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Childhood adversities and adult-onset asthma: a cohort study

Jyrki Korkeila,[1] Raija Lietzen,[2] Lauri H Sillanmäki,[3] Päivi Rautava,[4] Katariina Korkeila,[5] Mika Kivimäki,[6] Markku Koskenvuo,[7] Jussi Vahtera[8]

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For numbered affiliations see end of article.

Correspondence to
Dr Jyrki Korkeila;
jyrki.korkeila@utu.fi

ABSTRACT

Objectives: Childhood adversities may be important determinants of later illnesses and poor health behaviour. However, large-scale prospective studies on the associations between childhood adversities and the onset of asthma in adulthood are lacking.

Design: Prospective cohort study with 7-year follow-up.

Setting: Nationally representative study. Data were collected from the Health and Social Support (HeSSup) survey and national registers.

Participants: The participants represent the Finnish population from the following age groups: 20–24, 30–34, 40–44, and 50–54 years at baseline in 1998 (24 057 survey participants formed the final cohort of this study). The occurrence of childhood adversities was assessed at baseline with a six-item survey scale. The analyses were adjusted for sociodemographic characteristics, behavioural health risks and common mental disorders.

Primary and secondary outcomes: The survey data were linked to data from national health registers on incident asthma during a 7-year follow-up to define new-onset asthma cases with verified diagnoses.

Results: A total of 12 126 (59%) participants reported that they encountered a childhood adversity. Of them 3677 (18% of all) endured three to six adversities. During a follow-up of 7 years, 593 (2.9%) participants were diagnosed with incident asthma. Those who reported three or more childhood adversities had a 1.6-fold (95% CI 1.31 to 2.01) greater risk of asthma compared to those without childhood adversities. This hazard attenuated but remained statistically significant after adjustment for conventional risk factors (HR 1.33; 95% CI 1.06 to 1.67).

Conclusions: Adults who report having encountered adversities in childhood may have an increased risk of developing asthma.

ARTICLE SUMMARY

Article focus

- This study investigated, whether self-reported childhood adversities measured at adulthood are associated with the risk of incident asthma.
- And whether this risk was attributable to common mental disorders or behavioural health risk factors in a nationally representative sample with a longitudinal setting.

Key messages

- Self-reported childhood adversities were significantly associated to onset of asthma in adulthood. Psychiatric morbidity and other risk factors attenuated the association by 47%.

Strengths and limitations of this study

- The study was based on a nationally representative sample in a longitudinal setting. National registers with good data coverage and reliability were used to assess asthma diagnoses and psychiatric morbidity. The limitations of study are that assessment of adversities was based on self-reports, which, additionally, did not include items on abuse.

INTRODUCTION

It is increasingly recognised that childhood adversities may contribute to risk of various types of adult morbidity as well as poor health behaviour.[1–11] Most of the studies in this field of research have focused on exposures such as childhood sexual or physical abuse, or severe neglect. Several,[2–5 12 13] but not all[7] studies have found support for a dose–response relationship: the greater the number and severity of childhood adversities, the more unfavourable health outcomes. In the National Comorbidity Survey, childhood abuse was associated with increased physical health problems but controlling for the presence of subject's psychiatric illness substantially decreased the strength of this association.[7]

Many previous studies have found an association of anxiety disorders and also major depression with asthma,[14–21] and, additionally, with allergies and atopia.[22–26] Furthermore, this association seems to be generalisable across different cultural settings.[17] Mental disorders may influence the experience of asthma, quality of life related to asthma and adherence to treatment, hospitalisation rates and outcome in asthma.[19 27 28]

To our knowledge, only two previous longitudinal studies exist on the relation of mental disorders and asthma, supporting especially panic disorder as a risk factor for later the onset of asthma.[20 21 26]

