PSYCHOSOCIAL STRESS OVER THE LIFESPAN, PSYCHOLOGICAL FACTORS, AND CARDIOMETABOLIC RISK IN THE COMMUNITY

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ABSTRACT

Objective: The complex relationship between psychosocial stress over the lifetime, psychological factors and the cardiometabolic risk is still poorly understood. Accordingly, our aims were to 1) independently assess the associations between childhood adversity, life-event stress in remote (earlier than the last 5 years) and recent adulthood and the cardiometabolic risk, and 2) determine the role of psychological factors including personality, coping and depression in these associations.

Methods: The sample included 2674 adults, aged 35 to 66 year, randomly selected from urban area. Participants underwent a physical exam including the assessment of obesity markers, blood pressure as well as blood lipid and glucose levels. Stress during adulthood was determined using the severity scores of 52 stressful life events. Information on adverse childhood experiences and major depressive disorders was collected using semi-structured interviews, whereas personality traits and coping mechanisms were evaluated through questionnaires.

Results: Both childhood adversity and stress in remote adulthood were associated with elevated body mass index (β [95% confidence interval {CI}] = 0.249 [0.029 to 0.468]; 0.020 [0.006 to 0.034]), waist circumference (β [95% CI] = 0.061 [0.024 to 0.099]; 0.08 [0.04 to 0.11]), and the global cardiometabolic risk score (β [95% CI] = 0.278 [0.017 to 0.540]; 0.017 [0.001 to 0.033]) after adjustment for sociodemographic, lifestyle, and psychological factors. In addition, childhood adversity was associated with low high density lipoprotein levels (β [95% CI] = −0.021 [−0.042 to 0.000]), as well as increased fat mass and systolic blood sugar levels (β [95%CI] = 0.506 [0.165 to 0.846]; 0.952 [0.165 to 1.740]) and stress in remote adulthood with apolipoprotein B levels (β [95% CI] = 0.607 [0.312 to 0.901]). Psychological factors did not account for these associations and were not effect modifiers.

Conclusions: Our data demonstrate that psychosocial stress during childhood and remote adulthood favour adiposity and abnormal lipid metabolism.

Key words: cardiometabolic risk, childhood adversity, life events, major depressive disorder, personality, psychosocial stress

BMI = body mass index**, CVDs =** cardiovascular diseases**, DIGS** = Diagnostic Interview for Genetic Studies, **GHQ** = General Health Questionnaire, **HDL =** high density lipoprotein**, HPA-axis** = hypothalamic pituitary-adrenal axis, **MDD =** major depressive disorder**, SBP** = systolic blood pressure

INTRODUCTION

Epidemiological and clinical evidence has revealed that both CVDs and their risk factors are associated with psychosocial stress (1-4). Cardiometabolic abnormalities such as an increase in body weight, especially high fat distribution in the central region has been linked with chronic stress (5-8) Likewise, high levels of blood glucose and blood lipids have been found to be associated with life stress (4, 9, 10). Although findings vary, psychosocial stress has also been associated with high blood pressure (11). Research is also increasingly recognizing the role of stress during childhood as a risk factor for cardiometabolic abnormality in adulthood (12-16). Indeed, adverse childhood experiences like stressful life events, maladaptive family environments, sexual and physical abuse have been shown to be associated with cardiometabolic risk factors such as increased body weight (17) and diabetes (18, 19). Stress during childhood has also been shown to affect overall cardiometabolic functioning later on in life (20, 21).

Despite the growing body of evidence in this domain, exposure to psychosocial stressors over the entire life and the risk of cardiometabolic abnormality is only partially elucidated. One major limitation is that researchers often examine stress exposure within limited periods of time while stressors are ubiquitous and span over lifetime. Besides, the effect of stress during childhood and adulthood on the risk of adult cardiometabolic abnormality has been studied separately most of the time, which has impeded drawing conclusions regarding the independent effect stress within these distinct periods. In line with the stress sensitization hypothesis (22, 23), prior stress may amplify the risk of cardiometabolic abnormality in case of new exposure to life events. Life course epidemiology also depicts physical and/or social exposures at different periods in life have biological, behavioral and psychosocial pathways with lasting effects on body systems and implications for disease (24, 25). Indeed, personality traits and coping mechanisms have been shown to act as risk and resilience factors for the effect of stress (26-30). Studies have also revealed associations between psychosocial stress and major depressive disorder (MDD) (31) and between MDD and CVDs (32). Recent research suggests that the association between MDD and cardiometabolic risk factors are entirely attributable to the atypical depression subtype (characterized by increased appetite, increased sleep and leaden paralysis) (33-36). However, the interplay between psychosocial stress and psychological factors on the risk cardiometabolic abnormality has hardly been studied.

Accordingly, in order to better understand the link between lifetime psychosocial stress and the cardiometabolic risk, 1) we independently assessed the associations between childhood adversity, life-event stress in remote and recent adulthood and cardiometabolic risk indicators including obesity markers, blood glucose and lipid levels, blood pressure and a composite cardiometabolic risk score in a population-based sample; 2) we tested whether exposure to childhood adversity and adulthood life-event stress interact to affect the cardiometabolic risk measures; 3) we determined whether psychological factors such as personality traits, coping styles and MDD subtypes accounted for the associations between psychosocial stress and the cardiometabolic risk measures or modified their effects.

METHODS

I. Study sample and design

Data for the present study came from the ongoing population-based prospective cohort study CoLaus|PsyCoLaus, which was designed to study cardiovascular risk factors and mental disorders in the community (37, 38). A total of 6'733 randomly selected individuals, based on the civil registry, aged between 35 and 75 years, were recruited between June 2003 and May 2006 in the city of Lausanne (Switzerland). Sixty-seven percent of the 35 to 66 year-old participants who underwent the physical exam (n=5535) also accepted the psychiatric evaluation (n=3719), which took place from January 2004 to May 2009. For the present analyses, 2674 participants with complete information on psychosocial stress and cardiometabolic risk indicators as well as on personality traits, coping strategies and MDD could be included (figure 1). Participants who could not be included were more likely to be men, to be non-white, to have a lower educational level and to be physically inactive. The Institutional Ethics Committee of the University of Lausanne approved the CoLaus | PsyCoLaus study. All participants signed a written informed consent after having received a detailed description of the study.

II. Assessment

Cardiometabolic Measurements

The physical evaluation included anthropometric measurements and the collection of blood and urine samples (37). Body weight and height were measured, and the body mass index (BMI) was calculated. Waist circumference was measured at the narrowest point between the lowest rib and

the iliac crest. Body fat mass was assessed using bioelectrical impedance analysis. Blood pressure was measured three times on the left arm with 10 minute intervals; the average of the last two measures was then used. Venous blood samples (50ml) were drawn after an overnight fast and clinical chemistry assay was done within 2 hours of blood collection. High density lipoprotein (HDL) was assessed by cholesterol oxidase-phenol-aminophenazone + polyethylene glycol + cyclodextrin with a maximum interassay CV of 3.6% and a maximum intra-assay CV of 0.9%. Triglycerides were assessed by glucose oxidase-phenol-aminophenazone with a maximum inter-assay CV of 2.9% and a maximum intra-assay CV of 1.5%. Apolipoprotein B quantification was performed by turbidimetry with a maximum inter-assay CV of 8.7% and a maximum intra-assay CV of 7.6%. Glucose was assessed by glucose dehydrogenase with a maximum interassay CV of 2.1% and a maximum intra-assay CV of 1.0%. A continuous cumulative cardiometabolic risk score was also created on the basis of the cardiometabolic risk indicators including, BMI, waist circumference, body fat mass, levels of triglycerides, HDL (inversed levels), apolipoprotein B, glucose and systolic blood pressure (SBP). The continuous cardiometabolic risk score was the sum of the gender specific standardized z-scores of the indicators where the participant had valid measurements in all indicators (39). As most of the indicators had skewed distributions (see Supplementary A), appropriate power transformations were applied before calculating the scores (see Supplementary B). The suitability of aggregating indicators in a composite measure was tested using confirmatory factor analysis (see Supplementary C) which revealed an acceptable fit for a common factor solution (e.g. Root mean square error of approximation = 0.03, comparative fit index = 0.98, normed fit index =0.97).

Psychosocial Stress

Information about early life adversity was elicited using questions on childhood events from the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (40). The following stressful experiences until the age of 16 were considered as indicators of adversity: loss of close relatives (parents or siblings), divorce or separation of parents, witnessing of violence between parents, as well as sexual and physical abuse (41). According to the suggestion of Friedman et al. (14) exposure to childhood adversity was quantified by the sum of reported events. Stressful life events during adulthood were evaluated using the Amiel Lebigre's Life Event Questionnaire (42). The questionnaire comprises a list of 52 events related to the family environment, relationships, health issues, the social

environment, work and employment, the legal system, housing and economic problems (Table 1). When participants reported that they had been exposed to a specific adverse event, they were asked to provide the age of the first exposure to this event. If the event had occurred more than once, they also provided the age of the last exposure to this event. In addition, they were asked to rate the negative affective impact of the first and the last occurrences of the event by a score ranging from 0 (no negative impact at all) to 100 (maximal negative impact the participant could imagine). The questionnaire was previously evaluated by its originators in samples of depressed individuals and controls (42). The cumulative severity score of events of 200 or more for the two preceding years was found to indicate the presence of depression(43). Among depressive women and men, 56% and 74%, respectively, had a score of 200 and more, whereas in controls the respective proportions for these scores were only 30% and 12%. Given that participants provided us with the timing of each event, we could compute cumulative severity scores for the events reported for the five years preceding the interview (recent adult life-event stress) and for the period earlier than the five years preceding the interview (remote adult life-event stress). The 5-year cut-off was chosen according to the predictive power of the cumulative severity scores of stressors on the total score of the General Health Questionnaire (GHQ) (44, 45). By varying the duration of the exposure to stressors from the most recent one-year period up to a maximum of 10 years, we could establish that the prediction of the GHQ score did not further improve in terms of the area under the curve when an exposure period of longer than 5 years was considered. This cut-off was also confirmed using the Akaike Information Criterion within a linear model framework (see Supplementary table D). In order to increase the interpretability, we rescaled the scores to range from 0 to 100. Accordingly, one unit increase corresponds to a 1% increase of the maximum score in the sample.

