

**Childhood adversities and chronic conditions: Examination of mediators, recall bias and age at diagnosis**

Mashhood Ahmed Sheikh

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Health Services Research Unit, Department of Community Medicine, University of Tromsø, NO 9037 Tromsø, Norway

**Corresponding author:** Mashhood Ahmed Sheikh, Health Services Research Unit, Department of Community Medicine, University of Tromsø, 9037 Tromsø, Norway; Tel.: 0047-77620716; E-mail: [mashhood.a.sheikh@uit.no](mailto:mashhood.a.sheikh@uit.no); [senor\\_massao@hotmail.com](mailto:senor_massao@hotmail.com)

**Reprint request author:** Mashhood Ahmed Sheikh

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**Abbreviations:** CSES: childhood socioeconomic status; CA: childhood abuse; RR: relative risk; CI: cumulative inequality; CI: confidence interval; SE: standard error

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## **INTRODUCTION**

There is an increasing recognition that stressors in childhood may contribute to pathophysiological processes that can lead to several chronic conditions in later life (Danese et al. 2009). The allostatic load theory suggests that childhood adversities may permanently alter the neurobiological stress management systems (Björkenstam et al. 2015; Carroll et al. 2013). Previous studies have shown that childhood adversities are associated with long-term changes in the nervous, endocrine, and immune systems (Danese and McEwen 2012). In particular, there has been a great amount of research on how childhood socioeconomic status (CSES) and childhood abuse (CA) relate to chronic conditions in later life, and reviews have shown reasonable associations between these variables (Kalmakis and Chandler 2015; Pavalko and Caputo 2013; Spencer et al. 2013). Several previous studies have consistently shown that childhood adversities are associated with asthma (Exley et al. 2015), bronchitis (Springer et al. 2007), hypothyroid (Post et al. 2013), migraine (Post et al. 2013), and psychiatric disorders (Sheikh et al. 2014; Sheikh et al. 2016a; Sheikh et al. 2016b) in later life. These reports suggest there may be an early life stress-related etiology for these outcomes (Slopen et al. 2010). Other evidence suggests that childhood adversities are associated with stress dysregulation, immune dysfunction, and inflammation in later life (Yang et al. 2017), which may confer increased vulnerability to several chronic conditions (Bonaccio et al. 2017; Runsten et al. 2014).

The stress proliferation model (Pearlin et al. 2005) suggests that low CSES is a reflection of low parental SES, which can lead to secondary stressors such as CA, which, either along with or in place of CSES, can prompt chronic conditions in later life. A relationship between CSES and chronic conditions is of interest not only in its own right but also as a potential confounder of the relationship between CA and chronic conditions. The association between CA and chronic conditions may not be causal. It may instead be a function of shared risk

factors, such as CSES, parental history of chronic conditions, or other shared environmental factors (Plant et al. 2015). However, no previous study from Norway has shown the independent effect of CSES and CA on the prevalence of asthma, bronchitis, hypothyroid, migraine, and psychiatric disorders in later life.

Despite the growing interest in assessing the long-term influence of CSES, the mediating mechanisms by which CSES affects chronic conditions remain unclear. Most previous studies assessed socioeconomic and behavioral factors in adulthood as mediators in the association between CSES and chronic conditions in adulthood (de Sousa Andrade et al. 2017; Frenz et al. 2017; Sheikh et al. 2014). However, when assessing mediation one must assume a lack of intermediary confounders (Sheikh et al. 2016b), i.e., that there are no variables (measured or unmeasured) affecting both the mediator(s) and the outcome that are affected by the exposure itself (Sheikh et al. 2016b). CSES may affect health in early adulthood, which may in turn affect both socioeconomic status and health later in adulthood (Sheikh et al. 2016b; Zajacova et al. 2015). Being raised in an environment with ample monetary and parental resources may expose children to experiences and styles of interacting that are beneficial for educational achievement and intellectual performance (Martinez-Pons 1996). By the same token, habits adopted in adulthood, such as smoking and alcohol intake, are likely influenced by parental behavioral patterns and by the social environment one is exposed to during adolescence (Campbell et al. 2016; Lorant et al. 2017; Sheikh et al. 2016a). Due to the long time period between CSES and the development of health-related life style (e.g., smoking and alcohol intake) and adult socioeconomic status, many potential intermediary confounders may be present (Sheikh et al. 2014; Sheikh et al. 2016b), making the ‘no intermediary confounding’ assumption difficult to satisfy. Such is the case when assessing mediators from adulthood in the association between CSES and chronic conditions in later life.

The cumulative inequality (CI) theory proposes that even if genetic predispositions are accounted for, those with adverse childhood experiences have a higher risk of experiencing subsequent adversities (Ferraro and Shippee 2009). A key axiom in the CI theory is that “disadvantage increases exposure to risk...” (Ferraro and Shippee 2009, p. 335). As Hertzman and Boyce noted, “social causation is iterative and recursive... in which one traumatic event follows from others, giving rise over time to intensely negative and stressful social contexts” (Hertzman and Boyce 2010, p. 331). Previous studies have shown that children from low socioeconomic backgrounds are at a higher risk of experiencing CA (Ono and Honda 2017; Romens et al. 2015), and CA may have a long-term impact on chronic conditions (Ni et al. 2016; Sheikh et al. 2016b). In this way, CSES may influence chronic conditions partly through CA (i.e., mediation). However, a literature search revealed that only a few previous studies (Danese et al. 2009; Goosby 2013; Oshio et al. 2013; Park et al. 2013; Sheikh et al. 2016b) have assessed the mediating role of CA in the association between CSES and chronic conditions. In this study, the association between CSES and prevalence of the chronic conditions asthma, bronchitis, hypothyroid, migraine, and psychiatric disorders was assessed, as well as the mediating role of CA in these associations. Furthermore, some previous studies suggest that childhood adversities may affect health more at younger ages (Campbell et al. 2016). Therefore, the associations between CSES, CA, and chronic conditions, stratified by median age at diagnosis were also assessed.

