Early Life Stress and Physical and Psychosocial Functioning in Late Adulthood

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Abstract

Background: Severe stress experienced in early life may have long-term effects on adult physiological and psychological health and well-being. We studied physical and psychosocial functioning in late adulthood in subjects separated temporarily from their parents in childhood during World War II.

Methods: The 1803 participants belong to the Helsinki Birth Cohort Study, born 1934–44. Of them, 267 (14.8%) had been evacuated abroad in childhood during WWII and the remaining subjects served as controls. Physical and psychosocial functioning was assessed with the Short Form 36 scale (SF-36) between 2001 and 2004. A test for trends was based on linear regression. All analyses were adjusted for age at clinical examination, social class in childhood and adulthood, smoking, alcohol intake, physical activity, body mass index, cardiovascular disease and diabetes.

Results: Physical functioning in late adulthood was lower among the separated men compared to non-separated men ($b = -0.40$, 95% confidence interval [95% CI]: -0.71 to -0.08). Those men separated in school age (>7 years) and who were separated for a duration over 2 years had the highest risk for lower physical functioning ($b = -0.89$, 95% CI: -1.58 to -0.20) and ($b = -0.65$, 95% CI: -1.25 to -0.05), respectively). Men separated for a duration over 2 years also had lower psychosocial functioning ($b = -0.70$, 95% CI: -1.35 to -0.06). These differences in physical and psychosocial functioning were not observed among women.

Conclusion: Early life stress may increase the risk for impaired physical functioning in late adulthood among men. Timing and duration of the separation influenced the physical and psychosocial functioning in late adulthood.

Introduction

Physical and mental health varies individually through the life course and decreases with age, which might cause decline in physical functioning and well-being later in life [1]. Health-related behaviours such as smoking and sedentary lifestyle as well as low educational attainment accelerate health decline in old age [2,3]. However, decline in health in later life is not only related to biological and environmental factors occurring in adult life, but might also track back to early life experiences. Studies suggest that traumatic experiences in childhood such as childhood abuse, neglect, maltreatment and parental separation cause early life stress (ELS) and might serve as antecedents of health decline

throughout the lifespan [4,5]. Low childhood socioeconomic circumstances have also been associated with poor general health and physical function in later life [6–10]. A growing number of retrospective studies have reported that physical health and mental well-being in adulthood and at old age might stem from non-optimal growth and exceptional conditions during sensitive periods of growth and development early in life [4,11–16].

Roughly 70 000 Finnish children experienced ELS in the form of temporary separation from their parents in two Finnish-Soviet wars during World War II (WWII). Children were evacuated to foster care in Sweden and Denmark. The Finnish Government carried out evacuations to protect the children from the strains of war. We have shown in our previous reports based on findings

from the Helsinki Birth Cohort Study (HBCS) that the effect of war-time separation experience during childhood increased the risk for health problems later in life including hypertension, coronary heart disease (CHD) and type 2 diabetes [17–19], as well as depressive symptoms and hospitalisation for mental disorders [20,21]. In the present study we hypothesize that, people who had experienced ELS have reduced physical and psychosocial functioning in later life. The current study investigates the differences in physical and psychosocial functioning in late adulthood according to war-time separation status as an indicator of stress experienced in early life. We use unique longitudinal data from HBCS in which a proportion of the participants had been separated from their parents during WWII.

Materials and Methods

Participants

The 1803 participants in this study belong to an epidemiological cohort, which includes 4630 men and 4130 women [22]. They were born in Helsinki University Central Hospital between 1934 and 1944, had visited child welfare clinics in the city and were still living in Finland in 1971, when a unique personal identification number was allocated to each member of the Finnish population. As previously described, we used random-number tables to select a subset of people who attended a clinical examination during 2001–2004. Of the 2902 invited subjects, 2003 men and women participated in the examination [23]. Of these, 189 subjects did not have reliable information on war time separation and because of this they were excluded from the analyses [24]. 1803 subjects had data on war time evacuation and physical and psychosocial functioning in late adulthood.

Ethics Statement

The study protocol was approved by the ethical committee of the National Public Health Institute in Helsinki. Written informed consent was obtained from each participant before any study procedures were carried out.

Early Life Stress (ELS)

Of the participants, 267 (14.8%) had been evacuated unaccompanied by their parents ("separated") to Sweden or Denmark during WWII. Details of the historical context of the separations have been described elsewhere [25]. Data on evacuation were collected from a register in the Finnish National Archives, which gives full documentation of the children (n = 48628) evacuated by the Finnish Government. Information on age at and duration of the evacuation were obtained from the register. In addition, approximately 20000 children were evacuated abroad through personal contacts during WWII. These have not been officially registered. To identify these subjects, during the clinical survey in 2001–2004 we also collected information related to evacuation by asking the participants directly [20]. The remaining subjects ("non-separated"), who did not experience separation during WWII served as controls (n = 1536).

