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The impact of adversities across the lifespan on psychological symptom profiles in late adulthood: a latent profile analysis

C. E. Hilberdink[1,2,3], M. van Zuiden[1,2,4], M. Olff[1,2,5], T. J. Roseboom[3,6,7] and S. R. de Rooij[3,7,8]

[1]Amsterdam UMC Location University of Amsterdam, Psychiatry, Meibergdreef 9, Amsterdam, The Netherlands; [2]Amsterdam Neuroscience Research Institute, Mood, Anxiety, Psychosis, Stress and Sleep, Amsterdam, The Netherlands; [3]Department of Epidemiology and Data Science, University of Amsterdam, Amsterdam, The Netherlands; [4]Department of Clinical Psychology, Utrecht University, Utrecht, The Netherlands; [5]ARQ, National Psychotrauma Centre, Diemen, The Netherlands; [6]Department of Obstetrics and Gynaecology, University of Amsterdam, Amsterdam, The Netherlands; [7]Amsterdam Reproduction and Development, Amsterdam, The Netherlands and [8]Amsterdam Public Health research institute, Aging and Later Life, Health Behaviors and Chronic Diseases, Amsterdam, The Netherlands

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Corresponding author: C. E. Hilberdink;
Email: hilberdink@cyceron.fr

Abstract

People commonly face adverse circumstances throughout life, which increases risk for psychiatric disorders, such as anxiety, depression, psychosis, and posttraumatic stress disorder (PTSD). Adversities may occur during different periods in life. Especially adversity during early periods has been suggested to put individuals at risk for adverse mental health outcomes. Here, we investigated whether timing of adversity during the prenatal period, childhood, or mid-to-late adulthood differentially impacted classification into late adulthood symptom profiles. We performed sex-stratified Latent Profile Analysis to identify latent profiles regarding anxious, depressive, psychotic, and PTSD symptoms in $n = 568$ Dutch famine birth cohort members ($n = 294$ women, $n = 274$ men, mean age(SD) = 72.9(0.8)). Cross-sectional late adulthood symptomatology, childhood traumatic maltreatment, and adulthood trauma were based on self-report questionnaires. Prenatal adversity was considered present when individuals were prenatally exposed to the 1944-45 Dutch famine. In both men and women we identified one anxious/depressive profile and three profiles with approximately equal severity of all symptom types within each profile, yet differentiating in overall severity (low, mild, high) between profiles. We additionally found a PTSD symptom profile in women. In men, logistic regression models showed significant associations between prenatal, childhood and adulthood adversity, and profile classification, with differential effects depending on timing and most profound effects of child maltreatment. In women, childhood and adulthood adversity significantly increased classification probability into almost all profiles, with no significant effect of prenatal adversity. These findings support a time-dependent and sex-specific impact of adversity during different periods across the lifespan on psychological health, with consequences into late adulthood.

Introduction

People commonly face a variety of adverse circumstances throughout their lives, which may include physical or psychosocial environmental threats, e.g., poor nutrition, maltreatment, and traumatic accidents.[1] Although many psychological and biological factors are involved in determining an individual's mental health outcome upon exposure to adversity,[2,3] exposure to adversities per se is well known to increase the risk for a broad range of psychological problems later in life.[4,5] These psychological problems may go well beyond the psychiatric disorders formally recognized in the DSM-5 as being stressor- or trauma-related, such as posttraumatic stress disorder (PTSD), as exposure to adversity is associated with increased risk for subsequent mood-, anxiety-, schizophrenia spectrum, and other psychosis-related disorders.[6–10] Also, the risk for adverse mental health outcomes is commonly found to increase dose-dependently with increasing adversity severity and frequency.[11]

Adverse circumstances may occur during various periods in life. Adversities during early life periods are considered to particularly put exposed individuals at risk for developing unfavorable mental health outcomes, as the brain undergoes critical changes during these developmental periods which may render it particularly vulnerable to adverse circumstances.[12–14] These critical periods include the prenatal (*in utero*) period and childhood extending into adolescence.[15]

Regarding prenatal exposure, maternal exposure to both psychological and physical stressors as well as maternal psychological distress during pregnancy have been associated with an increased risk for mood and anxiety disorders, schizophrenia spectrum disorders,[9] and PTSD[7]

in the offspring during early adulthood. Additionally, famine exposure during the prenatal period has been associated with an increased risk for a multitude of mental disorders in adulthood, including depression, schizophrenia, and psychosis.[16–19] Findings from the Dutch famine birth cohort have demonstrated that specific outcomes may depend on timing of exposure during pregnancy and sex. Exposure to undernutrition during early gestation was associated with increased anxious and depressive symptoms in men in mid-adulthood, while no associations were found in men exposed during mid or late gestation, nor in women.[20]

Childhood adversities have also been demonstrated to have strong associations with adverse mental health outcomes, including all classes of mood and anxiety disorders,[8,21,22] as well as PTSD[10,23,24] and psychosis,[25,26] with persistent risk from childhood throughout mid-adulthood. Of note, specific subtypes of adversity during childhood have been shown to particularly increase the risk for mental health problems. Varied methodological approaches, such as the use of different categorizations and measuring methods,[22,27,28] may have led to inconsistent findings between studies. However, Sayyah et al[29] found differential effects and observed strong associations between childhood maltreatment and adult depressive, anxious, and PTSD symptoms, whereas adversities related to maladaptive family function less broadly predicted adult PTSD symptoms and not depressive and anxious symptoms.

Although not defined as a vulnerable developmental period, exposure to adversity during adulthood is also associated with increased risk for a broad range of subsequent psychological problems. For example, exposure to traumatic events in adulthood is associated with increased risk of subsequent onset or worsening of depressive symptoms,[30] presence of both anxious and depressive symptomatology,[31] PTSD prevalence,[32] onset and presence of psychotic symptoms,[6] and psychotic relapse.[33]

There is thus strong evidence that exposure to adversity during prenatal life, childhood, and adulthood increases the risk for a wide range of psychological symptoms and disorders in general, and particularly for mood-, anxiety-, schizophrenia spectrum and other psychosis-related disorders as well as the trauma-related disorder PTSD. However, as to the best of our knowledge, no studies have investigated the specific impact of adversity during multiple distinctively different periods in life, including the prenatal period, on mental health within the same study population across the entire lifespan until late adulthood. The ones that did measure multiple distinct life periods, measured cumulative exposure to adversity within and across these different life periods,[34] and did not study exposure within different periods across the lifespan separately. In addition, most studies investigating the effects of adversity on mental health, irrespective of the life period of exposure, focused either on specific psychological disorders and their respective symptoms without taking the absence or presence of other comorbid disorders and their respective symptoms into account,[8,23] or only investigated comorbidity between maximally two disorders at the same time.[7] Investigating comorbidity among a broad range of psychological disorders is relevant, as it may influence and exacerbate the course within disorders and outcome of symptoms.[35] Furthermore, comorbidity may interfere with diagnostic and treatment efficacy which consequently reduces symptom improvement and recovery.[36] It thus remains largely unknown whether exposure to adversity across different periods in life, including the prenatal period, childhood, and mid-to-late adulthood, increases risk for specific or comorbid psychological symptoms at an older age.