Retrospective reporting of CSES and CA might be subject to differential recall bias, and retrieval bias among those with psychiatric disorders (Fisher et al. 2009; Sheikh et al. 2016b). Similarly, the associations between CSES, CA and chronic conditions may be influenced by state of mind and mood based on respondent’s mental health (Hepp et al. 2006; Sheikh et al. 2016b). For instance, respondents with certain psychiatric disorders may have a tendency to form rather cynical and pessimistic perceptions of their childhood, but this perception does

not necessarily mean that their CSES was low or that they were abused in childhood (Sheikh et al. 2016b). Therefore, we also performed sensitivity analysis in which we controlled for self-reported diagnosis of psychiatric disorders.

## **METHODS**

### **Study population**

The Tromsø Study is a longitudinal prospective cohort study which contains data from 40,051 individuals, and its participants are considered representative of the adult population residing in the municipality of Tromsø (Jacobsen et al. 2012). Between 1974 and 2007-2008, six waves of the Tromsø Study were conducted (referred to as Tromsø I-VI) (Jacobsen et al. 2012). Tromsø IV took place in 1994-1995 (participation rate: 77%), and Tromsø VI took place in 2007-2008 (participation rate: 65.7%).

The current analyses are based on the 10,325 individuals who participated in both Tromsø IV and Tromsø VI. The study sample included respondents aged 25-74 years at Tromsø IV and 38-87 years at Tromsø VI. All respondents provided written informed consent after receiving a complete description of the Tromsø Study.

### **Study variables**

#### *Exposure (childhood socioeconomic status):*

Self-rated childhood financial condition was used as the indicator of CSES, and was measured in the Tromsø IV questionnaire by the question, “How was your family's financial situation during childhood?” on a 4-point scale (1 = very good, 2 = good, 3 = difficult, 4 = very difficult). Those who answered very good or good were considered to have high CSES, while those who answered difficult or very difficult were considered to have low CSES. The reliability of CSES (between Tromsø IV and Tromsø VI) was good (Kappa: 0.61, 95% confidence interval [CI]: 0.59, 0.63) in this sample (Sheikh et al. 2016b).

#### *Mediator (childhood abuse):*

Self-reported information on CA was collected in the Tromsø VI questionnaire by two questions: “Have you over a long period experienced any of the following? (as a child)”. The possible responses included: i) ‘Being tormented, or threatened with violence’; and ii) ‘Being beaten, kicked, or the victim of other types of violence’. Respondents could tick one or both responses. CA showed an acceptable degree of internal reliability in this sample (Cronbach’s alpha: 0.67, mean inter-item correlation: 0.50). Using responses to both questions, a separate cumulative variable of CA was constructed as: 0 = not exposed to CA, 1 = exposed to one CA (some), and 2 = exposed to both CAs (severe).

#### *Outcomes: chronic conditions*

Self-reported diagnoses from cohort studies in Norway are fairly reliable (Sheikh et al. 2016c) and valid (Engstad et al. 2000; Falkegård et al. 2015; Rylander et al. 2014). The questions on self-reported diagnosis of asthma, bronchitis, hypothyroid, migraine, and psychiatric disorders were included in the Tromsø VI questionnaire; there was a separate question for each chronic condition: *Do you have, or have you had asthma/ bronchitis/hypothyroid/ migraine/psychiatric disorders?*

#### *Confounders (Tromsø IV)*

The potential confounding variables age, gender, living in Norway at age 1 year (yes, no), exposure to passive smoke in childhood (yes, no), mother’s/father’s history of psychiatric disorders, parental history of heart attack, angina pectoris, cerebral stroke/brain hemorrhage, osteoporosis, stomach/duodenal ulcer, asthma, diabetes, and dementia were chosen based on *a priori* knowledge of the association between the exposure, mediator, and outcomes under study (Sheikh et al. 2016b; Ukawa et al. 2017). Valid information on age and gender was obtained from Statistics Norway by using the unique personal identification number of each

participant. The test-retest reliability (between Tromsø IV and Tromsø VI) of mother's history of psychiatric disorders and father's history of psychiatric disorders in this sample were Kappa: 0.57 (95% CI: 0.52, 0.62) and Kappa: 0.61 (95% CI: 0.53, 0.69), respectively. The test-retest reliability (between Tromsø IV and Tromsø VI) of exposure to passive smoke in childhood was good (Kappa: 0.76, 95% CI: 0.74, 0.84) in this sample.

### **Statistical analysis**

All analyses were conducted using Stata version 14. Multiple imputation (with chained equations) was used, and one hundred multiple datasets were generated. A comparison between the complete-case (excluding missing) and the imputed dataset is presented with proportions (%), and mean (standard error) (Table 1).

The comorbidity between asthma, bronchitis, hypothyroid, migraine, and psychiatric disorders was assessed by Poisson regression analysis. Relative risks (RRs) and their corresponding 95% CIs are presented (Table 2). The association between all covariates and CA, and between all covariates and chronic conditions was assessed by Poisson regression analysis with a robust error variance. All statistically significant ( $p < 0.05$ ) associations are presented in Table 3 and Table 4. The remaining variables that were not significantly ( $p > 0.05$ ) associated with CA and chronic conditions, were included in all models as confounding variables (Table 3 and Table 4). No statistically significant multiplicative interactions were observed between CSES, CA, gender, and age at diagnosis in this sample.