Psychological Factors

MDD was assessed using the French version of the semi-structured Diagnostic Interview for Genetic Studies (DIGS) (46, 47), which revealed excellent inter-rater (kappa = 0.93) and adequate 6 weeks test-retest reliability (kappa = 0.62) for MDD, tested in a clinical sample (46). Interviewers were required to be master-level psychologists, who were trained for one to two months. The DIGS information also elicits the criteria for the atypical and melancholic characteristics of major depressive episodes. According to the lifetime history of these episodes, subtypes with MDD were classified into

the atypical, melancholic, combined and unspecified subtypes as suggested by Angst et al (34, 48, 49). The personality dimensions of Neuroticism and Extraversion were evaluated using the Eysenck Personality Questionnaire (50).The originator of this instrument reported Cronbach's α coefficients of 0.78–0.87 for Neuroticism and 0.72 to 0.82 for Extraversion using three different samples in France (51). Coping strategies were evaluated using the coping section of the problem resolution strategy questionnaire (52). According to principal component analysis, factors Emotion-focused coping, Help-seeking behaviors, and Problem-focused coping were identified. Using the CoLaus|PsyCoLaus baseline sample we established standardized Cronbach's α coefficients for these dimensions of 0.65, 0.69 and 0.44, respectively.(53). As Emotion-focused coping was highly correlated with Neuroticism ($r = 0.63$; $p<0.0001$) we could not include it in our analyses.

Sociodemographics, Lifestyle Factors and Other Covariates

Data on sociodemographic characteristics (gender, age, education, and income), health-related lifestyle factors (alcohol consumption, smoking status, and physical inactivity), cardiometabolic abnormalities in first-degree relatives (diabetes, hypertension or hypercholesterolemia) and the use of physician-prescribed medication (anti-diabetic, anti-hypertensive, lipid-lowering and other weight-increasing medications) were collected through a standardized interview. Education was categorized into 5 levels: 1) compulsory school (maximum 10 school years); 2) apprenticeship; 3) upper secondary education (maximum 13 school years); 4) higher education except for university; and 5) university. Yearly income was assessed in Swiss Francs in six categories: 1) <30,000; 2: 30,000-49,000; 3) 50,000-69,000; 4) 70,000-89,000; 5) 90,000-110,000; 6) >110,000. Alcohol consumption was determined through the type and number of alcoholic beverage units consumed on a weekly basis (54). Self-reported tobacco consumption was used to determine smoking status. Participants were classified as non-smokers if they had never regularly smoked, as former smokers if they had a history of smoking in past but had stopped smoking and as current smokers if they reported a current regular consumption. Participants were considered to be physically active if they reported to perform physical activity for at least 20 minutes twice a week.

III. Statistical analysis

First, marginal associations between childhood adversity, adulthood remote and recent stress and cardiometabolic variables (BMI, waist circumference, body fat mass, triglycerides, HDL,

apolipoprotein B, fasting blood glucose, SBP and the cumulative cardiometabolic risk score) were established using robust linear regression models (M-estimation). Then, the conditional effects of childhood adversity and both remote and recent adulthood stress on these cardiometabolic indicators were assessed within models with adjustment for sociodemographic characteristics, family history of cardiometabolic risk, lifestyle factors and the use of medication (Model 1); we also tested whether the effects of childhood and adulthood stress interacted regarding the cardiometabolic risk indicators. In the next series of models, psychological factors including personality traits, coping style and MDD subtypes were entered (Model 2). Potential effect modification by psychological factors was tested by adding interaction terms of these psychological factors and childhood adversity or adulthood stress to the models. The percentage of change in the effects of stress variables after including a group of potential confounding variables or potential mediators in the model was calculated using the formula $\Delta = \left(\frac{\beta \text{ Model with adjustments } - \beta \text{ Reference model}}{\beta \text{ Model with adjustments}}\right) \times 100\%$.

In all analyses, observations were weighted by their inverse probability of being in the sample. This inverse probability was derived from a model that included sociodemographic (age, gender, educational level, income level, race) and life style (smoking status, physical activity, alcohol consumption) predictors of participation. Missing information on the covariates were attributed by multiple imputations (n=100; Markov Chain Monte Carlo (MCMC) method) under the missing-at-random assumption; observations with missing information in the outcome variables were dropped from the analysis. Statistical significance throughout the analyses was maintained at the 0.05 alpha levels and a 0.01 alpha level was used to test interactions. Analyses were carried out using the Statistical Analysis System (SAS), version 9.3 (SAS institute Inc., Cary, NC, USA) and R (www.cran.r-project.org).

RESULTS

Table 2 provides the description of the sample. Nearly half of the participants in our sample were overweight (BMI ≥ 25). The median score for the cumulative cardiometabolic risk was -0.29 ranging from -16.3 to 23.5, where 620 participants had a score above 3, representing the upper risk quartile. Nearly a third of the participants (31.2%) reported at least one adverse event during childhood. Among them, a quarter was exposed to two or more events. The most frequently reported event was witnessing of violence between parents (13.8%), followed by divorce or separation of parents

(12.9%), death of a parent (8.0%), death of a sibling (2.5%), sexual abuse (2.4%) and physical abuse (0.8%). Half of the sample had also experienced up to eleven life events in their adulthood; only 3% reported not having experienced any event. Most of the reported events were described to have happened between the ages of 25 and 45. As many as 42.8% met lifetime criteria for MDD, of which half of them met criteria for the unspecified subtype.

Results of the multiple covariate regression models did not provide evidence for interactions between childhood adversity and remote or recent adulthood, and between remote and recent adult stress regarding the cardiometabolic risk outcomes. Similarly, there were no significant interactions between psychological factors and childhood adversity or adulthood stress. However, these models revealed that participants exposed to childhood adversity had significantly increased BMI, waist circumference and body fat (Table 3, Model 1) as well as increased SBP levels (Table4, Model 1) and cumulative cardiometabolic risk score (Table 5, Model 1). These associations also remained significant after adjustment for psychological variables, which hardly diminished the established effect sizes. The association between childhood adversity and decreased levels of HDL only reached statistical significance after adjustment for the psychological variables (Table 4, Model 2). Regarding adulthood stress, remote life-event stress was positively associated with BMI, waist circumference (Table 3, Model 1), apolipoprotein B level (Table 4, Model 1) and the cumulative cardiometabolic risk score (Table 5, Model 1). The adjustment for psychological factors had a very limited effect on the measured effect sizes for these associations. In contrast, recent adulthood stress was associated with lower waist circumference, lower apolipoprotein B level and lower systolic blood pressure with and without adjustment for psychological characteristics (Table 4).

DISCUSSION

Using a population-based study, which relied on thorough physical and psychiatric evaluations, the key findings of the present analyses were the following: 1) childhood adversity and adult life-event stress were independently associated with increased levels of obesity markers, abnormal blood lipids and a higher cumulative cardiometabolic risk score; 2) only life-event stress in remote but not in recent adulthood was associated with elevated levels of these outcomes; 3) personality traits, coping strategies or MDD subtypes did not account for the associations between stress and the cardiometabolic risk and these psychological factors were not modifiers of these associations.

Stress During Childhood and Cardiometabolic Risk

Exposure to one more adverse childhood event was significantly associated with elevated BMI, waist circumference, fat mass, SBP, cardiometabolic risk score and low HDL levels after adjustment for sociodemographic, lifestyle and psychological factors, which is particularly remarkable given the advanced age of our sample. Our findings are in line with growing evidence showing associations between stress during early life and the risk of cardiometabolic abnormality (14, 21). A review by Danese and Tan (17), for example, has summarized findings on childhood maltreatment and obesity, and concluded that childhood adversity is a potential risk factor for abnormal weight. A study by Lee et al. (55) has shown that individuals with a history of abuse during childhood (emotional, physical, and sexual) have a greater risk of developing the metabolic syndrome. Similarly, Winning et al. (21) found that psychological distress in childhood was associated with a higher cardiometabolic risk later on in life. A 20-year follow-up study has also revealed that participants who were exposed to multiple adverse childhood experiences had greater increase of SBP levels in young adulthood (56). In addition to these studies, we could show that the association between childhood adversity and cardiometabolic risk was independent of later life stress, personality traits, coping mechanisms and the occurrence of a MDD.

It has often been hypothesized that stress during childhood affects the cardiometabolic functioning indirectly by precipitating health-related behaviors such as sedentary lifestyle, poor diet, smoking and heavy alcohol use that may persist all through adulthood (16, 57). As far as lifestyle factors were assessed in our study, our results did not support their mediating role. However, lifestyle factors can change over the lifespan and earlier lifestyle factors may have been more relevant as mediators of the effect of adverse childhood events on cardiometabolic outcome variables than the lifestyle factors that we assessed at an already more advanced age. Moreover, we were lacking data on diet and only had information on regular physical exercise at the time of the interview rather than on overall physical activity. Nevertheless, the fact that childhood adversity remained significantly associated with cardiometabolic variables after accounting for such health related lifestyle suggests other pathways that could be related to the biological system (58). Childhood is a sensitive period where exposures can have adverse effects on structures and functioning of the body system (59). Continuous exposure to stressors during this period may affect the biological stress response and/or

produce epigenetic changes (58), which could lead to cardiometabolic abnormalities later on in life. These stress-related biological processes and their links to the subsequent cardiometabolic risk need to be elucidated in future research.

Stress during adulthood and the cardiometabolic risk

Regarding stress during adulthood, we found remote rather than recent life-event stress to be a risk factor for elevated levels of cardiometabolic risk indicators. The differential effect of stress in function of the five-year dichotomy is likely to be explained by the duration/exposure window. Indeed, there may be an interval of several years between the occurrence of stress and the manifestation of significant weight increase or before developing other cardiometabolic risk factors. According to our data, the short-term effect of stress may be rather the converse. Indeed, increased stress during the five years prior to the assessment was associated with decreasing waist circumference, apolipoprotein B levels and SBP. The observed decrease in waist-circumference suggests that the negative associations between stress and apolipoprotein B concentrations and SBP could be attributable to decreased appetite and subsequent weight loss in stressful periods (60, 61). Our finding of negative associations between recent stress and three cardiometabolic outcome variables are in line with a Swedish study that also found negative correlations between the number of negative life events experienced during the year preceding the assessment and waist circumference, blood pressure and lipid levels in white-collar workers (62). In contrast to the results of this Swedish study and ours, reviews and meta-analyses have rather revealed a tendency for positive associations between stress and obesity markers(4), dyslipidemia and hypertension(4, 11). However, studies included in the review and the meta-analysis that predominantly focused on chronic stressors hardly distinguished between recent and remote life stress.