Short Form 36 Physical and Psychosocial Functioning

Physical and psychosocial functioning was assessed with the physical component summary and the psychosocial component summary of the Finnish validated version of the RAND 36-Item Health Survey 1.0 (Short Form 36 [SF-36]) [26–29]. The physical component summary included four subscales: physical functioning, role limitations due to physical problems, pain and general health (Cronbach's alpha = 0.80) and the psychosocial component summary included four subscales: role limitations due to emotional problems, energy, emotional well-being and social functioning (Cronbach's alpha = 0.82). Each subscale included 2 to 10 items and item scores were summed and transformed to a scale from 0 to 100. Physical and psychosocial component summaries are continuous scales and range from 0 to 100, with a median score of 82.5 for the physical component summary and 87.3 for the psychosocial component summary. Higher scores imply better physical and psychosocial functioning.

Socioeconomic Variables

Childhood socioeconomic status was evaluated based upon father's highest occupational status, which was extracted from birth records, child welfare clinic and school health care records. Childhood socioeconomic status was categorized into three groups (senior clericals, junior clericals, manual workers) using a social classification originally devised by Statistics Finland [30]. Highest socioeconomic status in adulthood was based on register data from the Finnish Population Register Centre, which was obtained at 5-year intervals between 1970 and 1995. This was categorized into upper middle class, lower middle class, self-employed, and labourer.

Confounding Variables

A clinical examination was performed by a team of 3 trained research nurses between 2001 and 2004, described in detail elsewhere [23]. Information on smoking, alcohol intake and physical activity were obtained from a questionnaire that the participants filled in during the clinical examination. Heights and weights were measured and the participants' body mass index (BMI) was calculated (kg/m^2). Cardiovascular disease (CVD) was defined as self-reported physician-diagnosed coronary heart disease and/or stroke. The participants came to the examination after an overnight fast and glucose tolerance was assessed using a 2-hour 75-g oral glucose tolerance test. The World Health Organization criteria for disturbances in glucose regulation were applied, in order to diagnose disturbances in glucose regulation [31].

Statistical Analyses

Baseline differences for categorical variables were tested with logistic regression and continuous variables were compared by analysis of covariance (ANCOVA) adjusted for age and by the Mann-Whitney U test. The distributions of the physical and psychosocial component summaries were highly skewed. The rank transformation was used to normalize the distributions where SF-36 physical and psychosocial component summary scores divided into 6 equal sized gender-specific categories and they were coded with the numbers 1–6. The cut-off for the lowest category was 45.72 and highest 95.91 in men, and lowest 38.63 and highest 95.09 in women for the physical component summary, respectively. The cut-off for the lowest category in the psychosocial component summary was 53.57 and highest 97.48 in men, and lowest 43.58 and highest 96.34 in women, respectively. Differences in physical and psychosocial functioning between the separated and non-separated participants were investigated with multivariate linear regression. The analyses were first adjusted for age at clinical examination and highest social class in childhood and adulthood. Second, we added smoking, alcohol intake, physical activity and body mass index (BMI) to the model and finally CVD and diabetes. In addition, we tested whether age at separation and duration of separation was associated with physical and psychosocial functioning using the non-separated as controls. We split age at separation into 4 categories: infancy (<2 years); toddlerhood (2−4 years); early childhood (4−7 years) and school age (>7 years)

and duration of separation into 3 categories: <1 years, 1 –2 years and >2 years which we have used in our previous studies [17,19,20]. Interaction between gender and separation status on physical functioning was $P = 0.05$ and on psychosocial functioning $P = 0.06$, thus men and women were analysed separately. Statistical analyses were performed using SPSS (Statistical Package for Social Sciences) version 19.0 (SPSS, Armonk, NY, USA) for Windows.

Results

Baseline differences according to separation status in childhood are presented in Table 1. Participants who had experienced separation from their parents were older than the non-separated. The separated had a significantly higher prevalence of CVD and diabetes compared to the non-separated, $P = 0.006$ and $P = 0.007$, respectively. Those who had been separated during war time had lower childhood and adulthood socioeconomic status compared to the non-separated ones, $P = 0.001$ and $P = 0.09$, respectively. There were no significant differences in alcohol consumption, smoking, physical activity or BMI according to the separation status. The most common periods of separation were during toddlerhood and early childhood (mean = 4.8 years, SD = 2.4) and for approximately half of the separated participants, the duration was 1–2 years (mean = 1.7 years, SD = 1.0).