### **Assessing recall bias due to respondent's mental health**

The % attenuation in the estimates of the association between all self-reported covariates and CA after controlling for self-reported diagnosis of psychiatric disorders is presented in Table 3. The % attenuation in estimates of the association between self-reported covariates and



chronic conditions after controlling for the self-reported diagnosis of psychiatric disorders is presented in Table 4.

### **Assessing the influence of CSES and CA on chronic conditions stratified by age at diagnosis**

We divided the cases in two groups by median age at diagnosis for each outcome, and assessed the associations between CSES, CA, and chronic conditions (Supplementary material Table 1). The respondents that reported age at diagnosis other than the selected age at diagnosis range (below or above the median age at diagnosis), were excluded from the analysis, to avoid comparing the cases within the range with other cases (see Supplementary material Table 1).

### **Assessing direct and indirect effects (via childhood abuse) of childhood socioeconomic status on chronic conditions**

Mediation was assessed with the difference-in-coefficients method, assuming no exposure-mediator multiplicative interaction (Sheikh et al. 2016a; Sheikh et al. 2016b). No statistically significant ( $p < 0.05$ ) multiplicative interaction between CSES and CA was observed in this sample. Since the prevalence of asthma, hypothyroid, migraine, and psychiatric disorders was not rare ( $\geq 5\%$ ), odds ratios (logistic regression) are not suitable for assessing mediation (Sheikh et al. 2014; Sheikh et al. 2016a). Therefore, Poisson regression analysis (RR) with robust error variance was used to estimate the total ( $RR_{\text{Total Effect}}$ ) and direct effect ( $RR_{\text{Direct Effect}}$ ) of CSES on chronic conditions.

CA was included in the models to assess the indirect effect and the proportion of mediated effect (%). Four estimates are presented: total effects (adjusted for confounding variables), direct effects (adjusted for confounding variables and CA), indirect effects, and proportion

mediated (%). 95% CIs were calculated for all estimates using a bias-corrected accelerated bootstrap method with 5000 re-samplings.

## RESULTS

Among the 10,325 individuals in this study sample, the majority were aged 45 years or older (61.9%) at Tromsø IV and 54% were women. One-third (33.6%) of the study sample reported having difficult or very difficult financial conditions in childhood; 6.4% reported being exposed to one CA, and 3.5% reported being exposed to both CAs (Table 1). The prevalence of chronic conditions was 9.9% for asthma, 4.8% for bronchitis, 9.5% for hypothyroid, 13.8% for migraine, and 9.3% for psychiatric disorders (Table 1).

In the fully-adjusted models, significant associations were found between asthma and bronchitis (adjusted RR=7.32, 95% CI: 6.26, 8.70), hypothyroid (adjusted RR=1.35, 95% CI: 1.14, 1.61), migraine (adjusted RR=1.26, 95% CI: 1.09, 1.46), and psychiatric disorders (adjusted RR=1.60, 95% CI: 1.35, 1.88) (Table 2). Bronchitis was associated with hypothyroid (adjusted RR=1.55, 95% CI: 1.26, 1.91), migraine (adjusted RR=1.45, 95% CI: 1.20, 1.76), and psychiatric disorders (adjusted RR=1.75, 95% CI: 1.39, 2.20). Similarly, significant associations were found between hypothyroid and migraine (RR=1.37, 95% CI: 1.19, 1.57), between hypothyroid and psychiatric disorders (adjusted RR=1.42, 95% CI: 1.18, 1.70); and between migraine and psychiatric disorders (adjusted RR=1.41, 95% CI: 1.21, 1.63) (Table 2).

Lower age and parental history of dementia were associated with CA (Table 3). Compared to men, women had a 58% higher risk of CA ( $p<0.01$ ) (Table 3). History of mother's psychiatric disorders (RR=1.56, 95% CI: 1.30, 1.88) was also associated with CA ( $p<0.05$ ) (Table 3). Regarding the influence of CSES on CA, low CSES was associated with a 90% higher risk of CA (adjusted RR=1.90, 95% CI: 1.66, 2.18) (Table 3).

In order to estimate the extent of recall bias due to the mental health of the respondents, we adjusted for self-reported diagnosis of psychiatric disorders (Table 3). Only some (3.98%,  $p<0.05$ ) of the association between CSES and CA was driven by respondent's mental health

(Table 3). A substantial proportion of the association between mother's history of psychiatric disorders (20.57%,  $p < 0.05$ ), father's history of psychiatric disorders (41.42%,  $p < 0.05$ ), and CA was driven by respondent's mental health (Table 3). This suggests that respondent's psychiatric disorders may be a crude proxy for genetic disposition of psychiatric disorders.

CA was associated with a 16% higher risk of asthma (adjusted RR=1.16, 95% CI: 1.03, 1.31), a 48% higher risk of bronchitis (adjusted RR=1.48, 95% CI: 1.26, 1.74), a 23% higher risk of hypothyroid (adjusted RR=1.23, 95% CI: 1.07, 1.40), a 21% higher risk of migraine (adjusted RR=1.21, 95% CI: 1.10, 1.33), and a 58% higher risk of psychiatric disorders (adjusted RR=1.58, 95% CI: 1.44, 1.73) in later life (Table 4).

Compared to women, men had a higher risk of asthma, hypothyroid, migraine and psychiatric disorders ( $p < 0.05$ ) (Table 4). Parental history of asthma was associated with an increased risk of asthma and bronchitis ( $p < 0.05$ ) (Table 4). History of mother's psychiatric disorders and parental history of stomach or duodenal ulcer was associated with increased risk of migraine and psychiatric disorders ( $p < 0.05$ ) (Table 4). Similarly, history of father's psychiatric disorders and parental history of diabetes was associated with respondent's psychiatric disorders ( $p < 0.05$ ) (Table 4).

