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Post-trauma cardiovascular risk factors and subclinical atherosclerosis in young adults following the war in Bosnia and Herzegovina

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ABSTRACT

Background: Risk of cardiovascular disease (CVD) has been associated with stress from serving in a war, but it has not been established whether children who experience war-related stress are at increased CVD risk.

Objective: This study aimed to compare CVD risk factors in young adults according to whether they experienced traumatic events as children during the 1990–1995 war in Bosnia and Herzegovina, and whether those exposed to trauma have evidence of subclinical atherosclerosis.

Method: We examined 372 first-year medical students who were preschool children during the war (1990–1995) (average age 19.5 ± 1.7 years, 67% female) in 2007–2010. They completed the Semi-Structured Interview for Survivors of War. CVD risk factors and carotid intima-media thickness (CIMT) measurements were obtained and compared in individuals with and without trauma. We also examined whether increased CIMT was independently associated with trauma after adjustment for other risk factors.

Results: From multiple logistic regression, only elevated triglycerides (> 1.7 mmol/l) were associated with a 5.2 greater odds of having experienced trauma. The mean CIMT of subjects with trauma was greater than that of non-trauma-exposed subjects (0.53 mm vs 0.50 mm, $p = 0.07$). Moreover, trauma was independently associated with higher CIMT (difference = 0.036 mm, $p = 0.024$) after adjustment for CVD risk factors.

Conclusions: We show that most CVD risk factors are associated with post-war trauma in young adults, and, if present, such trauma is associated with higher triglycerides and higher levels of CIMT in multivariable analysis.

Factores de riesgo cardiovascular y aterosclerosis subclínica post-trauma en adultos jóvenes luego de la guerra en Bosnia y Herzegovina

Antecedentes: El riesgo de enfermedades cardiovasculares (ECV) ha sido asociado con el estrés del servicio en la guerra. No está establecido si los niños que han experimentado estrés relacionado a la guerra tienen un riesgo aumentado de ECV. Comparamos los factores de riesgo de ECV en adultos jóvenes, en función de si experimentaron eventos traumáticos en la niñez durante la guerra de 1990–1995 en Bosnia-Herzegovina, y si aquellos expuestos a trauma tienen evidencia de aterosclerosis subclínica.

Métodos: Examinamos a 372 estudiantes de medicina de primer año, quienes eran niños preescolares durante la guerra (1990–1995) (edad promedio 19.5±1.7 años, 67% mujeres) en 2007–2010. Completaron la Entrevista Semiestructurada para Sobrevivientes de Guerra. Se obtuvieron mediciones de factores de riesgo cardiovascular (ECV) y de Grosor Carotídeo de la Intima Media (CIMT por su sigla en inglés), se compararon en personas con y sin trauma y se examinó además si el incremento de CIMT se asociaba independientemente con trauma luego de ajustar por otros factores de riesgo.

Resultados: De la regresión logística múltiple, sólo la elevación de triglicéridos (> 1.7 mmol/L) se asoció a una probabilidad 5.2 veces mayor de tener trauma. La CIMT promedio de los sujetos con trauma fue mayor (0.53 mm vs 0.50 mm, $p=0.07$) que la de los sujetos no expuestos a trauma. Más aún, el trauma estaba independientemente asociado con mayor CIMT (diferencia=0.036 mm, $p=0.024$) luego del ajuste por otros factores de riesgo de ECV.

Conclusiones: Mostramos que la mayoría de los factores de riesgo de ECV estaban asociados con el trauma post-guerra en adultos jóvenes, pero si estaba presente, el trauma se asocia a mayores niveles de triglicéridos y de CIMT en los análisis multivariable.

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PALABRAS CLAVE

Enfermedad cardiovascular; factores de riesgo; trauma; niños

关键词

心血管疾病; 危险因素; 创伤; 儿童

HIGHLIGHTS

- Our investigation was to examine whether there are differences in cardiovascular risk factors and subclinical atherosclerosis in persons previously exposed compared to not exposed to trauma during the war in Bosnia and Herzegovina.
- We demonstrated that while traditional risk factors are not strongly related to the presence of post-war trauma in young adults, those with greater CIMT appear to have been more likely to have had been previously exposed to trauma.