Table 2 shows mean scores for SF-36 physical and psychosocial functioning among the separated and non-separated participants. The scores in physical functioning, role limitations due to physical health and general health subscales were statistically significantly lower among the separated men compared to the non-separated ($P = 0.005$, $P = 0.03$ and $P = 0.001$, respectively). There were no differences in physical or psychosocial functioning according to war time separation status among women.

Differences in SF-36 physical and psychosocial functioning according to gender among the separated and the non-separated are given in Table 3. Men who had been separated from their parents in childhood had an increased risk of decreased physical functioning in late adulthood ($b = -0.45$, 95% confidence interval [CI]: -0.78 to -0.13; $P = 0.007$). Adjusting the model further for smoking, alcohol intake, physical activity, BMI, CVD and diabetes did not change the results. Among men, the associations between the separation experience and psychosocial functioning in later life were similar and reached statistical significance also when adjusting the model further for smoking, alcohol intake, physical activity and body mass index ($b = -0.37$, 95% CI: -0.71 to -0.03; $P = 0.03$). Among women we did not find any associations between the separation experience and physical and psychosocial functioning. When the participants were further divided into two age groups (≤62 years and >62 years), the associations between the separation experience and physical and psychosocial functioning in later life remained the same.

Age at and duration of the separation also affected the outcomes studied (Table 4). The highest risk of lower physical functioning was observed among those men who were separated in school age compared to the non-separated participants (fully adjusted $b = -0.89$, 95% CI: -1.58 to -0.20; $P = 0.01$). Men who were separated for more than two years also had an increased risk of decreased physical functioning (fully adjusted $b = -0.65$, 95% CI: -1.25 to -0.05; $P = 0.03$). Among women, there were no differences in physical functioning according to age at or duration of separation. Table 5 shows that those men who were separated for more than two years were also at highest risk of lower psychosocial functioning compared with the non-separated (fully adjusted $b = -0.70$, 95% CI: -1.35 to -0.06; $P = 0.03$). Women

who were separated for less than one year showed better psychosocial functioning than the non-separated participants ($b = 0.69$, 95% CI: 0.02 to 1.35; $P = 0.04$). There were no differences in psychosocial functioning according to age at separation among the separated men and women compared with the non- separated.

Discussion

We studied the long term consequences of ELS on physical and mental functioning in later life in people who as children experienced temporary separation from their parents during WWII. Physical functioning differed between the separated and the non-separated men. Men separated in school age and separated for more than 2 years showed lower physical functioning compared to the non-separated. These associations were not seen among women. Duration of separation was also associated with psychosocial functioning, and those who had been separated for over 2 years had an increased risk of decreased psychosocial functioning when compared to the non-separated.

Our findings are consistent with other studies showing that ELS is associated with impaired physical and psychosocial functioning in later life [14,15]. However, Edwards et al. have reported opposite results in relation to gender. They reported that men who had experienced childhood maltreatment had better physical function than women who had experienced maltreatment [32]. These differences may be due to the heterogeneity of ELS experiences. For example, we have shown that the children who were separated from their fathers because the fathers served in the military during war did not have a higher prevalence of depressive symptoms as adults (20). Other factors including socioeconomic status and health behaviours are also known to be associated with health [2,9,33,34]. Both socioeconomic factors and health behaviours are important determinants of physical and mental functioning [9,33,35]. Some studies have shown, that physically active people with chronic diseases can maintain good physical functioning, supporting the importance of health behaviour [36,37]. In the present study the separated group belonged to the lower socioeconomic classes compared with the non-separated group. No significant differences in physical activity were observed between the groups. We have shown that the separated groups had significantly higher prevalence of chronic diseases than the non-separated. Our findings were independent of age, social class, smoking, alcohol intake, physical activity, body mass index, cardiovascular disease and diabetes.

Our study design cannot disentangle the underlying mechanisms behind the associations between ELS and physical and psychosocial functioning in later life. There may be a large number of physiological, social and psychological explanations acting both individually and together. Furthermore, developmental differences between men and women may play a role. ELS research has focused on the developmental processes of physiological changes and re-setting of hormonal levels [38]. The modulations in physiological stress regulation may increase vulnerability to psychopathologies [39,40]. ELS is known to influence the function of the hypothalamic-pituitary-adrenal axis (HPA) and consequently cortisol metabolism in adult life [25,41,42]. The stress experience and long term outcomes differ according to type of stress experienced, age at onset, duration but also gender seem to be an important factor. Gender is an important factor in disease vulnerability and there are sex-specific pathways to many mental and physical conditions, including coronary heart disease and aggressive behaviour, the prevalence of which is higher in men [43]. Gender differences may depend on

Table 1. Characteristics of the study cohort[a].

