

Hanna Alastalo

Early life stress and later health

Cardiovascular disease and general health
among former war evacuees

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“The past is not dead. In fact, it is not even past”
W. Faulkner

To my family

Abstract

Hanna Alastalo, Early life stress and later health - Cardiovascular disease and general health among former war evacuees. National Institute for Health and Welfare. Research 114. 130 pages. Helsinki, Finland 2013.

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Background. Experienced stress in childhood might have been so severe that it has effects throughout the life course. It has been suggested that early life stress may extend consequences on psychological and physical well-being. Previous findings focusing upon consequences of early life stress are, however, limited and mostly based upon retrospective studies. Still little is known about the consequences of early life stress, such as the separation of family members during time of war on physical health from a longitudinal aspect.

Aims. This thesis aimed to study cardiovascular mortality and morbidity in late adulthood among people who experienced separation from their parents to temporary foster care during World War II (WWII). Other study aims were to examine cardiovascular health, blood pressure levels and physical and psychosocial functioning in the separated participants. People who were not separated served as controls.

Subjects and methods. Participants in this study belong to the Helsinki Birth Cohort Study (HBCS) which includes 13,345 people born between 1934 and 1944 in Helsinki. They also visited child welfare clinics in the city. The epidemiological sub-study consists of 12,915 subjects who in 1971 were alive and living in Finland, of whom 1726 (13.4%) had experienced evacuation abroad. Data on parental separation was obtained from National Archives. In the epidemiological sub-study information on use of medication for coronary heart disease and hypertension was obtained from the National Register of Medication Reimbursement and information on coronary events, stroke and cardiovascular deaths from the Finnish National Hospital Discharge – and the Causes of Death Registers during a follow-up period from 1971-2002.

The original clinical study cohort consists of 2003 subjects who attended a clinical examination between the years between 2001 and 2004. The detailed clinical examination included anthropometric measurements (e.g. blood pressure and body composition), oral glucose tolerance test and other blood samples for assessment of glucose and lipids, questionnaires on medication, life style habits and physical and psychosocial functioning. The cardiovascular health sub-study included the original clinical study cohort, of whom 320 (16.0%) were separated participants. The participants in the blood pressure sub-study were 1361 non-obese subjects whose

body mass index (BMI) were $<30 \text{ kg/m}^2$. Of these 192 (14.1%) were separated participants. The sub-study of physical and psychosocial functioning included 1803 people, who had completed a Short Form 36 (SF-36) questionnaire during their clinical visit. Of these 267 (14.8%) had experienced parental separation during WWII. In all sub-studies the remaining participants who did not experience war separation in childhood served as controls.

Results. Among the participants who had been separated without their parents over one-third were separated in toddlerhood. Average age at separation was 4.6 years (standard deviation [SD] = 2.4 years) in the epidemiological sub-study and 4.8 (SD = 2.4-2.5) years in the clinical sub-studies. The mean duration of separation was 1.8 (SD = 1.1) years in the epidemiological sub-study and 1.6-1.7 (SD = 1.0) years in the clinical sub-studies. The separated participants were older than the non-separated participants; in the epidemiological sub-study the mean difference was 2.4 years (95% confidence intervals [CI] = 2.2-2.5 years) and in the clinical sub-studies the mean differences was 2.6-2.9 (95% CI = 2.7-2.9). Lower socioeconomic status in childhood and adulthood were more common among the separated participants than among the non-separated controls.

Of the 1726 separated participants in the epidemiological sub-study, 7.2% had medication for coronary heart disease (CHD) compared with the non-separated participants (4.5%). The risk for receiving CHD medication was 1.29 -fold among the separated compared with the non-separated (95% CI = 1.04-1.59, $P = 0.02$). Despite this the separated people did not required more hospitalization for coronary events or stroke. There was no significant association between war separation and cardiovascular mortality or all-cause mortality.

War separation was associated with cardiovascular disease, type 2 diabetes and blood pressure. The separated participants had a higher prevalence of cardiovascular disease compared with the non-separated participants (14.7% versus 7.9%; odds ratio [OR] = 1.7, 95% CI = 1.1-2.4). The prevalence of type 2 diabetes was 1.5 -fold in the separated compared with the non-separated (95% CI = 1.0-2.0). The separated participants were also more likely to be hypertensive. The non-obese separated showed significantly higher levels of systolic blood pressure than the non-separated (148.5 + 21.5 versus 142.2 + 19.6 mmHg, $P < 0.0001$) and the difference in systolic blood pressure levels was higher in the separated participants who were separated in early childhood (154.6 versus 142.2 mmHg, 95% CI = 2.6-14.7) and furthermore, they had higher diastolic blood pressure than the non-separated controls (90.8 versus 87.7 mmHg, 95% CI = 1.0-7.3). A higher systolic blood pressure was observed among those participants whose duration of separation was at least one year (151.7 versus 142.2 mmHg, 95% CI = 0.0-12.4).

Men at increased risk of lower physical functioning in late adulthood were more often among the separated participants than the non-separated participants ($P = 0.01$). The highest risk for lower physical functioning was observed among men who were separated in school age and also among those men whose duration of separation was over two years. The duration of over two years was also associated with lower psychosocial functioning. We did not observe differences in physical and psychosocial functioning in women.

Conclusions. These studies suggest that experienced stress in early life such as war separation may have consequences on cardiovascular health and general well-being through the lifespan. The war separation and its timing and duration are stressors, which could have long-term influence on critical development phases and thereby increase the risk of chronic non-communicable diseases in later life.

Keywords: blood pressure, cardiovascular disease, clinical study, early life stress, epidemiology, physical functioning, programming, war separation,

Tiivistelmä

Hanna Alastalo, Early life stress and later health - Cardiovascular disease and general health among former war evacuees [Varhainen stressi ja myöhemmän iän terveys – sydän- ja verisuonivaurio ja yleinen terveys entisillä sotalapsilla]. Terveyden ja hyvinvoinnin laitos. Tutkimus 114. 130 sivua. Helsinki, Finland 2013. ISBN 978-952-245-997-8 (painettu); ISBN 978-952-245-998-5 (verkkojulkaisu)

Tausta. Lapsuusiän stressikokemus voi olla vakava ja sen vaikutukset voivat ulottua yli koko eliniän vaikuttaen fyysiseen ja psyykkiseen hyvinvointiin. Aikaisemmat tutkimustulokset lapsuusiän stressin seurauksista ovat rajoittuneet enimmäkseen retrospektiivisiin tutkimuksiin. Vielä ei paljon tiedetä lapsuusiän stressin kuten lapsuusiässä vanhemmista eroon joutumisen seurauksista fyysiseen terveyteen pitkittäistutkimuksen näkökulmasta.

Tavoitteet. Tässä väitöskirjassa tavoitteena oli tutkia myöhäisen aikuisiän sydän- ja verisuonisairastavuutta ja –kuolleisuutta, kardiovaskulaariterveyttä, verenpainetasoja ja fyysistä ja psykososiaalista toimintakykyä aikuisiässä ihmisillä, jotka kokivat väliaikaisen erokokemuksen vanhemmistaan (sotalapsuuden) toisen maailmansodan aikana.

Aineisto ja menetelmät. Tutkimukseen osallistui Helsingin syntymäkohortti tutkimukseen kuuluneet 13,345 ihmistä, jotka syntyivät Helsingissä vuosina 1934-1944 ja jotka kävivät lapsena neuvolakäynneillä. Epidemiologiseen osatutkimukseen kuului 12,915 ihmistä, jotka olivat vuonna 1971 elossa ja asuivat Suomessa. Näistä sotalapsuuden oli kokenut 1726 (13.4%). Tiedot sotalapsuudesta saatiin Kansallisarkistosta. Epidemiologisessa osatutkimuksessa käytettyjen sepelvaltimo- ja verenpaineaudinlääkityksen tiedot saatiin kansallisesta erityislääkekorvausrekisteristä ja tiedot sydäntapahtumista, aivohalvauksista ja sydänkuolemista saatiin hoitoilmoitus- ja kuolemansyyrekistereistä seurantajaksolle 1971-2002.

Alkuperäinen kliininen tutkimusryhmä koostui 2003 osallistujasta, jotka vuosina 2001-2004 osallistuiivat kliiniseen tutkimukseen. Yksityiskohtainen kliininen tutkimus sisälsi antropometrisiä mittauksia (esim. verenpaine ja kehon koostumus), oraalisen sokerirasitustestin ja muita verinäytteitä verensokerin ja rasva-arvojen määrittämiseksi sekä kyselyjä lääkityksestä, elämäntavoista ja fyysisestä ja psykososiaalisesta toimintakyvystä. Kardiovaskulaariterveyttä koskevassa osatutkimuksessa oli mukana koko alkuperäinen kliininen tutkimusryhmä, joista sotalapsia oli 320 (16.0%). Verenpainetta koskevaan osatutkimukseen osallistui 1361 ei-lihavaa ihmistä, joiden painoindeksi (BMI) oli $<30 \text{ kg/m}^2$. Osallistujista 192 (14.1%) oli lähetetty sotalapsiksi. Fyysisen ja psykososiaalisen toimintakyvyn osatutkimus sisälsi 1803 ihmistä, jotka olivat täyttäneet terveystieteiden tutkimuksen (Short

Form 36 [SF-36]). Näistä sotalapsuuden oli kokenut 267 (14.8%) toisen maailmansodan aikana. Kaikissa osatutkimuksissa osallistujat, jotka eivät olleet kokeneet sotalapsuutta toimivat vertailuryhmänä.

Tulokset. Sotalapsista yli kolmasosa lähti sotalapsiksi 2-4 vuoden iässä. Sotalapsiksi lähdettiin epidemiologisessa osatutkimuksessa keskimäärin 4.6 vuoden iässä (keskihajonta = 2.4 vuotta) ja kliinisissä osatutkimuksissa keskimäärin 4.8 vuoden iässä (keskihajonta [SD] = 2.4-2.5). Sotalasten keskimääräinen sotalapsena oloaika oli epidemiologisessa osatutkimuksessa 1.8 vuotta (SD = 1.1) ja kliinisissä osatutkimuksissa 1.6-1.7 vuotta (SD = 1.0). Sotalapset olivat vanhempia kuin ei-sotalapset; epidemiologisessa osatutkimuksessa keskimääräinen ikäero oli 2.4 vuotta (95% luottamusväli [CI]= 2.2-2.5 vuotta) ja kliinisissä tutkimuksissa keskimääräinen ikäero oli 2.6-2.9 (95% CI = 2.7-2.9) vuotta. Alhaisempi lapsuusiän ja aikuisiän sosioekonominen asema olivat yleisempiä sotalapsilla.

Epidemiologiseen osatutkimukseen osallistuneista 1726 sotalapsesta sepelvaltimotaudin lääkityksellä oli 7.2% verrattaessa ei-sotalapsiin 4.5%. Sotalapsilla riski saada lääkitys sepelvaltimotautiin oli 1.29-kertainen verrattuna ei-sotalapsiin (95% CI = 1.04 -1.59, $P = 0.02$). Tästä huolimatta sotalapset eivät tarvinneet enempää sairaalahoitoa sydäntapahtumien ja aivohalvausten takia. Sotalapsilla ei löytynyt merkitsevää yhteyttä sodanaikaisen vanhemmista erottamisen ja kardiovaskulaarikuolleisuuden tai kokonaiskuolleisuuden välillä.

Sotalapsuus oli yhteydessä korkeampaan sydän- ja verisuonitautien sairastavuuteen verrattuna ei-sotalapsuuteen (14.7% versus 7.9%; kerroinsuhde (odds ratio) [OR] = 1.7, 95% CI = 1.1-2.4). Tyypin 2 diabeteksen esiintyvyys oli sotalapsilla 1.5-kertainen ei-sotalapsiin verrattuna (95% CI = 1.0-2.0). Sotalapsilla oli myös todennäköisemmin verenpainetauti. Ei-lihavilla sotalapsilla tämä esiintyi korkeampana systolisena verenpaineena verrattuna ei-sotalapsiin (148.5 + 21.5 versus 142.2 + 19.6 mmHg, $P < 0.0001$) Sotalapsilla, jotka olivat lähteneet sotalapsiksi varhaislapsuudessa, erot näkyivät systolisessa paineessa (154.6 versus 142.2 mmHg, 95% CI = 2.6-14.7) ja lisäksi heillä oli korkeampi diastolinen verenpaine (90.8 versus 87.7 mmHg, 95% CI = 1.0-7.3). Korkeampi systolinen verenpaine havaittiin myös sotalapsilla, jotka olivat sotalapsina vähintään vuoden (151.7 versus 142.2 mmHg, 95% CI = 0.0-12.4).

Myöhemmän aikuisiän lisääntynyt riski alhaisempaan fyysiseen toimintakykyyn oli yleisempää sotalapsuuden kokeneilla miehillä kuin ei-sotalapsilla ($P = 0.01$). Suurin riski alhaisempaan fyysiseen toimintakykyyn oli miehillä, jotka kokivat sotalapsuuden kouluikässä ja myös miehillä, jotka olivat sotalapsina yli kaksi vuotta. Sotalapsena olo yli kaksi vuotta liittyi myös alhaisempaan psykososiaaliseen

toimintakykyyn. Sotalapsuuden kokeneilla naisilla ei havaittu eroja fyysisessä ja psykososiaalisessa toimintakyvyssä verrattuna ei-sotalapsiin.

Päätelmät. Väitöskirjan tutkimukset viittaavat siihen, että varhaisiällä koetulla stressillä kuten sodanaikaisella erokokemuksella vanhemmista voi olla elinikäisiä vaikutuksia kardiovaskulaariterveyteen ja yleiseen hyvinvointiin. Sotalapsuus sekä sen ajoitus ja kesto ovat stressitekijöitä, joilla voi olla kriittisessä kehitysvaiheessa pitkäaikaisia vaikutuksia ja voivat näin lisätä kroonisten ei-tarttuvien tautien riskiä myöhemmällä iällä.

Avainsanat: fyysinen toimintakyky, kohortti tutkimus, ohjelmoituminen, sodan aikainen evakuointi, sydän- ja verisuonisairaus, varhainen stressi, verenpaine

Sammandrag

Hanna Alastalo, Early life stress and later health - Cardiovascular disease and general health among former war evacuees. [Avhandlingens Namn på svenska]. Institutet för hälsa och välfärd. Forskning 114. 130 sidor. Helsingfors, Finland 2013. ISBN 978-952-245-997-8 (tryckt); ISBN 978-952-245-998-5 (nätpublikation)

Bakgrund. Upplevd stress i barndomen livslånga effekter. Det har föreslagits att stress upplevd tidigt i livet kan påverka såväl det psykiska och fysiska välbefinnandet. Tidigare studier som fokuserat på konsekvenserna av tidigt upplevd stress är dock begränsade och mestadels retrospektiva. Fortfarande är lite känt om konsekvenserna av stress upplevd tidigt i livet, såsom långvarig effekter av separation p.g.a. krig på fysisk hälsa ur ett livscykelperspektiv.

Målsättningar. Denna avhandling studerar kardiovaskulär mortalitet och morbiditet i sen vuxen ålder hos personer som upplevt separation utan sina föräldrar till tillfälliga fosterhem under andra världskriget (WWII). Andra syften hade var att undersöka kardiovaskulär hälsa, blodtryck och fysisk och psykosocial funktion i vuxen ålder. De personer som inte separerades fungerade som kontroller.

Material och metoder. Deltagarna i denna studie tillhör Helsingfors Födelsekohortstudie (HBCS) som omfattar 13 345 personer födda mellan 1934 och 1944 i Helsingfors och som också besökte barnrådgivningar i staden. Den epidemiologiska delstudien består av 12 915 personer som 1971 var vid liv och bodde i Finland, varav 1726 (13.4%) hade upplevt evakuering utomlands från sina föräldrar. Uppgifter om föräldrarnas separation erhöles från Riksarkivet. I den epidemiologiska delstudien användes uppgifter om användning av läkemedel för hjärt-och kärlsjukdomar och högt blodtryck som erhöles från det nationella registret över specialersättning för läkemedel och information om koronarsjukdom, stroke och kardiovaskulära dödsfall från Sjukhusutskrivningsregistret och Dödsfallsregistret - och dödsorsaker registrerar under en uppföljningsperiod 1971-2002.