Latent Profile Analysis (LPA) is a statistical approach that can be used to identify groups of individuals with similar symptom patterns based on their occurrence and severity levels[37] and to study specificity and/or comorbidity of a broad range of psychological symptoms in a comprehensive manner. In the present study, we used LPA to identify latent profiles of anxious, depressive, psychotic, and PTSD symptoms and subsequently investigated whether exposure to adversity at different periods across the lifespan impacted classification into the observed symptom profiles measured in late adulthood. This was done in the Dutch famine birth cohort, a historical birth cohort of men and women born around the time of the 1944–1945 Dutch famine in Amsterdam, the Netherlands, aiming to investigate effects of prenatal famine exposure on adult health.[38] This cohort provides the unique opportunity to measure impact of adversities during three different periods across the lifespan, specifically during the prenatal period, early childhood, or mid-to-late adulthood, on a wide range of psychological symptoms and their comorbidity within the same population. Of note, we specifically focussed on profiles of anxious, depressive, PTSD- and psychotic symptoms as their occurrence in adulthood has frequently been associated with exposure to adversity during these three life periods and they are often comorbid.[39–41] Furthermore, we performed our analyses in men and women separately, as previous studies showed differences in the impact of specific adversities on risk for subsequent psychological problems between men and women, including in the cohort currently investigated.[20] Also, there is evidence that classification of participants into these latent profiles is biased if within-pattern sex differences were not accounted for.[42]

Methods

Participants

Participants were members of the Dutch famine birth cohort consisting of men and women born as term singletons in the Wilhelmina Gasthuis in Amsterdam around the time of the Dutch famine (1 Nov 1943–28 Feb 1947). At the start of the study, a total of $N = 2414$ eligible participants were included (complete overview of cohort establishment and following data collection waves[38,43]). Data for the current study were collected in follow-up wave-V, starting in 2018. Eligible cohort members ($N = 1207$) were invited by mail to participate in a paper-and-pencil survey. A total of $N = 595$ (49.3%) cohort members provided written informed consent to participate and completed the survey (flowchart in Supplementary Figure S1, with no differences in rates of exposure to undernutrition between participating and nonparticipating cohort members (men $X^2(3) = 4.96$, $p = 0.175$, women $X^2(3) = 0.41$, $p = 0.937$). Finally, $N = 568$ (47.1%, $n = 294$ women, $n = 274$ men) completed the relevant questionnaires for this study. Descriptive overview of participant's demographics, characteristics, exposure to adversities, and late adulthood psychological symptoms are displayed in Table 1. The Medical Ethics Committee of the Academic Medical Center, Amsterdam, the Netherlands, concluded that a full review and official approval of this study wave was not required according to Dutch law for medical research.

Measures

Adversity during different periods in life

Prenatal undernutrition. Prenatal undernutrition was considered present if average daily maternal rations during any 13-week period of gestation were below 1000 calories.[43,44] Periods of 16

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Table 1. Participant characteristics

	Men ($n = 274$)	Women ($n = 294$)	Statistics
Age *(years)*	72.8 (0.9)[8]	72.9 (0.8)	$U = 41{,}585.00$, $p = 0.456$
PSYCHOLOGICAL SYMPTOMS			
HADS depression subscale[1]	3.3 (3.4)	3.5 (3.3)	$U = 41{,}343.50$, $p = 0.582$
Probable depression (score ≥ 8)	26 (9.5%)	33 (11.2%)	$X^2(1) = 0.46$, $p = 0.498$
HADS Anxiety subscale[1]	3.1 (3.3)	4.2 (3.8)[8]	$U = 46{,}951.00$, $p < 0.001$*
Probable anxiety (score ≥ 8)	24 (8.8%)	53 (18.0%)	$X^2(1) = 10.40$, $p = 0.001$*
PCL5 PTSD symptoms[2]			
Cluster B – Intrusions	1.5 (2.5)[9]	2.6 (3.6)[10]	$U = 46{,}856.50$, $p < 0.001$*
Cluster C – Avoidance	0.7 (1.3)[9]	1.0 (1.6)[12]	$U = 43{,}446.00$, $p = 0.012$*
Cluster D – Negative Cognitions and Mood	2.7 (3.9)[10]	3.1 (4.2)[12]	$U = 42{,}582.50$, $p = 0.066$
Cluster E – Arousal and Reactivity alterations	3.7 (3.2)[8]	4.7 (3.8)[8]	$U = 46{,}021.50$, $p = 0.002$*
Probable PTSD (total score ≥ 31)	9 (3.3%)	20 (6.8%)	$X^2(1) = 3.62$, $p = 0.057$
PQ-16 Psychotic symptoms[3]			$U = 41{,}626.50$, $p = 0.212$
Total score	1.7 (2.5)[8]	1.7 (1.9)[12]	$X^2(1) < 0.01$, $p = 0.986$
Probable psychosis (score ≥6)	15 (5.5%)	16 (5.4%)	
LIFE ADVERSITIES			
Prenatal undernutrition			
Early gestation	24 (8.8%)	25 (8.5%)	
Mid gestation	26 (9.5%)	48 (16.3%)	
Late gestation	48 (17.5%)	46 (15.6%)	
Unexposed controls	176 (64.2%)	175 (59.5%)	
Childhood traumatic maltreatment[4]			
Emotional Abuse	6.7 (3.1)	7.5 (4.1)[8]	$U = 42{,}719.50$, $p = 0.144$
Physical Abuse	5.8 (2.3)	5.8 (2.6)[8]	$U = 38{,}672.00$, $p = 0.264$
Sexual Abuse	4.5 (2.0)	5.0 (2.8)[8]	$U = 43{,}634.50$, $p = 0.004$*
Emotional Neglect	11.5 (5.0)	12.1 (6.0)[11]	$U = 40{,}634.50$, $p = 0.639$
Physical Neglect	7.3 (2.7)[8]	8.0 (3.1)[10]	$U = 43{,}570.00$, $p = 0.042$*
Total score	35.9 (11.4)[8]	38.1 (13.8)[11]	$U = 41{,}996.50$, $p = 0.211$
Minimization/Denial	0.7 (1.0)	0.7 (1.0)[10]	$U = 38{,}424.00$, $p = 0.390$
Mid-to-late Adulthood trauma[5]			
Number of traumatic events (<15 years)	1.0 (1.6)	1.2 (1.5)	$U = 43{,}684.50$, $p = 0.065$
Aging sensory impairements *(n(%))*[6]	29 (10.6%)	40 (13.6%)	$X^2(1) = 1.21$, $p = 0.271$
Educational level[7]	5.0 (1-7)[9]	5.0 (1-7)[9]	$U = 34{,}137.50$, $p = 0.002$*
Marital status *(n(%))*			
Single *(Divorced/unmarried)*	29 (10.6%)	51 (17.4%)	$p < 0.001$*
Long-term relationship *(Married/living together-unmarried)*	224 (81.8%)[9]	174 (58.1%)[10]	
Widow(er)/partner passed away	19 (6.9%)	66 (22.4%)	
Perceived SES during childhood			
Low	93 (34.0%)	95 (32.3%)	$p = 0.108$

(*Continued*)

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Table 1. (*Continued*)

	Men ($n = 274$)	Women ($n = 294$)	Statistics
Medium	84 (30.7%)	76 (25.9%)	
High	97 (35.4%)	121 (41.1%)[9]	
Received help with questionnaire (*n(%)*)	13 (4.7%)[8]	19 (6.5%)[8]	$X^2(1) = 0.79$, $p = 0.375$

