



Killing pain? A prospective population-based study on trauma exposure in childhood as predictor for frequent use of over-the-counter analgesics in young adulthood. The HUNT study

Monica Baumann-Larsen^{a,b,*}, John-Anker Zwart^{a,b}, Grete Dyb^{b,c}, Tore Wentzel-Larsen^{c,d}, Helle Stangeland^{b,c}, Kjersti Storheim^{a,e}, Synne Øien Stensland^{a,c}

^a Department of Research and Innovation, Division of Clinical Neuroscience, Oslo University Hospital, Oslo, Norway

^b Institute of Clinical Medicine, University of Oslo, Oslo, Norway

^c Norwegian Centre for Violence and Traumatic Stress Studies, Oslo, Norway

^d Centre for Child and Adolescent Mental Health, Eastern and Southern Norway, Oslo, Norway

^e Department of Rehabilitation Science and Health Technology, Oslo Metropolitan University, Oslo, Norway

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ABSTRACT

Frequent and increasing use of over-the-counter analgesics (OTCA) is a public health concern. Pain conditions and psychological distress are related to frequent OTCA use, and as exposure to potentially traumatic events (PTE) in childhood appears to increase risk of experiencing such symptoms, we aimed to assess childhood PTEs and related symptoms in adolescence as predictors for frequent OTCA use in young adulthood. Prospective population survey data were used ($n = 2947$, 59.1% female, 10–13 years follow-up). Exposure to PTEs, symptoms of post-traumatic stress, anxiety and depression, musculoskeletal pain and headache were assessed in adolescence (13–19 years). Use of OTCA was assessed in young adulthood (22–32 years) and use of OTCA to treat musculoskeletal pain and headache served as separate outcomes in ordinal logistic regression analyses. Overall, exposure to childhood PTEs, particularly direct interpersonal violence, was significantly and consistently related to more frequent use of OTCA to treat musculoskeletal pain and headaches in young adulthood. Adjusting for psychological symptoms and pain attenuated associations, indicating that these symptoms are of importance for the relationship between traumatic events and OTCA use. These findings emphasize the need to address symptomatology and underlying causes at an early age.

1. Introduction

Use of over-the-counter analgesics (OTCA) is common (Dale et al., 2015; Paulose-Ram et al., 2005; Samuelsen et al., 2015) and increasing (Koushede et al., 2011; Samuelsen et al., 2015; Sarganas et al., 2015) in general populations, and many young adults report frequent use (Koushede et al., 2011). Chronic pain and pain-related conditions are leading causes of disability and disease globally (Cohen et al., 2021) and are reported as the main reasons for OTCA use (Dale et al., 2015; Turunen et al., 2005). OTCA are considered safe within recommended doses for otherwise healthy young adults, however, frequent use can cause medication overuse headache and can contribute to the onset, maintenance or exacerbation of chronic pain (Luchting and Heyn, 2019; Parisien et al., 2022; Zwart et al., 2003a). Even within recommended doses,

OTCA use can severely impair kidney and liver function and gastrointestinal health in at-risk individuals (Donati et al., 2016; Lucas et al., 2019; Schjerning et al., 2020). High intake of easily available OTCA, including acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), causes the majority of medication poisonings, which have increased over the past decades and are often unintentional (Blieden et al., 2014; Shadman et al., 2022). Thus, restricted use is recommended, and the increasing frequency of use among young people poses a serious public health concern.

Behavioral patterns, including medication use patterns, are established at an early age (Andersen et al., 2009), and it is important to identify early predictors for frequent OTCA use in young adulthood. Early predictors may represent targets for timely interventions that can help adolescents escape adverse trajectories for OTCA use at an age

* Corresponding author at: Department of Research and Innovation, Division of Clinical Neuroscience, Oslo University Hospital, Oslo, Norway.

E-mail address: monica.baumann-larsen@studmed.uio.no (M. Baumann-Larsen).