Den ursprungliga kliniska kohorten består av 2003 personer som deltog en klinisk undersökning mellan åren mellan 2001 och 2004. I den klinisk undersökningen ingår antropometriska mått (bl.a. blodtryck och kroppssammansättning), oral glukostolerans test- och andra blodprov för bedömning av glukos och lipider, enkäter om medicinering, levnadsvanor och livsstil och fysisk och psykosocial funktion. Substudien om kardiovaskulär hälsa inkluderade den ursprungliga kliniska studiekohorten, av vilken 320 (16,0%) var separerade deltagare. Deltagarna i blodtrycks delstudien var 1361 icke-feta människor vars viktindex (BMI) var <30 kg/m². Av dessa var 192 (14,1%) separerade deltagare. I substudien om fysisk och psykosocial funktion ingår 1803 personer, som hade besvarat en Short Form 36 (SF-

36) enkät under deras kliniska besök. Av dessa hade 267 (14,8%) upplevt föräldrarnas separation under andra världskriget. I samtliga delstudier hade deltagarna som inte upplevt krigs separation i barndomen fungerat som kontroller.

Resultat. Bland deltagarna som hade separerats utan sina föräldrar separerades över en tredjedel i småbarn ålder. Medelåldern var 4,6 år (standardavvikelse [SD] = 2,4 år) i den epidemiologiska delstudien och 4,8 (SD = 2,4–2,5) år i kliniska delstudierna. Medellängden av separationen var 1,8 (SD = 1,1) år i den epidemiologiska delstudien och 1,6–1,7 (SD = 1,0) år i de kliniska delstudierna. De separerade deltagarna var äldre än de icke-separerade deltagarna, i den epidemiologisk delstudien var den genomsnittliga skillnaden = 2,4 år (95% konfidensintervall [CI] = 2,2–2,5 år) och i de kliniska delstudierna var de genomsnittliga skillnaderna = 2.6 -2.9 (95% KI = 2,7–2,9). Lägre socioekonomisk status i barndomen och vuxenlivet var vanligare bland de separerade deltagarna än bland de icke-separerade kontrollerna.

Av de separerade 1726 deltagare i den epidemiologiska delstudien, hade 7,2% medicinering för kranskärslsjukdom (CHD) jämfört med de icke-separerade deltagare 4,5%. Risken för användning av CHD medicinering var 1,29-faldigt i den separerade jämfört med den icke-separerade gruppen (95% konfidensintervall = 1,04–1,59, P = 0,02). Trots detta hade de separerade inte använt mer sjukhusvårdtjänster för koronarsjukdom eller stroke. Det var inget signifikant samband mellan krigsseparationen och kardiovaskulär mortalitet eller mortalitet av alla orsaker.

Krigsseparation var associerad med hjärt-och kärlsjukdomar, typ 2-diabetes och blodtryck. De separerade deltagarna hade en högre prevalens av hjärt- och kärlsjukdom jämfört med de icke-separerade deltagarna (14,7% mot 7,9%; oddskvot [OR] = 1,7, 95% CI = 1,1–2,4). Förekomsten av typ 2-diabetes var 1,5-faldigt bland de separerade jämfört med de icke-separerad (95% CI = 1,0–2,0). De separerade deltagarna var också mer benägna att vara hypertensiva. De icke-feta separerade deltagarna uppvisade signifikant högre nivåer av systoliskt blodtryck än de icke-separerade (148,5 + 21,5 versus 142,2 + 19,6 mmHg, p <0,0001) och skillnaden i systoliskt blodtryck nivåer var högre bland de separerade deltagarna som var separerade i den tidiga barndomen (154,6 jämfört 142,2 mmHg, 95% CI = 2,6–14,7) och dessutom hade de högre diastoliskt blodtryck än icke-separerade kontroller (90,8 kontra 87,7 mmHg, 95% CI = 1,0–7,3). Ett högre systoliskt blodtryck observerades bland de deltagare vars separation varade minst ett år (151,7 jämfört 142,2 mmHg, 95% CI = 0,0-12,4).

Men som upplevt separation i barndomen hade en ökad risk för lägre fysisk funktion i vuxen ålder än de icke-separerade deltagare (P = 0,01). Den största risken för lägre

fysisk funktion sågs bland de separerade män som var åtskilda i skolåldern och även bland de män vars separation varade över två år. En duration på över två år var också associerad med lägre psykosocial funktion. Vi har inte observerat skillnader i fysisk och psykosocial funktion hos kvinnor.

Slutsatser. Dessa studier tyder på att stress upplevd i tidig ålder såsom krigsseparation kan ha långt gående konsekvenser för kardiovaskulär hälsa och allmänt välbefinnande genom hela livet. Krigsseparation och dess tidpunkt och varaktighet är stressfaktorer, vilket kan ha en långvarig inverkan på de kritiska utvecklingskedan och därmed ökar risken för kroniska icke smittsamma sjukdomar senare i livet.

Nyckelord: blodtryck epidemiologi, fysisk funktion, hjärt- och kärlsjukdomar, klinisk studie, krigsseparation, programmering, upplevd stress,

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List of original papers

This thesis is based on the following original publications, which are referred to in the text by the Roman numerals.

- I Alastalo H, Räikkönen K, Pesonen AK, Osmond C, Barker DJ, Heinonen K, Kajantie E & Eriksson JG. Cardiovascular morbidity and mortality in Finnish men and women separated temporarily from their parents in childhood – a life course study. *Psychosomatic Medicine* 2012; 74(6): 583-587.
- II Alastalo H, Räikkönen K, Pesonen AK, Osmond C, Barker DJ, Kajantie E, Heinonen K, Forsén TJ & Eriksson JG. Cardiovascular health of Finnish war evacuees 60 years later. *Annals of Medicine* 2009; 41(1): 66-72.
- III Alastalo H, Räikkönen K, Pesonen AK, Osmond C, Barker DJ, Heinonen K, Kajantie E & Eriksson JG. Early life stress and blood pressure levels in late adulthood. Published online: *Journal of Human Hypertension* 2013 Feb; 27(2):90-4. doi: 10.1038/jhh.2012.6. Epub 2012 Feb 16.
- IV Alastalo H, von Bonsdorff M, Räikkönen K, Pesonen AK, Osmond C, Barker DJ, Heinonen K, Kajantie E & Eriksson JG. Early life stress and physical and psychosocial functioning in late adulthood. *PLoS ONE* 2013; 8(7): e69011. doi:10.1371/journal.pone.0069011.

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Abbreviations

BP	Blood Pressure
BMI	Body Mass Index, Weight/Height ²
CHD	Coronary Heart Disease
CI	Confidence Intervals
CVD	Cardiovascular Disease
ELS	Early Life Stress
FPG	Fasting Plasma Glucose
HBCS	Helsinki Birth Cohort Study
HDL	High Density Lipoprotein
HDR	Hospital Discharge Register
HPA-axis	Hypothalamic-Pituitary-Adrenal axis
HR	Hazard Ratio
ICD	International Classification of Disease
IDF	International Diabetes Federation
IGT	Impaired Glucose Tolerance
LDL	Low Density Lipoprotein
M	Mean
MCS	Mental Component Summary
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
PCS	Physical Component Summary

SD	Standard Deviation
SES	Socioeconomic Status
SF-36	Short Form 36
WWII	World War II
β	Regression Coefficient

1 Introduction

Stress is an important factor and it is needed during development in order to develop skills to cope with and adapt to different situations through life. However severe stress can have a negative effect on child development and health (National Scientific Council on the Developing Child 2005, Middlebrooks, Audage 2008, Shonkoff, Boyce & McEwen 2009).

Early life stress including e.g. childhood maltreatment, parental separation and poverty is increasingly becoming important phenomenon, which may have physiological and psychological impact on health in adulthood. There are studies that have shown an association between early life stress and later life health including cardiovascular disease, diabetes and psychological wellbeing (Felitti et al. 1998, Chartier, Walker & Naimark 2009, Chartier, Walker & Naimark 2010, Fuller-Thomson, Brennenstuhl & Frank 2010, Greenfield 2010).

Childhood parental separation is an event that profoundly increases the child's annoyance and vulnerability (Bowlby 1982). The consequences of separation depend on several aspects: the child's age at time of the separation, duration of separation, and reason for separation; divorce, death or other reasons. Studies of separation from parent(s) in childhood have usually focused on parental death or divorce (Kendler et al. 2002, Huurre, Junkkari & Aro 2006, Mustonen et al. 2011, Brent et al. 2012, Luecken, Roubinov 2012).

An increasing number of studies have focused upon the effect of separations from parents during exceptional conditions like during war time (Foster, Davies & Steele 2003, Andersson 2011, Rääkkönen et al. 2011, Lahti et al. 2012, Pesonen, Rääkkönen 2012). Despite this, very little is known about the effects of war time separation in the long-term consequences of physical health in later life. This thesis focuses on the long-term consequences of early life stress on later life health in the Helsinki Birth Cohort Study (HBCS) among people born between 1934 - 1944. The aim was to explore cardiovascular mortality and morbidity in late adulthood among people who experienced wartime separation from parents during WWII. The aims were also to study the separated participants' cardiovascular health, blood pressure levels and physical and psychosocial functioning by using a control group consisting of people who were not separated.

2 Review of the literature

2.1 Early life stress

Stress is part of normal life and we have experienced it even before we were born. Stress is a wide concept and therefore there is no unambiguous definition. One of the most generic definitions of stress is Hans Selye's definition "stress is the nonspecific response of the body to any demand" (Selye 1973). Lazarus (1985) defined stress as the disruption of an individual's physical, mental or emotional condition that has internal or external influence when an individual's coping resources are not sufficient (Lazarus 1985). In general, stress is associated with negative emotional experiences which can manifest as physiological, psychological and cognitive changes (Baum 1990). Minor as well as major stressful events may influence health and prolonged stress can cause illness.

Early life stress (ELS) has been defined as the social, psychological and physical events which infiltrate into a child's normal physical and psychosocial life experiences. ELS, acutely or chronically, affects the child's physiological or psychological balance by creating insecurity and by distorting the child's physical or mental development (Sandberg 2007). ELS is an adverse experience which occurs within the developmental period from gestation to puberty (LaPrairie et al. 2010).

Non-optimal and poor pre- and postnatal development increase vulnerability to various health problems. One of the first to report the association between poor living conditions, slow foetal and infant growth and ischemic heart disease was David Barker. Many studies based on Barker's expanded theory of the Developmental Origins of Health and Disease (DOHaD) (Barker 2004) have shown that programming during foetal life and infancy is associated with health outcomes in adult life including cardiovascular disease, and type 2 diabetes (Forsen et al. 2000, Lawlor et al. 2005, Barker 2008, Eriksson 2011).

Early life stress experiences commonly occur from childhood to school age whereby the child is the most vulnerable to the effects of the environment and events (Knudsen 2004, Flaherty et al. 2006). Different changes occur throughout childhood, and the reactions to them vary accordingly and adaption varies at different developmental levels (Kendall-Tackett, Williams & Finkelhor 1993). The vulnerability to early life stress may lead to dysfunction of the child's development which may result in impairment, problems in adjusting to the stressful experience, or it occurs as problems later in development.

Early life stress in animal models

Animal studies largely form the basis to understand the pathological consequences of early life stress. It has been observed in many animal studies that pre- and postnatal stress is related to neurobiological changes (Graham et al. 1999, Vallée et al. 1999, Kaufman et al. 2000). Stress in early life can alter the development and function of the corticotrophin-releasing-factor (CRF)-containing neurons, the hypothalamic–pituitary–adrenal axis (HPA-axis), and the sympathetic nervous system (Kaufman et al. 2000, Nemeroff 2004).

Maternal separation - where the pups are separated from maternal care and their normal attachment behaviour is disrupted - in an animal is one of the most severe forms of experimental stress. This is causing intense stress to the pups and an increasing sensitivity to the effects of stress in later life (Plotsky, Meaney 1993). Studies from different animal species have reported that early stress experiences such as maternal separation affect later function of the HPA axis and thus influence later wellbeing and health (Coplan et al. 1996, Anisman et al. 1998, Ladd et al. 2000, Cotella et al. 2013, Martisova et al. 2013). Consequently, maternal separation affects stress responsiveness. Also the behaviour of the mother, when the pups return to the mother, has major effects. Prolonged stress has been shown to be related to worse stress responses in later life while short-term stress has been associated with adaptive stress responses later in the life (Grossman et al. 2003).

Even if animal studies in many ways form the basis for human studies, it is difficult to conclude how widely they can be used to explain the effects of childhood stress in humans. Stress experienced by humans may be more complicated than in other species. In humans, besides the stress experience itself several other factors are important including environmental, stress types, frequency, age at exposure, duration and severity.

Types of early life stress

Early life stress can be divided into three stress types/forms i.e. positive, tolerable and toxic (National Scientific Council on the Developing Child 2005, Middlebrooks, Audage 2008). The normal childhood and development include events which pose positive stress. This kind of stress is short-term and may be associated for instance with normal situations of interaction with other children. Positive stress can cause minor physiological changes like higher heart rate, blood pressure and increase in hormone levels, but decreases to a normal level with support from adults (National Scientific Council on the Developing Child 2005, Middlebrooks, Audage 2008, Shonkoff, Boyce & McEwen 2009).

More serious is the tolerable stress, which can be due to changes in the family, death in the family or the relatives or external events of the family like natural phenomena. Tolerable stress takes place during a temporary period and this experience can change direction towards positive stress and become a part of the child's normal development with supportive environments. However, without a supportive atmosphere, physiological changes can increase to an abnormal level and can change for the worse towards toxic stress (National Scientific Council on the Developing Child 2005, Middlebrooks, Audage 2008, Shonkoff, Boyce & McEwen 2009).

Toxic stress is the most severe and prolonged adverse experiences that may be sustained over a long time period and may activate the physiological stress response systems (National Scientific Council on the Developing Child 2005). A child is not able to manage this kind of strong stress itself. It is postulated that a toxic stress could in children influence comprehensively several body systems and organs, metabolic and regulatory systems during critical developmental periods (Garner et al. 2012, Shonkoff et al. 2012). The effects of toxic stress could continually keep the stress hormone levels elevated and could therefore in children lead to permanent changes in brain structure and function (McEwen 2006, Middlebrooks, Audage 2008). Toxic stress can manifest itself as serious problems in the family as several forms of abuse, neglect and maltreatment.

2.1.1 Maltreatment in childhood

Childhood maltreatment is a multidimensional problem and its focus is on the child and the child's living environment. Maltreatment may continue for a long period, occurs commonly inside the family, is caused by parents or other family members and furthermore is one of the least visible forms in parent-child relationships. Child maltreatment can also occur by others like caregivers, friends, strangers or other children.

Maltreatment was for the first time described scientifically in 1946 when diagnosed children's fractures had no known explanation (Caffey 1946). Today, World Health Organization (WHO) has defined maltreatment as including physical, sexual and social abuse, neglect which uses the confidence and the power against the children and which has an impact on the children's health and development (Krug et al. 2002). The different forms of maltreatment are usually difficult to distinguish from each other because they are often related. Maltreatment in all forms of abuse and neglect experiences leaves an indelible mark and exposes the child to chronic stress (Carpenter et al. 2007).

Childhood abuse

Childhood abuse is the most serious form of maltreatment. Physical and sexual abuse can range in severity from minor to major events and physiologically damage the child (Norman et al. 2012). Physical abuse is defined as the event that appears as non-accidental injuries because of adult action. These incidents range from too harsh penalties to physical violence (Zigler, Hall 1989). Sexual abuse goes to the deepest level of domination and it involves different forms of severity. One of the definitions of sexual abuse is that it involves a sexual activity which the child is not able to fully understand, developmentally ready for and is not able to give informed an consent (World Health Organisation 1999). Sexual abuse is known to occur more among girls than boys (Barth et al. 2012).