Scores are displayed as mean(SD) for continuous variables or *n* (%) for categorical variables. Age was calculated based on date of birth and date of filling out the questionnaires (in case this was missing (*n*=7 men, *n*=18 women), date of signing Informed Consent was used). SES: social economic status, $p < 0.05$.
[1]Measured with HADS: Hospital Anxiety and Depression Scale.
[2]Measured with PCL5: PTSD Checklist for DSM5.
[3]Measured with PQ-16: Prodromal Questionnaire.
[4]Measured with CTQ: Childhood Trauma Questionnaire.
[5]Measured with LEC-5: Life Events Checklist, number of experienced traumatic event types in the past 15 years when experienced personally, witnessed it, learned about it happening to close family members or friends, or if it happened at work.
[6]Aging sensory problems are defined as being present in case of neurological problems, loss of hearing, loss of vision, or dizziness with falling.
[7]Educational level is displayed as median (ranges min-max), defined by the following levels, 1: Less than 6 primary school classes, 2: 6 primary school classes, 3: More than primary school/primary school with uncompleted further education, 4: Practical training, 5: Secondary vocational education, 6: Pre-university education, 7: University/higher professional education.
[8]$n = 1$ missing.
[9]$n = 2$ missing.
[10]$n = 3$ missing.
[11]$n = 4$ missing.
[12]$n = 5$ missing.

weeks were delineated to differentiate between those who were mainly exposed during late gestation (born between 7 Jan and 28 Apr 1945), mid gestation (born between 29 Apr and 18 Aug 1945), and early gestation (born between 19 Aug and 8 Dec 1945; for overview, see Supplementary Figure S2)). People born before 7 Jan 1945 and conceived after 8 Dec 1945 were considered unexposed to famine in utero and acted as control group.

Childhood traumatic maltreatment. We used the Dutch self-report Childhood Trauma Questionnaire (CTQ, 27 items, range 1–5 "Never true" to "Very often true"[45–47]) to measure traumatic maltreatment experiences during childhood and adolescence, which includes five subscales: Emotional; Sexual; and Physical Abuse; Emotional; and Physical Neglect. Reliability of CTQ subscales showed mostly good internal consistency (all $\alpha > 0.774$) in men and women, except for Physical Neglect, which showed poor internal consistency (men: $\alpha = 0.497$, women: $\alpha = 0.427$). One item (item 24) was excluded from analyses because of previous invalid translation.[46] We calculated sum scores to measure total reported childhood traumatic maltreatment and subscale scores to measure reported childhood maltreatment subtypes. The Minimization–Denial subscale (MD; range 0–3) was calculated to determine response bias for possible underreporting childhood maltreatment by recoding its three items; 1 till 4 = 0 and 5 = 1.

Adulthood trauma exposure. We measured mid-to-late adulthood trauma exposure using the Dutch self-report Life Events Checklist (LEC-5[48]) including 17 traumatic event types, either directly experienced, witnessed, encountered in the line of work, or occurring to close family members/friends. We specifically inquired on events in the past 15 years to be able to investigate parallel changes in anxiety and depression symptom severity (planned future research), measured over this 15-year period. We calculated sum scores (range 0–17) to measure total number of types experienced.

Late adulthood psychological symptoms

We measured depression and anxiety symptoms in the past month using the Dutch Hospital Anxiety and Depression Survey (HADS, 14 items, range 0–4, higher scores indicating more symptoms[49]) that contains Anxiety and Depression subscales (both seven items). We assessed PTSD symptoms in the past month using the Dutch PTSD Checklist for DSM-5 (PCL5, 20 items, range 0–4, higher scores indicating more symptoms[50]) measuring four DSM-5 diagnostic symptom clusters: Cluster B – *Intrusions;* Cluster C – *Avoidance;* Cluster D – *Negative Cognitions and Mood;* Cluster E – *Arousal and Reactivity alterations.* We assessed (sub)clinical psychotic symptoms using the shortened Dutch Prodromal Questionnaire (PQ-16, 16 items, 0 = Disagree 1 = Agree[51]) measuring perceptual abnormalities/hallucination (9 items); unusual thought content/delusional ideas/paranoia (5 items), and negative symptoms (2 items).

Statistical analysis

All analyses were performed in women and men separately. A maximum of one missing item per questionnaire was allowed (2 for LEC-5), in which case the missing item was imputed by the participant's mean score on the other items (cases imputed: $n = 1$ for HADS Depression and PCL5 Cluster E; $n = 3$ for HADS Anxiety, PCL5 Cluster B and C; $n = 2$ PCL5 Cluster D; $n = 19$ for PQ-16; $n = 63$ for LEC-5). Participants were excluded from all subsequent analyses due to suspected unreliable answers combined with psychotropic medication use and extremely high scores on HADS and PQ-16 questionnaires ($n = 1$); multivariate outliers on psychological symptom scores (Mahalanobis Distances; men $n = 20$, women $n = 11$); or in case of missing Mahalanobis Distances if additionally > 25% of items to calculate sub- or total scores were missing and these scores were univariate outliers ($Z \geq 3.29$; men $n = 4$, women $n = 6$). In the remaining $N = 526$ participants (88.1%, $n = 277$ women, $n = 249$ men) we performed LPA in Mplus (v8.6[52]) to identify psychological symptom profiles based on cross-sectional continuous HADS, PQ-16, and PCL5 total and subscale scores. We followed a recommended 3-step procedure.[53–55] Model evaluation was based on pre-identified indicators of best-fitting model by testing fit of a 1-profile model and subsequently increase profile number by 1, until addition of a profile was no longer optimal or improved.[56] Indicators were Bayesian Information Criterion, Akaike Information Criterion (AIC), and adjusted-AIC (lower value: better fit), entropy (>.80:

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Table 2. Estimated mean total- and subscores for anxiety, depression, PTSD and psychotic symptom profiles of best-fitting models in men and women

Men	Low symptoms ($n = 183$)	Anxiety/Depression symptoms ($n = 15$)	Mild symptoms ($n = 42$)	High symptoms ($n = 9$)	
Depressive symptoms[1]	2.0 (0.2)	8.1 (7.1)	4.1 (0.5)	9.7 (1.2)	
Anxious symptoms[1]	1.8 (0.3)	7.0 (2.9)	4.3 (0.6)	11.1 (0.7)	
PTSD symptoms[2]					
Cluster B - *Intrusions*	0.5 (0.1)	1.1 (2.5)	3.8 (0.4)	5.2 (0.7)	
Cluster C - *Avoidance*	0.2 (0.0)	0.3 (0.2)	2.3 (0.8)	2.8 (0.5)	
Cluster D - *Negative Cognitions and Mood*	0.8 (0.1)	4.4 (2.9)	5.3 (1.1)	11.4 (1.2)	
Cluster E - *Arousal and Reactivity alterations*	2.3 (0.3)	5.5 (2.3)	5.9 (0.9)	9.9 (0.5)	
Psychotic symptoms[3]	1.0 (0.1)	2.0 (0.6)	2.1 (0.3)	7.1 (1.2)	
Women	Low symptoms (n = 162)	Anxiety/Depression symptoms (n = 27)	Mild symptoms (n = 56)	High symptoms (n = 13)	PTSD symptoms (n = 19)
Depressive symptoms[1]	2.1 (0.2)	7.3 (0.7)	3.6 (0.4)	10.6 (1.2)	4.5 (0.8)
Anxious symptoms[1]	2.2 (0.2)	9.4 (1.2)	4.6 (0.4)	11.5 (0.8)	7.9 (0.7)
PTSD symptoms[2]					
Cluster B - *Intrusions*	0.8 (0.1)	2.6 (0.6)	3.8 (0.4)	11.9 (1.0)	6.9 (0.7)
Cluster C - *Avoidance*	0.1 (0.0)	0.5 (0.2)	1.9 (0.1)	5.6 (0.3)	3.7 (0.2)
Cluster D - *Negative Cognitions and Mood*	0.9 (0.1)	5.8 (0.8)	3.5 (0.4)	14.6 (1.0)	7.5 (0.8)
Cluster E - *Arousal and Reactivity alterations*	2.7 (0.2)	8.4 (0.5)	4.6 (0.4)	13.2 (0.9)	8.9 (0.6)
Psychotic symptoms[3]	1.0 (0.1)	3.3 (0.6)	2.1 (0.3)	4.1 (0.7)	2.5 (0.4)