The association between mental disorders and asthma could possibly be explained by shared risk factors, such as childhood adversity. Anxiety and depressive disorders are associated with childhood adversities.[29 30] There is some evidence linking asthma to childhood adversities. The studies have either been cross-sectional[31–37] or used childhood social adversity as exposure in a longitudinal setting.[36 38] The outcome has been measured using self-reports of physician-diagnosed asthma[36] or symptoms or use of services in adolescence as outcome measure.[20] One prospective study on early-life financial adversity and respiratory function in middle age used objective measurement of lung function.[38] However, we are aware of no previous large-scale studies with a prospective design that would have used register-based data of incident asthma in adulthood and taken into account factors underlying the association between childhood adversities and the onset of asthma, such as common mental disorders and health risk behaviours. It is so far uncertain, whether the association between preceding mental disorder and subsequent asthma could be accounted for by mental disorders, and whether childhood adversities could have an independent influence on incident asthma.

In this study, we aimed to investigate whether self-reported childhood adversities measured at adulthood are associated with the risk of incident asthma and whether this risk was attributable to mental disorders or behavioural health risk factors at baseline in a large prospective population sample.

METHODS

Population

Data were collected from the Health and Social Support (HeSSup) study, a longitudinal study on a population sample representative of the Finnish population in the following four age groups: 20–24, 30–34, 40–44 and 50–54 years at baseline in 1998. The initial response rate of the postal survey was 40%. According to the non-response analysis, no significant selective health-related factors could be identified.[39] Of all 25 901 respondents, 24 057 (93%) gave their written consent for health register linkages. Out of that pool, we excluded all participants with asthma (n=3446) and deceased (n=4) before the beginning of the follow-up. Thus, the final sample consisted of 20607 participants (8622 males and 11 985 females). They were followed for a 7-year period from national health registers in order to detect the onset of new asthma cases (1 January, 1999–31 December 2005). The Turku University Hospital Ethics Committee considered that a statement of approval was not required. The subjects originated from a random population sample. While agreeing to participate in the study, the subjects filled up an informed consent form.

Measures

Childhood adversities

The occurrence of childhood adversities was assessed at baseline with a six-item survey scale with questions on long-term financial difficulties, divorce or separation of the parents, serious conflicts in the family, severe illness of a family member, frequent fear of a family member and alcohol problem of a family member.[40] The subjects were asked to respond either 'yes', 'no' or 'cannot say' to each item. The items were analysed as a summary variable with three values (0, 1–2 or 3–6 adversities).

Case definition for asthma

Using the unified personal identification code system, which covers all Finnish citizens, we linked the survey responses to records from three independent and comprehensive Finnish national health registers in order to identify incident cases of asthma. The identification of cases was based on the clinical diagnosis from the Drug Reimbursement Register or the Hospital Discharge Register or detailed information about purchases of the prescribed medication for asthma from the Drug Prescription Register. A participant was classified as having incident asthma when the event was verified for the first time from any of the three data sources between 1 January 1999 and 31 December 2005.

First, we used the Drug Reimbursement Register of the Social Insurance Institution of Finland, which contains information on persons entitled to special reimbursement for certain chronic diseases, such as asthma. Patients who apply for special reimbursement must attach a detailed medical certificate prepared by the treating physician, who also provides data to confirm the diagnosis. The application is then reviewed by a physician in the Social Insurance Institution to determine whether the uniformly defined requirements for the disease are met. From this register, participants were defined as incident asthma cases if they were recorded in the Central Drug Register as eligible for asthma treatment for the first time during the follow-up.

Second, we used prescription data to assess the beginning of medical treatment for asthma. In Finland, the National Social Insurance Scheme at the Social Insurance Institution provides basic reimbursement (currently 42%) for all filled outpatient prescriptions that are recorded in the Drug Prescription Register according to the WHO's Anatomical Therapeutic Chemical (ATC) Classification[41] and by date of purchase. We identified all participants with two or more prescriptions for drugs for obstructive airway diseases (ATC code R03) in any year during the follow-up by using the day of the first purchase as an indicator of the onset of asthma.