In contrast to recent stress, we found a positive association between remote stress and increased BMI and waist circumference, whereas the associations for the fat mass did not reach the threshold of statistical significance. Our finding of an association between stress and adiposity markers is consistent with those of several previous studies (4-6). Interestingly, we also found a positive association between remote life-event stress and apolipoprotein B blood concentrations, an indicator of the number of circulating atherogenic lipid particles in the blood. No study has previously assessed the association between psychosocial stress and apolipoprotein B, although recent research

suggested that higher apolipoprotein B levels could be the most important predictor of cardiovascular events (63-65). Accordingly, our finding of a positive association between life-event stress and apolipoprotein B concentrations provides additional evidence for a potential pathway from stress to cardiovascular outcomes, which could be via abnormal lipid metabolism. We also found a significant association between remote life-event stress and the aggregated cardiometabolic risk measure. This finding highlights the considerable effect of life events in the overall cardiometabolic functioning, which, in consequence, may culminate in cardiovascular and metabolic disease. The significant associations with the cumulative risk measure, and the other cardiometabolic risk indicators were all independent of sociodemographic, lifestyle factors and psychological factors. However, the relationship between stress, the socioeconomic factors income and education and the cardiometabolic risk is complex and there is overlap, particularly between events related to unemployment or economic problems and income. Accordingly, adjustment for socioeconomic variables is likely to provide a conservative estimate of the effect of stress (66).

Lifetime psychosocial stress and the cardiometabolic risk

According to the stress sensitization hypothesis, early life stress increases responsiveness to subsequent stressors by imposing biological alterations (23, 24), whereas other hypotheses posit that stress in early life and later periods have a cumulative effect on the cardiovascular risk (16, 67). Our observation of independent effects of childhood adversity and adulthood stress on cardiometabolic risk indicators, together with the absence of an interaction between childhood and adulthood stress regarding the cardiometabolic outcomes, provides support for additive effects of life stressors rather than for the stress sensitization hypothesis. Moreover, our data revealed that personality traits, coping style and MDD subtypes did not changed the magnitude of the established associations between stress and cardiometabolic risk outcomes, suggesting that these psychological characteristics are hardly mediators of the observed life course associations. The lifetime prevalence of more than 40% for MDD was high in our sample. As discussed in a recent article (68), this high prevalence was likely to be attributable to our recruitment in an urban area and the use of a semi-structured diagnostic interview conducted by trained psychologist rather than a fully structured interview conducted by lay interviewers. In addition, our semi-structured interview used a low threshold in the screening questions to enter the depression section in order to also assess disorders

below the diagnostic threshold of MDD. However, considering that we found significant associations between MDD subtypes and cardiometabolic variables in our analyses, the absence of an effect of MDD subtypes on the associations between life event stress and cardiometabolic variables is hardly attributable to the high prevalence of MDD. Hence, the absence of an effect of MDD subtypes on these associations is rather explained by the absence of an association between life event stress and the atypical subtype (36), whereas this subtype has repetitively been shown to be associated with cardiovascular risk factors (33-36). Conversely, the unspecified MDD subtype is likely to be strongly associated with life event stress (36) but not with the cardiovascular risk (34, 35, 49).

STRENGTH AND LIMITATIONS

The strengths of our analyses were the assessment of stressful events over lifetime as well as the personal evaluation of the stressfulness of adult life events. Indeed, the bulk of previous studies have used the number of stressful events as a proxy measure of stress exposure. However, this approach does not take into account inter-individual differences in the perception of the stressfulness of events. We also analyzed our data using the number of events as a measure of the exposure to adulthood stress rather than the scores that included perceived stressfulness. The results of these analyses (see Supplementary E) generally revealed slightly lower associations with cardiometabolic outcome variables, which provide additional support to the use severity score. Indeed, adult life events were no longer associated with obesity markers and the cumulative cardiometabolic risk score. However, the associations with adipolipoprotein B and systolic blood pressure remained significant and significant associations appeared with the high density lipoprotein. Our analyses also relied on a large population-based sample that was thoroughly evaluated with respect to cardiovascular risk factors, psychiatric disorders and other psychological characteristics, which allowed us to evaluate the effect of life event stress on cardiometabolic variables accounting for psychological factors.

However, the results of the study must also be viewed in the light of several limitations. First, data were assessed retrospectively and the recall of stressful events that partially occurred several decades prior to the assessment is likely to be incomplete and could have been biased by the participant's current state. Nonetheless, according to the recently published results of the population-based Dunedin cohort study, there is moderate agreement between retrospective and prospective

measures of adverse childhood experiences, and both measures reveal associations with physical, mental, cognitive and social health at midlife (69). Second, given the cross-sectional nature of data collection, it was not possible to determine the temporal sequence between life events and the onset of cardiometabolic abnormalities. Third, we had no data on diet and only self-reported information on regular physical exercise at the time of the interview rather than on overall physical activity, although both diet and physical activity could be potential mediators of the association between stress and the cardiometabolic risk. Fourth, we had no data on the functioning of the hypothalamic pituitary-adrenal axis (HPA-axis) and catecholamine. Indeed, chronic activation of the HPA-axis, triggered by repeated or continued exposure to stressful experiences over an extended period of time, could lead to a cascade of changes in the biological set-points that finally result in cardiometabolic changes (70). Fifth, data were collected in an urban sample in Switzerland, which may limit the generalizability of the findings.

CONCLUSIONS

Our findings provide additional insight into the complex relationship between life course psychosocial stress and the cardiometabolic risk by showing that psychosocial stress in childhood as well as during adulthood are independently associated with adiposity and abnormal lipid profiles. The role of psychological factors in these associations seems to be trivial. Furthermore, stress encountered during these distinct periods may add up to affect overall cardiometabolic functioning, suggesting that individuals exposed to childhood adversity and high levels of stress during adulthood could particularly benefit from early screening of cardiovascular risk factors. However, our findings still need to be confirmed by longitudinal research.

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FIGURE AND TABELS

Figure 1 Sample flow chart

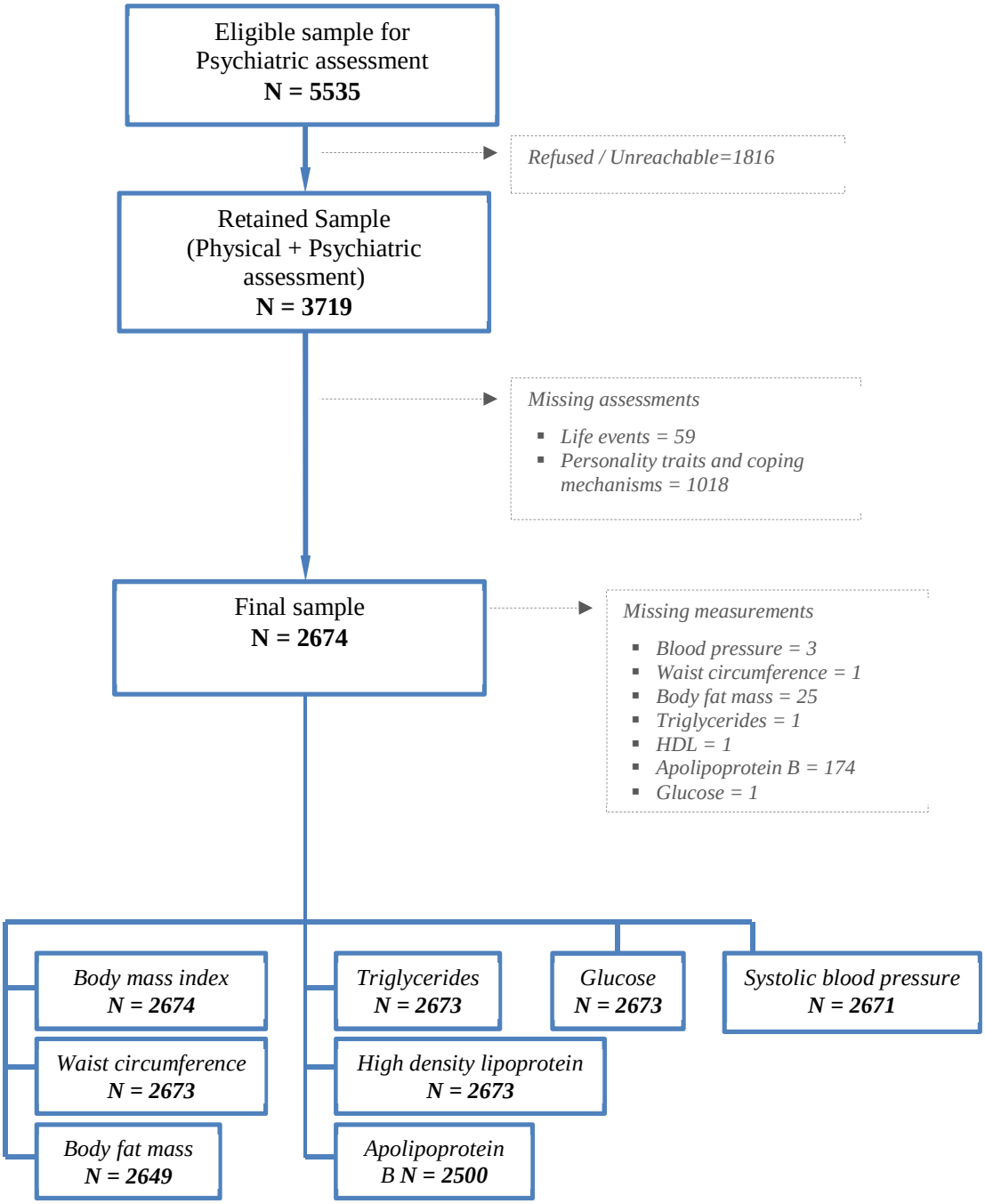


Table 1. Stressful life events

Events related to family environment
- *Alcoholism in a close family member*
- *Suicide of a close family member*
- *Death of a close family member*
- *Severe accident or disease within the close family*
- *Arrival of a new family member in the home*
- *Pregnancy*
- *Increased arguments with one or more members of close family*
- *Problem with family other than close family members (e.g. in-laws)*
- *Child leaving home*
- *Necessity to have others look after children*
- *Behavioural problems with children*
Events with spouse or partner
- *Unwanted pregnancy by one of the partners*
- *Sexual problems within the couple*
- *Marriage*
- *Increased arguments with spouse or partner*
- *Death of partner*
- *Divorce or separation from partner*
- *Separation from partner imposed by circumstances*
- *Extramarital/extra-partner affair*
- *Breakup of relationship*
- *Infidelity of partner*
- *Reconciliation with partner*
Events related to health / psychological problems
- *Disease or severe injury requiring hospitalization*
- *Disease or accident requiring medical treatment*
- *Sudden severe hearing or visual handicap*
- *Miscarriage*
- *Abortion*
- *Problems related to alcohol and drug*
Events related to social environment and other psychosocial problems
- *Retirement*
- *Moving*
- *Change of neighbours*
- *Quarrel with neighbours*