Scores are displayed as mean (SE).
[1]HADS: Hospital Anxiety and Depression Scale, both range 0–28.
[2]PCL5: PTSD Checklist for DSM-5, ranges Cluster B - *Intrusions* 0–20, Cluster C - *Avoidance* 0–8, Cluster D - *Negative Cognitions and Mood* 0–28, Cluster E - *Arousal and Reactivity alterations* 0–24.
[3]PQ-16: Prodromal Questionnaire, range 0–16.

indicates adequate profile division[57]), Lo–Mendell–Rubin-adjusted likelihood ratio test (LMR-A), and bootstrap likelihood ratio test (BLRT), for both tests $p < 0.05$ indicates the complex model is relatively better-fitted than a simpler model.[58,59] Models were estimated with multiple initial random starts and final stage optimizations to reduce risk of reaching local maximum that introduces bias in each bootstrap sample.[54] For BLRT, we requested 500 starting value sets in the first and 200 in the second step of optimization to avoid local likelihood maxima. Robust maximum likelihood estimator was used as this allowed for inclusion of participants with missing data with robustness against non-normality and non-independence of observations.

To assess associations between adversity during different life periods and symptom profile assignment, we subsequently performed multinomial logistic regression modeling on symptom profile assignment after investigating indicators for its assumptions (male model, minimum tolerance: 0.57, maximum VIF: 1.77; female model, minimum tolerance: 0.47, maximum VIF: 2.15).[60] We ran separate models with differential effects dependent on timing of prenatal undernutrition (dummy-coded; early, mid, and late gestation versus controls), childhood traumatic maltreatment (continuous, CTQ total scores), childhood maltreatment subtypes (continuous, CTQ subscale scores), and adulthood trauma (continuous, LEC total score) as predictors. Several continuous and dummy-coded covariates extracted from questions about demographics and aging-related sensory impairments within the survey were included: educational level (continuous), marital status (2 dummies; widow(er) versus long-term relationship, single versus long-term relationship), aging sensory impairments (in case of neurological problems, or problems with hearing or vision, or dizziness with falling; dichotomous), and receiving help filling out the questionnaire (dichotomous). We additionally included covariates for perceived social economic status during childhood (SES; continuous) and MD scores (continuous) in the models with childhood traumatic maltreatment as predictor. As sensitivity analyses, we performed all logistic regression models in men and women without any covariates (details are provided in Supplementary Materials S4–S5).

Parameters were fixed in case of empty cells in the joint distribution of predictors, covariates, and latent profile variables.[61] Results are given as log odds indicating the probability likelihood for classification into the target profile versus the reference low-symptom severity profile (Tables 3 and 4). A False Discovery Rate threshold (5%) was applied to correct the alpha value for significance for multiple comparisons.[62]

Results

Latent symptom profile labels

Results for latent profile model estimation are described in Supplementary Materials S3. For men, the best-fitting model consisted of 4-profiles and for women 5-profiles (Fig. 1).

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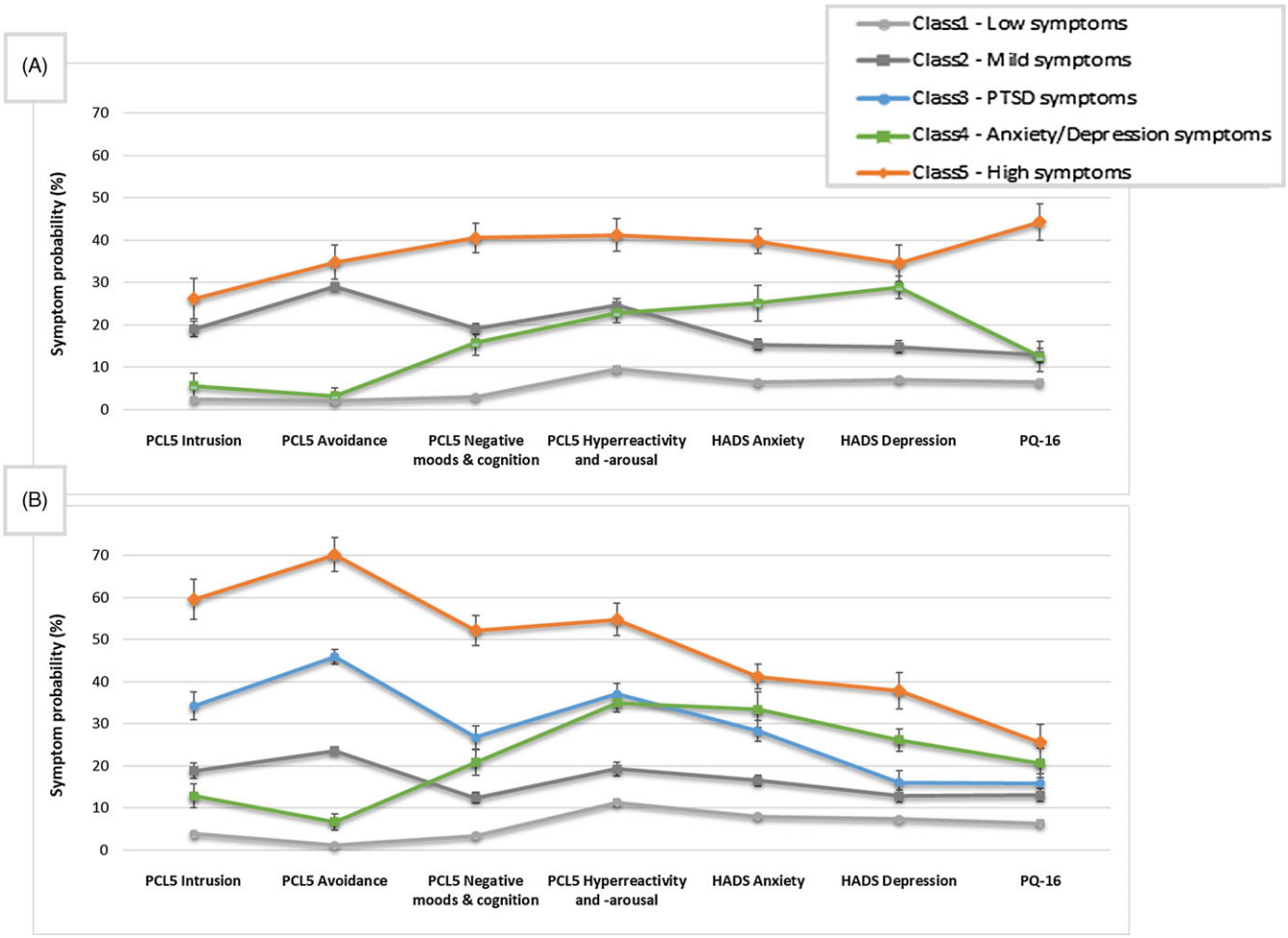

Figure 1. Latent symptom profiles based on standardized psychological symptom levels in men (A) and women (B). Symptom probability is based on the probability (%) of the relative symptom score within-profile based on questionnaire subscores of the PCL5 for PTSD-related DSM-5 symptoms, HADS anxiety and depression subscores for anxious and depressive symptoms, and total score of PQ-16 for psychotic symptoms. Error bars indicate standard errors.