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when change is still welcome and achievable (Sawyer et al., 2012). Previous research on OTCA use in adolescence has identified higher age, female sex and lower socioeconomic status as potential risk factors for more frequent use (Hansen et al., 2003; Kirkeby et al., 2014). Young people experiencing higher levels of psychological distress report using OTCA more frequently than their peers, and not explained by their reported pain, indicating that OTCA are also used to alleviate psychological distress (Algarni et al., 2021; Hansen et al., 2008; Jonassen et al., 2021; Koushede et al., 2011; 2012).

Recent studies on the co-occurrence of depression, anxiety and pain in young people have found that shared genetic and environmental factors may explain the co-occurrence, rather than mutual causation (Battaglia et al., 2020; Khan et al., 2020; Scaini et al., 2022). Exposure to potentially traumatic events (PTEs) may be one of the environmental factors of importance. PTEs represent a particularly important source of distress, and exposed adolescents commonly suffer from posttraumatic stress reactions and symptoms of depression, anxiety (McLaughlin et al., 2013; Turner et al., 2006), headache or musculoskeletal pain (Due et al., 2005; Stensland et al., 2013; 2014). They also appear to be at increased risk of OTCA use, as compared to their non-exposed peers (Baumann-Larsen et al., 2023). Studies on adults indicate that exposure to childhood PTEs may increase risk of chronic pain and mental health disorders, including substance use disorder (Hailes et al., 2019; Moore et al., 2017; Norman et al., 2012). Exposure to interpersonal violence, such as physical or sexual abuse or bullying (Krug et al., 2002), seems to be particularly detrimental (Alisic et al., 2014; McLaughlin et al., 2013), however, most studies on the long-term health consequences of childhood PTEs are based on retrospective reports of PTEs collected after health outcomes of interest have been established. The potential impact of exposure to PTEs and associated symptoms on future pain alleviation in the form of OTCA remains unexplored.

In this prospective cohort study of young people, we aimed to explore whether childhood exposure to interpersonal violence and other PTEs increase the risk of frequent OTCA use as young adults, and the potential effect of adjustment for headaches, pain and psychological distress in adolescence.

2. Methods

This prospective study uses data collected in The Trøndelag Health Study (HUNT) in the Young-HUNT3 Survey (2006–2008) (Holmen et al., 2014) and the follow-up HUNT4 Survey (2017–2019) (Åsvold et al., 2022) (Supplementary Fig. 1). Participation in the HUNT surveys was voluntary, and the surveys have been approved by the Regional Committee for Medical Research Ethics and the Data Inspectorate of Norway. Inclusion was based on written consent from participants 16 years of age or older, and from the parents of those under 16 years of age, in accordance with Norwegian law. The current study has been approved by the Regional Committee for Medical Research Ethics.

In Young-HUNT3 (between October 2006 and June 2008) all 10 464 adolescents in the region of Norway formerly called Nord-Trøndelag were invited to participate. The participation rate in Young-HUNT3 was 78% ($n = 8199$). Most adolescents completed the self-administered questionnaire during school hours, and a validated semi-structured clinical headache interview was conducted within the following month. In HUNT4 (between August 2017 and February 2019), all adult inhabitants in the same region were invited to participate, as well as participants in previous waves of the survey who had moved out of the region. Of the participants in Young-HUNT3, 37% also participated in HUNT4, creating a cohort of $n = 3032$. Participants who reported having received a diagnosis of juvenile rheumatoid arthritis from a physician in Young-HUNT3 and/or arthritis (including spondyloarthritis and gout) or cancer in HUNT4 (2.8%, $n = 85$) were excluded due to their medical reasons for using analgesics, leaving a study population of $n = 2947$ (59.1% females).

Patient and public involvement

Adolescent and adult participant representatives, representatives from local school authorities and local physicians were involved in planning the HUNT survey. The contents of questionnaires, clinical examinations, implementation of results and privacy concerns were discussed with these representatives.

2.1. Measures

Data on age and sex were obtained from the Norwegian National Population Registry. As adolescents (Young-HUNT3, 2006–2008), participants were asked two questions regarding household structure, and they were categorized as “living with both parents” or “living in other type of household” for the variable *Household structure*. The adolescents were asked whether they perceived their family economy as below average, average or above average and were grouped into “family economy average or better” and “family economy below average” for the variable *Family economy*.