波斯尼亚和黑塞哥维那战争后青年的创伤后心血管危险因素和亚临床动脉粥样硬化

背景：心血管疾病（CVD）的风险与战争服役中的应激有关。但还未确定的是，经历过与战争有关的应激的儿童的风险是否增加。我们根据被试在1990–1995年波斯尼亚-黑塞哥维那（Bosnia-Herzegovina）战争期间是否经历过童年创伤事件以及有创伤暴露的被试是否有亚临床动脉粥样硬化，来比较青年CVD危险因素。

方法：我们在2007年至2010年期间考察了372名一年级医学生（平均年龄 19.5 ± 1.7 岁，67%女性），他们在战争期间（1990–1995）还是学龄前儿童。他们完成了战争幸存者的半结构化面试。我们测量了心血管（CVD）危险因素和颈动脉内膜中层厚度（CIMT），并对有创伤和无创伤的人进行了比较。我们还考察了在控制其他风险因素后，增加的CIMT是否与创伤独立相关。

结果：多重逻辑回归分析显示，只有升高的甘油三酯（ > 1.7 mmol/L）与5.2%的创伤几率相关。创伤被试的平均CIMT比无创伤暴露被试更大（ 0.53mm vs 0.50mm , $p = 0.07$ ）。此外，在控制CVD风险因素后，创伤与较高的CIMT（差异= 0.036mm , $p = 0.024$ ）独立相关。

结论：我们发现大多数CVD风险因素与青年的战后创伤有关；如果有战后创伤，这种创伤与多变量分析中甘油三酯较高和CIMT水平较高有关。

1. Introduction

War and its consequences can be potent sources of stress. The war that occurred in Bosnia and Herzegovina in 1990–1995 negatively impacted people's lives for many years. Those most affected were people who observed deaths, suffered injury, or were forced from their homes, often in violent situations. This resulted in major traumatic events and subsequent psychological consequences causing adverse changes in the behaviour of the community (Gilbert et al., 2015; Vulic, Secerov, Tasic, & Burgic, 2012a). The definition of trauma requires actual or threatened death, serious injury, or sexual violence (American Psychiatric Association, 2013). How a person reacts to stress differs from individual to individual and frequently depends on their cognitive and affective characteristics and the extent to which defence mechanisms are present. Investigations in children and adolescents show both direct and indirect psychosocial effects resulting from a traumatic event, with some reports showing permanent negative effects in children which can make them more vulnerable than adults. Children who have gone through war have been shown to exhibit depression, post-traumatic stress disorder (PTSD), and difficulty responding to stressful situations, showing responses including anger and hostility (Kolaitis, 2017; Srinivasa Murthy, 2007; Williams, 2007).

Psychosocial stress can portend greater risk for future cardiovascular disease (CVD) and may be mediated by stress soliciting increases in catecholamines and corticosteroid levels, which, in turn, can promote higher blood pressure and atherosclerosis. Stress can also be associated with unhealthy behaviours such as smoking and alcohol abuse, which can also lead to CVD (Coughlin, 2011; McFarlane, 2010; Vulic et al., 2012a, 2012b; Wong, 2012).

Few studies have studied the relationship between negative psychological factors in youth and risk factors and the development of atherosclerosis later in

life. One study in Finland examined how negative psychosocial experiences in childhood may relate to atherosclerosis, evaluated from carotid intima-media thickness (CIMT) in adulthood (Hakulinen et al., 2016). Also, children experiencing trauma more often have adverse health outcomes in adulthood, such as heart disease, cancer, liver disease, obesity, hypertension, hypercholesterolaemia, chronic lung disease, and increased levels of inflammation (Gilbert et al., 2015).

We sought in this study to examine whether certain CVD risk factors are more common, as well as increased subclinical atherosclerosis as assessed by CIMT, in medical students who were exposed to trauma as children during the war in Bosnia and Herzegovina during 1990–1995. We hypothesize that such students previously exposed to trauma would have higher levels of CVD risk factors as well as higher values of CIMT, and that certain CVD risk factors and CIMT measurements would be independently associated with a higher odds of having had prior trauma.

2. Methods

2.1. Study sample

We examined 372 first-year medical students who were preschool children during the war (1990–1995) [average age 19.5 ± 1.7 years (mean \pm SD), 67% female] in 2007–2010.