Descriptive profile labels were based on means of sub- and total scores that determined profile membership (Table 2). In men, we interpreted the resulting profiles as (Fig 1a); "low symptoms" (73.5%) with lowest levels for all four psychological symptom types relative to the other profiles; "anxious/depressive symptoms" (6.0%) with relatively highest levels for anxious and depressive symptoms relative to lower levels for PTSD and psychotic symptoms within-profile and compared to the low and mild symptoms profiles; "mild symptoms" (16.9%) with moderate levels for all four symptom types compared to the other profiles; "high symptoms" (3.6%) with relatively highest levels for all four symptom types compared to the other profiles. In women, similar profiles occurred (Fig. 1b, "low symptoms" (58.5%), "anxious/depressive symptoms" (4.7%), "mild symptoms" (20.2%), "high symptoms" (4.7%)), with one additional profile; "PTSD symptoms" (6.9%) with relatively highest levels for PTSD symptoms compared to the other symptom scores within-profile and compared to the low, mild, and anxious/depressive symptom profiles.

Associations between life adversity and profile assignment

Prenatal undernutrition

We found a significant association between undernutrition in early gestation and profile assignment in men (Table 3). Findings suggested that in men exposed to famine during early gestation, probability was higher for classification into the mild- than low-symptom profile compared to unexposed men.

Childhood traumatic maltreatment

We found significant associations between childhood traumatic maltreatment and profile assignment in men (Table 3) and women (Table 4). Findings suggested that men who reported to have experienced more childhood maltreatment were associated with higher probability for classification into the anxious/depressive and high- than the low-symptom profile. In case they reported more emotional abuse, the probability was higher for classification into the mild-symptom, but lower for classification into the anxious/depressive than low-symptom profile. In case they reported more physical neglect, the probability was higher for classification into the high- than low-symptom profile. In women, reports of more childhood traumatic maltreatment was associated with higher probability for classification into the mild-, PTSD, and high- than low-symptom profile. Reports of more emotional abuse was associated with higher probability for classification into the mild-symptom profile, but when women reported more sexual abuse, the probability was higher for classification into the high- than low-symptom profile.

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Table 3. Multinomial regression analysis for associations between life adversities and probability of profile assignment in men

	Anxiety/Depression symptoms				Mild symptoms				High symptoms			
	Versus low symptoms				Versus low symptoms				Versus low symptoms			
Men ($N = 249$)	Odds	SE Odds	95% CI Odds	*p*	Odds	SE Odds	95% CI Odds	*p*	Odds	SE Odds	95% CI Odds	*p*
Model 1 ($N = 246$) Prenatal undernutrition due to famine exposure												
Early gestation	3	2.9	0.5–19.8	0.256	3.8	2.4	1.1–13.3	0.039*	3	3.7	0.3–34.0	0.371
Mid gestation	0.6	0.6	0.1–3.8	0.575	0.9	0.7	0.2–3.9	0.875	1.4	1.6	0.1–14.0	0.777
Late gestation	0.3	0.4	<0.1–2.8	0.31	0.9	0.5	0.3–2.5	0.882	0.8	0.9	0.1–7.5	0.843
Educational level	0.8	0.2	0.5–1.4	0.454	1.4	0.2	1.0–1.8	0.031*	1.2	0.3	0.7–1.4	0.606
Marital status												
Single vs long-term relation	0.9	0.8	0.2–5.1	0.928	2.3	1.3	0.8–6.7	0.125	***	***	***	<.001*
Widower vs long-term relation	1.7	1.2	0.5–6.5	0.423	0.4	0.3	0.1–1.8	0.262	265.4	<0.1	265.4–265.4	1
Other health problems	0.5	0.7	<0.1–7.6	0.648	1.3	0.7	0.4–3.9	0.662	1.2	1.4	0.1–11.5	0.898
Received help with questionnaire	1.5	1.9	0.1–19.0	0.761	1.3	1.6	0.1–15.9	0.862	4.5	5.6	0.4–52.1	0.232
Model 2 ($N = 245$) Childhood traumatic maltreatment												
Childhood maltreatment[1]	1.1	<0.1	1.0–1.1	0.010*	1.1	<0.1	1.0–1.1	0.051	1.2	<0.1	1.0–1.2	.032*
Educational level	0.8	0.3	0.5–1.5	0.554	1.4	0.2	1.1–1.9	.016*	1.3	0.3	0.7–1.9	0.486
Marital status												
Single vs long-term relation	0.8	0.8	0.1–5.3	0.843	4.5	2.7	1.4–14.6	0.013*	***	***	***	<.001*
Widower vs long-term relation	1.6	1.2	0.4–6.6	0.53	0.3	0.2	0.1–1.0	0.054	157.2	<0.1	157.2–157.2	1
MD score - *Response bias CTQ*	1.1	0.5	0.5–2.5	0.88	0.6	0.2	0.3–1.3	0.187	0.5	0.3	0.2–1.6	0.251
Perceived SES during childhood	1.2	0.4	0.7–2.2	0.468	0.7	0.1	0.5–1.0	0.061	1.1	0.3	0.7–1.8	0.612
Other health problems	0.8	0.9	0.1–8.3	0.827	1.4	0.8	0.5–4.3	0.579	1.5	1.7	0.2–14.4	0.73
Received help with questionnaire	1.8	2.5	0.1–17.1	0.676	1.4	1.8	0.1–17.1	0.814	4.9	7.1	0.3–83.6	0.276
Model 3 ($N = 245$) Childhood traumatic maltreatment subtypes												
Emotional abuse[1]	0.8	0.1	0.7–2.0	0.036*	1.2	0.1	1.0–1.4	0.032*	1.3	0.2	1.0–1.8	0.08
Physical abuse[1]	1.2	0.2	0.9–1.6	0.158	0.9	0.1	0.7–1.1	0.275	0.6	0.2	0.4–1.1	0.123
Sexual abuse[1]	1.1	0.2	0.8–1.4	0.757	0.9	0.2	0.7–1.2	0.513	1.1	0.4	0.5–2.2	0.879
Emotional neglect[1]	1.1	0.1	0.9–1.3	0.28	1	0.1	0.9–1.2	0.754	0.9	0.1	0.7–1.2	0.507
Physical neglect[1]	1.3	0.2	1.0–1.7	0.103	1.1	0.1	0.9–1.4	0.398	1.4	0.2	1.1–1.9	.008*
Educational level	<1.0	0.3	0.5–2.0	0.951	1.4	0.2	1.1–2.0	.023*	1.3	0.4	0.8–2.3	0.344
Marital status												
Single vs long-term relation	<1.0	1.2	0.1–9.9	0.985	3.9	2.1	1.3–11.4	0.015*	***	***	***	<.001*
Widower vs long-term relation	1.4	1.1	0.3–6.2	0.699	0.3	0.2	0.1–1.0	0.055	***	***	***	1
MD score - *Response bias CTQ*	1	0.5	0.4–2.5	0.941	0.7	0.3	0.3–1.4	0.276	0.3	0.2	0.1–1.1	0.075
Perceived SES during childhood	1.3	0.4	0.7–2.4	0.481	0.7	0.1	0.5–1.1	0.087	1.4	0.5	0.8–2.6	0.254