- *Social life diminution*
- *Death of a close friend*

Events related to work and employment

- *Unemployment (a participant)*
- *Unemployment (a partner)*
- *Problems with boss or colleagues*
- *Job change of the same type*
- *Job change of different type*
- *Change of work hours or conditions*
- *Promotion or increased responsibility at work*
- *Professional failure*
- *Partner starting or stopping his/her job*

Events related to housing/economic problems

- *Significant income increment*
- *Significant income decrement*
- *Becoming highly indebted*
- *Small financial difficulties*
- *Loss of object with high personal value*
- *Homelessness for a certain time*

Events related to the legal system

- *Sentenced to imprisonment*
- *Participation in a fight*
- *Imprisonment*

Table 2. Sample characteristics (n = 2674)

Socio-demographics		
Females, n (%)		1479 (55.3%)
Age, mean (± s.d)		50.4 (±8.8)
Income level, n (%)	< 30,000 CHF	152 (5.8%)
	30,000-49,999 CHF	393 (15%)
	50,000-69,999 CHF	584 (22.3%)
	70,000-80,999 CHF	513 (19.6%)
	90,000-110,000 CHF	386 (17.7%)
	> 110,000 CHF	598 (22.6%)
Educational level, n (%)	Compulsory school	411 (15.3%)
	Apprenticeship	1005 (37.5%)
	Upper secondary school	245 (9.2%)
	Higher education except for university	427 (16%)
	university	586 (22%)
Family history of cardio-metabolic risk [a], n (%)		1321 (49.4%)
Health related lifestyle		
Smoking status, n (%)	Non-smoker	1073 (40.1%)
	Former smoker	717 (26.8%)
	Current smoker	884 (33.1%)
Physically inactive (<20 minutes twice a week), n (%)		1119 (41.9%)
Number of alcoholic drinks per week, median (range)		4 (0-76)
Cardio-metabolic risk indicators		
Body Mass Index [kg/m^2], mean (±s.d)		25.4 (±4.5)
Waist circumference [cm] , mean (±s.d)		87.6 (±13.3)
Body fat mass [%], mean (± s.d)		28.5 (±8.7)
Triglycerides [mmol/l], mean (± s.d)		1.3 (±1.1)
High density lipoprotein [mmol/l] , mean (±s.d)		1.6 (±0.4)

Apolipoprotein B [mg/dl], mean (±s.d)		166 (±122.6)
Fasting blood glucose [mmol/l], mean (±s.d)		5.5 (±1.1)
Systolic blood pressure [mmHg], mean (±s.d)		125.4 (±16.5)
Cumulative cardio-metabolic risk score [b], mean (±s.d)		0.006 (±4.8)
Psychosocial stress		
Adulthood life-event stress [c], median (range)		310 (0-2520)
Recent (<5yrs) life-event stress [c], median (range)		70 (0-825)
Remote (>5yrs) life-event stress [c], median (range)		215 (0-2250)
Childhood adverse events, n (%)	No event	1242 (68.8%)
	One event	1047 (23.5%)
	Two events	301 (6.4 %)
	Three or more events	84 (1.3%)
Psychological factors		
Neuroticism score, mean (±s.d)		9.7 (±5.8)
Extraversion score, mean (±s.d)		11.9 (±5.0)
Problem-focused coping score, mean (±s.d)		7.7 (±1.8)
Help-seeking coping score, mean (±s.d)		4.3 (±2.6)
Major depressive disorder subtypes		
Atypical, n (%)		184 (6.9%)
Melancholic, n (%)		287 (10.7%)
Combined, n (%)		137 (5.1%)
Unspecified, n (%)		538 (20.1%)

s.d: standard deviation

CHF: Swiss franc

[a] History of either diabetes, hypertension or hypercholesterolemia in first degree relatives.

[b] The sum of gender-specific standardized z-scores of body mass index, waist circumference, body fat mass, triglycerides, high density lipoprotein, apolipoprotein B, fasting blood glucose and systolic blood pressure.

[c] cumulative severity scores of life events.

Table 3. Associations between psychosocial stress and obesity markers in bivariate and multiple covariate regression models

	Bivariate	Model-1		Model-2	
	Beta (95%CI)	Beta (95%CI)	Δ	Beta (95%CI)	Δ
Body Mass Index (kg/m^2)					
(N=2674)					
Recent (<5yrs) life-event stress	-0.018* (-0.033 - -0.004)	-0.009 (-0.022 - 0.005)		-0.012 (-0.025 - 0.002)	
Remote (>5yrs) life-event stress	0.012 (-0.002 - 0.026)	0.019** (0.006 - 0.033)	19%	0.020** (0.006 - 0.034)	5%
Childhood adversity	0.262* (0.063 - 0.462)	0.276* (0.056 - 0.495)	-5%	0.249* (0.029 - 0.468)	-5%
Neuroticism	-0.149 (-0.310 - 0.011)			-0.049 (-0.219 - 0.121)	
Extraversion	0.164* (0.001 - 0.326)			0.290*** (0.136 - 0.443)	
Problem-focused coping	0.017 (-0.143 - 0.177)			0.012 (-0.139 - 0.163)	
Help-seeking coping	-0.353*** (-0.512 - -0.194)			-0.032 (-0.187 - 0.123)	
Atypical depression	0.715* (0.041 - 1.390)			1.355*** (0.715 - 1.994)	
Melancholic depression	-1.024*** (-1.527 - -0.521)			-0.335 (-0.846 - 0.175)	
Combined depression	-0.236 (-1.046 - 0.574)			0.038 (-0.739 - 0.815)	
Unspecified depression	-0.518* (-0.915 - -0.120)			-0.149 (-0.540 - 0.242)	
Waist circumference (cm)					
(N=2673)					
Recent (<5yrs) life-event stress	-0.123*** (-0.173 - -0.073)	-0.039* (-0.076 - -0.001)	-209%	-0.044* (-0.082 - -0.007)	11%
Remote (>5yrs) life-event stress	0.017 (-0.031 - 0.065)	0.060** (0.023 - 0.097)	90%	0.061** (0.024 - 0.099)	1%
Childhood adversity	0.264 (-0.439 - 0.966)	0.648* (0.044 - 1.253)	40%	0.608* (0.001 - 1.215)	-6%
Neuroticism	-1.038*** (-1.595 - -0.481)			-0.213 (-0.684 - 0.258)	
Extraversion	0.362 (-0.203 - 0.928)			0.541* (0.117 - 0.966)	
Problem-focused coping	0.189 (-0.372 - 0.751)			-0.058 (-0.474 - 0.358)	
Help-seeking coping	-1.726*** (-2.278 - -1.174)			0.048 (-0.380 - 0.477)	
Atypical depression	0.850 (-1.531 - 3.230)			3.153*** (1.383 - 4.922)	
Melancholic depression	-4.410*** (-6.149 - -2.670)			-0.554 (-1.966 - 0.858)	
Combined depression	-1.786 (-4.667 - 1.094)			0.395 (-1.754 - 2.544)	
Unspecified depression	-2.709*** (-4.092 - -1.326)			-0.531 (-1.615 - 0.553)	
Body fat mass (%)					
(N=2649)					
Recent (<5yrs) life-event stress	0.010 (-0.024 - 0.043)	-0.004 (-0.025 - 0.017)	340%	-0.008 (-0.029 - 0.013)	33%
Remote (>5yrs) life-event stress	0.160*** (0.129 - 0.191)	0.020 (-0.001 - 0.040)		0.016 (-0.006 - 0.037)	-6%

Childhood adversity	1.076*** (0.611 - 1.542)	0.555** (0.215 - 0.896)	-95%	0.506** (0.165 - 0.846)	-4%
Neuroticism	0.947*** (0.575 - 1.319)			0.023 (-0.240 - 0.286)	
Extraversion	0.068 (-0.309 - 0.445)			0.350** (0.112 - 0.589)	
Problem-focused coping	0.236 (-0.134 - 0.605)			0.264* (0.030 - 0.499)	
Help-seeking coping	0.545** (0.174 - 0.915)			0.197 (-0.043 - 0.438)	
Atypical depression	4.345*** (2.807 - 5.882)			2.036*** (1.046 - 3.026)	
Melancholic depression	1.278* (0.098 - 2.457)			-0.302 (-1.095 - 0.491)	
Combined depression	4.429*** (2.572 - 6.285)			1.000 (-0.200 - 2.199)	
Unspecified depression	1.142* (0.215 - 2.069)			0.055 (-0.552 - 0.663)	

- CI = confidence interval; BMI = body mass index.
- Model-1: model with psychosocial stress variables adjusted for socio-demographics (sex, age, income level, educational level), family history of cardio-metabolic risk, health-related lifestyle factors (alcohol consumption, smoking status, physical inactivity) and the use of weight-increasing medication;
- Model-2: model-1 with psychological factors (personality traits, coping strategies and major depressive disorder subtypes).
- Betas associated with recent and remote stress are a one percent increase in the range of that variable;
- Betas associated with Neuroticism, Extraversion, Problem-focused coping, Help-seeking coping are one standard deviation increase for that variable;
- * p<0.05, ** p<0.01, ***p<0.001;
- $\Delta = \left(\frac{\beta \text{ Model with adjustments } - \beta \text{ Reference model}}{\beta \text{ Model with adjustments}}\right) \times 100\%$

Table 4. Associations between psychosocial stress lipids, blood glucose and systolic blood pressure in bivariate and multiple covariate regression models