	Separated	Non-separated	
	(n = 267)	(n = 1536)	
	Mean (SD) or %	Mean (SD) or %	P
Men (%)	50.2	46.9	0.18
Age at clinical examination (years)	63.7 (2.9)	60.9 (2.7)	<0.0001
Current smoker (%)	22.6	24.7	0.56
Weekly alcohol intake (%)	53.0	52.6	0.40
Exercise frequency ≥3 times/week (%)	49.4	42.5	0.33
BMI (kg/m^2)	27.9 (4.4)	27.6 (4.8)	0.30
Prevalence of CVD (%)	15.1	7.8	0.006
Prevalence of diabetes (%)	21.4	15.3	0.007
Father's highest social class in childhood (%)			0.001
Senior clericals	10.2	18.6	
Junior clericals	24.5	22.0	
Manual worker	65.3	59.3	
Highest social class in adulthood (%)			0.09
Upper middle	43.1	49.6	
Lower middle	39.0	37.7	
Self-employed	2.6	3.6	
Labourer	15.4	9.1	
Age at separation (years)[b]	4.8 (2.4)		
Infancy, <2 years (%)	9.9		
Toddlerhood, 2–4 years (%)	38.6		
Early childhood, 4–7 years (%)	28.8		
School age, >7 years (%)	22.7		
Duration of separation (years)[c]	1.7 (1.0)		
<1 year (%)	24.1		
1−2 years (%)	48.2		
>2 years (%)	27.6		

Abbreviation: BMI, body mass index.
[a]Categorical variables were tested with logistic regression and continuous variables were compared by the analysis of covariance (ANCOVA) and adjusted for age.
[b]Available for 87.0% of the separated.
[c]Available for 85.1% of the separated.
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the effects of sex hormones [44]. Gender differences may also depend on the stress reactivity of the HPA axis and the sympathetic nervous system, which can differ between the genders [45].

In this study, we used a longitudinal study design and well-characterized clinical data. We were able to use register data on socioeconomic status in childhood and adulthood. We also used reliable register data to define ELS and its timing. Despite this, we are aware that some children were evacuated via private routes and classified as non-separated [20]. The existence of the false controls would only diminish, not increase the observed group differences. The data on physical and mental functioning were self-reported based on the SF-36 form. The SF-36 has been found to be a valid and reliable health-related quality of life measurement in the Finnish population [26]. The present findings on physical and psychosocial functioning are comparable with the ones reported nationally. The limitations and possible selection bias of the Helsinki Birth Cohort Study have been discussed earlier [23]. Our study was restricted to people who had attended child welfare clinics, which were voluntary. Because of this the study could be unrepresentative of all people living in Helsinki. At that time, participation in child welfare clinics may have been related to families' socioeconomic situations. However at the time of birth, social class distribution was similar to that in the city as whole. Likewise, there were exceptional nutrition and living conditions in Finland around the time of the Second World War, malnutrition was not uncommon and the evacuated children may have experienced better nutritional conditions. In addition to food shortages, families sent the children abroad for opportunity get to children safely away from aerial bombardments. These unusual background conditions, may limit the general application of our results.

Some other limitations of the study should also be noted. ELS may occur as a one-time exposure or it could include many adverse early experiences. Children who are in temporary foster care may have experienced at least two displacements, the first at the separation and the other upon returning home. In our study temporary separations took place during WWII and some of the separated children were separated two or more times during the war. The effect of ELS on adult physical and mental function can

Table 2. Physical and psychosocial component subscales scores among separated (n = 267) and non-separated (n = 1536) participants[a].

