Childhood Psychosocial Adversity and Adult Neighborhood Disadvantage as Predictors of Cardiovascular Disease: A Cohort Study

Running title: Halonen et al.; Social predictors of cardiovascular disease

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Abstract

Background—Childhood adverse psychosocial factors (e.g., parental divorce, long-term financial difficulties) and adult neighborhood disadvantage have both been linked to increased cardiovascular disease (CVD). However, their combined effects on disease risk are not known.

Methods and Results—Participants were 37,699 adults from the Finnish Public Sector study whose data were linked to a national neighborhood disadvantage grid using residential addresses between years 2000 and 2008 and who responded to a survey on childhood psychosocial adversities and adult CVD-risk behaviors in 2008/09. Survey data were also linked to national registers on hospitalization, mortality, and prescriptions to assess CVD-risk factors in 2008/09 and to ascertain incident CVD (coronary heart disease or cerebrovascular disease) between the survey and the end of December 2011 (mean follow-up time 2.94 years, SD=0.44). Combined exposure to high childhood adversity and high adult disadvantage was associated with CVD risk factors (hypertension, dyslipidaemia, diabetes, obesity, smoking, heavy alcohol use, and physical inactivity), and with a 2.25-fold (95% Confidence Interval (CI) 1.39–3.63) hazard of incident CVD compared to a low childhood adversity and low adult disadvantage. This hazard ratio attenuated by 16.6% but remained statistically significant after adjustment for the CVD risk factors (1.96, 95% CI 1.22–3.16). Exposure to high childhood adversity or high adult neighborhood disadvantage alone was not significantly associated with CVD in fully-adjusted models.

Conclusions—These findings suggest that individuals with both childhood psychosocial adversity and adult neighborhood disadvantage are at an increased risk of CVD. In contrast, those with only one of these exposures have little or no excess risk after controlling for conventional risk factors.

Key words: cerebrovascular disease, coronary heart disease, epidemiology, risk factor, circulation
Research on predictors of cardiovascular disease (CVD) has increasingly focused on exposures to risk factors other than the conventional behavioral (i.e. smoking, heavy alcohol use, physical inactivity and unhealthy diet) and biological (e.g. hypertension, dyslipidaemia, diabetes, and obesity) ones. One of the potential predictors beyond the conventional risks is exposure to childhood psychosocial adversities, such as financial difficulties, serious conflicts and long-term disease in the family. In a recent longitudinal study of 1089 participants, childhood psychosocial adversity was associated with poorer cardiovascular health, as defined by American Heart Association metrics. Studies have also reported associations between childhood adversity and adulthood CVD risk factors and cardiovascular morbidity, although the underlying mechanisms linking childhood exposure to adult disease remain unclear.

It is possible that childhood adversity sets an individual on a risk pathway leading to adverse future exposures. Those exposed to psychosocial adversity in childhood may not only be at an increased risk of experiencing various adversities in adulthood, but may also perceive these events as more burdensome. Thus, adult neighborhood disadvantage may drive the link between childhood experiences and adult health, representing a pathway model. An important source of adversity experienced in adulthood is residence in a socioeconomically disadvantaged neighborhood, which has been shown to be associated with CVD risk factors or morbidities such as obesity, ischemic heart disease, myocardial infarction and cerebrovascular diseases. In our prior cross-sectional analyses childhood psychosocial adversity and adult neighborhood disadvantage, in combination, were associated with the co-occurrence of adult CVD risk behaviors such as smoking, heavy alcohol use, and physical inactivity. However, we are aware of no longitudinal studies on the combined effect of childhood psychosocial adversity and adult neighborhood disadvantage on CVD endpoints such as fatal and nonfatal
coronary heart disease (CHD) or cerebrovascular diseases.

In this longitudinal study, we used survey in addition to register data to examine whether exposure to certain adverse psychosocial factors in childhood and to neighborhood disadvantage in adulthood are associated with an increased risk of CVD in a large adult population. In accordance with the pathway model (Figure 1), we hypothesized that the effects of the two exposures are such that individuals with both psychosocial adversity in childhood and neighborhood adversity in adulthood would have a higher CVD risk than those with only one or none of such exposures. We also hypothesized that these associations are only partially accounted for by conventional CVD risk factors.

Methods

Study population

Participants were from the Finnish Public Sector study (FPSS).25 The register cohort of the FPSS includes all employees of ten towns and six hospital districts who had a minimum of six months employment in the participating organizations between 1991 and 2005 (n=151 901). These employees are in a wide range of occupations, from city administrators and doctors to semiskilled cleaners. The survey cohorts of the FPSS comprise employees with a job contract at the time of the survey, as indicated by the employers’ registers with responding being voluntary.