	Bivariate	Model-1		Model-2	
	Beta (95%CI)	Beta (95%CI)	Δ	Beta (95%CI)	Δ
Triglycerides [mmol l $^{-1}$] (N=2673)					
Recent (<5yrs) life-event stress	-0.001 (-0.003 - 0.001)	0.001 (-0.002 - 0.003)		0.000 (-0.002 - 0.003)	
Remote (>5yrs) life-event stress	0.001 (-0.001 - 0.003)	0.000 (-0.002 - 0.002)		0.000 (-0.002 - 0.002)	
Childhood adversity	-0.011 (-0.035 - 0.013)	0.000 (-0.034 - 0.033)		-0.001 (-0.034 - 0.033)	
Neuroticism	-0.019* (-0.039 - 0.000)			-0.007 (-0.033 - 0.019)	
Extraversion	0.011 (-0.008 - 0.031)			0.042*** (0.019 - 0.065)	
Problem-focused coping	-0.018 (-0.037 - 0.001)			-0.003 (-0.026 - 0.020)	
Help-seeking coping	-0.029** (-0.048 - -0.009)			0.010 (-0.014 - 0.033)	
Atypical depression	0.032 (-0.048 - 0.113)			0.040 (-0.058 - 0.137)	
Melancholic depression	-0.047 (-0.108 - 0.014)			0.009 (-0.069 - 0.086)	
Combined depression	-0.132** (-0.229 - -0.035)			-0.036 (-0.154 - 0.082)	
Unspecified depression	-0.028 (-0.075 - 0.020)			0.015 (-0.044 - 0.075)	
High density lipoprotein [mmol l $^{-1}$] (N=2673)					
Recent (<5yrs) life-event stress	-0.001 (-0.002 - 0.001)	-0.001 (-0.002 - 0.000)		-0.001 (-0.002 - 0.000)	
Remote (>5yrs) life-event stress	0.000 (-0.001 - 0.002)	-0.001 (-0.002 - 0.001)		-0.001 (-0.002 - 0.001)	
Childhood adversity	-0.014 (-0.037 - 0.009)	-0.020 (-0.041 - 0.001)		-0.021* (-0.042 - 0.000)	*6%*
Neuroticism	0.012 (-0.006 - 0.030)			-0.001 (-0.017 - 0.016)	
Extraversion	-0.016 (-0.034 - 0.003)			-0.015 (-0.029 - 0.000)	
Problem-focused coping	-0.009 (-0.028 - 0.009)			0.010 (-0.004 - 0.025)	
Help-seeking coping	0.025** (0.008 - 0.043)			-0.007 (-0.022 - 0.008)	
Atypical depression	0.052 (-0.027 - 0.130)			0.054 (-0.008 - 0.115)	
Melancholic depression	0.090** (0.032 - 0.148)			-0.003 (-0.052 - 0.046)	
Combined depression	0.076 (-0.019 - 0.170)			-0.004 (-0.078 - 0.071)	
Unspecified depression	0.021 (-0.025 - 0.068)			0.015 (-0.023 - 0.052)	
Apolipoprotein B [mg dl $^{-1}$] (N=2500)					

Recent (<5yrs) life-event stress	-0.344** (-0.580 - -0.109)	-0.443** (-0.728 - -0.157)	-0.437** (-0.724 - -0.150)
Remote (>5yrs) life-event stress	0.265* (0.034 - 0.496)	0.626*** (0.338 - 0.913)	0.607*** (0.312 - 0.901)
Childhood adversity	-1.924 (-5.969 - 2.121)	-0.504 (-5.273 - 4.265)	-0.125 (-4.918 - 4.668)
Neuroticism	-1.730 (-4.390 - 0.931)		-1.853 (-5.446 - 1.740)
Extraversion	-0.940 (-3.620 - 1.740)		0.303 (-2.956 - 3.562)
Problem-focused coping	-2.085 (-4.741 - 0.572)		-1.984 (-5.167 - 1.200)
Help-seeking coping	-3.609** (-6.296 - -0.923)		-0.453 (-3.819 - 2.912)
Atypical depression	-8.415 (-19.761 - 2.932)		-2.016 (-15.903 - 11.871)
Melancholic depression	-4.370 (-12.888 - 4.148)		-0.737 (-11.751 - 10.277)
Combined depression	2.582 (-10.913 - 16.078)		22.707** (6.227 - 39.188)
Unspecified depression	4.997 (-1.628 - 11.622)		10.938* (2.586 - 19.290)
Fasting blood glucose [mmol l^{-1}] (N=2673)			
Recent (<5yrs) life-event stress	-0.002* (-0.004 - 0.000)	-0.001 (-0.003 - 0.001)	-0.001 (-0.003 - 0.001)
Remote (>5yrs) life-event stress	0.000 (-0.002 - 0.002)	0.001 (-0.001 - 0.003)	0.001 (-0.001 - 0.003)
Childhood adversity	0.006 (-0.021 - 0.032)	0.012 (-0.019 - 0.044)	0.012 (-0.020 - 0.043)
Neuroticism	-0.034** (-0.055 - -0.012)		-0.001 (-0.026 - 0.023)
Extraversion	0.000 (-0.021 - 0.022)		0.012 (-0.010 - 0.034)
Problem-focused coping	-0.008 (-0.029 - 0.013)		-0.010 (-0.032 - 0.011)
Help-seeking coping	-0.050*** (-0.071 - -0.029)		-0.005 (-0.027 - 0.017)
Atypical depression	-0.069 (-0.158 - 0.020)		0.018 (-0.073 - 0.110)
Melancholic depression	-0.106** (-0.173 - -0.038)		-0.028 (-0.102 - 0.045)
Combined depression	-0.060 (-0.167 - 0.048)		0.027 (-0.085 - 0.138)
Unspecified depression	-0.087** (-0.140 - -0.034)		-0.071* (-0.128 - -0.015)
Systolic blood pressure [mmHg] (N=2671)			
Recent (<5yrs) life-event stress	-0.151*** (-0.209 - -0.092)	-0.059* (-0.107 - -0.011)	-0.059* (-0.107 - -0.010)
Remote (>5yrs) life-event stress	-0.002 (-0.057 - 0.054)	-0.035 (-0.083 - 0.013)	-0.030 (-0.079 - 0.019)
Childhood adversity	0.025 (-0.786 - 0.835)	0.974* (0.191 - 1.757)	0.952* (0.165 - 1.740)
Neuroticism	-1.575*** (-2.221 - -0.929)		-0.577 (-1.185 - 0.031)
Extraversion	-0.222 (-0.877 - 0.433)		-0.065 (-0.617 - 0.488)
Problem-focused coping	0.554 (-0.093 - 1.201)		0.610* (0.071 - 1.149)
Help-seeking coping	-1.899*** (-2.536 - -1.262)		-0.159 (-0.713 - 0.395)
Atypical depression	-1.058 (-3.773 - 1.658)		1.233 (-1.063 - 3.530)

Melancholic depression	-3.373** (-5.428 - -1.317)	-0.386 (-2.221 - 1.449)
Combined depression	-2.774 (-6.056 - 0.508)	0.098 (-2.690 - 2.885)
Unspecified depression	-2.291** (-3.899 - -0.683)	-0.270 (-1.675 - 1.135)

- Model-1: model with psychosocial stress variables adjusted for socio-demographics (sex, age, income level, educational level), family history of cardio-metabolic risk, health-related lifestyle factors (alcohol consumption, smoking status, physical inactivity) and the use of weight-increasing medication;
- Model-2: model-1 with psychological factors (personality traits, coping strategies and major depressive disorder subtypes).
- Betas associated with recent and remote stress are a one percent increase in the range of that variable;
- Betas associated with Neuroticism, Extraversion, Problem-focused coping, Help-seeking coping are one standard deviation increase for that variable;
- * p<0.05, ** p<0.01, ***p<0.001;
- CI: confidence interval
- $\Delta = \left(\frac{\beta \text{ Model with adjustments } - \beta \text{ Reference model}}{\beta \text{ Model with adjustments}}\right) \times 100\%$

-

Table 5. Associations between psychosocial stress and the cumulative cardio-metabolic risk score in bivariate and multiple covariate regression models

	Bivariate	Model-1		Model-2	
	Beta (95%CI)	Beta (95%CI)	Δ	Beta (95%CI)	Δ
Cardio-metabolic risk score† (N=2478)					
Recent (<5yrs) life-event stress	-0.030** (-0.049 - -0.011)	-0.011 (-0.026 - 0.005)		-0.012 (-0.027 - 0.004)	
Remote (>5yrs) life-event stress	0.048*** (0.030 - 0.067)	0.016* (0.001 - 0.032)	-183%	0.017* (0.001 - 0.033)	7%
Childhood adversity	0.371** (0.103 - 0.639)	0.268* (0.007 - 0.528)	-28%	0.278* (0.017 - 0.540)	-4%
Neuroticism	-0.034 (-0.246 - 0.179)			-0.093 (-0.289 - 0.103)	
Extraversion	0.076 (-0.138 - 0.291)			0.250** (0.073 - 0.428)	
Problem-focused coping	-0.023 (-0.235 - 0.189)			-0.013 (-0.186 - 0.161)	
Help-seeking coping	-0.365*** (-0.579 - -0.151)			0.074 (-0.109 - 0.257)	
Atypical depression	0.575 (-0.327 - 1.477)			0.664 (-0.090 - 1.418)	
Melancholic depression	-0.903** (-1.584 - -0.222)			-0.372 (-0.973 - 0.229)	
Combined depression	0.567 (-0.499 - 1.633)			0.328 (-0.566 - 1.222)	
Unspecified depression	-0.290 (-0.824 - 0.244)			-0.010 (-0.465 - 0.445)	

- † The sum of gender specific standardized z-scores of body mass index, waist circumference, body fat mass, triglycerides, high density lipoprotein (inversed levels), apolipoprotein B, fasting blood glucose and systolic blood pressure.
- Model-1: model with psychosocial stress variables adjusted for socio-demographics (sex, age, socioeconomic level), family history of cardio-metabolic risk, health related lifestyle factors (alcohol consumption, smoking status, physical inactivity) and the use of medication (anti-diabetic, anti-hypertensive, lipid-lowering and other weight-increasing medication);
- Model-2: model-1 with psychological factors (personality traits, coping strategies and major depressive disorder subtypes).
- Betas associated with recent and remote stress are a one percent increase in the range of that variable;
- Betas associated with Neuroticism, Extraversion, Problem-focused coping, Help-seeking coping are one standard deviation increase for that variable;
- * p<0.05, ** p<0.01, ***p<0.001;
- CI: confidence interval
- $\Delta = \left(\frac{\beta \text{ Model with adjustments} - \beta \text{ Reference model}}{\beta \text{ Model with adjustments}}\right) \times 100\%$

SUPPLMENTARY MATERIAL

Supplementary A

Table A. Distribution of gender specific cardio-metabolic risk indicators

Variable	Males					
	Mean (±SD)	Min	1st quartile	Median	3rd quartile	Max
Body Mass Index (kg/m^2)	26.2 (±3.8)	16.2	23.6	25.7	28.1	47.2
Waist circumference (cm)	94.4 (±10.8)	64.0	87.0	94.0	100.0	150.0
Body fat mass (%)	22.8 (±5.7)	7.0	19.0	22.8	26.0	44.9
Triglycerides (mmol l^{-1})	1.6 (±1.3)	0.3	0.9	1.3	1.9	20.7
High density lipoprotein (mmol l^{-1})	1.4 (±0.3)	0.6	1.2	1.4	1.6	3.2
Apolipoprotein B (mg dl^{-1})	168.8 (±109)	24.0	102.0	142.0	203.4	1162.2
Fasting blood glucose (mmol l^{-1})	5.6 (±1.0)	0.3	5.2	5.5	5.9	21.2
Systolic blood pressure (mmHg)	130.5 (±15.6)	93.0	120.0	128.0	138.5	219.0