Childhood emotional abuse and neglect

Overall neglect is defined as the child's caregiver's inability and disregard to care for the child's nutrition, safe living conditions, health and emotional development (World Health Organisation 1999). Emotional abuse and neglect are forms of psychological maltreatment. Emotional abuse includes verbal abuse, harsh nonphysical punishments, or threats of maltreatment (Kaplan, Pelcovitz & Labruna 1999). Whereas emotional neglect includes the child's emotional prohibition and lack of social support or an inability to prevent a child from being exposed to domestic violence (Kaplan, Pelcovitz & Labruna 1999, Kairys, Johnson & Committee on Child Abuse and Neglect 2002). Psychological maltreatment is also described as a repeated exposure which damage interactions between the child and parent(s) and it may occur as a separate event, but is commonly known as a consequence of physical and sexual abuse (Kairys, Johnson & Committee on Child Abuse and Neglect 2002).

Usually most of the maltreated children have experienced several forms of maltreatment (Higgins, McCabe 2001, McGee, Wolfe & Olson 2001, Mennen et al. 2010). Social disadvantage and disruptions in the family are also associated with child maltreatment (Mullen et al. 1996, Glaser 2005). Factors which may have to be taken into account in association with childhood maltreatment are timing, age at onset, severity and duration or chronicity. In particular timing and age at onset of maltreatment have an effect on numerous problems (Bolger, Patterson & Kupersmidt 1998, Thornberry, Ireland & Smith 2001) like difficulties in peer relationships (Bolger, Patterson & Kupersmidt 1998) and poorer skills in daily living when the first event occurs in early age (English et al. 2005). Severity and duration or chronicity of maltreatment helps to assess the intensity and the level of maltreatment (Thornberry, Ireland & Smith 2001, Jonson-Reid, Kohl & Drake 2012). Experience

of maltreatment in childhood is suggested to endanger a child's overall wellbeing (Roscoe 1990, Kaplan 1992, Kaplan, Pelcovitz & Labruna 1999, Hildyard, Wolfe 2002) causing consequences in physical and psychological health in adult life (Kendall-Tackett 2002, Irving, Ferraro 2006, Springer et al. 2007, Wegman, Stetler 2009, Fuller-Thomson, Brennenstuhl & Frank 2010, Hager, Runtz 2012).

2.1.2 Childhood adversity

A child's life can be affected, in addition to maltreatment, also by other types of negative life event and adversities. Negative life events and adversities include serious exposures within the family for instance a death of a family member or relatives, parental divorce or separation from the parents, a child's own or a family member's serious or life-threatening disease, natural disaster, traumatic event and physical violence affecting another family member and war time. Furthermore negative life events can encompass poor childhood conditions like lower socioeconomic status, long-term financial difficulties and living environment such as alcohol problems or substance abuse in the family. Some studies have defined these adversities and the negative events of the household dysfunction (Korkeila et al. 2004, Flaherty et al. 2006).

Parental separation

Parental separation in early life is a stressor which a child can experience when losing a parent e.g. when a parent dies, as a consequence of divorce or by being separated from the parents during exceptional conditions like war time. Separation from parent(s) in childhood is a deeply upsetting event in a child's life and it has a negative impact during childhood and increases vulnerability to later adversity (Bowlby 1982). Rutter (1995) has suggested that the most important risk factors for the child are the circumstances both before and after the loss (Rutter 1995). A few studies have concluded that the child's circumstances after parental death had a more strong long-term influence (Harris, Brown & Bifulco 1986, Sandler 2001).

Loss itself does not necessarily affect the child's development or wellbeing but rather loss internalizing may cause them (Vaillant 1985, Breier et al. 1988, Amato, Booth 1996, Luecken, Fabricius 2003). Parental divorce, can be seen as a child being exposed into a negative family atmosphere and thus to poor parental care (Tennant 1988). Clarke-Stewart et al. (2000) found that parental separation itself did not affect the psychological development in early aged children but did affect in relation to mother's financial difficulties, education and behaviour (Clarke-Stewart et al. 2000).

Further the association between childhood parental separation and elevated risks for adolescent problems social and contextual confounding factors influenced the outcome (Fergusson, Horwood & Lynskey 1994). Parental death is as an event even worse than parental divorce, but parental separation in divorce is seen to influence more widely later life problems (Maier, Lachman 2000, Mack 2001).

Timing of separation from the parent is important because it affects the child's vulnerability (Palosaari, Aro 1994). Parental separation affects children differently when taking place at various ages. It is known that the effects of separation are strongest around the time of the separation (Furstenberg 1990). Allison et al. (1989) examined the effects of separation from infancy to early childhood and found that the separation might have detrimental effects on a younger child (Allison et al. 1989, Woodward, Fergusson & Belsky 2000). There are also opposite findings suggesting that the separation experience in later childhood is more adverse to the child (Amato, Keith 1991, Fergusson, Horwood & Lynskey 1994, Chase-Lansdale, Cherlin 1995). Recently, this view has been challenged and it has been suggested that gender differences might not exist and parental separation effects on boys and girls might be similar (Allison et al. 1989, Amato, Keith 1991, Fergusson, Horwood & Lynskey 1994, Woodward, Fergusson & Belsky 2000).

The long-term consequences of parental separation are several and observed both in relation to parental death (Tennant, Bebbington & Hurry 1980, Tennant, Hurry & Bebbington 1982, Breier et al. 1988, Finkelstein 1988, Kendler et al. 1992, Kendler et al. 2002, Brent et al. 2012, Luecken, Roubinov 2012) and divorce (Kulka, Weingarten 1979, Huurre, Junkkari & Aro 2006, Mustonen et al. 2011) studies. Increasingly studies focus on long term effects of war time parental separation. Most of these studies have focused the psychological aspects (Birtchnell, Kennard 1984, Räsänen 1988, Foster, Davies & Steele 2003, Pesonen et al. 2007a, Rusby, Tasker 2008, Rusby, Tasker 2009, Pesonen et al. 2010, Andersson 2011, Rääkkönen et al. 2011, Pesonen et al. 2011a, Pesonen et al. 2011b, Lahti et al. 2012), but little is studied about war separation effects in physical health (Räsänen 1988). Studies on psychological aspects found that wartime separation experience in childhood increased risk for lower levels of psychological wellbeing (Foster, Davies & Steele 2003) and depressive symptoms (Pesonen et al. 2007a, Rusby, Tasker 2009) or other severe mental disorders (Rääkkönen et al. 2011, Lahti et al. 2012) in later life. There are also two studies which did not find difference in mental health between people who experienced childhood war separation and people who did not experience separation (Birtchnell, Kennard 1984, Räsänen 1988).

Negative life events

Negative childhood life events such as long-term financial difficulties, problems with relationships, serious diseases in the family and parental substance abuse are examples of childhood social stressors. Negative life events have been shown to contribute to disease processes (Berkman, Kawachi 2000) and they can be seen as confounding factors influencing childhood maltreatment, adversity and parental divorce (Amato 2001). Vanaelst et al. (2012) in the IDEFICS study stressed the importance to focus on a child's familial and social environment underlying the stress experiences. They observed that negative life events varied between the children. Most children did not experience negative life events, but a small group of children experienced multilevel adversities and these adversities in childhood made it possible for the stress to accumulate (Vanaelst et al. 2012b). Socioeconomic status (SES) is one of the most widely studied negative life events, which is known to associate strongly with health and disease (Rahkonen, Lahelma & Huuhka 1997, Cohen et al. 2010, Conroy, Sandel & Zuckerman 2010).

Cumulative maltreatment and adversity in childhood

Cumulative childhood stress can be defined as chronic stress, when the stress factors are prolonged or individuals are experiencing them more than once e.g. childhood adverse exposures. The Adversity Childhood Experiences childhood (ACEs) study is one of the largest studies focusing upon multiple forms of childhood adversity including some or all forms of adversity of childhood stress such as childhood abuse, neglect and household dysfunction including parental separation and negative life events (Middlebrooks, Audage 2008). There are studies where cumulative childhood adversity is defined differently by for example excluding maltreatment (Korkeila et al. 2004, Korkeila et al. 2010a, Korkeila et al. 2010b).

A growing body of evidence suggests that two or more experiences of childhood adversity had a higher impact on childhood and late life consequences such as smoking (Vander Weg 2011), alcohol abuse (Dube et al. 2002, Dube et al. 2006), sleeping problems (Chapman et al. 2013), health problems (Moeller, Bachmann & Moeller 1993, Felitti et al. 1998, Dube et al. 2003, O'Rand, Hamil-Luker 2005, Flaherty et al. 2006, Dube et al. 2009, Korkeila et al. 2010a) and psychological wellbeing (Forehand 1998, Chapman et al. 2004, Korkeila et al. 2004, Schilling, Asetline & Gore 2007, Danese et al. 2009, Clark et al. 2010, Korkeila et al. 2010b, Tietjen et al. 2010, Vanaelst et al. 2012a).

2.1.3 Coping with stress in early life

Coping and adapting to stress is continually changing behavioural, cognitive and emotional processes to manage external and/or internal adversity events in an individual's life (Folkman, Lazarus 1980). The process is acting as a mediator in the individual's personality development and affects the individual's ability to adapt and to operate in difficult situations (Holahan, Moos 1987). Individuals can cope with stress in various ways like by attempting to change their own conception of an exposure (cognitive coping strategy) or reducing the stress effects (behavioural coping strategy) or both attempting to protect and to regulate stress (approach coping strategy) and attempting to prevent negative feelings (avoidance coping strategy) (Roth, Cohen 1986, Holahan, Moos 1987) or a combination of these strategies (Moos 1995). People have different personal capabilities, resources and resilience to manage stress and maintain normal physical and psychological functioning. People with strong resources are able to use more active coping and they need less of the avoidance coping.

The experience of severe childhood stress varies individually and may affect the development of a stress response system. The developmental environments, social support, relationships with the family, child's personality trait and cognitive skills can have significant effect on children's ability in coping with stress (Compas 1987, Wu et al. 2013). Secure developmental environments offer protective effect against a stressful situation and security allows the child to deal with stress and to develop the capacity to face other stressful events (Rutter 1985, Streeck-Fischer, van der Kolk 2000). Without a safe environment, such as in child abuse situations, the child may not necessarily get the required support and stress can become unmanageable, the benefit of the child may be unable to address (Streeck-Fischer, van der Kolk 2000). Children who have experienced maltreatment in comparison with those who do not have maltreatment experience have a worse base to cope with stress (Cicchetti, Rogosch 2012).

Children can use the uncontrollable stress situations, the fight or flight reactions, which activates the peripheral autonomic nervous system and its adrenocorticotrophic hormone and cortisol, and the immune system of the HPA axis (Perry et al. 1995). Prolonged stressful situations may reduce the child's cognitive understanding about events or even change it, despite the fact that the child otherwise behaves normally in many situations and the child who experienced prolonged stress is internally restless. Cognitive behaviour modification can persist into adulthood, and low self-esteem can predict poor health as an adult (Trzesniewski et al. 2006). It is noted that although some children are vulnerable

when they are facing the changes and after adverse events, others can be more adaptive to life changes and stressful life events.

2.2 Cardiovascular disease

2.2.1 Definition and prevalence of cardiovascular disease

Cardiovascular disease (CVD) is a chronic disorder which usually develops slowly throughout the lifespan. CVD is a collective term for diseases that affect the heart and circulatory system. The more common forms are diseases often involving an atherosclerotic process such as coronary heart disease (CHD), hypertension and stroke (Mendis, Puska & Norrving 2011).

According to the World Health Organisation, the major risk factors for the CVD are unhealthy lifestyle habits such smoking, unhealthy dietary habits, excess alcohol intake and reduced physical activity (Marmot 1988, World Health Organization 2003, Mendis, Puska & Norrving 2011). In addition to these CVDs are associated with metabolic risk factor (elevated blood pressure and lipids, and elevated blood glucose) and other risk factors like psychosocial stress, family history, age and gender (Marmot 1988, Mendis, Puska & Norrving 2011).

Coronary heart disease

Coronary heart disease (CHD) is one main form of CVD. CHD usually manifests in three forms: angina pectoris, myocardial infarction and/or sudden death, which may be symptomatic or asymptomatic. Risk factors for CHD are dyslipidaemia and elevated blood pressure, smoking, diabetes and unhealthy dietary habits (Greenland et al. 2003). Greenland (2003) have shown that in people, who present with two or more of these risk factors, are more prone to develop CHD (Greenland et al. 2003). Psychosocial and chronic stress and psychological characteristics like personality and cognition have been shown to predict CHD (Greenwood et al. 1996, Rozanski, Blumenthal & Kaplan 1999, Cohen, Janicki-Deverts & Miller 2007, Steptoe, Kivimäki 2012).

Hypertension and stroke

Hypertension is common risk factor for cardiovascular events (Stamler, Stamler & Neaton 1993). Definition of hypertension has changed during the past years.

Generally hypertension has been defined as a blood pressure level exceeding 140/90 mmHg. This level of blood pressure doubles the risk of developing CVD, but the Joint National Committee have been argued that high systolic blood pressure (above 140 mmHg) is a more important CVD risk factor than diastolic blood pressure for people over 50 years of age (Chobanian et al. 2003). Also lower levels than those are generally defined and often called high-normal blood pressure and are also associated with an increase in the risk of CVD (Vasan et al. 2001, Chobanian et al. 2003). Risk factors for hypertension are similar to those for CVD including impaired glucose regulation, dietary habits, and smoking (Kannel 1989). Negative effects such as mood disorders (Jonas, Lando 2000, Meng et al. 2012) and psychosocial stress (Brotman, Golden & Wittstein 2007) have also been shown to be strongly and consistently associated with hypertension.

Stroke is a cerebrovascular disease strongly related to high blood pressure, but smoking and diabetes are also important modifiable risk factors (Donnan et al. 2008). In addition, other risk factors are old age and dyslipidaemia. Psychosocial stress and particularly self-reported chronic stress is an independent risk factor and is known to significantly increase the risk of stroke (Ohlin et al. 2004).

Prevalence of cardiovascular disease

CVD is the most common cause of death worldwide (Mendis, Puska & Norrving 2011) and in Europe it accounts for nearly half (47%) of the deaths. The main forms of CDV are CHD and stroke (Nichols et al. 2012). In Finland the diseases of circulatory systems caused 40% of all deaths in 2011 and of these over 55% of deaths caused CHD (Statistics Finland 2012).

2.2.2 Early life stress and cardiovascular disease

Childhood socioeconomic disadvantage, but also various other forms of childhood adversity such as abuse, neglect and household dysfunction are suggested to be important determinants of later life cardiovascular disease (Felitti et al. 1998, Dong et al. 2004, Goodwin, Stein 2004, O'Rand, Hamil-Luker 2005, Sumanen et al. 2005, Galobardes, Smith & Lynch 2006, Wegman, Stetler 2009, Cohen et al. 2010, Korkeila et al. 2010a). In cumulative childhood adversity studies it has been shown that people who experienced 3 or more childhood adversities compared to those who did not experience adversities in childhood had greater risk for heart disease (Felitti et al. 1998, Scott et al. 2011). However, it should be noted that also one single form of childhood stress can lead to disease. In Fuller-Thomson's study, childhood

maltreatment was associated with cardiovascular diseases and the association remained strong, even when controlled for age, gender, and ethnicity in addition to risk behaviour in adulthood, childhood stressors, depression and a high blood pressure (Fuller-Thomson, Brennenstuhl & Frank 2010).

Socioeconomic status and positions in early life predict adult cardiovascular disease, lower levels of father's occupational or educational level are associated with elevated risk for cardiovascular events in adulthood (Wannamethee et al. 1996, Wamala, Lynch & Kaplan 2001, Singh-Manoux et al. 2004, Nandi et al. 2012) and the findings were pronounced in men (Wannamethee et al. 1996, Singh-Manoux et al. 2004). The Wroclaw growth study found opposite results suggesting that childhood socioeconomic status was significantly associated with the appearance of cardiovascular disease among women not in men (Lipowicz et al. 2007). However, in men childhood socioeconomic status was significantly associated to stroke as well as parental divorce was seen in men to increase the risk of a stroke three-fold (Hart, Hole & Smith 2000, Fuller-Thomson, Dalton 2012). Brunner et al. (1999) reported opposite findings about the association between childhood/adulthood socioeconomic positions and cardiovascular disease risk. Socioeconomic position in adulthood was a stronger cardiovascular risk factor than father's social position during childhood (Brunner et al. 1999).