	ALL	Separated	Non-separated	
	Mean (SD)	Mean (SD)	Mean (SD)	P
Physical component subscales				
Physical functioning				
Men	85.7 (17.7)	82.5 (18.6)	86.3 (17.5)	0.005*
Women	79.1 (20.1)	77.6 (19.1)	79.4 (20.2)	0.07
Role limitations due to physical health				
Men	84.4 (29.5)	80.2 (31.7)	85.2 (29.0)	0.03
Women	77.3 (34.8)	77.3 (33.8)	77.3 (35.0)	0.68
Pain				
Men	82.9 (21.3)	80.0 (22.4)	83.4 (21.0)	0.06
Women	79.0 (22.0)	79.5 (20.4)	78.9 (22.3)	0.99
General health				
Men	62.8 (18.3)	58.5 (18.0)	63.6 (18.3)	0.001*
Women	62.3 (18.5)	62.1 (17.2)	62.4 (18.7)	0.70
Psychosocial component subscales				
Role limitations due to emotional problems				
Men	86.3 (28.2)	83.1 (30.8)	86.9 (27.6)	0.16
Women	80.5 (33.0)	80.5 (33.9)	80.5 (32.9)	0.76
Energy/fatigue				
Men	73.7 (18.8)	70.8 (19.8)	74.2 (18.5)	0.08
Women	67.4 (20.2)	67.9 (19.2)	67.3 (20.4)	0.94
Emotional well-being				
Men	83.1 (14.6)	81.1 (16.3)	83.5 (14.2)	0.14
Women	79.3 (15.7)	79.3 (15.0)	79.3 (15.8)	0. 73
Social functioning				
Men	91.2 (16.5)	89.9 (16.7)	91.4 (16.4)	0.24
Women	87.9 (19.1)	89.6 (17.8)	87.6 (19.3)	0.22

[a]Mann-Whitney U test.
*p-value <0.05 after Bonferroni correction.
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Table 3. Differences (95% confidence intervals (CIs)) in SF-36 physical and psychosocial component summaries according to gender among participants who were separated in childhood compared to the non-separated*.

	Model 1		Model 2		Model 3	
	Differences (95%CI)	P	Differences (95%CI)	P	Differences (95%CI)	P
Physical component summary[a]						
Men	−0.45 (−0.78 to −0.13)	0.007	−0.46 (−0.78 to −0.14)	0.004	−0.40 (−0.71 to −0.08)	0.014
Women	0.16 (−0.17 to 0.49)	0.33	0.13 (−0.18 to 0.45)	0.41	0.20 (−0.11 to 0.52)	0.21
Psychosocial component summary[b]						
Men	−0.37 (−0.72 to −0.03)	0.03	−0.37 (−0.71 to −0.03)	0.03	−0.32 (−0.66 to 0.02)	0.06
Women	0.27 (−0.06 to 0.60)	0.11	0.27 (−0.07 to 0.60)	0.12	0.30 (−0.03 to 0.63)	0.08

Abbreviations: SF-36, short form 36.
Model 1 was adjusted for, age at the testing time, highest social class in childhood and adulthood.
Model 2 was adjusted for model 1+ smoking, alcohol intake, physical activity and body mass index.
Model 3 was adjusted for model 2+ presence of cardiovascular disease and diabetes.
[a]Models adjusted R square varied among men between 6% and 16% and among women between 2% and 11%.
[b]Models adjusted R square varied among men between 2% and 6% and among women between 1% and 3%.
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Table 4. Differences (95% confidence intervals (CIs)) in SF-36 physical component according to age and duration of separation among the separated compared with the non-separated.