Variable	Females					
	Mean (±SD)	Min	1st quartile	Median	3rd quartile	Max
Body Mass Index (kg/m^2)	24.7 (±4.8)	15.7	21.3	23.6	26.9	59.1
Waist circumference (cm)	82.0 (±12.4)	58.0	73.0	80.0	89.0	162.0
Body fat mass (%)	33.0 (±7.9)	4.0	28.0	33.0	38.0	64.9
Triglycerides (mmol l^{-1})	1.1 (±0.6)	0.2	0.7	1.0	1.3	13.3
High density lipoprotein (mmol l^{-1})	1.8 (±0.4)	0.8	1.5	1.8	2.0	3.4
Apolipoprotein B (mg dl^{-1})	163.6 (±132.1)	21.0	92.0	130.1	186.3	1
Fasting blood glucose (mmol l^{-1})	5.2 (±1)	0.6	4.9	5.1	5.5	20.2
Systolic blood pressure (mmHg)	121.5 (±16.1)	86.5	110.0	119.5	130.5	193.0

SD:standard deviation

Supplementary B

Table B: Box-Cox power transformation

Variable Name	Box-Cox power	Transformed variable
Body Mass Index	-0.94	Body Mass Index $^{-0.94}$
Waist circumference	-0.46	Waist circumference $^{-0.46}$
Body fat mass	0.58	Body fat mass $^{0.58}$
Triglycerides	-0.38	Triglycerides $^{-0.38}$
High density lipoprotein	0.06 ~ Log	Log (High density lipoprotein)
Apolipoprotein B	-0.14	Apolipoprotein B $^{-0.14}$
Fasting blood glucose	0.3	Fasting blood glucose $^{0.3}$
Systolic blood pressure	-0.86	Systolic blood pressure $^{-0.86}$

Supplementary C

Analyses to identify factors underlying cardio-metabolic risk indicators

Objective

Factor analysis was performed on 8 normalized and standardized cardio-metabolic risk indicators (body mass index (BMI), waist circumference, body fat mass, triglycerides, high density lipoprotein (HDL), apolipoprotein B (ApoB), fasting blood glucose and systolic blood pressure (SBP)). The objective was to assess the plausibility of aggregating the indicators to create a composite measure representing an overall cardio-metabolic risk.

Procedure

First, analyses were performed to determine the appropriate number of factors that better explain the variance in the data. The optimal number of factors were identified based on a combination of criteria including Kaiser-Guttman rule (eigen-value > 1), parallel analysis and a scree test acceleration factor (1). Based on the identified number of factors, exploratory factor analysis was run in a training dataset (n=803) and factors were extracted using oblique rotation and the weighted least-square estimation method. The relation between the respective indicators and the factor was evaluated by the rotated factor loadings; variables with factor loadings above 0.3 were considered important. Finally, a confirmatory factor analysis was performed in the remaining dataset (n=1871) to test whether relationships among the observed variables were explained by specifying the factor structure that connects them. Weighted least square estimation method, with list-wise deletion for the missing data was used. The latent factors were standardized, allowing free estimation of all factor loadings. Model fit measures were obtained to assess how well the proposed model captured the covariance between all the variables in the model; model fit was evaluated using modification indices and improved accordingly.

Results

According to the criterion of an eigen-value greater than 1.0 and a parallel analysis 2-3 factors were suggested; however, no abrupt change in the slope after the second factor was observed. Hence, a one factor model where there was a maximal acceleration factor was considered appropriate.

In the exploratory factor analysis with one factor, 31% of the total variance in the data could be explained, whereas with two factors, the cumulative percent of variance accounted for by the two factors together was only 39%. In addition, the two factors were positively correlated (Coef=0.44) (see figure C1). The factor loading patterns of both the one and two factor models are presented in Table C1 and figure C2. The relative importance of BMI, waist circumference, glucose and SBP increased considerably in the one factor model compared to each of them in different factors; whereas, body fat mass, HDL and triglycerides decreased in the one factor model. ApoB had very little importance in each factor model.

Results of the confirmatory factor analysis show that the model fit for the one-factor model was acceptable (see Table C2). The one-factor model that allows covariance among variables fit the data significantly better than the model with no residual covariance. As expected, all indicators showed significant factor loadings, with standardized coefficients ranging from 0.08 (ApoB) to 0.94 (waist circumference) (see Table C3).

Taken together, the results were consistent in both exploratory and confirmatory factor analyses; one common factor was reasonably sufficient to explain as much of the total variance in the data. With respect to the relative importance of each variable corresponding to a one-factor model, they also seemed to underline the cumulative cardio-metabolic construct. Therefore, it is plausible to combine these indicators together and construct a composite cardio-metabolic risk index.

Figure C2. Factor plots based on exploratory factor analysis

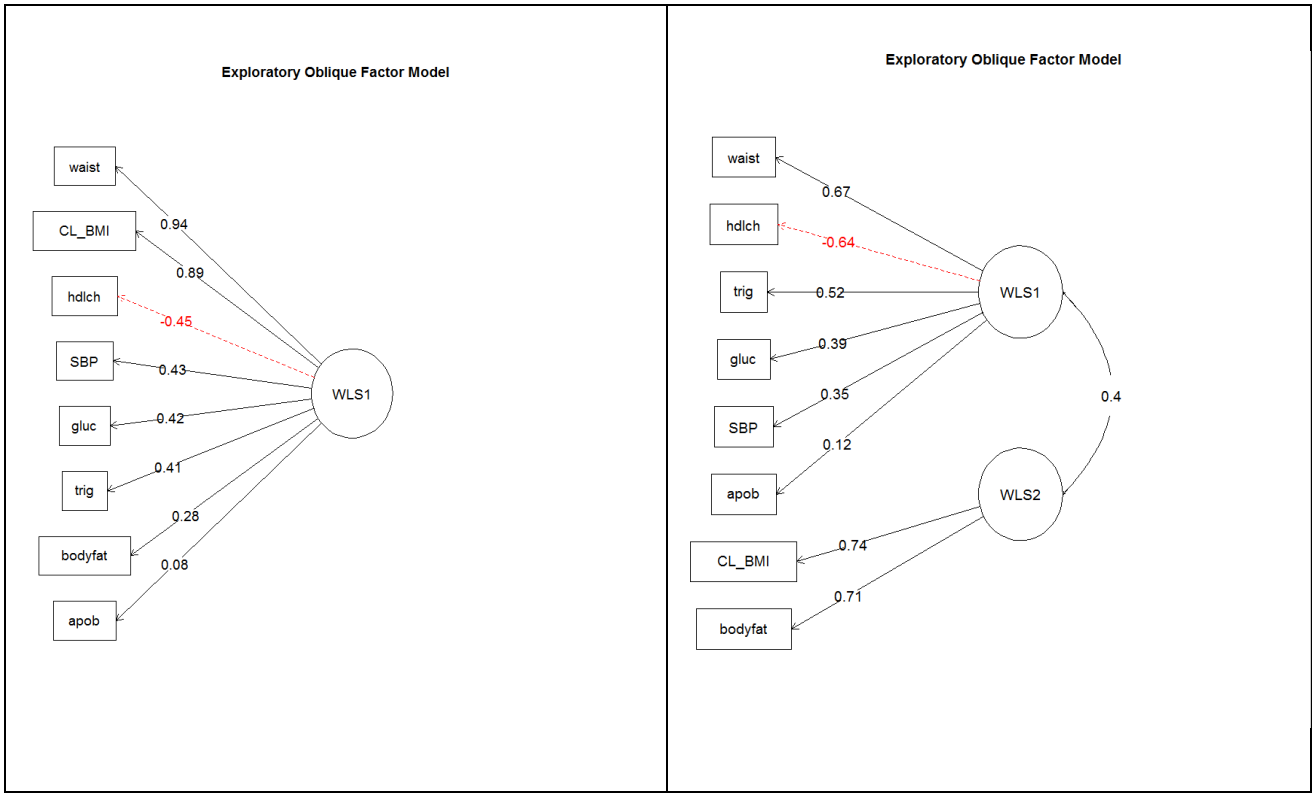


Table C1. Exploratory factor analysis, factor solutions

Cardio-metabolic risk indicators	One factor		Two factors		
	Loadings (Factor-1)	Communality	Loadings (Factor-1)	Loadings (Factor-2)	Communality
Body mass index	0.89	0.78	0.37	0.74	0.90
Waist circumference	0.94	0.88	0.67	0.41	0.83
Body fat mass	0.28	0.07	-0.27	0.71	0.42
High density lipoprotein	-0.45	0.20	-0.64	0.13	0.36
Triglycerides	0.41	0.16	0.52	-0.05	0.25
Apolipoprotein B	0.08	0.006	0.12	-0.04	0.01
Fasting blood glucose	0.42	0.17	0.39	0.09	0.18
Systolic blood pressure	0.43	0.18	0.35	0.16	0.19

Table C2. Confirmatory factor analysis, goodness-of-fit indices of one-factor cardio-metabolic risk model

Goodness-of-fit statistics	Values	Desired range of values for a good fit
Absolute fit measures		
Chi-square test	<0.001	p-value > 0.05
Goodness of fit index	0.99	> 0.9
Degrees of freedom	17	0
Root mean square error of approximation (RMSEA)	0.03	< 0.08
Incremental fit measures		
Adjusted good-of -fit index (AGFI)	0.982	> 0.9
Tucker-Lewis index (TLI)	0.978	> 0.9
Normed fit index (NFI)	0.98	> 0.9
Comparative fit index (CFI)	0.987	> 0.9
Parsimonious fit measures		
Parsimonious normed fit index (PNFI)	0.595	> 0.5
Parsimonious goodness-of-fit index (PGFI)	0.468	> 0.5

Table C3. Confirmatory factor analysis, parameter estimates of one-factor cardio-metabolic risk model

Cardio-metabolic indicators	Estimates	R^2
Body mass index	0.89	0.78
Waist circumference	0.94	0.88
Body fat	0.28	0.07
High density lipoprotein	-0.45	0.20
Triglycerides	0.41	0.16
Apolipoprotein B	0.08	0.006
Fasting blood glucose	0.42	0.17
Systolic blood pressure	0.43	0.18

Supplementary D

Analyses to determine the best proxy measure

Objective

An ancillary analysis was performed to understand how chronic stress could be better measured in our sample. We also wanted to characterize the temporal course of stress, i.e., at which exposure window stress could have a considerable effect on actual psychological distress.