Figure 2 shows a flow chart of the sample selection for the present study. We obtained the latitude and longitude coordinates of the residential addresses for the register cohort from the Population Register Center for dates from January 1, 2000 to the date of administration of our survey (hereafter 2008/09 survey), which took place between September 1, 2008 and November 30, 2009. For 1462 participants, the addresses were unknown. Of the register cohort, 60 061 participants were eligible for the 2008/09 survey on childhood adversities whereas 60 370 were
not eligible as they were not anymore employed by the organizations at the time of the survey(s). Furthermore, part of questionnaires did not include items on childhood adversity, leaving a further 26 053 participants out of the analytic cohort. We excluded from the cohort 18 653 nonresponders (response rate 69%) and those participants either with a CVD event (CHD or cerebrovascular disease) five years before the 2008/09 survey (n=374), with an incomplete residential history (n=2883), or with missing data on childhood psychosocial adversities (n=452), leading to a final sample size of 37 699 participants with detailed information on exposure to neighborhood disadvantage between 2000 and the 2008/09 survey. This sample was followed for major coronary heart and cerebrovascular events from the 2008/2009 survey until December 31, 2011, and for all-cause mortality until June 30, 2014 through national health registers. Register and cohort data were linked using personal identification codes that for confidentiality purposes were then re-coded into research identification codes to be used in the analyses. The analyzed sample did not differ markedly from the eligible survey cohort of 60 061 participants in terms of mean age (50 years in the sample vs. 49 in the eligible cohort), sex (78% vs. 78% females), or level of education (10% vs. 11% low; 36% vs. 38% intermediate; 54% vs. 50% high). The Ethics Committee of the Helsinki and Uusimaa Hospital District approved the study.

Measures of Exposure

Childhood psychosocial adversity

In the 2008/09 survey, childhood psychosocial adversity was assessed retrospectively using six questions modified from the Survey of Living Conditions developed by Statistics Finland, as in earlier studies. The respondents were asked whether they had experienced the following in their childhood: divorce/separation of the parents, long-term financial difficulties in the family, serious conflicts in the family, frequent fear of a family member, serious or chronic illness of a
family member, and alcohol problem of a family member. Response categories for each item were: no=0; yes=1; or “cannot say”, which was coded as missing data. We calculated a summary variable for childhood psychosocial adversity (range 0 to 6).

Adult neighborhood disadvantage

Data for adult neighborhood disadvantage were obtained from the Statistics Finland’s grid database for years 2000 and 2008. This database contains information for all Finnish residents on social and economic characteristics shown at the level of 250m×250m grids at the time of data collection.\textsuperscript{27} We used information on income (coded inversely), unemployment rates, and the proportion of those with a low level of education in 2008 as the determinants of neighborhood (i.e., for each 250m×250m grid) disadvantage. For each of the three variables we derived a standardized z-score (mean = 0, standard deviation = 1). A total disadvantage score was then calculated by taking the mean value across all z-scores;\textsuperscript{23} the mean of the score in the study population was 0.297 (range 2.03 to 6.78), a higher score indicating a higher disadvantage. We linked these data to the cohort participants’ home addresses between 2000 and the date of survey completion using the latitude and longitude coordinates. The participants had lived in 14,885 different neighborhoods between 2000 and the survey date; the average total population per neighborhood was 153.5, and there were on average 4.9 participants per grid. For the analyses we calculated exposure to neighborhood disadvantage as a residential time-weighted disadvantage score over a minimum of 3200 days (8.9 years) preceding the 2008/09 survey.

Outcome measures

Cardiovascular risk factors in adulthood

Using national registers and standard questionnaire measurements in the 2008/09 survey, we measured the following CVD risk factors:\textsuperscript{28} hypertension, dyslipidaemia, diabetes, obesity,
smoking, high alcohol intake, and physical inactivity. To identify cases of hypertension, dyslipidaemia, and diabetes we used data on prescription purchases for antihypertensive medication, lipid-lowering medication (statins), and antidiabetes medication. In Finland, drugs for the treatment of these conditions are available by prescription only: national health insurance provides coverage for the prescription drugs to all residents living in the community and all the reimbursed prescriptions are registered in the Finnish Prescription Register managed by the Social Insurance Institution. For each drug prescription, the dispensing date, the World Health Organization Anatomic Therapeutic Chemical (ATC) code, and the quantity dispensed are recorded. For antihypertensive medication we used ATC codes C02, C03, C07, C08, and C09; for statins the code C10AA, and for antidiabetes drugs code A10. As in our earlier studies, participants having hypertension or type 2 diabetes were additionally identified based on eligibility for special medication reimbursement for these conditions. From the Finnish national sickness insurance scheme, we obtained data on all patients who had been granted special reimbursement for medications, including anti-hypertensive and antidiabetes drugs. To be eligible for this reimbursement due to hypertension, the patient needs to have a severe (at least stage 2) or complicated form of hypertension. The corresponding eligibility criteria for reimbursement for antidiabetes medication are diabetes-specific symptoms and repeated plasma glucose levels above 7.0mmol/l.