2.2. Trauma questionnaire

Each respondent filled out the Semi-Structured Interview for Survivors of War (SISOW), a questionnaire to monitor post-traumatic predictors of CVD in young adults. The SISOW is modified from a previous version designed for survivors of torture, including a section on demographic characteristics. Demographics, trauma characteristics, and direct social impacts of war and

displacement on economic, social, family, occupational, and educational functioning were also assessed with the SISOW. The SISOW comprises an Exposure to War Stressors Scale (EWSS) which solicits information on 54 war-related stressors (e.g. experience of combat, torture, witnessing atrocities, internal or external displacement, and loss of close ones) as well as the extent of distress and control perceived from each event. Each of these stressors was rated by a Global Distress Rating (0 = not at all distressing, 4 = extremely distressing) and a Global Sense of Control Rating (0 = completely in control, 4 = not at all in control/entirely helpless) to assess the extent of distress or loss of control perceived from each war stressor. Also included were five variables that assessed the impact of trauma on economic, social, family, occupational, and educational life (0 = no impact at all, 4 = extremely severe impact) (Başoğlu et al., 1994).

After completing the questionnaire, the students were divided into two groups: those exposed to psychotrauma (based on a score of 1 or greater) and those not exposed (control group). In the control group were students who did not experience a traumatic event during the war, such as exposure to shelling, prisoner experience, torture or injury, death of a close person, or witness to the murder of another person.

2.3. Demographic and clinical characteristics

We examined demographic risk factors, including age and gender, and behavioural and other factors including smoking, weight, height, body mass index (BMI), waist-to-hip ratio, and measured blood pressure, lipids, and glucose. Samples of blood from all respondents were taken and passed to Banja Luka Center for Medical Research (Banja Luka, Bosnia and Herzegovina), the location chosen as a reference centre for all biochemical research within the project. In the laboratory, the following parameters were measured in a fasting state: total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and blood sugar level. Total cholesterol, triglycerides, and blood sugar level were measured enzymatically. HDL-C was measured directly in the serum and LDL-C levels were calculated using the Friedewald formula.

2.4. Carotid ultrasound procedures

In the second phase, subjects were invited to an ultrasound examination of the carotid arteries, to which 149 responded. The carotid arteries were evaluated with high-resolution B-mode ultrasonography using a GE LOGIQ 400 MD system equipped with a 5–10 MHz linear array transducer. According to consensus, the intima–media complex was measured

on the back wall of the carotid artery in a longitudinal scan in the part where there are no plaques in the artery (Touboul et al., 2004). Four measurements were taken: CIMT in the right internal carotid artery, left internal carotid artery, right common carotid artery, and left common carotid artery. For each patient, a summary value was calculated as the average value of these four measurements.

2.5. Statistical analysis

All data were initially entered into a commercially available statistical program (SPSS 17.0 for Windows; SPSS, Chicago, IL, USA). Continuous variables were summarized as mean \pm SD or as frequency percentages. Categorical variables were expressed as a proportion (percentage). First, the Student's *t*-test (for continuous variables) or chi-squared test of proportions (for categorical variables) was utilized to compare demographic and clinical risk factors between those with and those without trauma. Next, the Student's *t*-test was used to compare CIMT measurements in those with versus those without trauma. Finally, multiple logistic regression examined for risk factors and CIMT measurements independently associated with the odds of trauma.

3. Results

Table 1 shows a comparison of demographic and risk factors between those defined with versus those without trauma. Overall, 54 people, or 14.5% of the overall sample, were defined as having trauma. Among our subjects, those with versus without trauma were less likely to be smokers (7.4% vs 17.6%, $p = 0.06$), had lower blood sugar (4.23 mmol/l vs 4.65 mmol/l, $p = 0.002$), and were less likely to have ideal HDL-C (> 1.0 mmol/l) (3.7% vs 12.9%, $p = 0.051$). Other risk factors did not differ significantly between those with and those without trauma (Table 1).