Third, we obtained data from the Hospital Discharge Register of National Institute for Health and Welfare, which includes records on all inpatient hospital admissions. This register is comprised of countrywide information on virtually all hospitalisations. We obtained the

discharge dates and the corresponding main diagnoses for hospitalisation due to asthma (ICD-10 J45). All individuals who were identified as having asthma in any of these registers at baseline in 1998 were excluded from the analysis, as well as all those who reported a lifetime diagnosis of asthma in the baseline survey.

Background variables

All background variables were measured at baseline in 1998. Gender, age group, level of education (basic/vocational/college/university) and marital status (single, divorced or widowed vs married or cohabiting) were included in the analysis as sociodemographic variables.

We assessed four behavioural health risks using standard questionnaire measurements. Smoking status was measured with a variable describing current regular smoking (current/never/ex-smoker). High alcohol intake was present with a weekly self-reported consumption of beer, wine, and spirits exceeding ≥175 g of alcohol for women and ≥263 g of alcohol for men.[42] Survey reports on height and weight were used to calculate the average body mass index (BMI) to identify underweight (BMI<20 kg/m^2), normal-weight (BMI 20 −<25 kg/m^2), overweight (25−<30 kg/m^2), and obese (BMI ≥30 kg/m^2) participants. Physical activity was calculated by the Metabolic Equivalent Task index to measure sedentary life style (<2 MET-hours/day).[43]

Psychological factors were measured from the questionnaire responses. To measure general feelings of stressfulness in daily life we used the Reeder stress inventory, a four-item questionnaire instrument with a five-point Likert format.[44] It consist of four statements: (1) 'In general, I am usually tense or nervous'; (2) 'There is a great amount of nervous strain connected with my daily activities'; (3) 'At the end of the day, I am completely exhausted mentally and physically' and (4) 'My daily activities are extremely trying and stressful'. The mean score of the four statements was divided into quartiles (low/medium low/medium high/high general feelings of stressfulness).

Symptoms of sympathetic nervous system (SNS) hyperactivity were measured using an eight-item scale.[45] This measure requests the occurrence of the following eight symptoms within the past month: (1) palpitation without exercise; (2) irregular heartbeat; (3) chest pain upon anger or emotion; (4) sweating without exercise; (5) flushing; (6) tremor of hands; (7) tremor of voice and (8) muscle twitching. The following four alternatives were given for each item: daily or almost daily, weekly, less often and never. The mean score of the eight statements was divided into quartiles (low/medium low/medium high/high symptoms of SNS hyperactivity).

Common mental disorders were measured from the questionnaire responses and the medication records. Symptoms of depression were measured with the Beck Depression Inventory (BDI). Depression (no/yes) was indicated by a BDI sum score of more than 18.[46] Using data from the National Drug Reimbursement Register we assessed antidepressant or antianxiety purchases in 1998 to identify individuals with more severe depressive and anxiety symptoms (no/yes). To identify participants with clinically significant depression we collected data on hospitalisations from the Hospital Discharge Register. We obtained the discharge dates before 1 January 1999 (no/yes) for the main diagnoses determined by ICD-10 codes F00–F99.

Other possible risk factors for the development of asthma that were considered in this study included exposure to pets, parents' smoking and allergy. Information about a pet was obtained by asking whether the participant has a pet (having a pet at home vs not having one). The participants reported whether their parents had smoked at home during the school-age (no/yes). Allergy (no/yes) was determined using prescriptions for drugs for allergy diseases (ATC-codes R01AC, R03BC).

Statistical analysis

All analyses were performed by using SAS release 9.2/2008. Descriptive statistics included the associations between the various background variables (demographics, psychological factors, asthma risk factors and health-related factors) and childhood adversities; differences were studied by using logistic regression.

The Cox proportional hazard models were used to analyse the association between the baseline childhood adversities and the onset of asthma. The time-dependent interaction terms between any childhood adversity and the logarithm of the follow-up period were all non-significant confirming that the proportional hazard assumptions were justified. Follow-up began on 1 January 1999, and ended upon the first occurrence of the outcome measure or censoring event death (the date of death was obtained from the Statistics Finland register) or the end of follow-up (31 December 2005), whichever came first. We calculated HRs and their 95% CI. The models were adjusted for background variables; first the various background variables separately and finally all background variables in the same model. The gender difference in the association of childhood adversities with the onset of asthma was assessed by entering the interaction term sex × childhood adversities into the model. Because no interaction was found ($p=0.12$), we analysed men and women together.