Procedure

We compared two possible proxy measures of stress: the number of events participants experienced and the severity scores provided for each event that occurred, against a known psychological distress measure. For both measures, we calculated a cumulative score by varying the duration of the exposure to stressors from the most recent one-year period up to a maximum of 10 years in retrospect. Participants' current state of psychological distress was evaluated by the 12-item General Health Questionnaire (GHQ-12) (2). Using the overall GHQ score (max=12), two groups with typical scores (<4) and evidence of distress (4 and above) were created. The performance of both measures in classifying (typical score and evidence of distress) was evaluated using the Receiver Operating Characteristic (ROC). The area under the curve (AUC) indicated the probability that a random score from a participant was indicative of psychological distress. Additionally, we ran linear regression models with each additional year score and the raw GHQ score, after which effect sizes were compared. The superiority of each model, relative to each of the other models, was also evaluated based on the Akaike Information Criterion (AIC) and adjusted Coefficient of determination (R^2). The AIC provides a relative estimate of the information lost when a given model is used compared to the previous model; the smaller the AIC is the better. The Adj.R2 evaluated the proportion of variance in the GHQ-12 score that was predictable from the proxy measures.

Results

Results are summarized in figure D1 & D2. Models that used the number of events as a proxy measure showed that events in the last three years classified psychological distress better than other periods with a 58.9 % of chance of being correctly classified. The number of events within the same exposure window explained about 3% of the variance in the overall GHQ score. In models using the cumulative severity score, psychological distress was better classified by scores within the last five years. The AUC was highest for the fifth year with no significant increase in magnitude after that year. The probability of correct classification was also about 0.64 and about 6% of the total variance in the GHQ score could be explained. Overall, in terms of their construct, both measures seemed to measure distress (significantly related to the GHQ score). However, life event severity scores within the last five years better classified psychological distress with a broader exposure window than the number of events.

Figure – D1. Model indicators, psychological distress and number life events per additional year

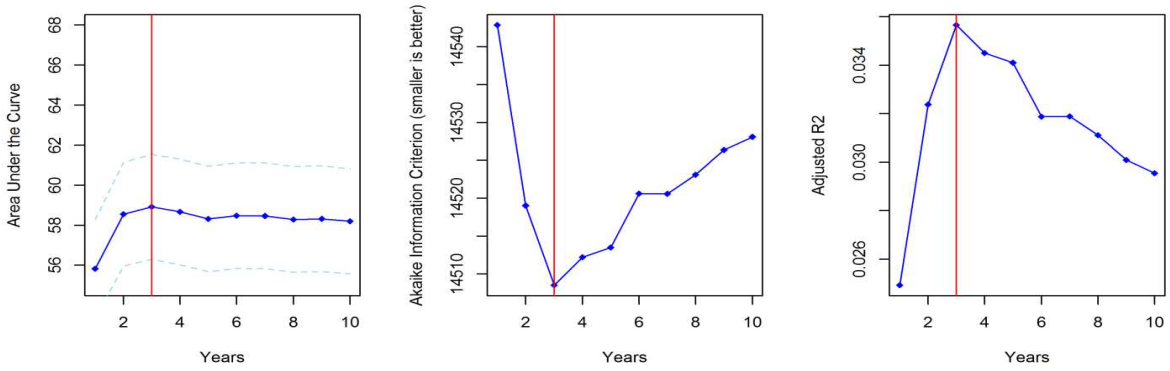
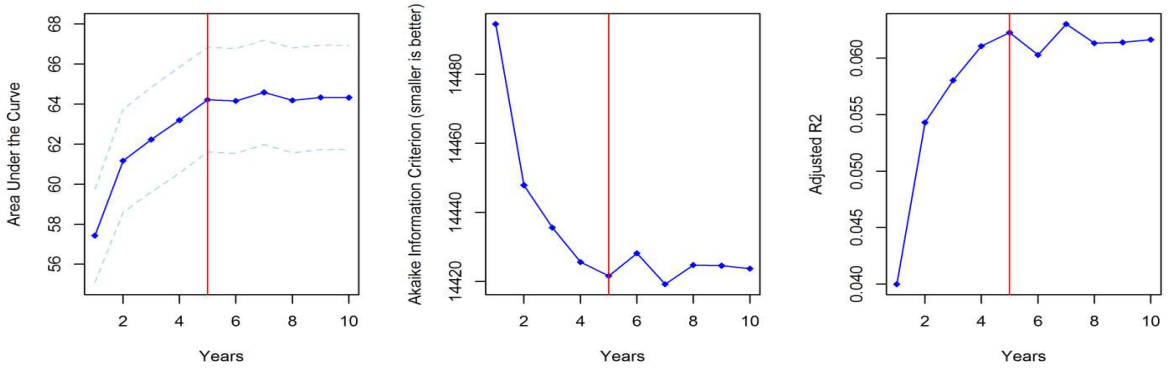


Figure- D2. Model indicators, psychological distress and life event severity scores per additional year



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2. Goldberg DP. The detection of psychiatric illness by questionnaire: a technique for the identification and assessment of non-psychotic psychiatric illness. illustrated ed: Oxford University Press, London; 1972.

Supplementary E

Table E1. Associations between psychosocial stress (count of events) and obesity markers in bivariate and multiple covariate regression models

	Bivariate	Model-1		Model-2	
	Beta (95%CI)	Beta (95%CI)	*Δ*	Beta (95%CI)	Δ
Body Mass Index (kg/m²) (N=2674)					
Number of Recent life-events	-0.089** (-0.152 - -0.025)	-0.008 (-0.068 - 0.051)		-0.022 (-0.082 - 0.037)	
Number of remote life-events	-0.015 (-0.042 - 0.013)	-0.010 (-0.035 - 0.015)		-0.007 (-0.032 - 0.018)	
Childhood adversity	0.251* (0.013 - 0.489)	0.309** (0.091 - 0.527)	***-39%***	0.276* (0.057 - 0.495)	**-5%**
Neuroticism	-0.149 (-0.310 - 0.011)			-0.026 (-0.194 - 0.142)	
Extraversion	0.164* (0.001 - 0.326)			0.300*** (0.146 - 0.453)	
Problem-focused coping	0.017 (-0.143 - 0.177)			0.022 (-0.129 - 0.172)	
Help-seeking coping	-0.353*** (-0.512 - -0.194)			-0.035 (-0.191 - 0.120)	
Atypical depression	0.717* (0.043 - 1.392)			1.363*** (0.724 - 2.001)	
Melancholic depression	-1.024*** (-1.527 - -0.521)			-0.259 (-0.766 - 0.248)	
Combined depression	-0.235 (-1.045 - 0.574)			0.169 (-0.601 - 0.939)	
Unspecified depression	-0.518* (-0.915 - -0.120)			-0.124 (-0.515 - 0.267)	
Waist circumference (cm) (N=2673)					
Number of Recent life-events	-0.355** (-0.574 - -0.136)	-0.003 (-0.167 - 0.161)		-0.031 (-0.195 - 0.134)	
Number of remote life-events	-0.039 (-0.136 - 0.058)	-0.013 (-0.082 - 0.056)		-0.008 (-0.076 - 0.061)	
Childhood adversity	0.388 (-0.451 - 1.226)	0.739* (0.136 - 1.342)	***9%***	0.683* (0.076 - 1.290)	**-6%**
Neuroticism	0.268*** (0.119 - 0.418)			-0.150 (-0.618 - 0.317)	
Extraversion	0.007 (-0.137 - 0.151)			0.570** (0.144 - 0.995)	
Problem-focused coping	-0.022 (-0.171 - 0.127)			-0.031 (-0.448 - 0.386)	
Help-seeking coping	-0.121 (-1.814 - 1.572)			0.043 (-0.387 - 0.473)	
Atypical depression	-0.775 (-1.958 - 0.408)			3.124*** (1.354 - 4.894)	
Melancholic depression	1.889 (-0.098 - 3.875)			-0.371 (-1.777 - 1.035)	
Combined depression	0.892 (-0.078 - 1.862)			0.757 (-1.377 - 2.892)	
Unspecified depression	-2.707*** (-4.090 - -1.324)			-0.473 (-1.558 - 0.612)	
Body fat mass (%) (N=2649)					
Number of recent life-events	-0.328*** (-0.474 - -0.182)	-0.023 (-0.115 - 0.070)		-0.033 (-0.124 - 0.059)	
Number of remote life-events	-0.010 (-0.074 - 0.054)	-0.017 (-0.056 - 0.021)		-0.016 (-0.054 - 0.022)	
Childhood adversity	1.328*** (0.775 - 1.880)	0.589*** (0.251 - 0.928)	***-137%***	0.548** (0.208 - 0.888)	**-8%**
Neuroticism	0.421 (-0.019 - 0.861)			0.042 (-0.218 - 0.302)	
Extraversion	0.033 (-0.392 - 0.458)			0.362** (0.123 - 0.600)	
Problem-focused coping	-0.081 (-0.520 - 0.358)			0.271* (0.036 - 0.505)	
Help-seeking coping	0.987 (-3.999 - 5.973)			0.196 (-0.044 - 0.436)	
Atypical depression	-3.200 (-6.685 - 0.285)			2.064*** (1.077 - 3.051)	
Melancholic depression	3.701 (-2.149 - 9.551)			-0.222 (-1.009 - 0.564)	
Combined depression	1.333 (-1.525 - 4.192)			1.106 (-0.081 - 2.294)	
Unspecified depression	1.143* (0.216 - 2.069)			0.082 (-0.524 - 0.688)	

- Model-1: model with psychosocial stress variables adjusted for socio-demographics (sex, age, income level, educational level), family history of cardio-metabolic risk, health related lifestyle factors (alcohol consumption, smoking status, physical inactivity) and the use of weight-increasing medication;
- Model-2: model-1 with psychological factors (personality traits, coping strategies and major depressive disorder subtypes);
- Betas associated with recent and remote life events are for one event increase;
- Betas associated with Neuroticism, Extraversion, Problem-focused coping, Help-seeking coping are one standard deviation increase for that variable;
- * p<0.05, ** p<0.01, ***p<0.001;
- CI: confidence interval
- $\Delta = \left(\frac{\beta \text{ Model with adjustments } - \beta \text{ Reference model}}{\beta \text{ Model with adjustments}}\right) \times 100\%$

Table E2. Associations between psychosocial stress (count of events), lipids, blood glucose and systolic blood pressure in bivariate and multiple covariate regression models