Moreover, in the subset of participants with CIMT measurements, the mean right internal CIMT was greater (0.54 mm vs 0.49 mm, $p < 0.01$) and left internal CIMT was slightly greater (0.53 mm vs 0.50 mm, $p = 0.07$) in those with versus without trauma; however, common CIMT measurements did not significantly differ between those with and those without trauma (Table 2).

From multiple logistic regression examining the adjusted odds of trauma according to risk factors (Table 3), only higher levels of triglycerides were independently associated with the odds of trauma [odds ratio (OR) = 5.3 for triglycerides ≥ 1.7 mmol/l vs < 1.7 mmol/l]. In Table 4, we examine both the unadjusted age and gender, and risk factor-adjusted odds of trauma according to each standardized CIMT measurement from logistic regression. In the adjusted analysis, all CIMT

Table 1. Levels of risk factors in students with vs without trauma.

Variable	With trauma (n = 54)	Without trauma (n = 318)	p
Age (years)	19.3 ± 1.69	19.5 ± 1.70	0.338*
Gender (male/female; % male)	17/37 (31.5)	105/213 (33.0)	0.824*
BMI (kg/m ²)	21.65 ± 3.04	21.59 ± 3.11	0.903*
Waist-to-hip ratio	0.78 ± 0.07	0.78 ± 0.06	0.952*
Smoking status (current smoker/not smoker; % smokers)	4/50 (7.4)	56/262 (17.6)	0.059*
SBP (mmHg)	113.4 ± 16.2	114.4 ± 14.5	0.644*
Target value of SBP (< 140 mmHg)	3/51 (5.6)	9/309 (2.8)	0.295*
DBP (mmHg)	71.2 ± 11.9	74.0 ± 10.2	0.112*
Target value of DBP (< 90 mmHg)	0/54 (0.0)	8/310 (2.5)	0.239*
Glucose in blood (mmol/l)	4.23 ± 0.67	4.65 ± 0.95	0.002*
Target value of glucose (< 6 mmol/l)	0/54 (0.0)	13/305 (4.1)	0.130*
Total cholesterol (mmol/l)	4.11 ± 0.76	4.18 ± 0.68	0.545*
Target value of total cholesterol (< 5 mmol/l)	6/48 (11.1)	36/282 (11.3)	0.964*
HDL-C (mmol/l)	1.54 ± 0.29	1.49 ± 0.36	0.407*
Target value of HDL-C (> 1.0 mmol/l in men; > 1.2 mmol/l in women)	2/52 (3.7)	41/277 (12.9)	0.051*
LDL-C (mmol/l)	2.21 ± 0.66	2.32 ± 0.62	0.220*
Target value of LDL-C (< 3 mmol/l)	6/48 (11.1)	49/269 (15.4)	0.411*
Triglycerides (mmol/l)	0.80 ± 0.49	0.79 ± 0.41	0.952*
Target value of triglycerides (< 1.7 mmol/l)	4/54 (7.4)	10/308 (3.1)	0.128*

Data are shown as mean ± SD or n/N (%). **p* < 0.001. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 2. Mean levels of carotid ultrasound measurements in those with vs without trauma.

Variable	With trauma (n = 27)	Without trauma (n = 122)	p
RCC	0.54 ± 0.09	0.51 ± 0.09	0.115
RIC	0.54 ± 0.10	0.49 ± 0.09	0.009
LCC	0.55 ± 0.07	0.52 ± 0.09	0.166
LIC	0.53 ± 0.08	0.50 ± 0.09	0.073

Data are shown as mean ± SD. RCA, right common carotid; RIC, right internal carotid; LCC, left common carotid; LIC, left internal carotid.

measurements were significantly associated with the odds of trauma (ORs of 1.7–2.2 per SD, *p* < 0.05 to *p* < 0.01), with the strongest relationship seen for the right internal carotid artery (OR = 2.3 per SD, *p* = 0.002) in age, gender, and risk factor-adjusted analyses.

Table 3. Odds of trauma according to age, gender, and risk factors from multivariable logistic regression (n = 372).