Gender is important when exploring links between childhood stress and physical health outcomes. Some studies found that gender differences between childhood stress and cardiovascular disease in maltreated women or women who lived under adverse social conditions in childhood had greater risk for cardiovascular events (Batten et al. 2004, Hamil-Luker, O'Rand 2007). Women who had experienced childhood maltreatment had a nine-fold risk of developing cardiovascular diseases (Batten et al. 2004).

Effect of hypertension

Results from several studies have shown that childhood adversities have an impact on later life blood pressure levels (Luecken 1998, Koupil et al. 2007, Lehman et al. 2009, Stein et al. 2010). Parental death was strongly associated with long-term higher blood pressure (Luecken 1998). Age at childhood adversity may have effect on developing hypertension. Koupil et al. (2007) studied people who suffered starvation during the siege of Leningrad. They found that the starvation effect on blood pressure levels differed between gender and age. Higher blood pressure levels were found in women aged from 6 to 8 years and in men aged from 9 to 15 years during the peak of starvation compared with those who only were born during the same period (Koupil et al. 2007).

2.2.3 Early life stress and cardiovascular disease mortality

Association between early life stress and cardiovascular mortality has been studied mostly in relation to childhood socioeconomic conditions and only few studies relate to parental divorce (Lynch et al. 1994, Schwartz et al. 1995, Lynch et al. 1996, Tucker et al. 1997, Smith et al. 1998, Martin et al. 2005, Power, Hyppönen & Smith 2005, Kauhanen et al. 2006). It has been shown that in men adverse childhood socioeconomic positions predicted a strongly increased risk for CVD and CHD deaths despite of controlling for adult socioeconomic position and other risk factors. In the mothers of the 1958 British birth cohort study low childhood socioeconomic position had impact on the cardiovascular events mortality (Power, Hyppönen & Smith 2005). Lynch et al. (1994) found that childhood socioeconomic position may not necessarily be an important factor for the risk of dying from cardiovascular disease. Socioeconomic position in childhood did not affect cardiovascular and all-cause mortality, when the comparison was made between people belonging to the lowest and the highest adult socioeconomic status (Lynch et al. 1994).

2.3 Type 2 diabetes

2.3.1 Definition and prevalence of type 2 diabetes

Type 2 diabetes is the most common form of diabetes. It is defined as a metabolic disorder in which people have insulin deficiency and insulin resistance (American Diabetes Association 2012). Diabetes may develop insidiously over a long time, and most of the people suffering impaired glucose tolerance (IGT) are not aware of it. International Diabetes Federation (IDF) has been estimated that among those who have 70% of IGT will develop diabetes (International Diabetes Federation 2003). In an oral glucose tolerance test (OGTT) plasma glucose concentration is measured and the diagnostic criterion for diabetes is exceeded when the fasting plasma glucose concentration (FPG) is ≥ 7.0 mmol/L, or the 2-h postload glucose is ≥ 11.1 mmol/L (World Health Organization, International Diabetes Federation 2006, American Diabetes Association 2012).

Obesity, especially abdominal obesity and physical inactivity are the main risk factors for type 2 diabetes. Aging is also a strong risk factor. It has also been shown that hypertension is an important risk factor for type 2 diabetes (Gress et al. 2000). There are a growing number of studies which have suggested that low birth weight is associated with an increased risk of type 2 diabetes later in adulthood (Whincup et al. 2008, Eriksson 2011, Li et al. 2012). Also, psychosocial stress can have an

adverse effect on glucose metabolism and may increase the risk of developing type 2 diabetes (Wales 1995, Rääkkönen et al. 1996, Pouwer, Kupper & Adriaanse 2010).

In Finland, according to the DEHKO 2D cross-sectional population-based survey the prevalence of type 2 diabetes among 45-74 year old men and women was 11% and 16%, respectively (Peltonen et al. 2006). In other words type 2 diabetes is one of the most common lifestyle associated with chronic diseases.

2.3.2 Early life stress and type 2 diabetes

Childhood socioeconomic status is known to associate with insulin resistance and general obesity (Lawlor et al. 2002), consequently it is associated with an increased risk of type 2 diabetes (Agardh et al. 2007, Maty et al. 2008, Tamayo, Christian & Rathmann 2010) and particularly among women (Agardh et al. 2007, Maty et al. 2008). The association between childhood socioeconomic positions and type 2 diabetes are not necessarily permanent. According to Agardh et al. (2007) the association between childhood socioeconomic positions and type 2 diabetes disappeared when adjusting for adult socioeconomic positions and adult risk factors of diabetes (Agardh et al. 2007).

There are only few studies focusing upon the association between other early life adversities and risk of obesity (Thomas, Hyppönen & Power 2008) and type 2 diabetes (Goodwin, Stein 2004, Thomas, Hyppönen & Power 2008). Goodwin and Stein (2004) found that childhood neglect, but not childhood physical abuse, has a strong association with a higher diabetes risk and the association was pronounced among women even when controlled for age, race, income, education and marital status (Goodwin, Stein 2004). Thomas et al. (2007) found that the association between childhood neglect or abuse and type 2 diabetes was mainly explained by adulthood mediators (Thomas, Hyppönen & Power 2008).

2.4 Physical and psychosocial functioning

An individual's physical and psychosocial functioning varies throughout life from negative states of diseases to more positive states of wellbeing. Ageing is a challenge for physical and psychosocial functioning and wellbeing and is usually associated with decline later in life (Rowe, Kahn 1987). Timing and the degree of decline is individual. These individual differences are partly due to lifestyles such as physical activity, smoking status and social circumstances including socioeconomic positions. It is known that the decline in health is faster during old age, among

people with poor health-related behaviours and from low social positions (Lantz et al. 1998, Willcox et al. 2006).

2.4.1 Measurement of physical and psychosocial functioning

Physical and psychosocial functioning is part of health-related quality of life. Health-related quality of life also includes the assessment of general health, physical symptoms, emotional and cognitive functioning, as well as role and social functioning. Physical and psychosocial functioning can usually be subjectively assessed. One of the most commonly used self-assessment measure is the Short form 36 questionnaire (SF-36) (Ware, Sherbourne 1992, Coons et al. 2000), which is a valid measure of physical and psychosocial health constructs (McHorney, Ware & Raczek 1993). Rand-36, a further development of the SF-36, is otherwise similar, but the general health and pain scales are different (Hays, Sherbourne & Mazel 1993).

The SF-36/RAND-36 scales were not designed to assess the physical and psychosocial functioning related to a specific disease, but rather to give an overall assessment of functional capacity. Measurement of self-assessed physical or psychosocial functioning requires several questions, which are combined to describe for example physical functioning. Other scales are physical role functioning, bodily pain, general health, mental health, emotional role functioning, vitality and social functioning and the scales each have scores ranging from 0 –100 where 0 reflects as maximal impairment and 100 reflects no impairment.

2.4.2 Early life stress and physical and psychosocial functioning

Past research has indicated that early life stress is related to several physical and mental health conditions. However, there are only few studies which examined the relationship between early life stress and later physical and psychosocial functioning (Walker et al. 1999, Edwards et al. 2004, Singh-Manoux et al. 2004, Afifi et al. 2007, Corso et al. 2008, Draper et al. 2008, Taylor, Way & Seeman 2011). Two of these studies showed that childhood abuse was associated with a greater risk of poor physical functioning (Afifi et al. 2007, Draper et al. 2008). Consequently childhood abuse is regarded as major determinant of later life physical and psychosocial functioning (Afifi et al. 2007). The Netherlands Mental Health Survey and Incidence Study also found that childhood neglect with childhood abuse is associated with mental functioning later in life (Afifi et al. 2007).

In studies were focus on for childhood maltreatment and cumulative early life stress has reported to two-way associations between the childhood stress, physical and psychosocial functioning and age. Corso et al. (2008) observed that the effects of childhood maltreatment on physical and psychosocial functioning were significant and the physical and psychosocial functioning declined continuously with age in people who had experienced childhood maltreatment (Corso et al. 2008) whereas Edwards et al. (2004) did not find the effect of age on physical functioning decline. (Edwards et al. 2004).

3 Aims of study

The overall aim of this study was to explore the associations between war-time separation status as an indicator of stress experienced in early life, and cardiovascular disease and general health in later adult life. Another focus was to study the associations of stress in early childhood and physical and psychosocial functioning among former war evacuees using a longitudinal study setting.

The specific aims were:

1. To examine morbidity and mortality from cardiovascular disease in individuals separated temporarily from their parents in childhood (Study I).
2. To assess prevalence of cardiovascular disease and diabetes in later life among individuals exposed to separation in early childhood (Study II).
3. To study long-term effects of separation on blood pressure levels in non-obese individuals who were separated temporarily in childhood from their parents (Study III).
4. To study the differences in physical and psychosocial functioning in late adulthood in subjects separated temporarily from their parents in childhood (Study IV).

4 Subjects and methods

4.1 Helsinki Birth Cohort Study

The study participants belong to the Helsinki Birth Cohort Study (HBCS) born 1934-1944. This cohort consists of 13,345 people, who were born in one of the two public maternity hospitals. 8760 were born in Helsinki University Central Hospital (HUCH) and 4585 in Kättilöopisto Maternity Hospital in Helsinki. All participants visited child welfare clinics in the city of Helsinki, the majority also went to school in Helsinki and they were alive and living in Finland in 1971 when a unique personal identification number was allocated for each member of the Finnish population. The cohort members, who migrated before January 1, 1971, were excluded from the study. Data on the sample sizes and exclusion criteria in the different substudies are presented in Figure 1.

4.2 Data on war separation in childhood

Finland fought two wars with the Soviet Union; the Winter War (November 1939 to March 1940) and the Continuation War (June 1941 to September 1944) during World War II (WWII). During 1939-1946 the Finnish Ministry of Social Affairs and Health organized the evacuation of children to foster families abroad primarily to Sweden, but also to Denmark. Approximately 70,000 Finnish children with various socioeconomic backgrounds were temporarily separated from their parents in order to protect them from the strains of war. In many families, the voluntary evacuations were seen as an opportunity to send the children to shelter from air bombardments and food shortage, which was severe particularly in 1942, and the war was expected to end soon. Children were evacuated as many reasons as there are children. Although the evacuations were voluntary, presumably the Finnish children's evacuations were related to unexpected interactions between political aspects and factors within the family (Pesonen et al. 2007a, Kavén 2010).

Information on parental separation was obtained from a register in the Finnish National Archives, which gives full documentation of the evacuated children ($n = 48,628$). Age at first separation and duration of separation was available from archive data (Pesonen et al. 2007a). After the war, the evacuated children were separated from their new foster families and sent back to their original families after a varying period. Some children experienced separation more than once.

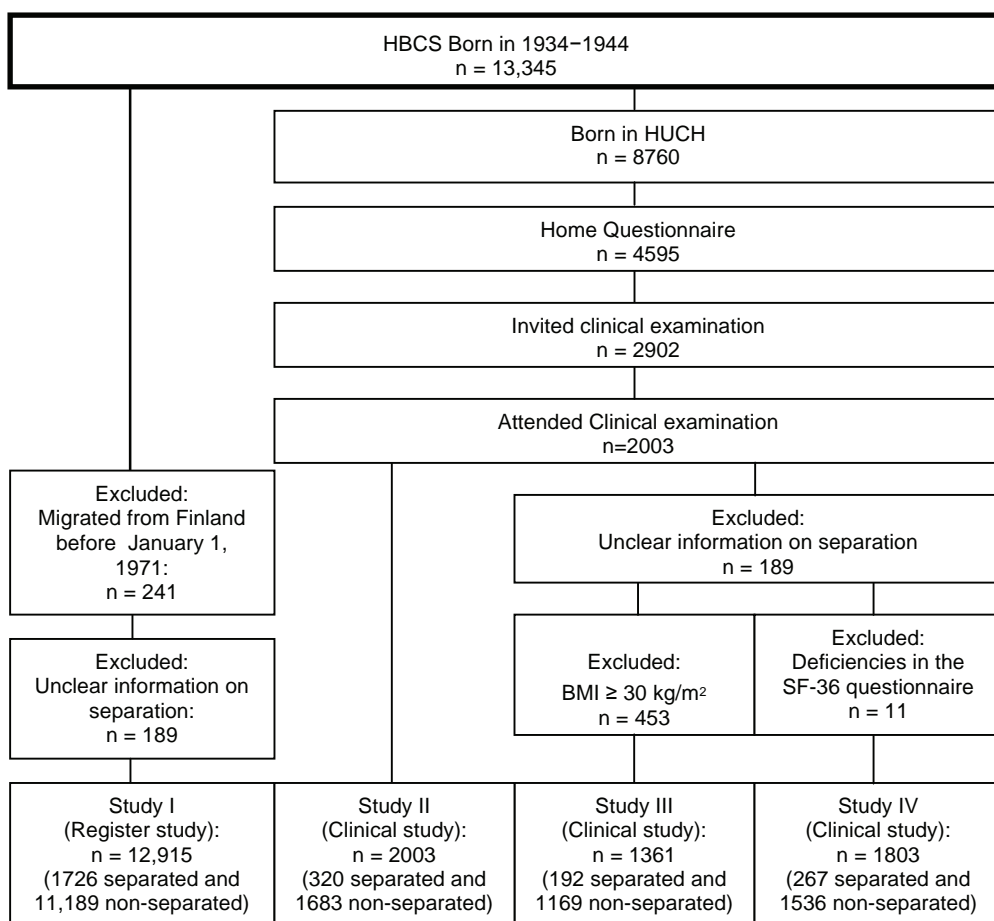


Figure 1. Data on study samples and war-time separation in participants included in the different studies.

In addition, roughly 20,000 children were separated from their parents through personal contacts of the families and through civil organizations during the WWII, which have not been officially registered. To identify these subjects, we also collected information relating to war-time evacuation during the clinical survey in 2001-2004 by a self-report questionnaire. People whose information on separation in wartime was uncertain ($n = 189$) were excluded from the analyses from studies I and III-IV.

Study I. The epidemiological study cohort consisted of 12,915 people. Of these 1726 (13.4%) had been evacuated abroad without their parents (“separated”) and of these 931 (53.9%) were men. The remaining 11,189 individuals did not experience separation from their parents (“non-separated”). Age at separation was available for

88% and data on duration of the separation was available for 89% of the separated. The mean age at separation was 4.6 (SD = 2.4) years and mean duration of the separation was 1.8 (SD = 1.1) years. When examining the possible effects, the age at evacuation and duration of the separation were taken into account, and were divided into four and three groups, respectively. The categorizations of age at separation were as follows: infancy, separated before 2 years; toddlerhood, from aged 2 years to less than 4 years; early childhood, from aged 4 years to less than 7 years; and school age, over 7 years. Similarly duration of the separation was divided into four groups in studies I-II; under 1 year, from 1 year to less than 2 years, from 2 years to less than 3 years and over 3 years. In studies III-IV duration of the separation was divided into three groups; under 1 year, from 1 year to less than 2 years and over 2 years. Data on age at separation and duration of separation are presented in table 1.

Study II. Of the 2003 participants 320 (16.0%) had been evacuated abroad and 49.7% (n = 159) were men. Participants (n = 1683) who did not separate from their parents during the war served as non-separated controls. Information on age at separation was available for 234 separated and duration time was available for 229 separated.

Study III. This sub-study included 1361 non-obese participants who had a BMI < 30 kg/m². Of these 192 (14.1%) were separated participants, who experienced temporary evacuation from their parents during the war. Age at the separation was available for 86.5% and data on duration of the separation was available for 83.9% of the separated. Average age at the separation was 4.8 (SD = 2.5) years and the duration of the separation was 1.6 (SD = 1.0) years. In separated participants 52.1% were men. The non-separated participants served as controls (n = 1169).