Participants who in the five years before the 2008/09 survey were eligible for special reimbursement for an antihypertensive drug or had at least one prescription for antihypertensive medication for a minimum of three months (>90 average daily doses) were counted as prevalent cases of hypertension. Correspondingly, the definition of prevalent case of diabetes was any participant who was eligible for special reimbursement for diabetes treatment or had at least one
prescription for diabetes medication for a minimum of three months, and a prevalent case of
dyslipidaemia was any participant who had had at least one statin prescription for a minimum of
three months in the five years before the 2008/09 survey. Incident cases of these conditions were
determined correspondingly from the date of granting special reimbursement or the date of the
first purchase of a prescribed drug after the 2008/09 survey until the occurrence of a CVD
outcome or until December 31, 2011.

In the 2008/09 survey we measured the following CVD risk factors: obesity, smoking,
alcohol intake and physical inactivity.\textsuperscript{23-25} Participants’ weight and height were requested to
determine if they were obese (\geq 30 \text{ kg/m}^2), and smoking status to identify current smokers. High
alcohol intake was indicated by self-reported average consumption of more than 210 g/week (of
pure alcohol) or having passed out due to heavy alcohol consumption at least once during the
past 12 months. Physical inactivity was assessed using the following questions: “How much did
you exercise per week on average during the past year?” and “Estimate whether the level of
intensity of the exercise corresponded to: walking, vigorous walking, jogging, or running”. The
time spent on activity at each intensity level in hours per week was multiplied by the average
energy expenditure of each activity, expressed in Metabolic Equivalent Task (MET) hours, less
than 2 MET hours per day was scored as indicating physical inactivity.

\textit{Cardiovascular outcomes}

The primary outcome was incident definite CVD events, including definite angina or myocardial
infarction (International Classification of Diseases [ICD] 10 codes I20.0, I21, and I22 for causes
of hospitalization, and codes I20-I25 for causes of death) and cerebrovascular disease (ICD 10
codes I60-I69 for causes of hospitalizations and deaths). Our secondary outcomes were any CVD
events (coronary heart disease [ICD 10 codes I20-I25] and cerebrovascular disease [ICD 10
\textit{Continued on next page.}}
codes I60-I69] for causes of hospitalization and death) and all-cause mortality that was used as an unbiased marker of outcome. Data on hospital admissions due to CVD events were obtained from the National Hospital Discharge Register, records on fatal CVD events were obtained from Statistics Finland, and records of all-cause mortality were obtained from the Population Register Center.

Covariates
The age and sex of the participants were obtained from the employers’ registers. Information about the participants’ highest educational degree was obtained from Statistics Finland and it was used as a three-class proxy variable for individual socioeconomic status (high= university degree, intermediate= high school or vocational school, low= comprehensive school). Marital status (living alone vs. married/cohabiting) was requested in the survey.

Statistical analyses
Using dichotomized variables for childhood psychosocial adversity (low=0-1, high=2-6) and for adult neighborhood disadvantage (low=standardized mean below zero, high=above zero), we classified the participants into four exposure categories: low childhood adversity/low adult disadvantage, low childhood adversity/high adult disadvantage, high childhood adversity/low adult disadvantage, and high childhood adversity/high adult disadvantage. To examine the pathway model, we assessed the associations between this combined exposure and conventional adult CVD risk factors (hypertension, dyslipidaemia, diabetes, obesity, smoking, high alcohol consumption, and physical inactivity) using log-binomial regression models with generalized estimating equations (GEEs). The findings are presented as risk ratios and their 95% confidence intervals (CI) for each combination category of the exposure variable where the combination of low childhood psychosocial adversity and low adult neighborhood disadvantage was used as the
reference. GEEs were used to take into account the intracluster dependence of individuals residing within the same municipalities.

To examine whether expected associations between CVD risk factors (hypertension, dyslipidaemia, diabetes, obesity, smoking, high alcohol intake, and physical inactivity) and the three outcomes (definite CVD event, any CVD event, all-cause mortality) were seen in these data, we used time-dependent marginal Cox proportional hazard models. We treated CVD risk factors as time-dependent predictors and followed participants until the outcome of interest, death, or end of follow-up (December 31, 2011), whichever occurred first. The results were reported as age- and sex-adjusted hazard ratios and their 95% CIs. In a preliminary analysis, we confirmed that proportional hazards assumptions were not violated. We adopted a GEE-like marginal approach to account for the intracluster dependence, and estimated regression parameters in the Cox model using the maximum partial likelihood estimates under an independent working assumption with a robust sandwich covariance matrix estimate.