RESULTS

The sample included 8556 (41.7%) men and 11 946 (58.3%) women. Altogether, 12 126 (59%) participants in our study reported that they encountered a childhood adversity. Of these participants, 8449 (41% of all participants) reported 1–2 adversities and 3677 (18% of all participants) 3–6 adversities. Table 1 shows the characteristics of the participants and the associations between childhood adversities by the baseline characteristics. Except for marital status, physical activity and allergy, the

Table 1 Baseline characteristics by childhood adversities

Characteristic	Number	Childhood adversities 0 (n=8376) Per cent	1–2 (n=8449) Per cent	>2 (n=3677) Per cent	Significance
Gender					<0.001
Men	8556	45	42	35	
Women	11 946	55	58	65	
Age group (years)					<0.001
20–24	5771	32	26	24	
30–34	4866	24	22	27	
40–44	4832	22	24	26	
50–54	5033	22	28	23	
Marital status					<0.001
Single/divorced/widowed	6781	34	32	34	
Married/cohabiting	13 707	66	68	66	
Occupational education					<0.001
Basic	6433	30	32	35	
Vocational school	4666	22	24	24	
College	6417	32	31	31	
University	2781	16	13	10	
Smoking					<0.001
Never	8667	53	44	35	
Ex-smoker	5214	25	29	33	
Current	4938	22	27	32	
Physical activity					0.667
No	4352	22	22	21	
Yes	15 718	78	78	79	
High alcohol intake (>16 drinks/week)					<0.001
No	19 294	95	95	92	
Yes	1179	5	5	8	
BMI (kg/m^2)					<0.001
<20	2055	11	9	10	
20–25	10 606	53	51	52	
25–30	5906	28	30	28	
>30	1823	8	10	10	
Pet					<0.001
No	11 979	60	58	55	
Yes	8523	40	42	45	
Parents' smoking					<0.001
No	9508	57	44	27	
Yes	10 994	43	56	73	
Prescribed antiallergy drugs					0.9669
No	18 958	93	92	92	
Yes	1544	7	9	8	
Symptoms of SNS hyperactivity (quartile)					<0.001
Lowest	4035	23	18	16	
Second	5288	28	26	22	
Third	6302	30	31	31	
Highest	4823	19	25	31	
General feeling of stressfulness (quartile) Reeder					<0.001
Low	5747	32	27	23	
Medium low	6333	33	31	29	
Medium high	4010	19	20	20	
High	4204	16	22	28	
Depression (BDI)					<0.001
No	19 534	98	95	92	
Yes	837	2	5	8	

Continued

Table 1 Continued

Characteristic	Number	Childhood adversities 0 (n=8376) Per cent	1–2 (n=8449) Per cent	>2 (n=3677) Per cent	Significance
Psychotropic medication					<0.001
No	19 421	96	95	92	
Yes	1081	4	5	8	
Hospitalisation due to psychiatric disorder					
No	20 382	99.7	99.3	99	<0.001
Yes	120	0.3	0.7	1	

BDI, Beck Depression Inventory; BMI, body mass index; SNS, sympathetic nervous system.

characteristics of the participants were associated with childhood adversities. In this cohort, women, older subjects, those with basic level education, who smoked, had higher alcohol intake and BMI, who reported symptoms of SNS hyperactivity, had a higher score on stressfulness measure and any indication of psychiatric morbidity reported an increased number of childhood adversities (p<0.001).

During a follow-up of 7 years, 593 participants were diagnosed with incident asthma. As shown in figure 1, the risk of adult onset asthma increased with increasing number of childhood adversities. The difference between the groups of no adversities, 1–2 adversities and 3–6 adversities became evident after 3 years of follow-up and widened during the course of time.