Study IV. Of the participants who filled completely the SF-36 questionnaire, 267 (14.8%) had been evacuated unaccompanied by their parents. Information on age at and duration of separation was available for 87.0% and 85.1% of the separated, respectively. The participants who did not experienced separation in the WWII served as controls (n = 1536).

Table 1. Age at separation and duration of separation in studies I and III-IV.

	Study I Separated ^a (n = 1726)	Study III Separated ^b (n = 192)	Study IV Separated ^c (n = 267)
	n (%)	Mean (SD)/ %	Mean (SD)/ %
<u>Age at separation</u>		4.8 (2.5)	4.8 (2.4)
Infancy (< 2 years)	222 (14.3)	11.4	9.9
Toddlerhood (2–4 years)	505 (32.6)	36.7	38.6
Early childhood (4–7 years)	517 (33.3)	27.1	28.8
School age (>7 years)	307 (19.8)	24.7	22.7
<u>Duration of separation</u>			
≤ 1 year	320 (21.2)		
1–2 years	726 (48.2)		
2–3 years	253 (16.8)		
> 3 years	208 (13.8)		
<u>Duration of separation</u>		1.6 (1.0)	1.7 (1.0)
< 1 year		26.1	24.1
1–2 years		49.7	48.2
>2 years		24.2	27.6

^a Available at least for 88.0% for each variable.

^b Available at least for 83.9% for each variable.

^c Available at least for 85.1% for each variable.

4.3 Socioeconomic covariates

Data of the participants' gender and year of birth were collected from hospital birth records. Information on the year of birth was used to define the participants' age in the register and was the base in study I and studies II-IV age was defined by age at clinical examination. Childhood socioeconomic status (SES) was based on father's highest attained occupational status for all four studies. It was abstracted from all childhood records; i.e. the birth, child welfare clinic and school health records. Childhood socioeconomic status was categorised into three groups using a social classification originally devised by Statistics Finland (Central Statistical Office of Finland 1989). In studies I and III-IV it was called manual workers, junior clericals and senior clericals, and in study II lower, middle and upper class.

Other socioeconomic covariates were educational attainment (studies II-III) and own occupational status (study IV). Participants' own level of educational attainment was

based on a question of schooling (education in years) in the clinical examination and was categorized into four groups; Elementary school, Vocational school, Senior high school and College or University degree. Data on participants' own highest occupational status was based on the Central Statistical Office of Finland registers and was obtained at 5-year intervals between 1970 and 1995. This was divided into four groups; labourer, self-employed, lower middle class and upper middle class. Data on socioeconomic and educational factors are presented in table 2.

4.4 Cardiovascular events: Medication Reimbursement-, Hospital Discharge- and Causes of Death Registers

The use of medication for coronary heart disease (CHD) and hypertension was extracted from the National Register of Medication Reimbursement and information was available until the end of year 2002. Consequently the follow-up period in study I was from 1971 to 2002. The data was linked by combining the records all people receiving reimbursement of drugs for CHD and hypertension by using the unique personal identification number. The partial reimbursement of drug costs are entitled to the people who have a physician's assent and the need for medication and diagnosis has been confirmed by the physician at the Social Insurance Institution.

Furthermore using the personal identification number information on coronary events and stroke were abstracted from the national Hospital Discharge Register (HDR) and the national Causes of Death Register (CDR). All information on all-cause mortality, cardiovascular and non-cardiovascular mortality was based on the national Causes of Death Register (CDR). Hospital admissions and deaths were recorded between years 1971 and 2003. The diagnoses in the HDR and the CDR were based on the International Classification of Diseases (ICD) codes according to ICD-8 until 1986; thereafter, ICD-9 was used until 1995, and ICD-10 was used until 2003.

The HDR and the CDR register data are confirmed to the coverage and the accuracy, and they are valid to use for epidemiological research (Keskimäki, Aro 1991, Lahti, Penttilä 2001). The HDR and the CDR registers are also validated to be reliable tools, showing high levels of specificity in coronary events (Rapola et al. 1997, Pajunen et al. 2005). They are also validated for stroke diagnoses (Leppälä, Virtamo & Heinonen 1999, Tolonen et al. 2007).

Table 2. Characteristics of the participants' socioeconomic status and educational levels in studies I-IV.

	Study I		Study II		Study III		Study IV	
	Separated (n = 1726) n (%)	Non- separated (n = 11189) n (%)	Separated (n = 320) n (%)	Non- separated (n = 1683) n (%)	Separated (n = 192) %	Non- separated (n = 1169) %	Separated (n = 267) %	Non- separated (n = 1536) %
<u>Father's occupational status in childhood^a</u>								
Senior clericals	184 (11.0)	1988 (18.2)	34 (10.7)	255 (15.3)	11.6	19.9	10.2	18.6
Junior clericals	375 (22.4)	2660 (24.4)	69 (21.8)	350 (20.9)	23.7	22.2	24.5	22.0
Manual workers	1118 (66.7)	6255 (57.4)	214 (67.5)	1067 (63.8)	64.7	57.9	65.3	59.3
<u>Level of educational attainment in adulthood^b</u>								
Elementary school			127 (39.7)	526 (31.3)	39.1	29.4		
Vocational school			63 (19.7)	336 (20.0)	19.3	19.1		
Senior high school			72 (22.5)	450 (26.8)	23.4	27.9		
College/university degree			58 (18.1)	366 (21.8)	18.2	23.7		
<u>Highest social class in adulthood^c</u>								
Upper middle							43.1	49.6
Lower middle							39.0	37.7
Self-employed							2.6	3.6
Labourer							15.4	9.1

^a The highest occupational status indicated by father's occupation, derived from birth, child welfare and school health-care records.

^b Based on a question related to schooling.

^c Based on occupation derived from the census data between 1970 and 1995.

Table 3 shows the ICD-codes used to define cardiovascular events and deaths. The first three digits from the cause of admission or primary cause of death were used to identify the occurrence of CHD, stroke, cardiovascular death and all other causes were included in the noncardiovascular death. Information on the overall morbidity and mortality of CHD were based on all three registers (the National Register of Medication Reimbursement, the HDR, and the CDR).

Table 3. International Classification of the Disease Codes on coronary events and deaths of the National Hospital Discharge Register or the Causes of the Death Register.

	Diagnostic codes from the International Classification of the Diseases 8 th , 9 th and 10 th
Coronary heart disease	ICD-8: 410-414 ICD-9: 410-414 ICD-10: I21-I25
Stroke	ICD-8: 430-434, 436-437 ICD-9: 430-434, 436-438 ICD-10: I60-I69
Cardiovascular death	ICD-8: 390-459 ICD-9: 390-459 ICD-10: I00-I99
Noncardiovascular death	ICD-8: 1-389, 460-999 ICD-9: 1-389, 460-999 ICD-10: A01-H99, J00-X99

In study I, 628 people who received reimbursement for CHD medication and 2530 people who received reimbursement for antihypertensive medication were identified. Also 408 people were identified being reimbursed for CHD medication but did not have any reimbursement for antihypertensive medication. For treatment of CHD beta-blocking agents and angiotensin-converting enzyme inhibitors are commonly used, but they are also frequently used for hypertension treatment. Thus, people could get the drugs reimbursement, but did not need a separate reimbursement permission for hypertension and vice versa. The HDR and the CHD registers, included the follow-up period from 1971 to 2003, and identified 1640 (12.3%) deaths of the cohort members. Cardiovascular disease (CVD) caused 494 deaths and of these 275 was due to deaths from CHD.

4.5 Clinical examination

The clinically examined subset of the HBCS cohort was traced by using the personal identification number. In the year of 2000 all 7079 individuals belonging to the cohort, still alive and living in Finland were sent a postal questionnaire, and of these 4595 responded to the questionnaire and gave permission to contact them. Randomly selected 2902 cohort members were invited to attend clinical examination, which included anthropometric measurements, blood tests and self-report questionnaires. Of them, 2003 subjects (928 men and 1075 women) participated during the years 2001-2004.

Participants in studies II-IV attended the clinical examination in the morning after an overnight fast. Before any study procedure, each participant gave written informed consent. The clinical examination was conducted by a trained research nurse team. The anthropometric measurements included height, weight and waist circumference. Blood pressure was measured. Height was measured to the nearest millimetre and weight was measured in light indoor clothing to the nearest 0.1 kilogram. Body mass index (BMI) was calculated (kg/m^2) and in study III participants with BMI $<30 \text{ kg/m}^2$ were defined as non-obese. Waist circumference was measured midway between the lowest ribs and the iliac crest and that of hip at the level of great trochanters with a soft tape. Blood pressure was measured after a 10 minutes rest from the right arm in a sitting position. The result from a standard sphygmomanometer (Omron Matsutaka Europe, Hoofddorp, the Netherlands) was recorded as the mean of two successive readings. Participants who used medication for hypertension were requested not to take their medication on the morning of clinic attendance. In study II pulse pressure was calculated according to the formula systolic pressure minus diastolic pressure and hypertension was defined when the systolic blood pressure was over 140 mmHg or diastolic blood pressure was over 90 mmHg and/or use of antihypertensive medication. Information on the use of antihypertensive medication and on hypertension diagnosed by a physician was collected from a questionnaire.

A 2-hour 75-g oral glucose tolerance test (OGTT) was performed after overnight fasting in the morning. Plasma glucose concentrations were measured by a hexokinase method from samples drawn at 0, 30 and 120 minutes. The results of OGTT were used to assess type 2 diabetes applying to the World Health Organization (WHO) criteria for disturbances in glucose regulation in studies II-IV (Alberti, Zimmet 1998). Insulin concentrations were determined by a two-site immunoradiometric assay. The homeostatic model assessment index of basal insulin resistance was calculated as the product of fasting glucose and insulin (mU/l) divided by 22.5. Furthermore, in studies II-III the participants' blood samples were

determined for the measurement of serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. These concentrations were measured by using standard enzymatic methods, and for apolipoprotein A and B and lipoprotein(a) were measured with the use a standard immunoturbometric methods (Lie et al. 1976, Fossati, Prencipe 1982, Sugiuchi et al. 1995). Low-density lipoprotein (LDL) cholesterol concentrations were also formed by the Friedewald formula (Friedewald, Levy & Fredrickson 1972). Characteristics of the blood pressure and lipid in studies II-III are shown in table 4.

Table 4. Blood pressure and blood lipids among the separated and non-separated participants in studies II-III.

	Study II		Study III	
	Separated (n = 320)	Non- separated (n = 1683)	Separated (n = 192)	Non- separated (n = 1169)
	Mean (SD) or n %	Mean (SD) or n %	Mean (SD) or n %	Mean (SD) or n %
Systolic blood pressure (mmHg)	149.4 (21.0)	144.7 (19.2)	148.6 (21.5)	142.2 (19.6)
Diastolic blood pressure (mmHg)	88.9 (10.5)	89.1 (10.4)	88.5 (11.0)	87.7 (10.3)
Systolic blood pressure > 140 mmHg	221 (18.6%)	99 (12.1%)		
Diastolic blood pressure > 90 mmHg	149 (16.3%)	171 (15.7%)		
Pulse pressure (mmHg)	60.5 (17.1)	55.6 (15.7)		
Use of blood pressure lowering medication	135 (18.7%)	185 (14.5%)		
Hypertension defined as systolic/diastolic blood pressure >140/90 mmHg and/or use of blood pressure lowering medication	263 (17.6%)	57 (11.1%)		
Hypertension diagnosed by a physician	122 (18.9%)	198 (14.6%)		
Total cholesterol (mmol/L)			5.9 (1.2)	5.9 (1.1)
HDL-cholesterol (mmol/L)	1.6 (0.4)	1.6 (0.4)	1.64 (0.44)	1.65 (0.44)
Triglycerides (mmol/L) *	1.5 (0.8)	1.5 (1.1)	0.27 (0.40)*	0.23 (0.44)*
Apolipoprotein A (mmol/L)	1.6 (0.3)	1.7 (0.3)		
Apolipoprotein B (mmol/L)	1.1 (0.3)	1.1 (0.3)		
Lipoprotein(a) (mmol/L)	19.2 (22.0)	16.2 (20.8)		

* Log transformed value

Data on chronic diseases were derived from a self-administered questionnaire, which the participants filled in during the clinical examination. Diseases like diabetes and CHD diagnosed by a physician and the use of medication for chronic disease were recorded. Cardiovascular disease was defined as self-reported physician diagnosed coronary heart disease and/or stroke. In addition to smoking habits, alcohol consumption and leisure-time physical activity were obtained from self-administered validated questionnaires and are presented in table 5.

At the clinical examination, the subjects completed the Finnish validated version of the RAND-36- Item Health Survey (Short Form 36 [SF-36]) (Hays, Sherbourne & Mazel 1993, Aalto et al. 1995, Aalto, Aro & Teperi 1999). The SF-36 questionnaire was used to examine physical and psychosocial functioning during the past month during the clinical examination and it was used in study IV. The physical functioning was assessed with the physical component summary, which included physical functioning, role limitations due to physical problems, pain and general health subscales. Psychosocial functioning was assessed with the psychosocial component summary, which included role limitations due to emotional problems, energy, emotional well-being and social functioning subscales. Each subscale included 2 to 10 items. Scores of items were summed and transformed to a scale from 0 to 100 and higher scores imply the better physical and psychosocial functioning.

Table 5. Data on variables of anthropometric measures, chronic disease and lifestyle habits in studies II-IV.

	Study II		Study III		Study IV	
	Separated (n = 320)	Non- separated (n = 1683)	Separated (n = 192)	Non- separated (n = 1169)	Separated (n = 267)	Non- separated (n = 1536)
	Mean (SD) or %	Mean (SD) or %	Mean (SD) or %	Mean (SD) or %	Mean (SD) or %	Mean (SD) or %
BMI (kg/m ²)	27.9 (4.4)	27.6 (4.7)	25.8 (2.7)	25.5 (2.6)	27.9 (4.4)	27.6 (4.8)
Waist circumference (cm)	96.5 (13.0)	95.4 (13.2)				
Prevalence of CVD	14.7	7.9			15.1	7.8
Prevalence of diabetes	19.7	14.8	16.8	10.5	21.4	15.3
Weekly alcohol intake			56.5	55.5	53.0	52.6
Exercise frequency > 3 times/week			51.0	46.1	49.4	42.5
Current smoker			25.0	24.4	22.6	24.7

4.6 Ethical aspects

The study plan was approved by the ethical committee at the National Public Health Institute and the Ethics Committee of Epidemiology and Public Health of the Hospital District of Helsinki and Uusimaa. Birth records and child welfare clinic records were reviewed with the permission of the Ministry of Social Affairs and Health. Each participant gave a written informed consent for the clinical studies.

4.7 Statistical methods

All statistical analyses were performed using SPSS (Statistical Package for Social Sciences). A p-value of <0.05 was considered to be statistically significant.

Study I. Analyses on register based cardiovascular disease morbidity and mortality between the separated and the non-separated individuals were based on Cox proportional hazard regression models. Models were stratified for gender and year of birth and adjusted for socioeconomic status in childhood. The register for medical reimbursement, hospital discharge and cause of death following up period began on January 1 in 1971 because data is available only from 1971 onward. Contributions to risk were censored at the earliest of 1) emigration date, 2) starting date of special reimbursement for medication 3) death, 4) December 31, 2002 updated date of the Medication Reimbursement register, or 5) December 31, 2003 updated date of the CDR and HDR. Interactions between war time separation and father's socioeconomic status in childhood were also tested. Association age at separation and duration of separation to morbidity and mortality were also tested by using non-separated as controls.

Study II. Test for differences in blood pressure, lipids and obesity between the separated and the non-separated controls were based on multivariate linear regression models. The proportions of other health variables (prevalence of cardiovascular disease and type 2 diabetes, diagnosed hypertension and subjects receiving antihypertensive medication) was analysed for logistic regression. Gender, age at testing time and social factors were treated as covariates and included in the analyses. Interaction between the war time separation status and gender were observed. Effects between age at separation and duration of separation and health were also tested. Non-linearity on age at and duration of separation were tested by entering squared terms of age at evacuation and duration of evacuation into regression equation together with the linear terms.