	Bivariate	Model-1		Model-2	
	Beta (95%CI)	Beta (95%CI)	Δ	Beta (95%CI)	Δ
Triglycerides (mmol l $^{-1}$) (N=2673)					
Number of Recent life-events	-0.009* (-0.016 - -0.001)	0.002 (-0.007 - 0.011)		0.001 (-0.008 - 0.010)	
Number of remote life-events	-0.001 (-0.004 - 0.003)	0.001 (-0.003 - 0.005)		0.001 (-0.003 - 0.005)	
Childhood adversity	0.003 (-0.026 - 0.032)	0.000 (-0.033 - 0.033)		0.000 (-0.033 - 0.033)	
Neuroticism	-0.043* (-0.084 - -0.001)			-0.006 (-0.032 - 0.019)	
Extraversion	0.024 (-0.014 - 0.062)			0.042*** (0.019 - 0.066)	
Problem-focused coping	-0.014 (-0.050 - 0.023)			-0.003 (-0.026 - 0.020)	
Help-seeking coping	-0.043* (-0.081 - -0.005)			0.010 (-0.014 - 0.033)	
Atypical depression	-0.113 (-0.542 - 0.317)			0.041 (-0.056 - 0.138)	
Melancholic depression	0.215 (-0.086 - 0.517)			0.010 (-0.067 - 0.087)	
Combined depression	0.550* (0.045 - 1.054)			-0.035 (-0.152 - 0.082)	
Unspecified depression	-0.028 (-0.075 - 0.020)			0.016 (-0.044 - 0.075)	
High density lipoprotein (mmol l $^{-1}$) (N=2673)					
Number of Recent life-events	-0.010** (-0.017 - -0.002)	-0.011*** (-0.016 - -0.005)	-35%	-0.010*** (-0.016 - -0.005)	-3%
Number of remote life-events	0.003 (0.000 - 0.006)	0.002 (0.000 - 0.004)		0.002 (0.000 - 0.004)	
Childhood adversity	-0.023 (-0.051 - 0.004)	-0.020 (-0.041 - 0.000)		-0.021 (-0.042 - 0.000)	
Neuroticism	-0.018 (-0.061 - 0.024)			-0.003 (-0.019 - 0.013)	
Extraversion	0.010 (-0.029 - 0.049)			-0.015 (-0.029 - 0.000)	
Problem-focused coping	0.012 (-0.025 - 0.050)			0.010 (-0.005 - 0.024)	
Help-seeking coping	0.016 (-0.023 - 0.056)			-0.007 (-0.021 - 0.008)	
Atypical depression	0.030 (-0.431 - 0.490)			0.054 (-0.007 - 0.115)	
Melancholic depression	-0.040 (-0.353 - 0.274)			-0.006 (-0.054 - 0.043)	
Combined depression	0.133 (-0.372 - 0.638)			-0.011 (-0.085 - 0.062)	
Unspecified depression	0.021 (-0.026 - 0.068)			0.014 (-0.024 - 0.051)	
Apolipoprotein B (mg dl -1) (N=2500)					
Number of Recent life-events	-1.767*** (-2.810 - -0.724)	-1.920** (-3.173 - -0.667)	-35%	-1.917** (-3.173 - -0.660)	0%
Number of remote life-events	0.450 (-0.005 - 0.906)	0.970*** (0.447 - 1.492)	2%	0.976*** (0.453 - 1.500)	
Childhood adversity	-1.924 (-5.969 - 2.121)	0.572 (-4.162 - 5.307)		0.727 (-4.041 - 5.495)	
Neuroticism	0.098 (-1.143 - 1.338)			-1.259 (-4.818 - 2.300)	
Extraversion	0.604 (-0.549 - 1.757)			0.812 (-2.446 - 4.070)	
Problem-focused coping	0.639 (-0.478 - 1.756)			-1.886 (-5.067 - 1.296)	
Help-seeking coping	0.164 (-0.984 - 1.311)			-0.362 (-3.728 - 3.004)	
Atypical depression	-2.448 (-7.536 - 2.641)			-1.064 (-14.921 - 12.793)	
Melancholic depression	-2.524 (-6.200 - 1.153)			0.920 (-10.021 - 11.861)	
Combined depression	2.848 (-3.117 - 8.813)			25.027** (8.733 - 41.322)	
Unspecified depression	5.096 (-1.540 - 11.731)			11.525** (3.194 - 19.856)	
Fasting blood glucose (mmol l $^{-1}$) (N=2673)					
Number of Recent life-events	-0.009* (-0.018 - -0.001)	-0.004 (-0.012 - 0.005)		-0.004 (-0.012 - 0.004)	
Number of remote life-events	0.002 (-0.002 - 0.006)	0.001 (-0.003 - 0.004)		0.001 (-0.003 - 0.004)	
Childhood adversity	0.006 (-0.025 - 0.038)	0.013 (-0.018 - 0.044)		0.013 (-0.018 - 0.044)	
Neuroticism	0.366** (0.115 - 0.618)			-0.001 (-0.026 - 0.023)	
Extraversion	0.318* (0.076 - 0.560)			0.012 (-0.010 - 0.035)	
Problem-focused coping	0.161 (-0.089 - 0.411)			-0.010 (-0.031 - 0.012)	
Help-seeking coping	-0.654 (-3.490 - 2.183)			-0.005 (-0.028 - 0.017)	
Atypical depression	-1.922 (-3.912 - 0.069)			0.018 (-0.073 - 0.110)	
Melancholic depression	4.700** (1.373 - 8.027)			-0.027 (-0.100 - 0.046)	
Combined depression	1.012 (-0.618 - 2.641)			0.028 (-0.082 - 0.138)	
Unspecified depression	-0.087** (-0.141 - -0.034)			-0.071* (-0.127 - -0.015)	

Systolic blood pressure (mmHg) (N=2671)					
Number of Recent life-events	-0.798*** (-1.053 - -0.544)	-0.320** (-0.531 - -0.108)	-175	-0.316** (-0.529 - -0.103)	1
Number of remote life-events	-0.087 (-0.199 - 0.026)	-0.003 (-0.092 - 0.086)		0.000 (-0.089 - 0.089)	
Childhood adversity	0.429 (-0.542 - 1.400)	0.911* (0.133 - 1.690)	5	0.918* (0.132 - 1.704)	-1
Neuroticism	-1.575*** (-2.221 - -0.929)			-0.075 (-0.270 - 0.119)	
Extraversion	-0.222 (-0.877 - 0.433)			0.261** (0.083 - 0.438)	
Problem-focused coping	0.554 (-0.093 - 1.201)			-0.004 (-0.178 - 0.169)	
Help-seeking coping	-1.899*** (-2.536 - -1.262)			0.067 (-0.116 - 0.250)	
Atypical depression	-1.058 (-3.773 - 1.658)			0.690 (-0.063 - 1.442)	
Melancholic depression	-3.373** (-5.428 - -1.317)			-0.290 (-0.887 - 0.308)	
Combined depression	-2.774 (-6.056 - 0.508)			0.465 (-0.420 - 1.350)	
Unspecified depression	-2.291** (-3.899 - -0.683)			0.023 (-0.431 - 0.478)	

- Model-1: model with psychosocial stress variables adjusted for socio-demographics (sex, age, socioeconomic level), family history of cardio-metabolic risk, health related lifestyle factors (alcohol consumption, smoking status, physical inactivity) and the use of medication (anti-diabetic, anti-hypertensive, lipid-lowering and other weight-increasing medication);
- Model-2: model-1 with psychological factors (personality traits, coping strategies and major depressive disorder subtypes);
- Betas associated with recent and remote life events are for one event increase;
- Betas associated with Neuroticism, Extraversion, Problem-focused coping, Help-seeking coping are one standard deviation increase for that variable;
- * p<0.05, ** p<0.01, ***p<0.001;
- CI: confidence interval
- $\Delta = \left(\frac{\beta \text{ Model with adjustments } - \beta \text{ Reference model}}{\beta \text{ Model with adjustments}}\right) \times 100\%$

Table E3. Associations between psychosocial stress (count of events) and the cumulative cardio-metabolic risk score in bivariate and multiple covariate regression models

	Bivariate	Model-1		Model-2	
	Beta (95%CI)	**Beta (95%CI)**	*Δ*	**Beta (95%CI)**	*Δ*
Cardio-metabolic risk score† (N=2478)					
Number of Recent life-events	-0.240*** (-0.323 - -0.157)	-0.037 (-0.114 - 0.040)		-0.042 (-0.119 - 0.035)	
Number of remote life-events	-0.025 (-0.061 - 0.012)	-0.017 (-0.049 - 0.015)		-0.015 (-0.047 - 0.017)	
Childhood adversity	0.523* (0.094 - 0.952)	0.473* (0.094 - 0.852)	***-15%***	0.467* (0.089 - 0.846)	***-2%***
Neuroticism	-0.034 (-0.246 - 0.179)			-0.126 (-0.344 - 0.091)	
Extraversion	0.076 (-0.139 - 0.291)			0.226* (0.026 - 0.426)	
Problem-focused coping	-0.023 (-0.235 - 0.189)			-0.028 (-0.222 - 0.167)	
Help-seeking coping	-0.365*** (-0.579 - -0.151)			0.120 (-0.084 - 0.325)	
Atypical depression	0.574 (-0.328 - 1.476)			0.648 (-0.197 - 1.492)	
Melancholic depression	-0.903** (-1.584 - -0.221)			-0.535 (-1.205 - 0.135)	
Combined depression	0.568 (-0.497 - 1.634)			0.628 (-0.361 - 1.617)	
Unspecified depression	-0.289 (-0.822 - 0.245)			0.140 (-0.372 - 0.651)	

- Model-1: model with psychosocial stress variables adjusted for socio-demographics (sex, age, socioeconomic level), family history of cardio-metabolic risk, health related lifestyle factors (alcohol consumption, smoking status, physical inactivity) and the use of medication (anti-diabetic, anti-hypertensive, lipid-lowering and other weight-increasing medication);
- Model-2: model-1 with psychological factors (personality traits, coping strategies and major depressive disorder subtypes);
- Betas associated with recent and remote life events are for one event increase;
- Betas associated with Neuroticism, Extraversion, Problem-focused coping, Help-seeking coping are one standard deviation increase for that variable;
- * p<0.05, ** p<0.01, ***p<0.001;
- CI: confidence interval
- $\Delta = \left(\frac{\beta \text{ Model with adjustments } - \beta \text{ Reference model}}{\beta \text{ Model with adjustments}}\right) \times 100\%$