In the main analysis, the association between combined exposure to high adversity and high disadvantage and the risk of incident definite CVD event was examined using time-dependent Cox proportional hazard models. We first estimated the effect with adjustment for demographic characteristics (age, sex, education, marital status). We then added the CVD risk factors to the model and calculated the percentage attenuation in the $\beta$ coefficient as: $100 \times (\beta_{\text{ref model}} - \beta_{\text{ref model + risk factors}})/\beta_{\text{ref model}}$. This proportion provides an estimate of the extent to which the association between the combined exposure and incident definite CVD event is mediated by adulthood CVD risk factors. Similar analyses were performed for the secondary outcomes, any CVD event and all-cause mortality. All analyses were performed with the statistical package SAS version 9.3.
Results

The mean age of the 37,699 healthy participants at the time of the 2008/09 survey was 49.9 years (SD=10.4). Other descriptive statistics of the study population by the four exposure categories are presented in Table 1. During the mean follow-up of 2.94 (SD=0.44) years, there were 201 definite CVD events. For all-cause mortality (n=381) the follow-up time was 5.43 (SD=0.50) years.

Exposure to either high childhood adversity or high adult disadvantage was associated with adult CVD risk factors (Table 2). The highest age- and sex-adjusted risk ratios for those exposed only to high childhood adversity were 1.28 (95% CI 1.21–1.36) for heavy alcohol use and 1.24 (95% CI 1.19–1.30) for smoking (Table 2). The highest risk ratios for exposure to high adult disadvantage only were 1.66 (95% CI 1.56–1.76) for smoking and 1.36 (95% CI 1.26–1.47) for obesity. Being exposed to high childhood adversity and high adult disadvantage was associated with all CVD risk factors, with risk ratios ranging from 1.10 (95% CI 1.02–1.18) for dyslipidaemia to 2.16 (95% CI 2.06–2.27) for smoking.

In the age- and sex-adjusted models the combination of high childhood adversity and high adult disadvantage was associated with a doubling of the risk of a definite CVD event at follow-up: the hazard ratio for the high/high versus the low/low exposure category was 2.53 (95% CI 1.72–3.74) (Table 3). As expected, all CVD risk factors were also associated with an increased risk of CVD, the only exception being heavy alcohol consumption (Table 3). These results were similar when the CVD risk factors were mutually adjusted (Supplemental Table 1). All CVD risk factors were associated with all-cause mortality, with the hazard ratios ranging from 1.32 (95% CI 1.04–1.69) for obesity to 2.57 (95% CI 1.94–3.39) for diabetes (Table 3).

In models adjusted for age, sex, education, and marital status, being in the high/high
exposure category was associated with a 2.25 -fold (95% CI 1.39–3.63) hazard for a definite CVD event (Table 4). For all-cause mortality the corresponding hazard ratio was 1.24 (95% CI 0.98–1.57) (data not shown). Adjustments for the CVD risk factors attenuated the association for definite CVD event by 16.6%, but it remained highly significant with hazard ratio of 1.96 (95% CI 1.22–3.16). An analysis using any CVD event as the outcome replicated these results (Table 4). Figure 3 shows cumulative hazards for definite and any CVD events by exposure category. The risk difference between exposure category groups increased across the entire follow-up period, suggesting the highest risk for those with a combined exposure.

Discussion

We found that exposure to high childhood psychosocial adversity and high adult neighborhood disadvantage was associated with a doubling of the risk of incident cardiovascular disease in adulthood when compared to the absence of such exposures. This association was not explained by factors included in conventional CVD risk assessment, such as smoking, hypertension, dyslipidaemia, or diabetes. Neither childhood psychosocial adversity nor adult neighborhood disadvantage alone were significantly associated with incident CVD in the fully-adjusted models, although they were associated with CVD risk factors.

Our findings on childhood psychosocial adversity and CVD are in agreement with the prior literature.\textsuperscript{11} In Finland, poor psychosocial and socioeconomic circumstances in childhood have been found to be associated with poor heart health as defined by the American Heart Association,\textsuperscript{2} and with an increased risk of acute ischemic heart or cerebrovascular disease in men.\textsuperscript{10} Elsewhere, a three-fold risk of stroke was found among men who had experienced parental divorce in comparison with those whose parents had not divorced.\textsuperscript{9} Associations
between early life adverse psychosocial experiences and CVD at the age of 50 years or over, and a dose-response relationship between exposure to adverse childhood psychosocial factors and ischemic heart disease have also been reported. However, only one cross-sectional study has reported the combined effects of childhood psychosocial adversity and neighborhood disadvantage, suggesting that living in an affluent neighborhood may protect from any negative health effects resulting from childhood psychosocial exposures.