	Model 1		Model 2		Model 3	
	Differences (95%CI)	P	Differences (95%CI)	P	Differences (95%CI)	P
Age at separation						
Men						
Non-separated	Referent		Referent		Referent	
Infancy (<2y)	−0.52 (−1.55 to 0.51)	0.32	−0.72 (−1.71 to 0.27)	0.15	−0.74 (−1.71 to 0.23)	0.14
Toddlerhood (2–4y)	−0.28 (−0.78 to 0.22)	0.27	−0.26 (−0.75 to 0.23)	0.30	−0.20 (−0.68 to 0.28)	0.41
Early childhood (4–7y)	−0.20 (−0.83 to 0.42)	0.52	−0.20 (−0.81 to 0.41)	0.52	−0.15 (−0.75 to 0.45)	0.62
School age (≥7y)	−0.88 (−1.59 to −0.17)	0.02	−0.94 (−1.63 to −0.25)	0.008	−0.89 (−1.58 to −0.20)	0.01
Women						
Non-separated	Referent		Referent		Referent	
Infancy (<2y)	0.52 (−0.41 to 1.44)	0.27	0.44 (−0.46 to 1.34)	0.34	0.49 (−0.40 to1.38)	0.28
Toddlerhood (2–4y)	0.32 (−0.18 to 0.83)	0.21	0.26 (−0.23 to 0.75)	0.30	0.30 (−0.19 to 0.79)	0.23
Early childhood (4–7y)	0.17 (−0.42 to 0.75)	0.58	0.24 (−0.33 to 0.80)	0.41	0.28 (−0.28 to 0.84)	0.32
School age (≥7y)	−0.06 (−0.78 to 0.66)	0.87	−0.09 (−0.80 to 0.61)	0.79	0.02 (−0.70 to 0.73)	0.96
Duration of separation (years)						
Men						
Non-separated	Referent		Referent		Referent	
≤1	−0.52 (−1.16 to 0.12)	0.11	−0.46 (−1.09 to 0.17)	0.15	−0.38 (−1.00 to 0.24)	0.23
≤2	−0.24 (−0.71 to 0.24)	0.33	−0.26 (−0.72 to 0.21)	0.28	−0.25 (−0.71 to 0.21)	0.29
>2	−0.64 (−1.27 to −0.01)	0.05	−0.73 (−1.34 to −0.12)	0.02	−0.65 (−1.25 to −0.05)	0.03
Women						
Non-separated	Referent		Referent		Referent	
≤1	0.33 (−0.33 to 0.98)	0.33	0.26 (−0.39 to 0.90)	0.43	0.29 (−0.35 to 0.93)	0.37
≤2	0.36 (−0.12 to 0.83)	0.14	0.28 (−0.18 to 0.74)	0.24	0.33 (−0.13 to 0.79)	0.16
>2	−0.07 (−0.65 to 0.52)	0.82	0.04 (−0.52 to 0.61)	0.88	0.11 (−0.46 to 0.67)	0.71

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be expected to affect the severity and frequency of the adverse exposures, type of stress, quality of early life environment and timing of the separation [46,47]. Unfortunately, we do not have information on the quality of foster care, which are likely to modulate the effect of ELS on adult physical and psychosocial functioning. Although early life stress was experienced in this

Table 5. Differences (95% confidence intervals [CIs]) in SF-36 psychosocial component according to duration of separation (years) among the separated compared with the non-separated.

	Model 1		Model 2		Model 3	
	Differences (95%CI)	P	Differences (95%CI)	P	Differences (95%CI)	P
Men						
Non-separated	Referent		Referent		Referent	
≤1	0.13 (−0.54 to 0.79)	0.71	0.16 (−0.51 to 0.82)	0.64	0.21 (−0.45 to 0.88)	0.53
≤2	−0.41 (−0.90 to 0.08)	0.10	−0.38 (−0.88 to 0.11)	0.13	−0.40 (−0.90 to 0.09)	0.11
>2	−0.72 (−1.37 to −0.06)	0.03	−0.78 (−1.42 to −0.13)	0.02	−0.70 (−1.35 to −0.06)	0.03
Women						
Non-separated	Referent		Referent		Referent	
≤1	0.69 (0.02 to 1.35)	0.04	0.59 (−0.08 to 1.26)	0.08	0.60 (−0.07 to 1.27)	0.08
≤2	0.37 (−0.11 to 0.86)	0.13	0.33 (−0.15 to 0.80)	0.18	0.34 (−0.14 to 0.82)	0.17
>2	−0.07 (−0.65 to 0.52)	0.82	0.07 (−0.51 to 0.65)	0.81	0.12 (−0.47 to 0.72)	0.68

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historical cohort under exceptional circumstances, the developmental significance of stress in childhood is not limited to this study. Today early life stress caused by child maltreatment, poverty, immigration or war are worldwide phenomena and consequently little is still known about the long-term effects of these severe stress experiences on later life physical functioning.

In conclusion, the current study suggests that people who experienced ELS may be at increased risk for impaired physical functioning in late adulthood, this was observed at least for men. Timing and duration of the separation experience influenced both physical and psychosocial functioning in late adulthood. The long term effects of early life stress can differ largely from one individual to another depending on the individual coping mechanisms [48]. Men who experienced separation at school age and who were

separated from their parents for more than two years are more vulnerable to the effects of early life stress. Therefore, future research should examine further gender differences in relation early life stress and take into account the cumulative effects of all life disadvantages.

Author Contributions

Conceived and designed the experiments: HA MBvB KR A-KP CO DJPB KH EK JGE. Performed the experiments: HA MBvB KR A-KP CO DJPB KH EK JGE. Analyzed the data: HA MBvB KR A-KP CO DJPB KH EK JGE. Contributed reagents/materials/analysis tools: HA MBvB KR A-KP CO DJPB KH EK JGE. Wrote the paper: HA MBvB KR A-KP CO DJPB KH EK JGE.