2.1.1. Use of OTCA for musculoskeletal pain and headaches in young adulthood

In HUNT4 (2017–2019), young adult participants were asked “How often during the past month have you used non-prescription medication to treat the following complaints? (medication not prescribed by a doctor, for instance, purchased at a pharmacy or grocery store) for i) muscle or joint pain and ii) headaches. Response alternatives were “never/rarely”, “1–3 times per week”, “4–6 times per week” and “daily”. We combined the frequency categories “4–6 times/week” and “daily” into one group (Dale et al., 2015; Dyb et al., 2006; Zwart et al., 2003a). Two ordinal outcome variables on self-reported use of over-the-counter-analgesics (OTCA) in young adulthood were computed: *Use of OTCA to treat musculoskeletal pain* and *Use of OTCA to treat headaches* with the frequency categories “never/rarely”, “1–3 times per week” (weekly), “≥4 times per week” (daily). Weekly or more frequent use in the past month is referred to in this article as “frequent use”.

2.1.2. Childhood exposure to potentially traumatic events (Young-HUNT3, 2006–2008)

Lifetime trauma screen. Lifetime exposure to PTEs was assessed in adolescence by a brief lifetime trauma screen derived from the UCLA PTSD Index for DSM IV, part I (Steinberg et al., 2004). The trauma screen used in Young-HUNT3 had been adapted to a Norwegian context, and specific questions related to gun violence and war were not asked. However, these and other events not assessed specifically could be reported under the item “other experience that was very frightening, dangerous or violent”. The original instrument does not contain a specific question on bullying, however, this was assessed in Young-HUNT3, in compliance with the WHO definition of interpersonal violence (Krug et al., 2002). All events were listed under the question “Did you ever experience any of these events?” (Supplementary Table 1). Response alternatives were “never”, “yes, during the past year” and “yes, during lifetime” for all items. Participants responding “yes, during the past year” and “yes, during lifetime” were labelled as exposed.

2.1.3. Direct interpersonal violence

Items on exposure to direct interpersonal violence included physical violence, bullying and sexual abuse. Participants were classified as exposed to *Physical violence* if they answered affirmatively to the question “been subjected to violence (beaten/injured)”. Participants who answered “yes” to the question “been threatened or physically harassed by fellow students at school over a period of time” were classified as exposed to *Bullying*. Exposure to sexual abuse was measured by two items worded “subjected to an unpleasant sexual act by a peer” and “subjected to an unpleasant sexual act by an adult”, and reports of exposure to either or both were categorized as *Sexual abuse*. A sum score (range 0–3) of the three items on direct interpersonal violence was

computed and labelled *Interpersonal violence, number of types*. For regression analyses, scores of 2 and 3 were combined due to low counts.

2.1.4. Other potentially traumatic events

Participants were asked if they had “seen someone else being subjected to violence”, responders answering in the affirmative were classified as *Witness to violence*. Responders answering “yes” to either “someone in your family was seriously ill” or “the death of someone close to you” were classified as exposed to *Severe illness or death of someone close*. Responders answering in the affirmative to experiencing “a disaster (fire, hurricane or similar)”, “a serious accident (e.g., serious car accident)”, “painful or frightening hospital treatment for a disease or an accident”, “other experience that was very frightening, dangerous or violent” were classified as exposed to *Other potentially traumatic event*.

2.1.5. Adolescent frequent musculoskeletal pain and headaches (Young-HUNT3, 2006–2008)

Frequent musculoskeletal pain. As adolescents, participants were asked “How often during the past 3 months have you experienced any of these complaints?”. The complaints were pain in eight locations (neck or shoulders, chest, upper back, lower back, left arm, right arm, left leg, right leg) (Supplementary Table 1). Response alternatives were “never/rarely”, “monthly”, “weekly”, “several times per week”, and “almost daily”. The questions are based on an instrument developed to assess musculoskeletal pain in adolescents (Mikkelsen et al., 1997). In compliance with measures of chronic multisite musculoskeletal pain in adolescents from other studies, we counted all the sites in which participants reported pain with a frequency of at least once a week (Al-Janabi et al., 2021; Bazett-Jones et al., 2019; Rathleff et al., 2013). We grouped responders based on number of pain sites (0, 1, 2 and 3 or more sites) for regression analyses, as higher numbers of pain sites have been shown to be associated with a higher extent of comorbidities (Skrove et al., 2015).