(*Continued*)

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Table 3. (*Continued*)

Men ($N = 249$)	Anxiety/Depression symptoms Versus low symptoms Odds	SE Odds	95% CI Odds	p	Mild symptoms Versus low symptoms Odds	SE Odds	95% CI Odds	p	High symptoms Versus low symptoms Odds	SE Odds	95% CI Odds	p
Other health problems	0.7	0.9	0.1–7.0	0.794	1.3	0.8	0.4–4.3	0.635	2.3	2.7	0.2–23.7	0.491
Received help with questionnaire	2.8	3.4	0.3–30.0	0.396	1.1	2.1	<0.1–45.3	0.953	5	10.3	0.1–273.4	0.428
Model 4 ($N = 246$) Adulthood trauma												
Adulthood trauma[2]	0.6	0.2	0.3–1.2	0.17	1.2	0.2	0.9–1.5	0.277	2	0.4	1.4–2.9	<.001*
Educational level	0.8	0.2	0.4–1.4	0.337	1.3	0.2	1.0–1.7	0.054	1.1	0.3	0.7–1.9	0.626
Marital status												
Single vs long-term relation	<1.0	0.8	0.2–5.0	0.98	1.8	0.9	0.7–4.8	0.218	***	***	***	<.001*
Widower vs long-term relation	1.6	1.1	0.4–6.0	0.493	0.5	0.3	0.3–1.7	0.285	332.3	<0.1	332.3–332.3	1
Other health problems	0.8	1	0.1–8.6	0.839	1.3	0.7	0.4–4.0	0.641	<1.0	1.3	0.1–14.0	0.983
Received help with questionnaire	1.8	2.3	0.2–21.5	0.646	0.9	1.4	0.2–16.9	0.96	4.2	6.1	0.3–71.0	0.317

[1]Childhood traumatic maltreatment subtypes was measured using the Childhood Trauma Questionnaire (CTQ).
[2]Adulthood trauma was measured with LEC-5: Life Events Checklist, number of experienced traumatic event types in the past 15 years when experienced personally, witnessed it, learned about it happening to close family members or friends, or if it happened at work; Odds indicates the B value corresponding to the log odds, with Odds>1 representing higher odds – higher probability for assignment into the target profile versus the low-symptom severity profile, and Odds<1 lower odds – lower probability for assignment into the target profile versus the low-symptom severity profile; SES: Social economic status, SE: Standard error, CI: Confidence interval of B log odds.
***missing values.

Mid-to-late adulthood trauma

We found significant associations between adulthood trauma and profile assignment in men (Table 3) and women (Table 4). In men, reports of experiencing more adulthood trauma was associated with higher probability for classification into the high- than low-symptom profile. In women, reports of more adulthood trauma was associated with higher probability for classification into all other symptom profiles compared to the low-symptom profile. Sensitivity analyses for all logistic regression models in men and women without any covariates showed that odds ratios and corresponding confidence intervals between regression models with and without covariates were largely overlapping (details are provided in Supplementary Materials S4–S5).

Discussion

In the Dutch famine birth cohort, we observed that in men exposure to undernutrition during early gestation, traumatic maltreatment in childhood, and trauma in mid-to-late adulthood were all associated with symptom profile classification. In women, classification was impacted by childhood maltreatment and adulthood trauma, while no effect of prenatal undernutrition was observed. Lastly, we found distinct associations between specific subtypes of childhood adversities and symptom profile classification in both men and women.

Observed psychological symptom profiles

We observed four different symptom profiles in men and five symptom profiles in women. In both men and women, we observed three profiles that included all symptom types of approximately equal severity within each profile, yet differentiated between profiles in terms of their overall severity into low, mild, and high severity. We also observed profiles that showed a clear prominence of specific symptom types. Firstly, there was a distinct profile for anxious/depressive symptoms in both men and women in the presence of low PTSD and psychotic symptoms. Within this distinct profile, the severity of anxious and depressive symptom levels were descriptively somewhat lower than within the high-symptom profile, and higher than within the low- and mild-symptom profiles. This particular profile was not unexpected as increased levels of anxious and depressive symptoms have consistently been shown to be comorbid, more so than with other psychiatric disorders,[63] and both symptoms increase the risk of subsequently developing the other disorder, regardless of variation in study methodology.[64] Secondly, a distinct PTSD symptom profile was identified in women only, implying that there was a subset of women specifically experiencing PTSD symptoms without comorbidity of the other investigated symptom types. Momartin et al,[65] who identified a pure PTSD profile next to a comorbid PTSD/depression and pure depression profile using diagnostic grouping in a community sample of Bosnian refugees and war survivors, discussed that this may depend on the character of the experienced trauma. For example, a life-threatening character of an experienced traumatic event solely predicted pure PTSD compared to three other dimensions describing specified traumatic events that were previously extracted from interviews within this sample. As females appear to report more perceived life threat than males after experiencing a similar trauma,[66] and it seems unclear how the likelihood of having pure PTSD or with any PTSD comorbidity is influenced by gender,[67–70] an explanation for identifying this profile only in females could be related to gender

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Table 4. Multinomial regression analysis of estimates and odds for associations between life adversities and probability of profile assignment in women