Controlling for self-reported diagnosis of psychiatric disorders suggests that only 5.54-8.71% ( $p < 0.05$ ) of the associations between CSES and asthma, bronchitis, hypothyroid, and migraine were driven by respondent's mental health (Table 4). Similarly, 9.51-19.52% ( $p < 0.05$ ) of the associations between CA and asthma, bronchitis, hypothyroid, and migraine were driven by respondent's mental health (Table 4).

Stratifying the associations between CSES and chronic conditions by median age at diagnosis showed that the associations were stronger among participants whose asthma, migraine, and psychiatric disorders were diagnosed earlier in life (Supplementary material

Table 1). However, for bronchitis and hypothyroid, the associations with CSES were stronger among those diagnosed later in life (Supplementary material Table 1). Similarly, the associations between CA and bronchitis, hypothyroid, and psychiatric disorders were stronger among those diagnosed earlier in life (Supplementary material Table 1). Furthermore, the association between CA and migraine was stronger among those diagnosed later in life (age at diagnosis: > 23 years) (Supplementary material Table 1). The association between CA and asthma remained the same (RR= 1.21,  $p<0.05$ ) for both age groups (Supplementary material Table 1).

### **Direct and indirect effect of childhood socioeconomic status on asthma, bronchitis, hypothyroid, migraine, and psychiatric disorders in later life**

Low CSES was associated with a 19% higher risk of asthma (RR<sub>Total effect</sub>=1.19, 95% CI: 1.09, 1.30), a 27% higher risk of bronchitis (RR<sub>Total effect</sub>=1.27, 95% CI: 1.17, 1.30), a 18% higher risk of hypothyroid (RR<sub>Total effect</sub>=1.18, 95% CI: 1.05, 1.31), a 18% higher risk of migraine (RR<sub>Total effect</sub>=1.18, 95% CI: 1.13, 1.22), and a 32% higher risk of psychiatric disorders (RR<sub>Total effect</sub>=1.32, 95% CI: 1.15, 1.40) (Table 5).

Decomposition of total effects showed that there was a direct as well as an indirect effect of CSES on chronic conditions (Table 5). CA mediated 10.86% (95% CI: 2.51, 17.54) of the association between CSES and asthma, 16.65% (95% CI: 11.44, 23.80) of the association between CSES and bronchitis, 9.58% (95% CI: 2.83, 31.59) of the association between CSES and hypothyroid, 12.58% (95% CI: 8.70, 14.48) of the association between CSES and migraine, and 25.06% (95% CI: 17.70, 44.10) of the association between CSES and psychiatric disorders (Table 5).

Estimating the associations separately for men and women showed that the associations (total effects) between CSES, and asthma and bronchitis were stronger for men (Supplementary material Table 2). However, the associations (total effects) between CSES, and migraine and psychiatric disorders were stronger for women (Supplementary material Table 2).

Estimating the associations separately for men and women showed that the direct effects of CSES on asthma, migraine and psychiatric disorders were stronger for women (Supplementary material Table 2). However, the direct effect of CSES on bronchitis was stronger for men (Supplementary material Table 2). The indirect effects of CSES on asthma, bronchitis, migraine, and psychiatric disorders were stronger among men (Supplementary material Table 2). CA mediated 17.97-31.35% ( $p < 0.05$ ) of the association between CSES and chronic conditions among men (Supplementary material Table 2). However, among women, CA mediated 5.62-24.09% ( $p < 0.05$ ) of the association between CSES and chronic conditions (Supplementary material Table 2).

## **DISCUSSION**

These findings suggest that CA mediates the associations between CSES and chronic conditions. Compared to men, women were at a lower risk of asthma, hypothyroid, migraine, and psychiatric disorders. However, the associations between CSES and asthma, migraine, and psychiatric disorders were stronger among women. On the contrary, the association between CSES and bronchitis was stronger among men. Due to the low prevalence of some outcomes and substantial differences in the distributions of age at diagnosis between the outcomes, we used the median age at outcome diagnosis as the cut-off. The results of this study suggest that negative effect of CSES may be more detrimental at younger ages for the chronic conditions asthma, migraine, and psychiatric disorders. Similarly, CA may have a stronger effect on bronchitis, hypothyroid, and psychiatric disorders at younger ages.

The two childhood adversities considered in this paper (CSES and CA) are independent predictors (adjusted for each other) of chronic conditions in later life. This shows that they cannot be used as proxies for each other. More research is needed to understand how each of these childhood adversities relate to other chronic conditions. The associations between self-reported parental history of psychiatric disorders and self-reported CA were attenuated substantially after adjusting for the self-reported diagnosis of psychiatric disorders. This may suggest that some of the association between parental history of psychiatric disorders and CA is driven by a respondent's perceptions about parental psychopathology and abuse suffered in childhood. Adjusting for self-reported diagnosis of psychiatric disorders significantly attenuated the associations between CSES, CA, asthma, bronchitis, hypothyroid, and migraine. This suggests that respondent's state of mind and mood (via mental health) does play a minor role in the recall of CSES and CA (Sheikh et al. 2016b).