References

1. Rowe JW, Kahn RL (1987) Human aging: usual and successful. Science 237(4811): 143–149.
2. Willcox BJ, He Q, Chen R, Yano K, Masaki KH, et al. (2006) Midlife risk factors and healthy survival in men. JAMA 296(19): 2343–2350.
3. Lantz PM, House JS, Lepkowski JM, Williams DR, Mero RP, et al. (1998) Socioeconomic factors, health behaviors, and mortality: results from a nationally representative prospective study of US adults. JAMA 279(21): 1703–1708.
4. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, et al. (1998) Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med 14(4): 245–258.
5. Repetti RL, Taylor SE, Seeman TE (2002) Risky families: family social environments and the mental and physical health of offspring. Psychol Bull 128(2): 330–366.
6. Adams J, White M, Pearce MS, Parker L (2004) Life course measures of socioeconomic position and self reported health at age 50: prospective cohort study. J Epidemiol Community Health 58(12): 1028–1029.
7. Lundberg O (1993) The impact of childhood living conditions on illness and mortality in adulthood. Soc Sci Med 36(8): 1047–1052.
8. Luo Y, Waite LJ (2005) The impact of childhood and adult SES on physical, mental, and cognitive well-being in later life. J Gerontol B Psychol Sci Soc Sci 60(2): S93–S101.
9. Singh-Manoux A, Ferrie JE, Chandola T, Marmot M (2004) Socioeconomic trajectories across the life course and health outcomes in midlife: evidence for the accumulation hypothesis? Int J Epidemiol 33(5): 1072–1079.
10. Rahkonen O, Lahelma E, Huuhka M (1997) Past or present? Childhood living conditions and current socioeconomic status as determinants of adult health. Soc Sci Med 44(3): 327–336.
11. Maier EH, Lachman ME (2000) Consequences of early parental loss and separation for health and well-being in midlife. Int J Behav Dev 24(2): 183–189.
12. Foster D, Davies S, Steele H (2003) The evacuation of British children during World War II: a preliminary investigation into the long-term psychological effects. Aging Ment Health 7(5): 398–408.
13. Krause N (1998) Early parental loss, recent life events, and changes in health among older adults. J Aging Health 10(4): 395–421.
14. Corso PS, Edwards VJ, Fang X, Mercy JA (2008) Health-related quality of life among adults who experienced maltreatment during childhood. Am J Public Health 98(6): 1094–1100.
15. Draper B, Pfaff JJ, Pirkis J, Snowdon J, Lautenschlager NT, et al. (2008) Long-term effects of childhood abuse on the quality of life and health of older people: results from the Depression and Early Prevention of Suicide in General Practice Project. J Am Geriatr Soc 56(2): 262–271.
16. Irving SM, Ferraro KF (2006) Reports of abusive experiences during childhood and adult health ratings: personal control as a pathway? J Aging Health 18(3): 458–485.
17. Alastalo H, Räikkönen K, Pesonen AK, Osmond C, Barker DJ, et al. (2009) Cardiovascular health of Finnish war evacuees 60 years later. Ann Med 41(1): 66–72.
18. Alastalo H, Räikkönen K, Pesonen AK, Osmond C, Barker DJ, et al. (2012) Cardiovascular morbidity and mortality in finnish men and women separated temporarily from their parents in childhood – a life course study. Psychosom Med 74(6): 583–587.
19. Alastalo H, Räikkönen K, Pesonen AK, Osmond C, Barker DJ, et al. (2012) Early life stress and blood pressure levels in late adulthood. J Hum Hypertens; doi: 10.1038/jhh.2012.6. Epub 2012 Feb 16.
20. Pesonen AK, Räikkönen K, Heinonen K, Kajantie E, Forsen T, et al. (2007) Depressive symptoms in adults separated from their parents as children: a natural experiment during World War II. Am J Epidemiol 166(10): 1126–1133.
21. Räikkönen K, Lahti M, Heinonen K, Pesonen AK, Wahlbeck K, et al. (2011) Risk of severe mental disorders in adults separated temporarily from their parents in childhood: The Helsinki birth cohort study. J Psychiatr Res 45(3): 332–338.
22. Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJ (2001) Early growth and coronary heart disease in later life: longitudinal study. BMJ 322(7292): 949–953.
23. Barker DJ, Osmond C, Forsen TJ, Kajantie E, Eriksson JG (2005) Trajectories of growth among children who have coronary events as adults. N Engl J Med 353(17): 1802–1809.