Variable	B	SE	p	OR	95% CI for OR	
					Lower	Upper
Age (years)	−0.100	0.117	0.392	0.905	0.719	1.138
Gender (male vs female)	0.468	0.388	0.228	1.597	0.746	3.418
Smoking (yes vs no)	−0.833	0.558	0.135	0.435	0.146	1.297
BMI (≥ 30 vs ≤ 30 kg/m ²)	0.721	0.429	0.093	2.056	0.888	4.765
Triglycerides (≥ 1.7 vs ≤ 1.7 mmol/l)	1.664	0.717	0.020	5.280	1.296	21.518
HDL-C (≥ 1.2 vs ≤ 1.2 mmol/l female; ≥ 1.0 vs ≤ 1.0 mmol/l male)	−1.419	0.802	0.077	0.242	0.050	1.165
LDL-C (≥ 3 vs ≤ 3 mmol/l)	−0.660	0.533	0.216	0.517	0.182	1.469
Glucose (≥ 6.0 vs ≤ 6.0 mmol/l)	−0.782	1.139	0.492	0.457	0.049	4.261
Constant	−0.592	2.300	0.797	0.553		

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; CI, confidence interval. For independent variables code 1 is given to risk and code 0 to no risk; gender: 1, male; 2, female.

Table 4. Odds of trauma according to carotid intima–media thickness (CIMT) measurements from logistic regression, unadjusted and adjusted for age, gender, and risk factors (n = 149).

Variable	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
All participants (n = 149)				
Z RCC	1.37 (0.92–2.04)	0.119	1.69 (1.02–2.79)	0.041
Z RIC	1.68 (1.12–2.53)	0.012	2.31 (1.35–3.94)	0.002
Z LCC	1.32 (0.89–1.97)	0.169	1.83 (1.06–3.15)	0.030
Z LIC	1.46 (0.96–2.21)	0.076	1.93 (1.13–3.31)	0.017

RCC, right common carotid; RIC, right internal carotid; LCC, left common carotid; LIC, left internal carotid.

Multivariate: adjusted for age, gender, smoking, body mass index, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glucose, and triglycerides.

Z: standardized values of variables to represent odds ratio (OR) and 95% confidence interval (CI) per 1 standard deviation (SD) change. The OR per 1 SD increase in the corresponding CIMT variables and the 95% CI were also calculated. We estimated ORs and their 95% CIs for an SD increment of each measurement (thereby facilitating comparisons of effect sizes for individual measurements).

4. Discussion

We studied whether there were differences in CVD risk factors and whether early atherosclerosis measured by CIMT was present in people who had previously been exposed to trauma during the war in Bosnia and Herzegovina. We found that traditional risk factors (except for elevated triglycerides) are not strongly related to post-war trauma in young adults, but those with greater CIMT are more likely to have been previously exposed to trauma, after adjustment for major risk factors.

The war in Bosnia and Herzegovina has made psychological and mental adjustment difficult for the population, with PTSD not an uncommon occurrence (Vulic et al., 2012a, 2012b). PTSD can have a major impact on various diseases, with stress often being traumatic (Hakulinen et al., 2016). Reactions to stress can be physical, emotional, and cognitive. While about 40% of the population is exposed to intense stress, about 10% might develop PTSD (Gilbert et al., 2015). Moreover, PTSD is associated with greater CVD risk, such as premature heart attack or stroke (Boscarino, 2008; Dobie et al., 2004; Kubzansky, Koenen, Spiro, Vokonas, & Sparrow, 2007; Rozanski, 2011; Turner, Neylan, Schiller, Li, & Cohen, 2013; Vaccarino et al.,

2013). While the exact mechanism causing CVD is not established (Wentworth et al., 2013), possible contributors include a dysfunctional hypothalamic–pituitary–adrenal axis or abnormal sympathetic activation (Boscarino, 2011). Age also affects resilience and vulnerability to stress; for instance, younger people react more easily to stress and often have more dramatic reactions and poorer outcomes. In addition, how one reacts to stress as a child can greatly affect emotional development in the future, compromising responses of the neuroendocrine and motor system (Theorelli, Kristensen, Kornitzer, & Orth-Gomer, 2006). Whether this may portend the development of CVD risk factors or subclinical atherosclerosis is not known, and thus was the subject of our investigation.