Study III. Multivariate linear regression analyses were used to test for differences in the blood pressure levels between the separated and the non-separated. The group differences were adjusted for gender, age at testing time, socioeconomic status in childhood and educational attainment in adulthood and further adjustments were BMI, use of blood pressure medication and lifestyle habits. Interactions between separation and socioeconomic factors were also observed. In addition, effects of age at separation and duration of separation to blood pressure levels were also tested using the non-separated as controls.

Study IV. Differences in physical and psychosocial functioning between the separated and non-separated were tested with multivariate linear regression analysis. Distributions of SF-36 physical and psychosocial functioning variables were highly skewed. The rank transformation provides a more normal distribution where SF-36 physical and psychosocial component summary scores divided into 6 equal sized gender-specific categories and they were coded with numbers 1-6. The basic models were adjusted for age at clinical examination and highest social class in childhood and adulthood. Additional analysis included the adjustments for smoking, alcohol intake, physical activity and BMI, CVD and diabetes. There were also tested if, among the separated, age at separation and duration of separation associated with physical and psychosocial functioning. Interactions between separation status and gender on physical functioning and psychosocial functioning were found, thus the analyses were performed separately for men and women.

5 Results

5.1 Temporary separation from parents and cardiovascular morbidity and mortality in adult life

The register-based follow-up time was from 1971 to 2003, with the longest overall individual follow-up time being 69 years (Mean = 57.5 years; standard deviation [SD] = 9.5). Two-thirds of the separated participants had lower socioeconomic status in childhood and they were older than the non-separated participants (mean difference = 2.4 years, 95% confidence interval [CI] = 2.2-2.5 years).

Table 6 shows the prevalence rates for CHD, hypertension and stroke according to separation status. Those participants who experienced separation in childhood had a 1.29-fold higher risk for receiving medication for CHD than those who were not separated (7.2% versus 4.5%, respectively; 95% CI = 1.04-1.59). Despite of this, the separated participants did not experience more coronary events requiring hospitalization. No association was observed between the separation status and hypertension in this register-based study. By the end of the follow-up period (2003), 12.3% (n = 1640) of the cohort members had died. No association between separation status and all-cause mortality (hazard ratio [HR] = 1.04, 95% CI = 0.90-1.20) nor cardiovascular mortality (HR = 0.94, 95% CI = 0.72-1.21) was observed. Overall CHD morbidity and mortality among the separated participants were higher than those in the non-separated participants (10.9% versus 7.5%, HR = 1.19, 95% CI = 1.01-1.41, $P = 0.04$).

The participants who experienced separation in early childhood showed a 1.58 -fold higher CHD morbidity than the non-separated participants (Table 7). CHD morbidity was also higher in the participants whose duration of separation was 1 or 2 years (HR = 1.38, 95% CI = 1.03-1.84, $P = 0.03$) in comparison with the non-separated participants. Those who were separated in toddlerhood also showed higher overall CHD morbidity and mortality than the non-separated participants (HR = 1.34, 95% CI = 1.01-1.79, $P < 0.05$).

Table 6. Prevalence rates and Hazard Ratio (HR) of CHD, hypertension and stroke in separated and non-separated subjects based upon information on medication reimbursement, hospital admissions and deaths.

	Separated		Non-separated		Unadjusted model ^a		Fully adjusted model ^b	
	n	%	n	%	HR (95% CI)	P	HR (95% CI)	P
<u>Medication</u>								
Coronary Heart Disease	124	7.2	504	4.5	1.35 (1.09 – 1.65)	0.005	1.29 (1.04 – 1.59)	0.02
Hypertension	324	18.8	2206	19.7	0.91 (0.80 – 1.03)	0.12	0.89 (0.78 – 1.00)	0.06
<u>Hospital admission or death</u>								
Coronary event	158	9.2	745	6.7	1.13 (0.95 – 1.36)	0.17	1.10 (0.92 – 1.32)	0.30
Stroke	75	4.3	436	3.9	0.97 (0.75 – 1.26)	0.83	0.98 (0.76 – 1.27)	0.88
<u>Mortality</u>								
All-cause mortality	254	14.8	1386	12.4	1.06 (0.92 – 1.22)	0.41	1.04 (0.90 – 1.20)	0.59
Cardiovascular	77	4.5	417	3.7	0.96 (0.75 – 1.24)	0.78	0.94 (0.72 – 1.21)	0.61
Non-cardiovascular	177	10.3	969	8.7	1.11 (0.94 – 1.31)	0.22	1.09 (0.92 – 1.30)	0.30
<u>Overall coronary heart disease morbidity and mortality</u>	188	10.9	842	7.5	1.19 (1.01 – 1.41)	0.04	1.16 (0.98 – 1.37)	0.09

(95% CI= 95% confidence interval)

^a Stratified for year of birth and sex

^b Stratified for year of birth and sex and adjusted for father's occupational status in childhood.

Table 7. Prevalence rates [% (n)] and HR (95% CI) of CHD, hypertension and stroke in separated and non-separated subjects according to age at separation based upon information on medication reimbursement, hospital admissions and deaths ^a.

	Non-separated	Infancy (< 2 years)	Toddlerhood (2–4 years)	Early Childhood (4–7 years)	School age (7–11 years)
<u>Medication</u>					
Coronary Heart Disease	4.5% (504)	5.0% (11)	5.7% (29)	9.1% (47)	9.8% (30)
	1	1.06 (0.55–2.06)	1.19 (0.80–1.76)	1.58 (1.15–2.19)**	1.25 (0.81–1.91)
Hypertension	19.7% (2206)	15.8% (35)	15.2% (77)	19.7% (102)	27.0% (83)
	1	0.87 (0.61–1.22)	0.78 (0.62–0.98)*	0.88 (0.71–1.09)	1.12 (0.87–1.44)
<u>Hospital admission or death</u>					
Coronary event	6.7% (745)	5.4% (12)	9.1% (46)	10.1% (52)	12.4% (38)
	1	0.78 (0.42–1.47)	1.28 (0.94–1.75)	1.13 (0.84–1.52)	1.05 (0.72–1.52)
Stroke	3.9% (436)	2.3% (5)	3.6% (18)	5.2% (27)	5.9% (18)
	1	0.68 (0.28–1.64)	0.97 (0.60–1.57)	1.00 (0.66–1.52)	1.07 (0.63–1.83)
<u>Mortality</u>					
All-cause mortality	12.4% (1386)	13.1 (29)	12.4% (62)	15.9% (82)	18.6% (57)
	1	1.21 (0.84–1.76)	1.04 (0.80–1.34)	1.02 (0.81–1.29)	1.03 (0.77–1.39)
Cardiovascular	3.7% (417)	2.7% (6)	3.2% (16)	5.2% (27)	7.2% (22)
	1	0.89 (0.40–2.01)	0.81 (0.48–1.37)	0.94 (0.62–1.42)	1.07 (0.66–1.73)
Non-cardiovascular	8.7% (969)	10.4% (23)	9.1% (46)	10.6% (55)	11.4% (35)
	1	1.35 (0.88–2.06)	1.09 (0.81–1.48)	1.05 (0.79–1.40)	0.99 (0.67–1.47)
<u>Overall coronary heart disease morbidity and mortality</u>					
	7.5% (842)	6.8% (15)	10.5% (53)	11.6% (60)	15.0% (46)
	1	0.92 (0.53–1.59)	1.34 (1.01–1.79) **	1.13(0.86–1.50)	1.08 (0.77–1.52)

^a Regression models are stratified for year of birth and sex and adjusted for father's occupational status in childhood.

*P<0.05; **P=0.005

5.2 Temporary separation from parents and cardiovascular health

The clinical study participants who experienced separation were older at examination than the non-separated subjects (63.7 years versus 61.1 years, $SD = 2.8$ years, $P < 0.0001$) and their educational attainment was lower compared with the non-separated ones ($P = 0.03$). Figure 2 shows that the prevalence of cardiovascular disease among the separated participants was 1.7 -fold higher than among the non-separated subjects (95% CI = 1.1-2.4, $P = 0.01$). Type 2 diabetes was also more common among the separated participants (odds ratio [OR] = 1.5, 95% CI = 1.0-2.0, $P = 0.03$). Age at separation did not reach significant linear or non-linear effects on cardiovascular morbidity or type 2 diabetes. Duration of separation reached a significant, non-linear, J-shaped association in relation to the cardiovascular morbidity ($P = 0.02$ for the adjusted model) so that the prevalence of cardiovascular disease were highest among those separated participants who were separated over 3 years (19.6%, 10.0%, 5.7%, and 32.1% for those evacuated for less than 1, 1-2, 2-3, and over 3 years, respectively).

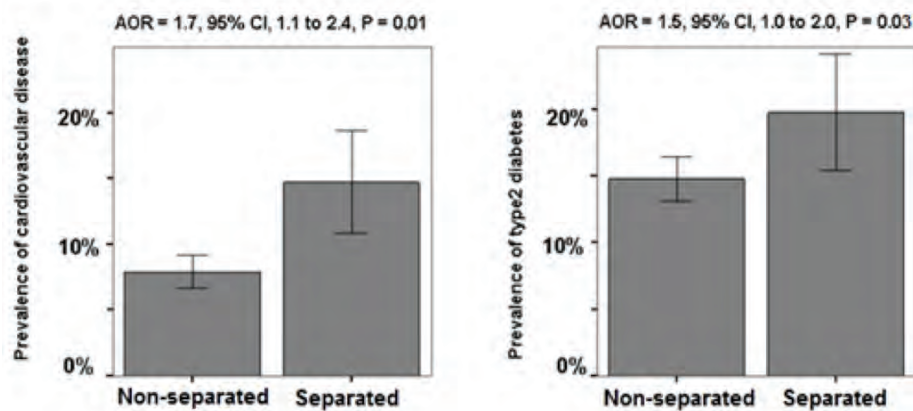


Figure 2. Prevalence of CVD and type 2 diabetes in the separated and the non-separated subjects. A model adjusting for sex, age at testing, father's occupational status in childhood and own attained level of education in adulthood. Error bars represent 95% confidence intervals. (Abbreviation: AOR = adjusted odds ratio)

Table 8 shows the differences in blood pressure levels, blood lipids and obesity. The separated participants were more hypertensive than the non-separated subjects, this was especially true for systolic blood pressure (OR = 1.3, 95% CI = 1.0 – 1.7, $P = 0.05$), but not diastolic blood pressure. Among the separated participants age at separation did not reach linear or non-linear significance on blood pressure. Hypertension diagnosed by a physician was linearly associated with duration of separation ($P = 0.04$ for the adjusted model) so that the highest prevalence of hypertension was seen among the separated whose duration was over 3 years (26.8%, 43.6%, 31.4%, and 51.7% for those evacuated for less than 1, 1–2, 2–3, and over 3 years, respectively).

In total cholesterol, HDL, LDL, and concentrations of triglyceride, apolipoprotein A and B we did not find differences between the separated and the non-separated participants (Table 8). However lipoprotein(a) was 17% higher among the separated participants (95% CI = 2.0-24.0, $P = 0.03$). There were no differences in obesity measures such as BMI and waist circumference according to war separation status. Further age at and duration of separation was not found to be associated with blood lipids and obesity.

Table 8. Differences (95% CI) in blood pressure levels, lipids, obesity and in risk of elevated blood pressure and hypertension between separated and non-separated subjects.

	Unadjusted model		Fully adjusted model ^a	
	Mean or % difference / OR (95% CI)	P	Mean or % difference / OR (95% CI)	P
Blood pressure				
Systolic blood pressure (mmHg)	4.8 (2.3 – 7.1)	< 0.0001	1.8 (-0.7 – 4.3)	0.16
Systolic blood pressure > 140 mmHg	1.3 (1.3 – 2.1)	< 0.0001	1.3 (1.0 – 1.7)	0.05
Diastolic blood pressure (mmHg)	-0.2 (-1.4 – 1.1)	0.80	0.2 (-1.0 – 1.6)	0.81
Diastolic blood pressure > 90 mmHg	1.0 (0.8 – 1.3)	0.83	1.1 (0.9 – 1.5)	0.37
Pulse pressure (mmHg)	4.9 (3.0 – 6.8)	< 0.0001	1.7 (-0.3 – 3.6)	0.10
Use of blood pressure lowering medication	1.4 (1.1 – 1.7)	0.01	1.2 (0.9 – 1.6)	0.15
Hypertension defined as systolic/diastolic blood pressure > 140/90 mmHg	1.7 (1.3 – 2.3)	0.001	1.4 (1.0 – 2.0)	0.03
and/or use of blood pressure lowering medication				
Hypertension diagnosed by a physician	1.4 (1.1 – 1.8)	0.01	1.3 (1.0 – 1.7)	0.05
Lipids				
Triglycerides (mmol/L)	1.4% (-4.1 – 7.1)	0.61	1.5% (-4.3 – 7.6)	0.60
HDL-cholesterol (mmol/L)	-1.7% (-4.9 – 1.4)	0.29	0.0% (-3.6 – 2.8)	0.81
Apolipoprotein A (mmol/L)	-1.1% (-3.4 – 1.0)	0.30	0.0% (-3.0 – 1.4)	0.47
Apolipoprotein B (mmol/L)	0.0% (-3.0 – 2.6)	0.90	-0.5% (-3.6 – 2.5)	0.75
Lipoprotein(a) (mmol/L)	20.0% (5.3 – 36.5)	0.006	17.0% (2.0 – 24.0)	0.03
Obesity				
Body mass index (kg/m ²)	0.3 (-0.3 – 0.8)	0.33	0.2 (-0.4 – 0.8)	0.48
Waist circumference (cm)	1.1 (-0.5 – 2.6)	0.19	0.5 (-1.1 – 2.0)	0.56

^a Fully adjusted refers to a model adjusting for sex, age at testing, father's occupational status in childhood and own attained level of education in adulthood.

5.3 Early life stress and adult blood pressure levels

Of the 2003 participants 1361 were non-obese (BMI <30 kg/m²), and of them 192 (14.1%) were separated abroad from their parents. Among the separated and the non-separated there were equally men and women. However the separated participants more commonly came from lower socioeconomic conditions in childhood and their educational attainment in adulthood was lower than that among the non-separated controls (Table 2).

Systolic blood pressure level was over 6 mmHg higher in adult life among the separated in comparison with the non-separated (148.6 + 21.5 versus 142.2 + 19.6 mmHg, $P < 0.0001$). The association between separation and blood pressure was little affected by adjustments (sex, age and SES in childhood and adult life) and further analysis with BMI and the use of blood pressure medication did not attenuate the findings even though the separated participants used more blood pressure lowering medication ($P = 0.03$). Also taking into account smoking, alcohol consumption and physical activity did not influence the findings.

Table 9 shows the differences in blood pressure levels according to age at separation among the separated and the non-separated non-obese participants. The systolic blood pressure was over 12 mmHg higher among those participants who were separated in early childhood (4-7 years) compared with the participants who did not experience separation in childhood ($P \leq 0.005$) and the association was strongest in men (regression coefficient [β] = 11.2, 95% CI = 2.5-20.0). In women we observed similar trends but it did not reach statistical significance. Furthermore, those separated in early childhood had higher diastolic blood pressure levels ($\beta = 4.2$, 95% CI = 1.0-7.3, $P = 0.01$) compared to the non-separated. These findings were still significant when adjusted for BMI, use of blood pressure medication, smoking, alcohol consumption and physical activity.

The differences in blood pressure levels according to the duration of separation among the separated and the non-separated are shown in table 10. Higher systolic blood pressure was more common among those who were separated for the duration of under 1 year ($P = 0.05$) compared with the non-separated and it was more obvious in women ($\beta = 10.5$ 95% CI = 1.5-19.6, $P < 0.03$). Diastolic blood pressure levels differ between men and women so that the highest diastolic blood pressure levels are seen in men who were separated for over 2 years ($\beta = 4.9$ 95% CI = 0.2-9.7, $P < 0.05$) and in women who were separated for under 1 year ($\beta = 4.9$ 95% CI = 0.3-9.5, $P < 0.05$) when compared with the non-separated controls. These findings were only

little attenuated when adjusted further for BMI, use of blood pressure medication, smoking, alcohol consumption and physical activity.