Except for our study on the co-occurrence of poor health behaviors, we are not aware of studies that have examined the effect of neighborhood disadvantage on CVD while taking into account childhood psychosocial exposures. However, there is evidence to support an association between neighborhood disadvantage and increased cardiovascular health risk. In an Australian study, for example, area-level deprivation was associated with obesity and smoking, although no statistically significant association was apparent with diabetes, at-risk alcohol use, physical activity, or CVD itself. At least one study of disease outcomes has reported an increased risk of stroke among whites aged 65 years or more in neighborhoods with the lowest compared with those in neighborhoods with the highest socioeconomic status, two independent ecological studies suggest associations between aspects of neighborhood disadvantage and the risk of stroke, and several studies have shown a link between neighborhood disadvantage and an increased risk of CVD, often independently of adult individual-level socioeconomic status.

Several plausible mechanisms may link these two exposures with health. Financial difficulties or parental distress, for example, may decrease health-promoting parenting, thus adversely affecting children’s health behaviors. Disadvantaged neighborhoods characterized by a high prevalence of smoking or public drinking may reduce motivation to initiate and maintain healthy behaviors. Common pathways, such as social stress may partly explain the observed
strong link for childhood psychosocial adversity and adult neighborhood disadvantage with one health behavior, namely smoking. This finding is consistent with the hypothesis that psychosocial and socioeconomic exposures from across the life course and at individual and neighborhood levels play an important role in smoking habits.

Policy implications of the present findings should be drawn cautiously. Factors included in a conventional CVD risk assessment did not explain the association between childhood psychosocial adversity, adult neighborhood disadvantage, and incident CVD, suggesting that tackling conventional risk factors might not remove the excess CVD risk among individuals exposed to childhood adversity and adult disadvantage. Setting childhood adversity and adult disadvantage as targets of CVD prevention is premature at this stage as we have little evidence of the potential benefits and harms of such interventions, and it is unknown whether these factors can realistically be modified in clinical settings in a cost-effective manner. While further research is needed to increase understanding about the nature of these associations in terms of CVD aetiology, the reduction of childhood adversity and adult disadvantage remains still an important goal for health policies.

**Limitations of the study**

Childhood psychosocial adversity was assessed retrospectively at the individual level whereas the measure of adult neighborhood disadvantage was an aggregate measure based on the population living in the same small-area. The first measure is subject to reporting and recall biases which may both under- and overestimate associations; area-based measures can be imprecise, potentially leading to an underestimation of associations. To improve accuracy, we defined neighborhood disadvantage using a long and detailed residential history (location in 250×250m grids over nearly nine years). There is also a chance of differential misclassification
error as we used a retrospective measure for childhood adversity and this may limit the validity of the data. There is some evidence that the reliability of the self-reported measure of childhood adversity is good,\textsuperscript{35} however, the validity of self-reported adversity can only be assessed by means of prospective studies beginning from childhood. The data came from a society based on a strong welfare state and a study population that was dominated by white female participants who were employed. The cohort is likely to have excluded those who suffered the most from childhood adversities as they might be less successful in finding a job. In combination, these facts may have resulted in the exclusion of those who are the worst off. Thus, the results need to be confirmed in other general populations, and in locations where the social security through life varies and neighborhood-level socioeconomic differences are larger. The strengths of this longitudinal study include the large study population, the comprehensive and valid register data for the outcomes, and the control for conventional CVD risk factors as well as for individual-level education. A further advantage was the use of accurate data for characterizing the accumulation of neighborhood-level exposure.

**Conclusions**

We found that combined exposure to high childhood psychosocial adversity and high adult neighborhood disadvantage was associated with an increased risk of major cardiovascular events such as coronary heart disease and cerebrovascular disease. The magnitude of this association was comparable to those for major CVD risk factors, but further research is needed to assess whether the association is replicable in other populations and whether it is causal or only indicative of other risk factors.
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**Conflict of Interest Disclosures:** None.

**References:**


Table 1. Demographic Characteristics of the Sample by Childhood Psychosocial Adversity and Adult Neighborhood Disadvantage.

