating mechanism has been demonstrated. This might indicate that life stress leads to arterial stiffness through the development of depressive and anxiety disorders. A possible explanation for the strong direct effect between job strain and arterial stiffness, which is independent of lifestyle and psychopathology, is an altered autonomic tone with more sympathetic and less parasympathetic activity. This may lead to metabolic dysregulations in general [53] and accentuated inflammation of the arterial wall and as a consequence to the formation of thrombosis [54–56]. These findings are indirectly supported by the effects of job strain on heart rate variability [54] while reduced heart-rate variability is associated with subclinical inflammation [55].

We found no significant associations between either childhood or recent life stress and carotid atherosclerosis. This is consistent with previous research in this sample [42], in which no significant associations were found between depressive and anxiety disorders and carotid atherosclerosis. It has been demonstrated that subclinical CVD probably does not affect all arterial beds in a uniform and contemporaneous manner [57]. This may due to a differential composition of the vascular wall, i.e., so-called elastic (e.g., large central arteries such as the carotid artery) versus muscular arteries (e.g., femoral artery) as well as the location of the arteries in the body. To our knowledge, stress experienced during childhood and subclinical atherosclerosis has not been investigated before. Some studies, however, have found significant associations between work stress and carotid atherosclerosis in men [21,22,25].

Several limitations of the current study have to be considered. Because of the cross-sectional design, definitive conclusions about causality cannot be drawn with regard to the associations between life stress and arterial stiffness. Furthermore, although direct and indirect effects were still present after adjustment for various covariates, the mediation analyses might still comprise residual confounding. We therefore performed sensitivity analyses to assess the robustness of estimates of indirect (mediation) effects with respect to the influence of unmeasured confounders. Furthermore, the associations in the mediation model were assumed to be linear and not tested, while non-linear mediation would have required another approach [58]. Because of the high percentage of participants with current psychopathology, recollections of childhood stress may be less reliable or less valid [59,60]. Plaque prevalence was low (14.6%) in our relatively young sample, which probably resulted in a lack of power in multivariate testing. Additionally, central augmentation index, which is based on applanation tonometry and a transfer function is rather an indirect than a direct measure of aortic stiffness, however, its prognostic value has been demonstrated [2]. Strengths of this study are the availability of various indicators of life stress and the assessment of subclinical CVD performed using

different state-of-the-art techniques. Besides, this study is one of the first to use advanced mediation models in order to determine the role of psychopathology, more specifically the severity of depressive and anxiety symptoms, as a pathway linking life stress to markers of subclinical CVD.

In conclusion, this study shows that life stress may have negative effects on cardiovascular health by increasing arterial stiffness. This association between life stress and arterial stiffness was partly mediated by depression and anxiety. Since a substantial part of life stress is inevitable, prevention should merely focus on early identification and management of emotional distress. This hopefully will slow down the development of CVD. This approach, consisting of early identification and management of emotional distress, may not be easy to study prospectively in large cohorts. However, given the high global prevalence of both stressful life events and psychopathology, these studies are needed to unveil potential novel strategies to further prevent or delay the development of CVD.

Declaration of interest

Prof. Diamant had disclosed advisory board membership for Eli Lilly & Co., Merck Sharp & Dohme, Novo Nordisk; consultancy for Astra Zeneca/BMS, Eli Lilly & Co., Merck Sharp & Dohme, Novo Nordisk, Sanofi Aventis; being on the speaker's buro for Eli Lilly & Co., Merck Sharp & Dohme, Novo Nordisk; receiving research support from Amylin Pharmaceuticals Inc., Eli Lilly & Co., Merck Sharp & Dohme, Novartis, Novo Nordisk, Takeda. All other authors declare to have no financial or other conflicts of interest, both in general and in relation to this study.

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