Table 9. Differences (95% CI) in blood pressure levels according to age at separation among separated compared with non-separated non-obese subjects^a.

	ALL			MEN			WOMEN		
	Mean	SD	Difference (95% CI)	Mean	SD	Difference (95% CI)	Mean	SD	Difference (95% CI)
<u>Systolic blood pressure (mmHg)</u>									
Non-separated	142.2	19.6	0	143.9	19.2	0	140.5	19.8	0
Infancy (< 2y)	142.5	23.7	0.3 (-8.6 - 9.2)	141.2	21.6	-1.9 (-14.6 - 10.8)	143.7	26.6	1.9 (-10.7 - 14.5)
Toddlerhood (2- 4y)	147.1	20.7	3.7 (-1.3 - 8.8)	149.5	19.6	4.0 (-3.1 - 11.2)	144.7	21.8	3.6 (-3.7 - 10.9)
Early childhood (4-7y)	154.6	21.8	8.7 (2.6 - 14.7)**	159.1	18.6	11.2 (2.5 - 20.0)*	150.8	23.9	6.4 (-2.1 - 14.9)
School age (≥ 7y)	148.7	21.2	-0.7 (-7.5 - 6.1)	148.5	18.0	-2.3 (-11.4 - 6.9)	148.9	25.2	1.9 (-8.5 - 12.3)
<u>Diastolic blood pressure (mmHg)</u>									
Non-separated	87.7	10.3	0	89.4	10.3	0	86.1	10.0	0
Infancy (< 2y)	88.8	10.4	0.8 (-3.8 - 5.5)	90.3	12.6	0.6 (-6.3 - 7.6)	87.4	8.4	0.9 (-5.4 - 7.3)
Toddlerhood (2- 4y)	88.8	11.4	1.5 (-1.1 - 4.2)	90.2	11.5	1.0 (-2.9 - 4.9)	87.5	11.4	2.0 (-1.7 - 5.6)
Early childhood (4-7y)	90.8	10.7	4.2 (1.0 - 7.3)*	93.3	9.7	4.4 (-0.3 - 9.2)	88.7	11.3	3.9 (-0.4 - 8.2)
School age (≥ 7y)	86.4	11.6	0.3 (-3.2 - 3.9)	88.1	10.9	0.5 (-4.4 - 5.5)	84.2	12.4	-0.2 (-5.4 - 5.0)

^a Adjusted for sex, age at testing time, father's occupational status in childhood and educational attainment in adulthood.

*P=0.01; **P≤0.005

Table 10. Differences (95% CI) in blood pressure levels according to duration of separation among non-obese separated compared with non-separated non-obese controls^a.

	ALL			MEN			WOMEN		
	Mean	SD	Difference (95% CI)	Mean	SD	Difference (95% CI)	Mean	SD	Difference (95% CI)
<u>Systolic blood pressure (mmHg)</u>									
Non-separated	142.2	19.6	0	143.9	19.2	0	140.5	19.8	0
< 1 year	151.7	22.0	6.2 (0.0 – 12.4)*	150.2	19.2	2.6 (-6.0 – 11.1)	153.4	25.1	10.5 (1.5 – 19.6)**
1–2 years	148.9	22.0	3.4 (-1.2 – 8.1)	151.4	16.9	4.2 (-2.4 – 10.8)	146.6	25.9	2.9 (-3.7 – 9.5)
>2 years	148.0	19.6	3.1 (-3.2 – 9.4)	154.4	21.6	7.8 (-0.9 – 16.5)	141.3	15.1	-2.3 (-11.6 – 6.9)
<u>Diastolic blood pressure (mmHg)</u>									
Non-separated	87.7	10.3	0	89.4	10.3	0	86.1	10.0	0
< 1 year	89.7	11.9	2.8 (-0.4 – 6.1)	89.7	10.2	0.8 (-3.9 – 5.4)	89.7	13.8	4.9 (0.3 – 9.5)*
1–2 years	87.7	11.3	0.9 (-1.5 – 3.4)	89.5	11.7	1.1 (-2.5 – 4.7)	86.0	10.8	0.7 (-2.7 – 4.0)
>2 years	90.2	10.3	3.0 (-0.3 – 6.3)	94.2	9.7	4.9 (0.2 – 9.7)*	85.9	9.2	0.7 (-4.0 – 5.4)

^aAdjusted for sex, age at testing time, father's occupational status in childhood and educational attainment in adulthood.

**P<0.03; *P < 0.05

5.4 Early life stress and physical and psychosocial functioning in adult life

The 1803 participants in the present clinical study completed the SF-36 questionnaire, and of these 267 were separated during childhood. In this clinical subset the separated subjects were older and their socioeconomic status in childhood and adult life were lower, and they also had higher prevalence of CVD ($P = 0.006$ adjusted for age) and diabetes ($P = 0.007$ adjusted for age) than the non-separated. In spite of these, there were no differences observed in BMI or lifestyle factors such as smoking, alcohol intake and physical activity (Table 5). The SF-36 physical and psychosocial functioning subscales scores among the separated and the non-separated participants are presented in table 11. The separated men had lower subscales scores on physical functioning ($P = 0.005$), role limitations due to physical health ($P = 0.03$) and general health ($P = 0.001$) than the non-separated controls. Among women similar trends for physical and psychosocial functioning were not observed.

Table 12 shows differences between the SF-36 physical and psychosocial functioning and the separation status separately for men and women. Men who were separated abroad without their parents in childhood showed lower physical functioning comparison with the non-separated ($\beta = -0.40$, 95% CI: -0.71 to -0.08 , $P = 0.01$). The associations between the psychosocial functioning in late life and the separation status among men showed similar trends, but it only reached significance when adjusted further for BMI, lifestyle factors ($\beta = -0.37$, 95% CI: -0.71 to -0.03 , $P = 0.03$). There were no associations between physical and psychosocial functioning in later life and the separation status in women. Furthermore the associations between physical and psychosocial functioning and separation status remained the same when the separated and the non-separated groups were divided into two age-groups (≤ 62 years and > 62 years).

Table 11. Physical and psychosocial component subscales scores according to separation status in men and women^a.

	Separated		Non-separated
	Mean (SD)	Mean (SD)	<i>P</i>
Physical component subscales			
<u>Physical functioning</u>			
Men	82.5 (18.6)	86.3 (17.5)	0.005
Women	77.6 (19.1)	79.4 (20.2)	0.07
<u>Role limitations due to physical health</u>			
Men	80.2 (31.7)	85.2 (29.0)	0.03
Women	77.3 (33.8)	77.3 (35.0)	0.68
<u>Pain</u>			
Men	80.0 (22.4)	83.4 (21.0)	0.06
Women	79.5 (20.4)	78.9 (22.3)	0.99
<u>General health</u>			
Men	58.5 (18.0)	63.6 (18.3)	0.001
Women	62.1 (17.2)	62.4 (18.7)	0.70
Psychosocial component subscales			
<u>Role limitations due to emotional problems</u>			
Men	83.1 (30.8)	86.9 (27.6)	0.16
Women	80.5 (33.9)	80.5 (32.9)	0.76
<u>Energy/fatigue</u>			
Men	70.8 (19.8)	74.2 (18.5)	0.08
Women	67.9 (19.2)	67.3 (20.4)	0.94
<u>Emotional well-being</u>			
Men	81.1 (16.3)	83.5 (14.2)	0.14
Women	79.3 (15.0)	79.3 (15.8)	0.73
<u>Social functioning</u>			
Men	89.9 (16.7)	91.4 (16.4)	0.24
Women	89.6 (17.8)	87.6 (19.3)	0.22

^a Mann-Whitney U test

Table 12. Differences (95% CI) in Short Form-36 physical and psychosocial functioning according to gender among participants who were separated in childhood compared to the non-separated.

	Model 1 ^a			Model 2 ^b			Model 3 ^c		
	Differences (95% CI)	P	Differences (95% CI)	P	Differences (95% CI)	P	Differences (95% CI)	P	
<u>Physical component summary</u>									
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)	0.01			
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			
<u>Psychosocial component summary</u>									
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			

^a Adjusted for, age at the testing time, highest social class in childhood and adulthood.

^b Adjusted for model 1 + smoking, alcohol intake, physical activity and body mass index.

^c Adjusted for model 2 + presence of cardiovascular disease and diabetes.

Differences in the SF-36 physical functioning scales according to age at separation and duration are presented in table 13. Separated men who were separated around school age (> 7 years) showed an increased risk for lower physical functioning compared to the non-separated ($\beta = -0.89$, 95% CI: -1.58 to -0.20 , $P = 0.01$). In addition the highest risk for decreased physical functioning was in those men who were separated for over two years ($\beta = -0.65$, 95% CI: -1.25 to -0.05 , $P = 0.03$). There were no observed differences between separation experience and physical functioning in later life in women.

Table 14 shows the effects on duration of separation and the SF-36 psychosocial functioning. Those men who were separated for a duration more than two years showed an increased risk for lower psychosocial functioning compared with the non-separated participants ($\beta = -0.70$, 95% CI: -1.35 to -0.06 , $P = 0.03$). Among women psychosocial functioning was better in those who were separated for less than one year compared to the non-separated ($\beta = 0.69$, 95% CI: 0.02 to 1.35 , $P = 0.04$). This finding remained significant after adjusting for age and socioeconomic status in childhood and adult. Further adjustment for BMI, lifestyle factors, and CVD and diabetes reduced the significance of the results. Age at separation did not effect the SF-36 psychosocial functioning among the separated men and women compared with the non-separated participants.

Table 13. Differences (95% CI) in Short Form-36 physical functioning according to age and duration (years) 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 to 1.38	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									
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

Table 14. Differences (95% CI) in Short Form-36 psychosocial functioning 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

6 Discussion

Separation abroad without parents in childhood during war circumstances represents an extreme form of early life stress, caused by exceptional circumstances. This thesis examined late life cardiovascular disease and general health among participants who experienced temporary separation abroad without their parents during WWII. We also tested whether the timing and the duration of the separation influenced cardiovascular health among the separated participants. The findings of this longitudinal study are consistent with previous findings which have been based on mostly retrospective reports.

In all sub-studies in this thesis, the participants separated from their parents in childhood were older than the non-separated participants. Furthermore among the separated, the childhood socioeconomic status, based on father's highest occupational status and their own educational attainment in adulthood was lower compare with the non-separated participants. However, the distribution of childhood social classes among the separated participants was similar to that in the city of Helsinki as a whole. These differences in age and socioeconomic status were taken into account in the analysis.

6.1 Cardiovascular morbidity and mortality in adult life among temporarily separated participants

In Finland, national health registers and well-documented information on child evacuations are unique resources to examine both early life stress and overall health outcomes from a life course perspective. The focus on this life course study was to examine morbidity and mortality from cardiovascular disease in the participants separated from their parents more than 60 years later.

Among the participants who experienced separation in childhood we found a significantly higher CHD morbidity compared with the participants who did not experience war separation in childhood. In addition, to this timing and duration of separation was associated with CHD morbidity. Age at separation in early childhood and furthermore the duration of one to two years and over three years increased CHD morbidity rates compared with the non-separated participants. These findings are consistent with other studies on cardiovascular disease and early life stress (Dong et al. 2004, O'Rand, Hamil-Luker 2005, Sumanen et al. 2005, Korkeila et al. 2010a). The Adverse Childhood Experiences study (ACEs) reported a strong association between adversity experienced in childhood and ischemic heart disease,

childhood adversity included abuse, neglect and household dysfunction (Dong et al. 2004). Two other studies found that the risk for CHD was increased in those working-aged people who were exposed to adversities in childhood (Sumanen et al. 2005, Korkeila et al. 2010a). In addition, Korkeila et al. (2010) showed higher risk for cerebrovascular disease among working-aged people who experienced childhood adversities (Korkeila et al. 2010a).

Räsänen (1988) found opposite results in relation to war separation and cardiovascular disease morbidity, the separated were somatically healthier and they had less cardiovascular diseases compared with the control group (Räsänen 1988). Explanations for a variety of research results with our study may be that in Räsänen's study most of the families sent to separation two or more children, and siblings travelled together to Sweden. Also average on age at the first separation was higher (6 years) in Räsänen's study compared with our study where the average age at the first separation was 4.6 years. Other explanations may be that during Räsänen's study the separated were working-aged compared with the separated in our study. Also the study sample was relatively small in Räsänen study, especially in the control group which may affect the comparability between the groups.

Stress experienced in childhood is an exposure which could influence mortality in later life. There are some studies showing that different exposures and stress in childhood could associate with mortality (Schwartz et al. 1995, Tucker et al. 1997, Martin et al. 2005, Koupil et al. 2007). The children who experienced parental divorce showed a higher risk of all-cause mortality. Koupil et al. (2007) studied men and women who experienced the siege of Leningrad in childhood. They found that the siege had a significant effect on mortality from ischemic heart disease and cerebrovascular disease in men. Also age at exposure to the siege influences the association. However, our study did not observe any association between war separation and hospital admissions for stroke or coronary events nor differences in all-cause or overall cardiovascular mortality.

Socioeconomic factors in childhood and adult life might also play important roles in affecting prevalence of chronic diseases such as cardiovascular disease, but also mortality. Most studies, which have investigated the association between socioeconomic circumstances in childhood and mortality, have found an association between mortality and lower childhood socioeconomic circumstances (Lundberg 1993, Lynch et al. 1996, Smith et al. 1998, Galobardes, Lynch & Davey Smith 2004, Power, Hyppönen & Smith 2005). Wannamethee et al. (1996) found childhood socioeconomic status and particularly father's social class to be strongly associated with CVD (Wannamethee et al. 1996). Despite this, the socioeconomic factors did not affect our findings. Our findings suggest that experience to stress in early life may increase coronary heart disease risk later in life.

6.2 Cardiovascular health and adult blood pressure levels and early life stress

Parental separation during wartime, a severe stressor, is not typical for a normal childhood. It is beyond the control of the child and therefore its processing and psychological and physical adaptation is an important challenge to the child. Previous studies on war separation are focused on psychological aspects and psychiatric morbidity (Birtchnell, Kennard 1984, Foster, Davies & Steele 2003, Pesonen et al. 2007a). Our aims in these clinical studies were to explore long-term effects of wartime parental separation on physical health in a longitudinal study setting.

We found the participants who experienced separation during the war had CVD diagnosed almost twice as often as the participants who did not experience parental separation. This was most marked in the separated that were separated over 3 years. Further the separated participants were 1.4 -fold more likely to develop type 2 diabetes than those participants who did not separate. For blood lipids, plasma lipoprotein(a) levels were higher in the separated compared with the non-separated. Elevated plasma lipoprotein(a) has been associated with an increased risk for CHD (Danesh, Collins & Peto 2000, Emerging Risk Factors Collaboration et al. 2009).

Systolic blood pressure levels among non-obese ($BMI < 30 \text{ kg/m}^2$) separated participants were higher when compared with the non-obese non-separated participants. Age at separation was not significant for the blood pressure levels, so that those separated in early childhood had significantly higher systolic blood pressure compared with those not separated. The association between systolic blood pressure and timing of separation was more evident in men. Also the duration of separation influenced blood pressure levels, but differently in women than in men. Women who were separated for at least one year exhibited higher systolic and diastolic blood pressure when compared with the non-separated participants. Men, separated for over two years showed higher diastolic blood pressure than the non-separated.