Much of the research on the effects of CA has focused on mental health (Sheikh et al. 2016a; Sheikh et al. 2016b). The results of this study showed that individuals with a history of

CA are also at a higher risk of developing physical chronic conditions in later life. Other studies (Björkenstam et al. 2015; Mock and Arai 2011) combined the variables of socioeconomic adversity and CA, by summing the number of childhood adversities. However, this type of scoring makes it impossible to disentangle the influence of socioeconomic and psychosocial disadvantage on health outcomes (Sheikh et al. 2016a; Sheikh et al. 2016b). Some population-based studies (Greenfield and Marks 2009; Mock and Arai 2011) have focused on the impact of CA on chronic conditions by assigning a score based on the number of chronic conditions, but again, this approach makes it difficult to establish whether CA is a risk factor for any specific chronic condition.

Although the Tromsø Study participants are considered representative of the age-group-specific populations residing in the municipality of Tromsø, Norway, the current sample may not be representative, since it includes only the respondents participating in both Tromsø IV and Tromsø VI. Previous estimates of the prevalence of CA in studies from Norway (Myhre et al. 2014; Sheikh et al. 2016a; Sørbo et al. 2013; Thoresen et al. 2015) are slightly lower than those observed in this study (6.4%), which may be partly due to selection bias. There is likely a substantial amount of unmeasured heterogeneity in the data, which in turn could lead to underestimated associations. Some of the potential exposure-outcome and mediator-outcome confounders that are missing in the analysis are parental history of bronchitis, hypothyroid, and migraine.

The mismeasurement, under-reporting, or under-ascertainment of CA would likely bias the estimates of direct effect upwards; while the indirect effect and ‘proportion mediated’ estimates would be biased downwards (Sheikh et al. 2016b). Therefore, the true value of indirect effects could be substantially higher (assuming that there is an indirect effect) (Sheikh et al. 2016b). The precise timing of CSES and CA was not measured and the temporal sequence between CSES and CA is assumed in this study.



The strengths of this study are its longitudinal design, large sample size, and the estimates of two different childhood adversities, CSES and CA, on the prevalence of five chronic conditions in later life.

This study contributes to the growing literature (Oshio et al. 2013; Park et al. 2013; Post et al. 2013; Spencer et al. 2013; Yang et al. 2017) on the assessment of life course pathways from CSES to chronic conditions in later life. The findings of this study suggest that low CSES is associated with a higher risk of asthma, bronchitis, hypothyroid, migraine, and psychiatric disorders in later life, and that CA mediates a minor proportion of these effects. Moreover, a minor proportion of these associations was driven by recall bias.

**Conflict of interest:** none

**Ethical approval:** This investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The Tromsø Study has been approved by the Regional Committee for Medical and Health Research Ethics, the Data Inspectorate, and the Norwegian Directorate of Health. Written informed consent was obtained from all individual participants included in the study.

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Table 1. General characteristics of the sample (Tromsø, Norway, 1994/1995-2007/2008).

Characteristics		Complete-	Imputed
		case dataset	dataset
		n (%)	(%)
Age (at baseline)	mean (SE)	47.03 (0.12)	-. <sup>b</sup>
	25-34	1987 (19.2)	-. <sup>b</sup>
	35-44	1944 (18.8)	-. <sup>b</sup>
	45-54	3630 (35.2)	-. <sup>b</sup>
	55-64	2016 (19.5)	-. <sup>b</sup>
	65-74	748 (7.2)	-. <sup>b</sup>
Gender	Men	4754 (46.0)	-. <sup>b</sup>
	Women	5571 (54.0)	-. <sup>b</sup>
History of psychiatric disorders, mother	Yes	676 (6.5)	-. <sup>b</sup>
	No	9649 (93.5)	-. <sup>b</sup>
History of psychiatric disorders, father	Yes	256 (2.5)	-. <sup>b</sup>
	No	10069 (97.5)	-. <sup>b</sup>
Parental history of Asthma	Yes	1164 (11.3)	-. <sup>b</sup>
	No	9161 (88.7)	-. <sup>b</sup>
Parental history of heart attack	Yes	1477 (14.3)	-. <sup>b</sup>
	No	8848 (85.7)	-. <sup>b</sup>
Parental history of angina pectoris	Yes	2360 (22.9)	-. <sup>b</sup>
	No	7965 (77.1)	-. <sup>b</sup>
Parental history of cerebral stroke or brain hemorrhage	Yes	2292 (22.2)	-. <sup>b</sup>
	No	8033 (77.8)	-. <sup>b</sup>
Parental history of osteoporosis	Yes	981 (9.5)	-. <sup>b</sup>
	No	9344 (90.5)	-. <sup>b</sup>
Parental history of stomach or duodenal ulcer	Yes	1550 (15.0)	-. <sup>b</sup>
	No	8775 (84.9)	-. <sup>b</sup>
Parental history of diabetes	Yes	1623 (15.7)	-. <sup>b</sup>
	No	8702 (84.3)	-. <sup>b</sup>
Parental history of dementia	Yes	1177 (11.4)	-. <sup>b</sup>
	No	9148 (88.6)	-. <sup>b</sup>
Exposure to passive smoke in childhood <sup>a</sup>	Yes	7589 (73.5)	73.5
	No	2731 (26.5)	26.5
Living in Norway at age 1 <sup>a</sup>	Yes	8962 (97.9)	97.9
	No	192 (2.1)	2.1
Childhood socioeconomic status <sup>a</sup>	Very good	352 (3.7)	3.8
	Good	5906 (62.6)	62.8
	Difficult	2946 (31.2)	31.1
	Very difficult	228 (2.4)	2.4
Childhood abuse	None	9310 (90.2)	-. <sup>b</sup>
	One	658 (6.4)	-. <sup>b</sup>
	Both	357 (3.5)	-. <sup>b</sup>
Asthma (median age at diagnosis: 40 years) <sup>a</sup>	Yes	992 (9.9)	10.0
	No	9065 (90.1)	90.0
Bronchitis (median age at diagnosis: 55 years) <sup>a</sup>	Yes	479 (4.8)	5.0
	No	9559 (95.2)	95.0
Hypothyroid (median age at diagnosis: 52 years) <sup>a</sup>	Yes	947 (9.5)	9.6
	No	9042 (90.5)	90.4
Migraine (median age at diagnosis: 23 years) <sup>a</sup>	Yes	1385 (13.8)	13.8
	No	8660 (86.2)	86.2



Psychiatric disorders (median age at diagnosis: 40 years) <sup>a</sup>	Yes	926 (9.3)	9.3
	No	9070 (90.7)	90.7

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<sup>a</sup>The numbers for some variables do not add up to 10,325 due to missing values.