	Mild-symptoms				PTSD symptoms				Anxiety/Depression symptoms				High symptoms			
	Versus low symptoms				Versus low symptoms				Versus low symptoms				Versus low symptoms			
Women ($N = 277$)	Odds	SE Odds	95% CI Odds	*p*	Odds	SE Odds	95% CI Odds	*p*	Odds	SE Odds	95% CI Odds	*p*	Odds	SE Odds	95% CI Odds	*P*
Model 1 (N=273) Prenatal undernutrition due to famine exposure																
Early gestation	0.6	0.5	0.1–2.7	0.508	0.6	0.7	0.1–5.1	0.646	1.5	1	0.4–5.8	0.556	0.9	0.9	0.1–7.2	0.889
Mid gestation	1.3	0.6	0.6–3.1	0.523	2.1	1.3	0.6–6.9	0.22	0.6	0.4	0.1–2.3	0.426	0.5	0.6	0.1–4.4	0.536
Late gestation	0.8	0.4	0.3–2.2	0.711	0.3	0.3	<0.1–2.8	0.285	0.3	0.3	0.1–1.7	0.175	0.6	0.4	0.1–2.2	0.396
Educational level	1.1	0.1	0.9–1.4	0.327	1.2	0.3	0.8–1.8	0.496	1	0.2	0.7–1.4	0.995	1.3	0.3	0.9–1.9	0.244
Marital status																
Single vs long-term relation	0.9	0.2	0.5–1.5	0.639	1.4	0.5	0.7–3.0	0.339	0.8	0.3	0.4–1.7	0.542	1.3	0.6	0.5–3.0	0.612
Widower vs long-term relation	1.5	0.4	0.9–2.6	0.129	0.7	0.4	0.3–1.9	0.517	1.1	0.5	0.4–2.7	0.863	1.4	0.7	0.6–3.5	0.478
Other health problems	0.7	0.4	0.2–2.2	0.506	1	0.9	0.2–6.1	0.972	1.7	1.2	0.5–6.7	0.422	3	1.8	0.9–9.6	0.067
Received help with questionnaire	0.2	0.3	<0.1–2.3	0.216	2	0.3	0.3–12.3	0.46	***	***	***	<0.001*	1.2	1.5	0.1–12.9	0.869
Model 2 ($N = 268$) Childhood traumatic maltreatment																
Childhood maltreatment[1]	1.1	<0.1	1.0–1.1	.002*	1.1	<0.1	1.0–1.1	0.030*	1	<0.1	0.9–1.1	0.916	1.1	<0.1	1.0–1.1	.013*
Educational level	1.2	0.2	0.9–1.5	0.233	1.2	0.3	0.8–1.8	0.525	<1.0	0.1	0.7–1.3	0.739	1.3	0.2	0.9–1.8	0.207
Marital status																
Single vs long-term relation	0.9	0.3	0.5–1.5	0.68	1.3	0.5	0.6–2.9	0.455	0.8	0.3	0.3–1.8	0.583	1.2	0.5	0.5–2.8	0.693
Widower vs long-term relation	1.5	0.5	0.8–2.7	0.201	0.7	0.4	0.5–2.2	0.591	1.1	0.5	0.5–2.7	0.795	1.5	0.8	0.5–4.1	0.435
MD score - *Response bias CTQ*	0.9	0.2	0.6–1.3	0.436	0.5	0.2	0.2–1.3	0.126	0.9	0.2	0.6–1.4	0.545	0.7	0.3	0.3–1.7	0.396
Perceived SES during childhood	1.3	0.2	1.0–1.8	0.048*	1.1	0.2	0.7–1.7	0.691	<1.0	0.2	0.7–1.4	0.858	1.1	0.3	0.6–1.9	0.806
Other health problems	0.6	0.4	0.2–2.0	0.377	0.7	0.7	0.1–4.5	0.711	1.5	0.9	0.4–5.1	0.527	2.4	1.7	0.6–9.5	0.22
Received help with questionnaire	0.3	0.4	<1.0–3.3	0.354	2	2.1	0.3–15.3	0.51	***	***	***	<.001*	1.6	1.8	0.2–15.4	0.697
Model 3 (N=266) Childhood traumatic maltreatment subtypes																
Emotional abuse[1]	1.1	0.1	1.0–1.3	.036*	1.1	0.1	0.9–1.3	0.627	1.2	0.1	<1.0–1.4	0.151	1.1	0.1	<1.0–1.3	0.155
Physical abuse[1]	0.9	0.1	0.8–1.2	0.52	1	0.1	0.8–1.3	0.987	<1.0	0.1	0.7–1.3	0.705	0.8	0.1	0.5–1.1	0.153
Sexual abuse[1]	1.1	0.1	<1.0–1.3	0.171	1.1	0.1	<1.0–1.3	0.08	0.9	0.2	0.6–1.4	0.642	1.3	0.1	1.0–1.6	.027*
Emotional neglect[1]	<1.0	0.1	0.9–1.1	0.872	1.1	0.1	<1.0–1.2	0.238	1	0.1	0.8–1.2	0.932	1.1	0.1	<1.0–1.3	0.121

Table 4. (*Continued*)

Physical neglect[1]	1.1	0.1	0.9–1.3	0.443	1	0.1	0.8–1.2	0.722	0.8	0.2	0.6–1.2	0.313	<1.0	0.1	0.7–1.2	0.666
Educational level	1.1	0.2	0.9–1.5	0.405	1.2	0.3	0.8–1.8	0.502	0.9	0.1	0.7–1.1	0.292	1.3	0.3	0.8–2.0	0.24
Marital status																
Single vs long-term relation	0.9	0.3	0.5–1.5	0.603	1.3	0.5	0.6–2.9	0.456	0.7	0.4	0.3–1.9	0.517	1.2	0.5	0.5–2.9	0.676
Widower vs long-term relation	1.6	0.5	0.8–3.0	0.183	0.7	0.4	0.2–2.3	0.596	1.3	0.6	0.5–3.2	0.638	1.4	0.8	0.5–4.2	0.575
MD score - *Response bias CTQ*	0.8	0.2	0.5–1.2	0.289	0.5	0.3	0.2–1.4	0.161	1	0.2	0.6–1.4	0.641	0.8	0.4	0.3–2.1	0.592
Perceived SES during childhood	1.4	0.2	<1.0–1.8	0.057	1.1	0.3	0.7–1.7	0.775	0.9	0.2	0.6–1.4	0.617	1	0.3	0.6–2.0	0.908
Other health problems	0.6	0.4	0.2–2.1	0.404	0.8	0.7	0.1–5.1	0.774	1.3	0.9	0.3–4.8	0.728	2.7	2.1	0.6–12.4	0.207
Received help with questionnaire	0.3	0.4	<0.1–3.7	0.368	2	2.1	0.3–15.9	0.509	***	***	***	<.001	1.8	2.2	0.2–19.1	0.623
Model 4 ($N = 273$) Adulthood trauma																
Adulthood trauma[2]	1.4	0.2	1.1–1.8	.021*	1.5	0.2	1.1–2.0	.015*	1.4	0.2	1.1–1.8	.015*	1.6	0.3	1.0–2.4	.037*
Educational level	1.1	0.1	0.8–1.4	0.736	1	0.2	0.6–1.6	0.946	0.9	0.1	0.7–1.2	0.387	1.1	0.2	0.7–1.7	0.709
Marital status																
Single vs long-term relation	0.8	0.2	0.5–1.4	0.4	1.3	0.5	0.6–2.9	0.553	0.7	0.3	0.3–1.6	0.419	1.1	0.4	0.5–2.3	0.838
Widower vs long-term relation	1.7	0.5	<1.0–3.0	0.064	0.8	0.4	0.3–2.2	0.667	1.3	0.6	0.5–3.0	0.591	1.8	0.8	0.7–4.5	0.217
Other health problems	0.6	0.4	0.2–1.9	0.367	0.7	0.6	0.1–3.5	0.646	1.4	0.9	0.4–4.9	0.626	2.4	1.6	0.7–8.8	0.185
Received help with questionnaire	0.2	0.3	<0.1–2.5	0.218	1.6	1.5	0.3–9.4	0.583	***	***	***	<.001*	<1.0	1.1	0.1–8.1	0.974

[1]Childhood traumatic maltreatment subtypes was measured using the Childhood Trauma Questionnaire (CTQ).
[2]Adulthood trauma was measured with LEC-5: Life Events Checklist, number of experienced traumatic event types in the past 15 years when experienced personally, witnessed it, learned about it happening to close family members or friends, or if it happened at work; Odds indicates the B value corresponding to the log odds, with Odds>1 representing higher odds – higher probability for assignment into the target profile versus the low-symptom severity profile, and Odds<1 lower odds – lower probability for assignment into the target profile versus the low-symptom severity profile; SE: Standard error, CI: Confidence interval of log odds.
*** missing values.

differences in trauma appraisal. Psychotic symptom levels were overall low across profiles, although levels covaried with severity across the three profiles consisting of all symptom types. The low levels suggest that cohort members experienced few psychotic symptoms which limited variance in PQ-16 scores for LPA, but is in line with what is expected given their low prevalence in a general population.[71]

Adversity and psychological symptom profiles in women

Within women, childhood and adulthood adversity both generally increased the probability for classification into all symptom profiles other than the low symptom profile in late adulthood. This corresponds with previous studies demonstrating strong predictive effects of childhood and adulthood traumatic adversity for several DSM-IV disorders in adult men and women, including our symptoms of interest, with little apparent specificity across disorders.[22,72–74] Yet, we observed that specific forms of childhood adversity in women had differential impact on symptom severity, as women who reported more emotional abuse had higher risk for classification into specifically the mild- compared to low-symptom profile, while risk was higher for the high-symptom profile after experiencing more sexual abuse. In line with our findings, several subtypes of childhood maltreatment were previously found to generically predict many types of psychological symptoms, although some types more than the other.[22,29,75,76] Krause et al[77] hypothesized that chronic inhibition of experiencing and expressing emotions as coping strategy can be functional during childhood to deal with maltreatment, but mediates the association between childhood maltreatment and a range of adult psychological disorders. Accordingly, it is possible that specific coping strategies in response to adversity may determine psychopathology severity, however, we did not assess this in our study.