Our findings are consistent with previous studies that reported the association between early life stress and a number of health problems (Ekeberg et al. 1990, Felitti et al. 1998, Maier, Lachman 2000, Dube et al. 2003, Batten et al. 2004, Dong et al. 2004, Korkeila et al. 2010a). Childhood overall abuse (physical, psychological or sexual) and household dysfunction have been found to associate with CHD, cancer, chronic lung and liver disease and people who have accumulated childhood adversities have a large number of diseases in adulthood (Felitti et al. 1998). Early stress in childhood and its multiple forms are known risk factor for heart disease (Batten et al. 2004, Caspi et al. 2006, Galobardes, Smith & Lynch 2006). In

addition, there are studies suggesting that cardiovascular health may be programmed in childhood (Eriksson, Forsen 2002, Barker et al. 2005). Further, these effects may have differences in programming between the genders (Jones et al. 2008).

A major risk factor for CVD is elevated blood pressure (Chobanian et al. 2003). Various childhood exposure predicted elevated systolic and diastolic blood pressure levels in adulthood (Luecken 1998, Lehman et al. 2009). There are studies reporting that subjects who experienced early life stress and had early-onset depressive symptoms had more hypertension (Stein et al. 2010). Our studies did not examine the relation between depressive symptoms and hypertension, but our previous studies in the HBCS have shown that parental separation during the war increased the risk of depressive symptoms (Pesonen et al. 2007a) and severe mental disorder (Räikkönen et al. 2011) later in life. Obesity is also known risk factor for CVD (DeFronzo, Ferrannini 1991, Björntorp 1992) and a risk factor for metabolic syndrome. Childhood adversities such as abuse, neglect, punishment increases risk for obesity and associate with glucose metabolism and therefore increased risk for type 2 diabetes (Thomas, Hyppönen & Power 2008).

Early life stress itself is a risk factor for heart disease such is discussed above but stressful life experiences during childhood are also shown to associate with numerous risk factors for health which lead to chronic diseases. Low socioeconomic circumstances in childhood predict increased blood pressure (Lehman et al. 2009). However, our findings were independent of the participant's socioeconomic status in childhood and in the adult life. The amounts of stress exposure in childhood increased risks for negative lifestyle habits such as smoking (Anda et al. 1999, Kestilä et al. 2006, Chartier, Walker & Naimark 2009), alcohol intake (Kendler et al. 1996, Anda et al. 2002, Enoch 2011, Keyes, Hatzenbuehler & Hasin 2011), physical inactivity (Felitti et al. 1998, Dong et al. 2004). Despite these, our findings were not explained by participants' age, sex and adult lifestyle such as smoking, alcohol consumption and physical activity. These findings demonstrate that stress in early life could extend over the lifespan and have effects on blood pressure levels, prevalence of CVD and type 2 diabetes.

6.3 Adult life physical and psychosocial functioning and early life stress

Impaired physical and psychosocial functioning in late adulthood is known to associate with early life stress (Biggs et al. 2004, Corso et al. 2008, Draper et al. 2008, Talbot et al. 2009). Our findings are consistent with these studies and show that the separated men who as children experienced temporary separation from their

parents during WWII showed different physical functioning compared with the non-separated. The separated men had an increased risk for lower physical functioning. This was common in men who were separated in school age and whose duration of separation was more than two years. Among women the association for physical or psychosocial functioning was not observed. In men, lower psychosocial functioning was observed among those whose separation time was over two years.

The heterogeneity of childhood stress experiences may underlay gender differences in the physical and psychosocial functioning. Strine et al. reported that among men the experience of parental separation or divorce were not a significant indicator for psychological distress on mental functioning (Strine et al. 2012). Childhood sexual abuse affected on the contrary. Men who had experienced sexual abuse in childhood had impaired mental functioning and a similar trend was observed in women (Najman, Nguyen & Boyle 2007). For physical functioning Edwards et al. (2004) found opposite results in relation to gender so that men who experienced childhood maltreatment had better physical functioning than women who experienced maltreatment in childhood (Edwards et al. 2004).

Socioeconomic status and lifestyle habits are factors, known to affect health (Martikainen et al. 1999, Singh-Manoux et al. 2004, Willcox et al. 2006, Lachman, Agrigoroaei 2010). Childhood circumstances may affect physical and mental functioning in the adult either directly or indirectly through other factors and later circumstances (Kuh et al. 2003, Pudrovska et al. 2005, Mäkinen et al. 2006, Laaksonen et al. 2007). Childhood circumstances such as parental education did not have direct effect on physical and mental functioning but has some effect via adult socioeconomic status (Mäkinen et al. 2006, Laaksonen et al. 2007). Nonetheless, father's occupational status was associated with low physical functioning (Guralnik et al. 2006). Other childhood circumstances like chronic disease in the child, parental mental problems and drinking problems were observed to associate with physical and psychosocial functioning (Mäkinen et al. 2006). However, in our study most of the separated participants belonged to lower socioeconomic classes in childhood and in adulthood compared with the non-separated participants but this did not affect the findings.

Some studies have shown that people who have chronic diseases, but who are physically active, can maintain the good physical functioning, supporting the importance of a healthy behaviour (DiPietro 1996, Spirduso, Cronin 2001). Our studies have shown that the separated participants had a significantly higher prevalence of chronic diseases than the non-separated, but our study did not observe significant differences in physical activity between the separated and the non-separated participants. Lifestyle habits such as smoking are associated with functional health (Strine et al. 2012). Our findings of war separation and physical

and psychosocial functioning were independent of smoking and alcohol consumption. Furthermore, age, a body mass index and chronic diseases as CVD and diabetes did not effect on the findings.

6.4 Possible underlying mechanisms explaining the effects between early life stress and cardiovascular health

There are several possible underlying mechanisms explaining the relationship between early life stress and late health. Our study design did not allow us to disentangle these mechanisms behind the association between early life stress and cardiovascular morbidity and mortality, cardiovascular health and physical and psychosocial functioning in later adulthood. These mechanisms can include a large number of physiological, social and psychological explanations acting both individually and together.

One potential mechanism that may underlie these associations is the hypothesis of biological embedding according to which stress experience in childhood may have an effect on alteration in physiological stress regulation. It is known from animal and human studies that a child's developmental period is crucial to the maturation of neuroendocrine systems and during "critical periods," small changes may have disproportionate effect on the function of biological systems. This may predispose an individual for adverse physical health consequences in late life (Bremne, Vermetten 2001, Sanchez, Ladd & Plotsky 2001, Cirulli, Berry & Alleva 2003, Korosi et al. 2012).

Inflammation is an important part of the stress process and it may be a possible mediating mechanism to explain the association between early life stress and later life health (Fagundes et al. 2011). Hence inflammation is a known risk factor for CVD (Ridker et al. 1997, Ridker et al. 2000, Avitsur, Hunzeker & Sheridan 2006, Danese et al. 2007) and type 2 diabetes (Ershler, Keller 2000, Libby 2007). In the Dunedin Multidisciplinary Health and Development Study the children who had experienced maltreatment such as maternal rejection, harsh discipline, disruptive caregiver changes, and physical and sexual abuse, showed elevated levels of inflammation in the adult life (Danese et al. 2011).

Early life stress and HPA axis function

Psychological stress in early life is known to modulate the function of the hypothalamic-pituitary-adrenal axis (HPA) and the dysfunction of the HPA axis is known to be a risk factor for CVD (Rosmond, Björntorp 2000). Early life stress has

been also associated with long-term alteration in the function of the HPA-axis and consequently cortisol metabolism in adult life (Gunnar 2000, Nemeroff 2004, Carpenter et al. 2007, Elzinga et al. 2008, Tyrka et al. 2008, Pesonen et al. 2010). Our previous study using a smaller subsample has shown that among the participants, evacuated abroad without their parents, the HPA axis responsiveness was changed in later life (Pesonen et al. 2010). Responsiveness of the HPA axis may have individual differences, because people experience different levels of early life stress and stress reactivity can vary (Boyce, Ellis 2005, Ellis, Essex & Boyce 2005, Gunnar, Fisher 2006, Gunnar, Quevedo 2007). For instance, Luecken et al. (1998) showed that the both experience of early parent loss and poor quality of family relationships associated with increased blood pressure, but the changes in stress responses were the opposite (Luecken 1998).

The effect of ELS on inflammation and HPA axis is probably mediated by epigenetic modification. The epigenetic changes may increase the risk of CVD and diabetes (Gluckman et al. 2009, Ling, Groop 2009, Turunen, Aavik & Ylä-Herttuala 2009, Wierda et al. 2010). Epigenetic changes affect the pattern of gene expression. DNA methylation is a common epigenetic mechanism behind gene-environment interactions and it underlies in relationships between early life events and later metabolic status and health problems (Weaver et al. 2004, Meaney, Szyf 2005, Gluckman et al. 2007, Crews 2010). DNA methylation has been implicated as an early stage in the development of atherosclerosis and type 2 diabetes (Waterland, Michels 2007). The data available to us does not, however, allow testing of whether these mechanisms may account for the associations we found.

Sex-specific developmental difference

The function of the HPA axis alteration, inflammation and morbidity in later adulthood could depend on individual psychological coping resources. Men and women differ in their ways of managing stress and an individual's own coping mechanisms may depend on the type of life-long effects of early life stress (Fagundes et al. 2011). Men can have a more active coping style to manage severe exposures while women's coping styles can be more passive (Groer, Thomas & Shoffner 1992, De Boo, Spiering 2010).

The type of stress experienced, age at exposure, duration and gender may be important factors influencing the stress experience and long-term outcomes. The effects of sex hormones can have major impact on gender differences (Otte et al. 2005). In addition, the stress reactivity of the HPA axis and the sympathetic nervous system may differ between genders (Tyrka et al. 2008, Gupta, Verma & Balhara 2011). Developmental gender differences in physiological changes and the re-setting

of hormonal levels may play a role in the vulnerability and sex-specific prevalence rates for several diseases (Miller, Chen & Parker 2011). Many physical and mental outcomes such as CHD and hostile behaviour show sex-related differences with higher prevalence in men (Kajantie, Phillips 2006). Sex-specific protective pathways have been found e.g. as in women; estrogen has a protective role in cardiovascular disease (Mendelsohn 2002). In our study gender-specific differences were observed in blood pressure and in physical and psychosocial functioning.

6.5 Strengths and limitations of the studies

6.5.1 Study population

This thesis studied people belonging to the longitudinal HBCS who were born in Helsinki from 1934 to 1944 and in childhood attended free and voluntary child welfare clinics in the city. They did not migrate from Finland, were alive in 1971 and lives in the city when all Finns were allocated personal identification number. In the clinical studies (studies II-IV), participants were born in the Helsinki University Central Hospital and therefore the clinical studies may not be representative of all people who were born in Helsinki.

Despite this, at birth, the distribution of socioeconomic status was quite similar among the participants as compared with whole city. Childhood socioeconomic status is based on father's occupations. Roughly 60% of men were labourers at that time in Helsinki. Similarly, in this study the same percentages of fathers were labourers (Barker et al. 2005).

Early life stress and war separation

Stress in early life is expressed in many ways and it could include an one-time adverse exposure or be the sum of many adverse early experiences. Every childhood abnormal event may interfere with the healthy development in childhood. Children in temporary foster care may have experienced displacements at least two times. The first displacement experience happens at the separation and the other when the children returned home years late (Harden 2004).

In this thesis temporary separations occurred during WWII and some of the separated children experienced separation two or more times during the war. During the WWII in Finland, the circumstances were unusual in contemporary Western setting. There were aerial bombardments, severe food shortage and malnourishment,

which may limit the generality of the results. Information about war separation is based upon the National Archives register, which data is reliable to define stress in early life and its timing. Despite this, we cannot, though ignore the possibility that the selection of the children for evacuation may not have been truly random (Pesonen et al. 2007b) and some of the children were classified as the non-separated, even though actually they were evacuated via private routes with the help of the families' personal contacts (Pesonen et al. 2007a). However, the existence of false controls would not increase but rather to diminish the differences between the observed groups.

Other potential limitations of the study are the quality of foster care and childhood diets, which we have not been able to control for. We do not have information on the quality of foster care, which may be relevant in an attempt to understand at the individual level of the stress exposure and the change effects of early stress on adult health. We do not either have information on the differences in childhood diets although is a possibility that the diets of the separated differed from those remaining in Finland. The association between early life stress and later life health would be expected to be affected by the severity and sum of the adverse exposures, the form of stress and further environmental variations and timing of the separation (Nemeroff 2004, Rusby, Tasker 2008). The impact of timing of the separation on late life health was obvious in the present study.

Furthermore clinical results were based upon internal comparisons within the sample and therefore it is unlikely that the association between war separation and cardiovascular health, blood pressure and physical and psychosocial functioning could be attributed to selection bias. Finally, this historical cohort had experienced the war and temporary separation without parents in exceptional circumstances which is not however limited to the developmental significance of stress in childhood in this study. In the contemporary world still occurs childhood stress experience for various reasons and therefore our findings in relation to ELS in historical circumstances during WWII and cardiovascular morbidity and mortality, cardiovascular health and general health can be seen in a broader review. In the world, millions of refugees are displaced and many of these are children who are separated from parents (UNHCR 2012).

6.5.2 Epidemiological study

Data of the early life stress and health factors are taken only from registers in the epidemiological sub-study. Validity of the study increases when register-based data is used compared to self-reported diagnoses. Early life stress on the war separation is

discussed above. The national health registers, the National Register of Medication Reimbursement, the HDR and the CDR have been validated. They have been evaluated as reliable and good in the epidemiological research (Keskimäki, Aro 1991, Lahti, Penttilä 2001).

The HDR and the CDR have shown to be highly specific and valid when evaluating coronary events (Rapola et al. 1997, Pajunen et al. 2005). They are also valid indicators of a stroke (Leppälä, Virtamo & Heinonen 1999, Tolonen et al. 2007). Although registers have been identified as accurate, they could underestimate especially the prevalence of hypertension. This limitation is to be noted because some people are not necessary eligible for the reimbursement of special medication if they have mild hypertension without complications and are thus not registered at the Medication Reimbursement register.

6.5.3 Clinical study

In Clinical studies (studies II-IV) we used well-characterized clinical data in assessing cardiovascular health, blood pressure and physical and psychosocial functioning among the separated participants. Data on chronic diseases like CHD and diabetes diagnosed by a physician and the use of medication for these, as well as lifestyle habits were derived from validated self-administered questionnaires. Diabetes was also defined by using data on OGTT and applying to the WHO criteria. The blood pressure levels based upon the mean of two consecutive measurements which was taken without antihypertensive medication, with held at the day of the examination. The data on physical and psychosocial functioning were obtained from a self-reported SF-36 questionnaire, which is validated in Finland (Aalto, Aro & Teperi 1999).

7 Conclusions

This longitudinal study showed that temporary parental separation in childhood may predispose to lifelong effects on health and well-being. Not only the separation itself but also the timing and the duration of the separation are important factors in affecting later life and overall well-being.

We found that, higher CHD morbidity, the prevalence of CVD and diabetes at the age of 60 was associated with the separation experience in early life. In addition early life stress among the separated participants predicted higher blood pressure levels in late adulthood and moreover increased the risk of impaired physical functioning. In spite of these findings, evidence of higher hospitalizations and mortality was not found. The effects of separation in overall health were more pronounced among the separated men than women.

Additionally, the timing and duration of the separation during a critical developmental phase seemed to be stress factors which affected health in later life. We found that the separation in early childhood (4-7 years) was associated with higher prevalence of CHD and blood pressure levels and in addition the separation in school age (≥ 7 years) was associated with lower physical functioning later in life. Duration of the separation influenced more widely. The separated participants whose duration of the separation was one to two years had higher CHD morbidity. However separation lasting over three years had strongest effects on health. These separated participants had highest CHD morbidity but also higher prevalence of CVD and hypertension. Interestingly, the participants who had been separated for less than a year had higher levels of systolic blood pressure. Decreasing physical and psychosocial functioning in late adulthood showed to associate for duration of over two years. The findings in the timing and duration of separation were commonly observed in men.

To conclude, early life separation abroad without parents increased the risk of chronic disease and decreases overall health. Despite this the separated itself showed adaptability towards life events for staying alive. Therefore, sex differences in relation to early life stress and further the timing and duration of separation seemed the factors which should be examined in future research with the cumulative effects of all life advantages.

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