Other investigators have studied how cardiovascular parameters relate to psychotrauma, such as by association with inflammation, which may lead to early atherosclerosis. For instance, a New Zealand study showed that children exposed to socioeconomic deficiency, maltreatment, and social isolation were more likely to be depressed and have higher levels of inflammation (Danese et al., 2009). Others have shown that elevated C-reactive protein levels may lead to increased CVD risk in young adults (Taylor, Lehman, Kiefe, & Seeman, 2006). In addition, higher levels of interleukin-6 following stressful childhood events may relate to future development of atherosclerosis (Danese et al., 2008; Danese, Pariante, Caspi, Taylor, & Poulton, 2007).

Our results show that higher levels of CIMT in this young population are associated with a greater odds of having trauma, even after adjustment for age, gender, and other risk factors. There are no prior studies in children linking increased CIMT with a greater likelihood of war stress, but other studies have examined how risk factors in children relate to increased CIMT. For example, in young overweight adults with diabetes, higher levels of CIMT have been shown (Urbina et al., 2009). While stress alone may not be sufficient to promote increased CIMT, its effect in combination with other risk factors may be sufficient (Botbol, 2012; Cobbe & Balle, 2010; Rozanski, Blumenthal, Davidson, Saab, & Kubzansky, 2005; Tounian et al., 2001). Roemmich et al. (2011) studied 25 boys and 23 girls with an average age 14 years, and showed that cardiovascular reactivity, especially stress-induced systolic blood pressure reactivity, was associated with increased subclinical atherosclerosis measured by CIMT. This showed that stress-induced cardiovascular reactivity can lead to the progression of subclinical CVD. While that study studied younger subjects than ours, their finding of stress-induced cardiovascular reactivity in relation to increased CIMT is consistent with our findings.

Conversely, others have not found increased CIMT to be related to stress. Dietz and Matthews (2011)

investigated the association between depression and CVD in adolescents, and demonstrated that while depression was related to compromised vascular elasticity, there was no association with CIMT. In another study, Low, Salomon, and Matthews (2009) examined 158 healthy adolescents who experienced chronic long-term stress, and showed chronic stress to be related to elevated blood pressure but not to increased CIMT. However, others have shown exposure to psychosocial environments, including unaffectionate interactions, conflict, cold, aggressive interpersonal behaviour, and neglect, to be associated with slightly increased CIMT in white, but not black participants (Loucks et al., 2014). Finally, Goetz et al. (2014) examined the association of combat exposure with CIMT in Vietnam War-era twins and the effect of PTSD, and found that both combat exposure and a lifetime history of PTSD were associated with increased CIMT. Others have also shown an association between occupational psychosocial stress and increased CIMT (Nordstrom, Dwyer, Merz, Shircore, & Dwyer, 2001; Rosvall et al., 2002).

Family conflict in early life has also been shown to relate to increased CVD risk in adulthood, explained partly by the shaping of adult social interactions (John-Henderson, Kamarck, Muldoon, & Manuck, 2016; Rooks et al. 2012). The role of stress as an isolated risk factor remains unclear. While stress itself does not appear to cause increased atherosclerosis, its synergistic effect in combination with other risk factors may lead to the development of atherosclerosis, reflected in increased CIMT. Future studies should further examine how stress as an isolated risk factor may lead to the development of cardiovascular risk factors. While cross-sectional studies relating stress with health can be useful, examining persistent or increasing stress longitudinally can be more informative, especially when studying populations that are experiencing rapid changes in CVD risk, such as children and adolescents.

Our study has certain limitations. Importantly, we had a single-time assessment of CIMT, which precludes our ability to make inferences about serial changes in atherosclerosis. The sample was also healthy, with restricted range for CIMT, and may not be representative of adolescents most at risk for cardiovascular morbidity. It is also possible that trauma-related risk factors may not develop until a later age than in those whom we studied, where we found limited differences in risk factors in those with versus those without trauma at a young age.

Our research, conducted among adolescents who were born or who were young (pre-school age) during the war period in Bosnia and Herzegovina, showed a significant presence of psychological trauma and signs of depression. We demonstrate that while most traditional risk factors are not strongly related to the presence of post-war trauma in young adults, the odds of post-war trauma does relate to greater subclinical

atherosclerosis as measured by CIMT, after adjustment for major risk factors. Investigation into whether other risk factors may mediate these findings is needed.

Disclosure statement

No potential conflict of interest was reported by the authors.

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