<table>
<thead>
<tr>
<th></th>
<th>Low childhood adversity, low adult disadvantage, (N=17 089) %</th>
<th>Low childhood adversity, high adult disadvantage, (N=6743) %</th>
<th>High childhood adversity, low adult disadvantage, (N=9460) %</th>
<th>High childhood adversity, high adult disadvantage (N=4407) %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>8031 (21.3)</td>
<td>22.5</td>
<td>22.7</td>
<td>19.6</td>
</tr>
<tr>
<td>Women</td>
<td>29 668 (78.7)</td>
<td>77.5</td>
<td>77.3</td>
<td>80.4</td>
</tr>
<tr>
<td><strong>Age group, y</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22 - 55</td>
<td>25 009 (66.3)</td>
<td>66.9</td>
<td>61.4</td>
<td>68.4</td>
</tr>
<tr>
<td>56 - 78</td>
<td>12 690 (33.7)</td>
<td>33.1</td>
<td>38.6</td>
<td>31.6</td>
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<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>High</td>
<td>20 445 (54.2)</td>
<td>62.1</td>
<td>42.9</td>
<td>56.0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>13 551 (36.0)</td>
<td>30.5</td>
<td>43.5</td>
<td>34.9</td>
</tr>
<tr>
<td>Low</td>
<td>3703 (9.8)</td>
<td>7.4</td>
<td>13.6</td>
<td>9.1</td>
</tr>
<tr>
<td><strong>Married or cohabiting</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>28 084 (74.9)</td>
<td>81.1</td>
<td>65.3</td>
<td>77.5</td>
</tr>
<tr>
<td>No</td>
<td>9412 (25.1)</td>
<td>18.9</td>
<td>34.7</td>
<td>22.5</td>
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</tbody>
</table>
Table 2. Risk Ratios* and 95% Confidence Intervals for Age- and Sex-Adjusted Associations of Childhood Psychosocial Adversity and Adult Neighborhood Disadvantage with Cardiovascular Risk Factors.

<table>
<thead>
<tr>
<th>Childhood adversity</th>
<th>Adult disadvantage</th>
<th>Hypertension†</th>
<th>Dyslipidaemia†</th>
<th>Diabetes†</th>
<th>Obesity</th>
<th>Smoking</th>
<th>Heavy alcohol use</th>
<th>Physical inactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low - Low (n=17089)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Low - High (n=6743)</td>
<td>1.11 (1.07 to 1.15)</td>
<td>1.06 (1.01 to 1.11)</td>
<td>1.26 (1.14 to 1.39)</td>
<td>1.36 (1.26 to 1.47)</td>
<td>1.66 (1.56 to 1.76)</td>
<td>1.10 (1.03 to 1.18)</td>
<td>1.17 (1.12 to 1.22)</td>
<td></td>
</tr>
<tr>
<td>High - Low (n=9460)</td>
<td>1.07 (1.03 to 1.11)</td>
<td>1.06 (1.00 to 1.14)</td>
<td>1.08 (0.96 to 1.22)</td>
<td>1.20 (1.11 to 1.30)</td>
<td>1.24 (1.19 to 1.30)</td>
<td>1.28 (1.21 to 1.36)</td>
<td>1.07 (1.03 to 1.11)</td>
<td></td>
</tr>
<tr>
<td>High-High (n=4407)</td>
<td>1.15 (1.09 to 1.20)</td>
<td>1.10 (1.02 to 1.18)</td>
<td>1.53 (1.37 to 1.70)</td>
<td>1.55 (1.40 to 1.72)</td>
<td>2.16 (2.06 to 2.27)</td>
<td>1.42 (1.35 to 1.51)</td>
<td>1.29 (1.21 to 1.37)</td>
<td></td>
</tr>
</tbody>
</table>

* Based on log-binomial regression models with GEE estimation taking into account the intracluster dependence of individuals residing within the same municipalities.
† Based on prescription registers.
Table 3. Age- and Sex-Adjusted Associations of Childhood Psychosocial Adversity, Adult Neighborhood Disadvantage, and Cardiovascular Risk Factors with Incident Cardiovascular Disease and All-Cause Mortality.*

<table>
<thead>
<tr>
<th></th>
<th>Definite CVD event†</th>
<th>Any CVD event#</th>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Participants</td>
<td>Events</td>
<td>Hazard ratio (95% CI)</td>
</tr>
<tr>
<td><strong>Childhood adversity</strong></td>
<td>Low</td>
<td>23 832</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>13 867</td>
<td>91</td>
</tr>
<tr>
<td><strong>Adult disadvantage</strong></td>
<td>Low</td>
<td>26 549</td>
<td>118</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>11 150</td>
<td>83</td>
</tr>
<tr>
<td><strong>Childhood adversity</strong></td>
<td>Low - Low</td>
<td>17 089</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Low - High</td>
<td>6743</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>High - Low</td>
<td>9460</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>High - High</td>
<td>4407</td>
<td>41</td>
</tr>
</tbody>
</table>