Exposure to 1–2 childhood adversities associated with 1.20-fold (95% CI 1.00 to 1.45) greater risk of asthma compared to participants who did not report any childhood adversities. However, after adjustments for the background variables this association became nonsignificant (table 2). Exposure to 3–6 childhood adversities associated with 1.6-fold (95% CI 1.31 to 2.01) greater risk of asthma. This excess hazard was attenuated by 19.4% to 1.50 (95% CI 1.21 to 1.86), when controlling for demographic information. Adjustment for psychiatric disorders attenuated the excess hazard by 22.6% to 1.48 (95% CI 1.19 to 1.84), for asthma risk factors by 8% to 1.57 (95% CI 1.26 to 1.95) and for health behaviours by 11.3% to 1.55 (95% CI 1.25 to 1.92). When all the different factors were concurrently adjusted for, the excess hazard was attenuated by 47% to 1.33 (95% CI 1.06 to 1.67) (table 2). To test the linear trend in the association between childhood adversities and incident asthma, we treated childhood adversities as a count variable; in the unadjusted model the HR was 1.12 (95% CI 1.07 to 1.19, p<0.001) and in the fully adjusted model 1.06 (95% CI 1.01 to 1.13, p=0.032).

Of the specific types of childhood adversities in the family, economical difficulties, severe conflicts and severe and long term illness were associated with 1.2–1.4 times higher hazard of asthma onset while the corresponding association of divorce, fear of family member and alcohol problem with asthma, although slightly elevated, remained non-significant (table 3).

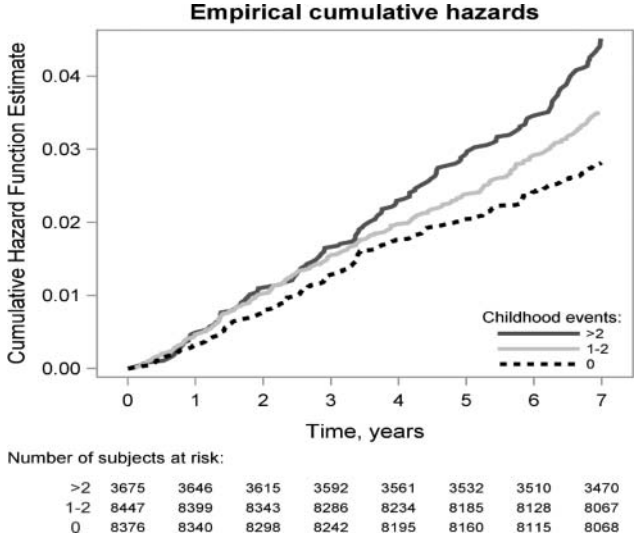

Figure 1 Cumulative hazard function curves according to the Cox model with adult onset asthma during the course of the follow-up (n=20 502).

DISCUSSION

In this study we found self-reported childhood adversities to be associated with register-verified asthma diagnoses. Our results suggest that about half of this association is mediated by several factors. Psychiatric morbidity attenuated the relative risk most, almost a quarter, and demographic factors by about a fifth, whereas asthma risk factors accounted for a smaller portion of the attenuation of the risk after adjustment. Our analyses suggest that psychiatric disorder, having no relationship, being female, belonging to an older age group, low level of education, having allergy or atopia, health behaviours contribute to the excess risk of adult onset asthma associated with childhood adversity. The fact that circa half of this association was not accounted for by the variables measured in this study may reflect an independent relation between childhood adversities and adult asthma or some other unaccounted factors.