<sup>b</sup>There were no missing values, so no imputations were made for these variables.

SE=standard error

1 Table 2. Comorbidity between asthma, bronchitis, hypothyroid, migraine, and psychiatric disorders (Tromsø, Norway, 2007/2008).

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		Dependent variable				
		RR (95% CI) <sup>a</sup>	RR (95% CI) <sup>a</sup>	RR (95% CI) <sup>a</sup>	RR (95% CI) <sup>a</sup>	RR (95% CI) <sup>a</sup>
Independent variable		Asthma	Bronchitis	Hypothyroid	Migraine	Psychiatric disorders
	<b>Asthma</b>	1.00	7.32 (6.26, 8.70)	1.35 (1.14, 1.61)	1.26 (1.09, 1.46)	1.60 (1.35, 1.88)
	<b>Bronchitis</b>	5.25 (4.63, 5.97)	1.00	1.55 (1.26, 1.91)	1.45 (1.20, 1.76)	1.75 (1.39, 2.20)
	<b>Hypothyroid</b>	1.36 (1.14, 1.62)	1.62 (1.28, 2.05)	1.00	1.37 (1.19, 1.57)	1.42 (1.18, 1.70)
	<b>Migraine</b>	1.29 (1.10, 1.51)	1.56 (1.24, 1.97)	1.38 (1.19, 1.60)	1.00	1.41 (1.21, 1.63)
	<b>Psychiatric disorders</b>	1.59 (1.35, 1.88)	1.87 (1.46, 2.41)	1.40 (1.17, 1.68)	1.38 (1.20, 1.58)	1.00

3 <sup>a</sup>Adjusted for age, gender, childhood socioeconomic status, childhood abuse, exposure to passive smoke in childhood, living in Norway at age 1 year, parental history  
4 of psychiatric disorders, heart attack, angina pectoris, cerebral stroke/brain hemorrhage, osteoporosis, stomach/duodenal ulcer, asthma, diabetes, and dementia.  
5 RR=relative risk, CI=confidence interval

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18 Table 3. Association between childhood socioeconomic status and childhood abuse (Tromsø, Norway, 1994/1995-2007/2008).

		Childhood abuse						% attenuation between Model 2 & Model 3 % (95% CI)
		Model 1		Model 2		Model 3		
		RR	95% CI	RR <sup>b,d</sup>	95% CI	RR <sup>c,d</sup>	95% CI	
<b>Childhood socioeconomic status</b>	Low	1.69 <sup>a</sup>	1.49, 1.93	1.95	1.63, 2.34	1.90	1.66, 2.18	3.98 (1.88, 6.36)
<b>Age</b>		-	-	0.96	0.96, 0.97	0.96	0.96, 0.97	- <sup>e</sup>
<b>Gender</b>	Female	-	-	1.51	1.28, 1.77	1.58	1.40, 1.79	- <sup>e</sup>
<b>History of psychiatric disorders, mother</b>	Yes	-	-	1.75	1.37, 2.24	1.56	1.30, 1.88	20.57 (15.82, 34.13)
<b>History of psychiatric disorders, father</b>	Yes	-	-	1.38	0.92, 2.07	1.21	0.89, 1.64	41.42 (30.45, 95.32)
<b>Parental history of dementia</b>	Yes	-	-	1.36	1.08, 1.71	1.35	1.13, 1.61	ns
<b>Self-reported diagnosis of psychiatric disorders</b>	Yes	-	-	-	-	2.11	1.80, 2.46	-

19 <sup>a</sup> Unadjusted20 <sup>b</sup> All estimates are adjusted for age, gender, exposure to passive smoke in childhood, living in Norway at age 1 year, childhood socioeconomic  
21 status, parental history of psychiatric disorders, heart attack, angina pectoris, cerebral stroke/brain hemorrhage, osteoporosis,  
22 stomach/duodenal ulcer, asthma, diabetes, and dementia.23 <sup>c</sup> All estimates are adjusted for age, gender, exposure to passive smoke in childhood, living in Norway at age 1 year, childhood socioeconomic  
24 status, parental history of psychiatric disorders, heart attack, angina pectoris, cerebral stroke/brain hemorrhage, osteoporosis,  
25 stomach/duodenal ulcer, asthma, diabetes, dementia, and self-reported diagnosis of psychiatric disorders.26 <sup>d</sup> The association between exposure to passive smoke in childhood, living in Norway at age 1 year, parental history of heart attack, angina  
27 pectoris, cerebral stroke/brain hemorrhage, osteoporosis, stomach/duodenal ulcer, asthma, diabetes, and childhood abuse was not statistically  
28 significant ( $p > 0.05$ ), and adjusting for respondent's psychiatric disorders did not significantly attenuated the estimates. Therefore, the  
29 estimates are not presented.30 <sup>e</sup> The % attenuation was not estimated for age and gender, because these variables were not self-reported.

31 Childhood socioeconomic status was measured in Tromsø IV (1994-95), while childhood abuse was measured in Tromsø VI (2007-2008).