**Biological risk factors**

- **Hypertension***
  - No: 28 183, 113, 1.00, 141, 1.00, 202, 1.00
  - Yes: 9516, 88, 1.73 (1.29 to 2.33), 139, 2.14 (1.67 to 2.74), 179, 1.71 (1.39 to 2.11)

- **Dyslipidemia***
  - No: 34 286, 158, 1.00, 195, 1.00, 306, 1.00
  - Yes: 3413, 43, 1.84 (1.29 to 2.62), 85, 2.94 (2.23 to 3.87), 75, 1.39 (1.07 to 1.81)

- **Diabetes***
  - No: 35 783, 173, 1.00, 234, 1.00, 319, 1.00
  - Yes: 1916, 28, 2.42 (1.60 to 3.68), 46, 2.88 (2.06 to 4.00), 62, 2.57 (1.94 to 3.39)

- **Obesity**
  - No: 30 545, 147, 1.00, 210, 1.00, 286, 1.00
  - Yes: 6217, 49, 1.51 (1.09 to 2.08), 65, 1.40 (1.06 to 1.85), 83, 1.32 (1.04 to 1.69)

**Behavioral risk factors**

- **Smoking**
  - No: 32 291, 132, 1.00, 200, 1.00, 289, 1.00
  - Yes: 5216, 68, 3.47 (2.57 to 4.68), 79, 2.72 (2.09 to 3.54), 89, 2.29 (1.79 to 2.91)

- **Heavy alcohol use**
  - No: 32 440, 164, 1.00, 234, 1.00, 292, 1.00
  - Yes: 5152, 37, 1.13 (0.78 to 1.64), 45, 0.96 (0.69 to 1.33), 87, 1.81 (1.41 to 2.32)

- **Physical inactivity**
  - No: 27 424, 107, 1.00, 146, 1.00, 206, 1.00
  - Yes: 10 106, 92, 2.00 (1.51 to 2.64), 131, 2.07 (1.63 to 2.62), 173, 1.96 (1.60 to 2.40)

* From marginal Cox-model approach taking into account the intraclass dependence of individuals residing within the same municipalities.
† Cardiovascular disease ICD-10 codes I20.1, I21-I22 and I60-I69. # Cardiovascular disease ICD-10 codes I20-I25 and I60-I69
Table 4. Sequentially Adjusted Associations of Combined Childhood Psychosocial Adversity and Adult Neighborhood Disadvantage with Incident Cardiovascular Disease.*

<table>
<thead>
<tr>
<th>Childhood adversity</th>
<th>Participants (events)</th>
<th>Hazard Ratio (95% Confidence Interval)* Adjusted for</th>
<th>OUTCOME: Definite CVD event#</th>
<th>OUTCOME: Any CVD event§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Demographic characteristics†</td>
<td>Demographics + biological risk factors†</td>
<td>Demographics + behavioral risk factors†</td>
</tr>
<tr>
<td>Low - Low</td>
<td>16 460 (66)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Low - High</td>
<td>6452 (40)</td>
<td>1.34 (1.01 to 1.77)</td>
<td>1.32 (1.01 to 1.74)</td>
<td>1.24 (0.92 to 1.68)</td>
</tr>
<tr>
<td>High - Low</td>
<td>9150 (46)</td>
<td>1.29 (0.93 to 1.79)</td>
<td>1.27 (0.92 to 1.77)</td>
<td>1.31 (0.93 to 1.84)</td>
</tr>
<tr>
<td>High - High</td>
<td>4231 (40)</td>
<td>2.25 (1.39 to 3.63)</td>
<td>2.13 (1.33 to 3.43)</td>
<td>1.98 (1.20 to 3.25)</td>
</tr>
<tr>
<td>Low - High</td>
<td>6452 (48)</td>
<td>1.04 (0.81 to 1.33)</td>
<td>1.01 (0.79 to 1.29)</td>
<td>0.98 (0.75 to 1.29)</td>
</tr>
<tr>
<td>High - Low</td>
<td>9150 (64)</td>
<td>1.14 (0.87 to 1.51)</td>
<td>1.13 (0.87 to 1.47)</td>
<td>1.16 (0.87 to 1.54)</td>
</tr>
<tr>
<td>High - High</td>
<td>4231 (52)</td>
<td>1.92 (1.26 to 2.94)</td>
<td>1.81 (1.19 to 2.76)</td>
<td>1.74 (1.12 to 2.71)</td>
</tr>
</tbody>
</table>

*From marginal Cox-model approach taking into account the intracluster dependence of individuals residing within the same municipalities.
†Demographic characteristics are age, sex, marital status, and education. Biological risk factors are hypertension, dyslipidaemia, diabetes, and obesity. Behavioral risk factors are smoking, high alcohol consumption, and physical inactivity.
# Cardiovascular disease ICD-10 codes I20.1, I21-I22 and I60-I69
§ Cardiovascular disease ICD-10 codes I20-I25 and I60-I69
Figure Legends:

**Figure 1.** Childhood psychosocial adversity and adult neighborhood disadvantage as distal risk factors for cardiovascular disease.