Table 2 Childhood adversities as the predictors of incident asthma

	Number of subjects in the analysis	Number of subjects with the event	Childhood adversities	
			0	1–2 Childhood adversities
Crude	17 894	593	1 1.20 (1.0–1.45)	1.62 (1.31–2.01)
Adjusted for demographics*	17 894	593	1 1.16 (0.96–1.40)	1.50 (1.21–1.86)
Adjusted for psychiatric disorders†	17 894	593	1 1.16 (0.96–1.40)	1.48 (1.19–1.84)
Adjusted for asthma risk factors‡	17 894	593	1 1.19 (0.98–1.43)	1.57 (1.26–1.95)
Adjusted for health behaviours§	17 894	593	1 1.17 (0.97–1.41)	1.55 (1.25–1.92)
Adjusted for all aforementioned	17 894	593	1 1.11 (0.92–1.34)	1.33 (1.06–1.67)

*Sex, age group, marital status, education.
†Sympathetic nervous system, Reeder, Beck, prescribed antidepressant or antianxiety, National Hospital Discharge Register F-diagnoses.
‡Pet, parents' smoking, prescribed antiallergy drugs.
§Smoking, body mass index, physical activity, high alcohol intake.

This is to our knowledge the first large-scale prospective, population-based study using various forms of childhood adversity as the exposure and comprehensive measures of asthma as the outcome, while controlling for sociodemographic factors, common risk factors, psychological distress and psychiatric morbidity. Our findings are consistent with previous longitudinal studies that reported an association between adverse childhood events and asthma.[20 36 38] However, the EPIC-Norfolk study used incident hospitalisation as outcome, but did not adjust for mental disorders.[36] The adversities measured in our study covered equally heterogeneous[20] or a more comprehensive[36 38] set of childhood adversities and the outcome measures of the present study were derived from reliable national registers comprehensively covering new asthma cases.

The study by Bartley *et al*[38] focused on lung function and found that financial adversity was associated with poor lung function partly through poor housing and partly through pathways involving continuities in social disadvantage and the associated environmental exposures and behaviours. In our cohort roughly a fifth of the association between adversities and asthma was mediated by sociodemographic factors. Additionally, socioeconomic status (SES) has been found to associate with the risk of mental disorders and poor health behaviours.[47 48] Hence, socioeconomic factors may operate on the micro level through these risk factors.

Likewise, our study is in line with the 10 cross-sectional population surveys conducted as part of the World Mental Health (WMH) surveys. In that particular study childhood adversities predicted adult-onset asthma with risk increasing with the number of adversities experienced (HR 1.49–1.71). However, the researchers of the WMH surveys also found that early-onset depression and anxiety disorders and childhood adversities both predicted adult-onset asthma after mutual adjustment.[37] In our study, psychiatric disorder was only used as a covariate. It was not studied as a risk factor for asthma.

Interestingly, low maternal childhood SES was found to associate with increased cord blood immunoglobulin E (IgE) levels and repeated wheeze through both direct and indirect effects.[49] Additionally, maternal cumulative interpersonal trauma was also associated with increased cord blood IgE levels. Psychoneuroimmunological pathway may be one key mechanism between adversity and asthma. Parenting difficulties have, likewise, been linked to childhood asthma and the risk seemed to be highest among those, who also had elevated IgE levels.[32] Adults who have exposed to childhood maltreatment have been found to have elevated levels of inflammation biomarkers.[10 50] Also anxiety disorders have been linked to inflammation.[51] It has been suggested that stress-related elevation in clinically relevant inflammation proteins could contribute to the biological embedding of childhood stress.[50]

Table 3 Associations (HR) between individual types of childhood adversities and adult onset asthma*

Childhood adversity	HR	95% CI	Significance
Parents' divorce	1.11	0.89 to 1.38	0.346
Economical difficulties	1.41	1.17 to 1.70	<0.001
Severe conflicts between parents	1.20	1.00 to 1.45	0.05
Fear of family member	1.21	0.96 to 1.51	0.104
Severe and chronic illness	1.29	1.05 to 1.51	0.013
Alcohol problem	1.19	0.99 to 1.43	0.066

*Adjusted for age, education, marital status and gender.