24. Pesonen A, Räikkönen K, Kajantie E, Heinonen K, Osmond C, et al. (2011) Intergenerational social mobility following early life stress. Ann Med 43(4): 320–328.
25. Pesonen AK, Räikkönen K, Feldt K, Heinonen K, Osmond C, et al. (2010) Childhood separation experience predicts HPA axis hormonal responses in late adulthood: A natural experiment of World War II. Psychoneuroendocrinology 35(5): 758–767.
26. Aalto AM, Aro AR, Teperi J (1999) Rand-36 as a Measure of Health-related Quality of Life, Reliability, Construct Validity and Reference Values in the Finnish General Population. National Research and Development Centre for Welfare and Health (STAKES).
27. Aalto AM, Aro S, Aro AR, Mähönen M (1995) RAND 36-Item Health Survey 1.0. Finnish version on the Health-related Quality of Life Questionnaire. National Research and Development Centre for Welfare and Health (STAKES) report 2/1995.
28. Hays RD, Sherbourne CD, Mazel RM (1993) The RAND 36-Item Health Survey 1.0. Health Econ 2(3): 217–227.
29. Ware JE Jr, Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30(6): 473–483.
30. Central Statistical Office of Finland (1989) Classification of Socioeconomic Groups: Handbooks 17. Helsinki, Finland: Central Statistical Office of Finland.
31. Alberti KG, Zimmet PZ (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 15(7): 539–553.
32. Edwards VJ, Anda RF, Felitti VJ, Dube SR (2004) Adverse childhood experiences and health-related quality of life as an adult. Washington, DC, US: American Psychological Association p. 81–94.
33. Martikainen P, Stansfeld S, Hemingway H, Marmot M (1999) Determinants of socioeconomic differences in change in physical and mental functioning. Soc Sci Med 49(4): 499–507.
34. Lachman ME, Agrigoroaei S (2010) Promoting functional health in midlife and old age: long-term protective effects of control beliefs, social support, and physical exercise. PLoS One 5(10): e13297.
35. Kaplan GA (1992) Maintenance of functioning in the elderly. Ann Epidemiol 2(6): 823–834.
36. Spirduso WW, Cronin DL (2001) Exercise dose-response effects on quality of life and independent living in older adults. Med Sci Sports Exerc 33(6 Suppl): S598–608; discussion S609–10.
37. DiPietro L (1996) The epidemiology of physical activity and physical function in older people. Med Sci Sports Exerc 28(5): 596–600.
38. Miller GE, Chen E, Parker KJ (2011) Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. Psychological bulletin JID - 0376473.
39. Korosi A, Naninck EFG, Oomen CA, Schouten M, Krugers H, et al. (2012) Early-life stress mediated modulation of adult neurogenesis and behavior. Behav Brain Res 227(2): 400–409.
40. Cirulli F, Berry A, Alleva E (2003) Early disruption of the mother-infant relationship: effects on brain plasticity and implications for psychopathology. Neurosci Biobehav Rev 27(1–2): 73–82.
41. Gunnar MR (2000) Early adversity and the development of stress reactivity and regulation. In: Nelson CA, editor. Mahwah, NJ US: Lawrence Erlbaum Associates Publishers p. 163–200.
42. Carpenter LL, Carvalho JP, Tyrka AR, Wier LM, Mello AF, et al. (2007) Decreased adrenocorticotropic hormone and cortisol responses to stress in

healthy adults reporting significant childhood maltreatment. Biol Psychiatry 62(10): 1080–1087.

43. Kajantie E, Phillips DI (2006) The effects of sex and hormonal status on the physiological response to acute psychosocial stress. Psychoneuroendocrinology 31(2): 151–178.

44. Otte C, Hart S, Neylan TC, Marmar CR, Yaffe K, et al. (2005) A meta-analysis of cortisol response to challenge in human aging: importance of gender. Psychoneuroendocrinology 30(1): 80–91.

45. Gupta C, Verma R, Balhara Y (2011) Gender differences in stress response: Role of developmental and biological determinants. Ind Psychiatry J 20(1): 4–10.

46. Rusby JS, Tasker F (2008) Childhood temporary separation: long-term effects of the British evacuation of children during World War 2 on older adults' attachment styles. Attach Hum Dev 10(2): 207–21.

47. Nemeroff CB (2004) Neurobiological consequences of childhood trauma. J Clin Psychiatry 65 Suppl 1: 18–28.

48. Fagundes CP, Bennett JM, Derry HM, Kiecolt-Glaser J (2011) Relationships and Inflammation across the Lifespan: Social Developmental Pathways to Disease. Social & Personality Psychology Compass 5(11): 891–903.