32 RR=relative risk, CI=confidence interval

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36 Table 4. Association between covariates and chronic conditions (Tromsø, Norway,  
37 1994/1995-2007/2008).

		<b>Asthma</b>		
		Model 1	Model 2	% attenuation between Model 1 vs Model 2
		RR (95%)	RR (95%)	% (95% CI)
<b>Childhood socioeconomic status</b>	Low	1.19 (1.04, 1.35) <sup>a</sup>	1.17 (1.03, 1.33) <sup>f</sup>	7.91 (1.18-14.24)
<b>Childhood abuse</b>	-	1.20 (1.07, 1.36) <sup>a,i</sup>	1.16 (1.03, 1.31) <sup>f</sup>	19.52 (13.01, 72.87)
<b>Age</b>	-	1.01 (1.01, 1.01) <sup>a</sup>	1.01 (1.01, 1.01) <sup>f</sup>	- <sup>h</sup>
<b>Gender</b>	Female	0.76 (0.68, 0.86) <sup>a</sup>	0.79 (0.70, 0.89) <sup>f</sup>	- <sup>h</sup>
<b>Parental history of Asthma</b>	Yes	2.72 (2.39, 3.10) <sup>a</sup>	2.71 (2.38, 3.08) <sup>f</sup>	0.62 (0.55, 1.00)
<b>Parental history of dementia</b>	Yes	0.79 (0.65, 0.97) <sup>a</sup>	0.80 (0.65, 0.97) <sup>f</sup>	ns <sup>g</sup>
<b>Psychiatric disorders</b>	Yes	-	1.59 (1.35, 1.88) <sup>a</sup>	-
		<b>Bronchitis</b>		
<b>Childhood socioeconomic status</b>	Low	1.24 (1.03, 1.50) <sup>b</sup>	1.22 (1.01, 1.48) <sup>f</sup>	8.71 (4.62, 15.03)
<b>Childhood abuse</b>	-	1.54 (1.32, 1.81) <sup>b,i</sup>	1.48 (1.26, 1.74) <sup>f</sup>	9.51 (6.00, 16.60)
<b>Age</b>	-	1.05 (1.05, 1.06) <sup>b</sup>	1.05 (1.05, 1.06) <sup>f</sup>	- <sup>h</sup>
<b>Parental history of Asthma</b>	Yes	2.01 (1.62, 2.50) <sup>b</sup>	1.99 (1.60, 2.48) <sup>f</sup>	ns <sup>g</sup>
<b>Psychiatric disorders</b>	Yes	-	1.87 (1.46, 2.41) <sup>b</sup>	-
		<b>Hypothyroid</b>		
<b>Childhood socioeconomic status</b>	Low	1.17 (1.03, 1.34) <sup>c</sup>	1.16 (1.02, 1.32) <sup>f</sup>	5.54 (3.11, 10.61)
<b>Childhood abuse</b>	-	1.26 (1.10, 1.44) <sup>c,i</sup>	1.23 (1.07, 1.40) <sup>f</sup>	11.44 (5.86, 25.18)
<b>Age</b>	-	1.03 (1.03, 1.04) <sup>c</sup>	1.03 (1.03, 1.04) <sup>f</sup>	- <sup>h</sup>
<b>Gender</b>	Female	0.31 (0.26, 0.36) <sup>c</sup>	0.31 (0.27, 0.37) <sup>f</sup>	- <sup>h</sup>
<b>Psychiatric disorders</b>	Yes	-	1.40 (1.17, 1.68) <sup>c</sup>	-
		<b>Migraine</b>		
<b>Childhood socioeconomic status</b>	Low	1.17 (1.05, 1.31) <sup>d</sup>	1.16 (1.04, 1.30) <sup>f</sup>	5.98 (4.22, 8.06)
<b>Childhood abuse</b>	-	1.24 (1.13, 1.36) <sup>d,i</sup>	1.21 (1.10, 1.33) <sup>f</sup>	12.60 (7.44, 19.39)
<b>Age</b>	-	0.99 (0.99, 0.99) <sup>d</sup>	0.99 (0.99, 0.99) <sup>f</sup>	- <sup>h</sup>
<b>Gender</b>	Female	0.36 (0.32, 0.41) <sup>d</sup>	0.37 (0.33, 0.42) <sup>f</sup>	- <sup>h</sup>
<b>History of psychiatric disorders, mother</b>	Yes	1.23 (1.04, 1.45) <sup>d</sup>	1.17 (0.99, 1.39) <sup>f</sup>	23.07 (14.16, 66.17)
<b>Parental history of stomach or duodenal ulcer</b>	Yes	1.26 (1.12, 1.42) <sup>d</sup>	1.25 (1.11, 1.41) <sup>f</sup>	3.25 (1.57, 7.05)
<b>Psychiatric disorders</b>	Yes	-	1.38 (1.20, 1.58) <sup>d</sup>	-
		<b>Psychiatric disorders</b>		
<b>Childhood socioeconomic status</b>	Low	1.23 (1.09, 1.32) <sup>e</sup>	-	-
<b>Childhood abuse</b>	-	1.58 (1.44, 1.73) <sup>e,i</sup>	-	-
<b>Age</b>	-	0.99 (0.98, 0.99) <sup>e</sup>	-	-
<b>Gender</b>	Female	0.62 (0.54, 0.71) <sup>e</sup>	-	-
<b>History of psychiatric disorders, mother</b>	Yes	2.21 (1.89, 2.59) <sup>e</sup>	-	-
<b>History of psychiatric disorders, father</b>	Yes	2.12 (1.70, 2.65) <sup>e</sup>	-	-
<b>Parental history of stomach or duodenal ulcer</b>	Yes	1.20 (1.03, 1.40) <sup>e</sup>	-	-
<b>Parental history of diabetes</b>	Yes	1.17 (1.01, 1.37) <sup>e</sup>	-	-
<b>Living in Norway at age 1</b>	Yes	0.68 (0.48, 0.94) <sup>e</sup>	-	-

38 <sup>a</sup> Adjusted for exposure to passive smoke in childhood, living in Norway at age 1 year, parental history of  
39 psychiatric disorders, heart attack, angina pectoris, cerebral stroke/brain hemorrhage, osteoporosis,  
40 stomach/duodenal ulcer, and diabetes.