METHODOLOGICAL ISSUES

In this study, the incidence of asthma was 2.9%, providing sufficient statistical power to adequately study the association between childhood adversities and adult-onset asthma. The strengths of our study are, first, reliable register-based information on the outcomes, and second, a large nationwide population sample with a prospective study design. The Finnish hospital

discharge and mortality registers provide virtually complete population-wide data on hospital discharge and mortality. In Finland, the validity of the national registers has been found to be high, reasonably accurate and highly reliable for epidemiological study purposes.[52 53]

The limitations of the present study include a relatively low baseline questionnaire response rate as well as a retrospective assessment of the childhood adversities based on self-reports. The non-response analysis of the cohort was based on two strategies: (1) comparisons made between early and late responders and (2) comparisons made between all responders and routine statistical data of the general population. The first analysis showed no significant differences in self-reports of physician-diagnosed illnesses including depression, panic disorder and eating disorder, and the second that there were no indications of selective physical health-related factors. Additionally, the subjects reporting physician-diagnosed panic disorder, heavy alcohol use and use of tranquillizers gave significantly more commonly than others (94.5% vs 90.9%, respectively) consent to use register-based data.[39] We deemed that a significant bias on important health-related was unlikely. However, it is known from other studies that persons with mental disorders are more likely to be among non-responders. As in the cohort of this study, consent to use register data was likely to compensate for mental disorder bias. As the linkage to register data on outcomes was almost complete (93%) we believe selection bias is an unlikely explanation for our findings.

The associations between asthma and mental disorder symptoms and disorders seem to be bidirectional.[20] Including psychiatric risk factors during the follow-up into our model could have attenuated further the association between asthma and mental health risk factors, but made it more cumbersome to settle on their temporal relationships. The same goes for behavioural risk factors as well.

There is some evidence to suggest that the childhood abuse reports by different informants such as children as victims, their parents and teachers may differ.[54] However, severe abuse is most often well recalled and false-positive reports are rather rare.[55 56] Less severe adversities may well be under-reported.[56] Furthermore, adjustment for adulthood depression may partly lead to over-control, as prospective cohort studies have shown that childhood adversities may increase the risk of depression, in particular when combined with genetic vulnerability.[57] Research on documented adverse childhood experiences indicates that their consequences are not merely artefacts of retrospective recall.[58] The reliability of the measure on childhood adversities has been previously assessed and found good, the κ-values of responses between 1998 and 2003 ranging from 0.56 ('severe illness of a family member') to 0.90 ('parents divorce').[59] Further prospective studies starting from childhood are needed to examine this issue in detail. Our findings on the relationships between adversities and incident asthma are not likely to be over-estimates.

CONCLUSIONS

In this prospective population-based study of Finnish adults, self-report of childhood adversities was associated with increased incidence of diagnosed asthma. Although further studies are needed to confirm this finding, the results emphasise the importance of early risk factors in the identification and treatment of risk groups for poor health outcomes. If confirmed, these findings suggest it would be of importance to provide resources to face or avoid psychosocial risk factors in the prevention of asthma at population level.

Author affiliations
[1]Department of Psychiatry, University of Turku, and Harjavalta Hospital, Satakunta Hospital District, Finland
[2]Department of Public Health, University of Turku, Turku, Finland
[3]Department of Public Health, University of Helsinki, Helsinki, Finland
[4]Department of Public Health, Clinical Research Centre, Turku University Hospital, University of Turku, Turku, Finland
[5]Department of Health Centre of Raisio, Raisio Municipal Health Care and Social Services, Raisio, Finland
[6]Department of Epidemiology and Public Health, University College London, London, UK
[7]Department of Public Health, University of Helsinki, Helsinki, Finland
[8]Department of Public Health, University of Turku and Turku University Hospital and Finnish Institute of Occupational Health, Helsinki, Finland

Competing interests JK has received honoraria for lectures from Eli Lilly, Lundbeck, Wyeth, Pfizer (related to the subject matter of depression and psychoses), and has participated three international congresses or symposia with Janssen-Cilag, Lundbeck, and Pfizer. All other authors: none.

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Jyrki Korkeila, Raija Lietzen, Lauri H Sillanmäki, Päivi Rautava, Katariina Korkeila, Mika Kivimäki, Markku Koskenvuo and Jussi Vahtera

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