Adversity and psychological symptom profiles in men

In men, child maltreatment seemingly had the most profound effect as it increased probability for classification into all other profiles than low symptoms, whereas exposure to famine in early gestation aspecifically and exclusively increased probability for mild rather than low symptoms and adulthood trauma increased probability for high compared to low symptoms. The association with exposure to undernutrition during early gestation was only observed amongst men and no associations were found in prenatally exposed women. This implies a time-dependent impact of adversity within the prenatal gestational period in addition to a sex-specific vulnerability to prenatal adversity in general. This latter observation conforms to existing literature on the increased vulnerability of males to prenatal adversity, probably due to faster *in utero* fetus growth.[78] It is essential to note that sample sizes of our prenatally exposed groups were limited, which could explain the absence of further significant associations. Yet, early gestation has been repeatedly demonstrated to be sensitive to famine exposure in relation to psychological health risk in later life,[7] also within our study cohort.[20,79] Our observations in men further support a time-dependent effect of adversity on psychological health, extending from the prenatal period through childhood into late adulthood, thereby adding to a growing literature.[80–83]

Notably and similar to what we found in women, specific subtypes of childhood adversity had differential impact in men, and not only affected overall symptom severity but also symptom type. For example, emotional abuse in men increased probability for mild rather than low symptoms, but lowered risk for anxious/depressive symptoms. In case of more physical neglect, probability was higher for high symptoms. As mentioned previously, specific stressor types experienced during childhood and adolescence distinctly predict specific adult psychopathology[72] and severity.[84] Although it is still unclear what underlies the differential impact of childhood trauma subtypes on long-term symptom specificity, a hypothetical pathway has been put forward by Sayyah et al.[29] They suggested that specific subtypes of childhood maltreatment interfere with the development of specific age-salient socio-emotional concepts that are formed during childhood and portend certain symptoms when disrupted. For example, interfering with the consolidation of attachment and emotion regulation could manifest in adult maladjustment of internalizing behavior (related to anxious and depressive symptoms) or traumatic stress (related to PTSD). Accordingly, childhood trauma subtypes differentially affect personality traits[85] and brain regions underlying specific affected cognitive-behavioral processes.[86]

The different associations we found in men and women with respect to adversity impact during the prenatal period, early childhood and mid-to-late adulthood, may be regulated by differential underlying neurobiological (epigenetic) mechanisms regarding the development and susceptibility of psychological symptoms. For example, the faster rate of growth in male fetuses,[87] protective characteristics of the female placenta during brain development,[78] and disparate brain maturation and aging[88] have previously been identified to be sex-dysmorphic vulnerability and protective factors for health outcomes. Although these sex-differential effects need further investigation and could be influenced by other factors, such as trauma accumulation or trauma type, our findings stress the importance of the use of the Sex and Gender Equity in Research (SAGER[89]) guidelines to study men and women separately in future research on psychological health.

Study implications

A major implication of our findings is that exposure to adversity across the lifespan still has measurable impact on psychological health into late adulthood, even when the adversity happened approximately 75 years ago as was observed in men exposed to undernutrition during early gestation. These findings seem to fit with the concept of developmental programing of mental health contending that adverse events in early life persistently impact risk for long-term psychopathology through disruption of neurobiological developmental processes that take place during these critical life periods.[90–95] Importantly, our findings highlight that long-term risk may also apply when adversity occurs outside of critical neurodevelopmental periods, during mid-to-late adulthood, independent of whether early life adversity was experienced. Yet, other additional factors such as genetic predisposition[96,97] may also be related to specificity of the type, complexity and severity of late adult symptoms.[98,99]

Strengths and limitations

A major strength of this study is that we assessed adversities during different periods across the lifespan, including the prenatal period, and their associations with a wide range of psychological symptoms, making it possible to study whether effects of adversity exposure on patterns of psychological symptoms depend on timing of exposure. Another strength is our multidimensional statistical approach of using LPA. This person-centered method utilizes

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multivariate continuous data and full ranges of symptoms of interest and their severity, as well as their interdependence instead of relying on dichotomous categorical diagnoses, allowing for comprehensive consideration of symptom specificity and comorbidity.[37,100] Furthermore, we stratified our analyses for men and women as recommended in the SAGER guidelines[89] and given previous findings on sex specificity of latent symptom profiles and impact of adversity thereon.[20,42] We indeed observed sex-specific effects, which may likely have gone undetected without performing this stratification.

Our study also has some limitations. First, although our cohort study is longitudinal in itself, psychological symptoms were assessed cross-sectionally. Consequently, we could not study potential differential effects regarding symptom chronicity and course. Future studies should adopt a longitudinal perspective to be able to investigate this. Another methodological limitation was that childhood and adulthood adversity were retrospectively assessed, possibly introducing memory bias with representation of inaccurate perceptions, interpretations, and recollections.[101] False positive memories in childhood adversity reports are rare,[102] but underreporting is more prevalent.[103] To account for potential underreporting, we included MD scores as covariate in our models regarding exposure to childhood adversity. Most CTQ subscales showed acceptable, good, and even excellent internal consistency in the present study and were comparable to previous reliability measures in several samples.[45,104,105] However, also in line with several previous studies,[105–107] internal consistency of the Physical Neglect subscale was poor and its reliability is thus likely suboptimal. Furthermore, women prenatally exposed to famine have overall higher mortality risk than unexposed women and exposed men.[108] This may have resulted in selective survival and participation of more healthy (female) cohort members. Additionally, our aging cohort members may have become physically and/or mentally ill, which could have increased loss to follow up of adults with poorer health. As those exposed to famine in early gestation have previously been shown to have increased risk for several adverse cardio-metabolic disease outcomes as well as other adverse mental and physical health outcomes, selective participation of this group of participants is likely and may have led to underestimation of effects in this study. Lastly, we did not take potential effects of accumulation of or interactions between several adversity types across the lifespan into account. Although it would have been valuable to assess the impact of multiple hits by adverse events across the lifespan on psychological symptoms, our modest sample size only allowed for reliable investigation of main effects for distinct exposure periods. Although the statistical method used in this study by performing multinomial regression analyses is most suitable for multiple categorical outcome variables, the statistical power of the present study might still have been negatively influenced by including categorical outcome measures.

Conclusion

We observed specific impact of adversity during different periods across the lifespan on psychological symptom profiles later in life, which appeared to be time-dependent as well as sex-specific. Effects of exposure to adversity during early gestation or during childhood were still visible in late adulthood suggesting an ongoing lifelong impact of adverse events that happened over 7 decades ago.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S2040174423000181.

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Ethical standard. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (SAGER guidelines) and with the Helsinki Declaration of 1975, as revised in 2008, and the Medical Ethics Committee of the Academic Medical Center, Amsterdam, the Netherlands, concluded that a full review and official approval of this study wave was not required according to Dutch law for medical research.

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