41 <sup>b</sup> Adjusted for gender, exposure to passive smoke in childhood, living in Norway at age 1 year, parental history  
42 of psychiatric disorders, heart attack, angina pectoris, cerebral stroke/brain hemorrhage, osteoporosis,  
43 stomach/duodenal ulcer, diabetes, and dementia.

44 <sup>c</sup> Adjusted for exposure to passive smoke in childhood, living in Norway at age 1 year, parental history of  
45 psychiatric disorders, heart attack, angina pectoris, cerebral stroke/brain hemorrhage, osteoporosis,  
46 stomach/duodenal ulcer, asthma, diabetes, and dementia.

47 <sup>d</sup> Adjusted for exposure to passive smoke in childhood, living in Norway at age 1 year, father's history of  
48 psychiatric disorders, parental history of heart attack, angina pectoris, cerebral stroke/brain hemorrhage,  
49 osteoporosis, asthma, diabetes, and dementia.

50 <sup>e</sup> Adjusted for exposure to passive smoke in childhood, parental history of heart attack, angina pectoris, cerebral  
51 stroke/brain hemorrhage, osteoporosis, asthma, and dementia.

52 <sup>f</sup> Adjusted for age, gender, exposure to passive smoke in childhood, living in Norway at age 1 year, parental  
53 history of psychiatric disorders, heart attack, angina pectoris, cerebral stroke/brain hemorrhage, osteoporosis,  
54 stomach/duodenal ulcer, asthma, diabetes, dementia, and self-reported diagnosis of psychiatric disorders.

55 <sup>g</sup> The % attenuation is not presented when  $RR < 1.00$  in Model 1 or Model 2, or when the estimate in Model 2  
56 was greater than the estimate in Model 1, or when the % attenuation was not statistically significant ( $p > 0.05$ )

57 <sup>h</sup> The % attenuation was not estimated for age and gender, because these variables were not self-reported.

58 <sup>i</sup> Childhood abuse: 0 = 9310 (90.2%), 1 = 658 (6.4%), and 2 = 357 (3.5%).  
59 RR=relative risk, CI=confidence interval

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65 Table 5. Direct and indirect effect (via childhood abuse) of childhood socioeconomic status on chronic conditions (Tromsø, Norway, 1994/1995-  
66 2007/2008).

	Total effect		Direct effect <sup>c</sup>		Indirect effect <sup>d</sup>		Proportion mediated <sup>e</sup>	
	RR	95% CI	RR	95% CI	RR	95% CI	%	95% CI
Childhood socioeconomic status <sup>f</sup>	<b>Asthma<sup>a</sup></b>							
	1.19	1.09, 1.30	1.17	1.03, 1.33	1.02	1.01, 1.03	10.86	2.51, 17.54
	<b>Bronchitis<sup>a</sup></b>							
	1.27	1.17, 1.30	1.22	1.01, 1.48	1.04	1.04, 1.06	16.65	11.44, 23.80
	<b>Hypothyroid<sup>a</sup></b>							
	1.18	1.05, 1.31	1.16	1.02, 1.32	1.02	1.01, 1.02	9.58	2.83, 31.59
<b>Migraine<sup>a</sup></b>								
	1.18	1.13, 1.22	1.16	1.04, 1.30	1.02	1.01, 1.03	12.58	8.70, 14.48
<b>Psychiatric disorders<sup>b</sup></b>								
	1.32	1.15, 1.40	1.23	1.09, 1.32	1.07	1.06, 1.09	25.06	17.70, 44.10

67 <sup>a</sup> Adjusted for age, gender, exposure to passive smoke in childhood, living in Norway at age 1 year, parental history of psychiatric disorders, heart attack, angina  
68 pectoris, cerebral stroke/brain hemorrhage, osteoporosis, stomach/duodenal ulcer, asthma, diabetes, and dementia, and self-reported diagnosis of psychiatric  
69 disorders.

70 <sup>b</sup> Adjusted for age, gender, exposure to passive smoke in childhood, living in Norway at age 1 year, parental history of psychiatric disorders, heart attack, angina  
71 pectoris, cerebral stroke/brain hemorrhage, osteoporosis, stomach/duodenal ulcer, asthma, diabetes, and dementia.

72 <sup>c</sup> Adjusted for confounding variables + childhood abuse.

73 <sup>d</sup>  $\beta_{\text{Indirect effect}} = \beta_{\text{Total effect}} - \beta_{\text{Direct effect}}$

74 <sup>e</sup> The percentages attenuation shows the proportion of reduction between  $\beta_{\text{Total effects}}$  and  $\beta_{\text{Direct effects}}$ .

75 <sup>f</sup> Low (reference = high)

76 CA: 0 = 9310 (90.2%), 1 = 658 (6.4%), and 2 = 357 (3.5%).

77 Childhood socioeconomic status was measured in Tromsø IV (1994-95). Chronic conditions were measured in Tromsø VI (2007-2008).

78 RR=relative risk, CI=confidence interval

79