**Figure 2.** Flow chart of the selection of the analyzed sample.

**Figure 3.** Cumulative hazard of definite* (A) and any† (B) cardiovascular disease events by the level of childhood psychosocial adversity and adult neighbourhood disadvantage. *ICD-10 codes I20.1, I21-I22 and I60-I69 † ICD-10 I20-I25 codes and I60-I69
Figure 1

- Childhood psychosocial adversity
- Adult neighborhood disadvantage
- CVD risk factors
- Fatal and non-fatal CVD event
Finnish Public Sector study cohort, 151,901 adults.

60,061 eligible to 2008/09 survey on childhood psychosocial factors and linked to their addresses with dates of moves between 2000 and study baseline 2008/09.

41,408 responded to 2008/09 survey on childhood adversities (response rate 69%).

37,699 healthy participants with complete residential history from 2000-2008/09.

3955 died before 2008/09.
60,370 participants were not employed by the organisations at the time of the survey.
For 26,053 participants, 2008/09 survey did not include items on childhood psychosocial factors.
1462 with unknown addresses in 2000 - 2008/09.

18,653 did not respond.

452 had not data on childhood psychosocial factors,
2883 had incomplete residential history,
374 had prevalent cardiovascular disease.

Follow-up for cardiovascular risk factors from prescription registers and 2008/09 survey:
- Hypertension, dyslipidaemia, diabetes, obesity, smoking, heavy alcohol use, physical inactivity.

Follow-up for disease endpoints from national registers:
- Incident coronary heart and cerebrovascular disease from 2008/09 to 31 December 2011; mean follow-up 2.94 (SD=0.44) y.
- All deaths from 2008/09 to June 2014; mean follow-up 5.43 (SD=0.50) y.

Figure 2
Figure 3A
Childhood Psychosocial Adversity and Adult Neighborhood Disadvantage as Predictors of Cardiovascular Disease: A Cohort Study
Jaana I. Halonen, Sari Stenholm, Jaana Pentti, Ichiro Kawachi, S.V. Subramanian, Mika Kivimäki and Jussi Vahtera

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SUPPLEMENTAL MATERIAL

Childhood Psychosocial Adversity and Adult Neighborhood Disadvantage as Predictors of Cardiovascular Disease: A Cohort Study

Jaana I. Halonen Ph.D., Sari Stenholm Ph.D., Jaana Pentti B.Sc., Ichiro Kawachi M.D., SV. Subramanian Ph.D., Mika Kivimäki Ph.D., Jussi Vahtera M.D.
**Supplemental Table 1.** Independent Effects of Adult Neighborhood Disadvantage, Childhood Psychosocial Adversity and Cardiovascular Risk Factors on Definite Vascular Events*. Hazard Ratios (95% confidence intervals) Adjusted for Age, Sex, Education, Marital Status, and All Other Predictors.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Childhood adversity</strong></td>
<td></td>
</tr>
<tr>
<td>Adult disadvantage</td>
<td></td>
</tr>
<tr>
<td>Low - Low</td>
<td>1.00</td>
</tr>
<tr>
<td>Low - High</td>
<td>1.28 (0.92 to 1.77)</td>
</tr>
<tr>
<td>High - Low</td>
<td>1.22 (0.93 to 1.61)</td>
</tr>
<tr>
<td>High - High</td>
<td>1.96 (1.22 to 3.16)</td>
</tr>
<tr>
<td><strong>Hypertension†</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>1.37 (1.09 to 1.73)</td>
</tr>
<tr>
<td><strong>High lipids†</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>1.54 (1.15 to 2.07)</td>
</tr>
<tr>
<td><strong>Diabetes†</strong></td>
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<tr>
<td>No</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>1.64 (1.12 to 2.42)</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
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</tr>
<tr>
<td>No</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>1.05 (0.80 to 1.39)</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>3.05 (2.23 to 4.16)</td>
</tr>
<tr>
<td><strong>Heavy alcohol use</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>0.86 (0.57 to 1.28)</td>
</tr>
<tr>
<td><strong>Physical inactivity</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>1.62 (1.22 to 3.16)</td>
</tr>
</tbody>
</table>

* ICD-10 codes I20.1, I21-I22 and I60-I69
† From marginal Cox-model approach taking into account the intracluster dependence of individuals residing within the same municipalities.