Frequent headaches. The interview part of the Young-HUNT3 survey included a validated headache interview (Zwart et al., 2003b). Participants were asked if they had experienced headaches in the past 12 months, and if they had experienced reoccurring headaches in the past 12 months. Further, they were asked about headache characteristics to assess type of headache (migraine, tension-type headache or other headache). Headache frequency was assessed for each type of headache, with the following response alternatives: “<1 day per month”, “1–3 days per month”, “1–3 days per week” and “more than 4 days per week”. Participants reporting weekly or more frequent headaches of any type were classified as having *Frequent headaches* (Dyb et al., 2006; Zwart et al., 2003a) (Supplementary Table 1).

Pain-related disability. Level of pain-related disability in adolescence was measured using a disability index by Mikkelsen et al. (1997). Five specific complaints were listed, and the adolescents were asked to assess whether each statement was a true or false description of their disability due to pain. These complaints were “pain makes it difficult to fall asleep”, “pain disrupts my sleep at night”, “pain makes it hard for me to be in lectures in school”, “pain makes it hard for me to walk more than one kilometer”, “due to pain, I have problems with physical education classes”. The item on leisure activity was worded slightly differently than in the original instrument – as a question, not a statement: “all things considered, has pain made it difficult to do daily leisure activities?” instead of “pain limits my leisure activities” (Hoftun et al., 2012). The two questions about sleep were combined to give one point for an affirmative answer to either or both questions in compliance with the original index ranging from 0 to 5, as in previous studies on pain-related disability in this population (Hoftun et al., 2011).

Frequent adolescent OTCA use. Use of OTCA in adolescence was assessed by frequency of use (never, ≤ 1 day per week, 2 days per week, 3 days per week, ≥ 4 days per week) to treat headache, stomach ache, backache and musculoskeletal pain. Participants reporting OTCA use 2 days per week or more were defined as using OTCA frequently.

2.1.6. Adolescent psychological symptoms (Young-HUNT3, 2006–2008)

Posttraumatic stress symptoms (PTSS). Participants who reported exposure to any of the events in the brief lifetime trauma screen were asked three questions about posttraumatic stress symptoms (Supplementary Table 1). The questions were derived from the UCLA PTSD Reaction Index, part III, for children and adolescents in collaboration with the authors of the original instrument (Steinberg et al., 2004). Two items assessed the common posttraumatic symptom intrusion: “I have upsetting thoughts, pictures or sounds of what happened come into my mind when I do not want them to” and “When something reminds me of what happened I get very afraid, upset or sad”. The third question assessed avoidance, also a common posttraumatic symptom: “I try not to talk about, think about or have feelings about what happened”. Questions were answered with “yes” or “no”. A sum score ranging from 0 to 3 for posttraumatic stress symptoms was used in regression analyses. The score was set to 0 for participants reporting no trauma exposure.

Psychological distress. Psychological distress in adolescence was measured using a validated five-item short version of the Hopkins Symptoms Checklist (SCL-5) (Strand et al., 2003; Tambs and Moum, 1993). SCL-5 includes items on i) feeling fearful, ii) nervousness or shakiness inside, iii) feeling hopeless about the future, iv) feeling blue and v) worrying about things too much (Supplementary Table 1). Participants were asked to rate the extent to which they had been bothered by each item in the past 14 days on a 4-point Likert scale where “not bothered” = 1, “a little bothered” = 2, “fairly bothered” = 3 and “very bothered” = 4. A mean score was calculated, and a score > 2.0 was used as a cutoff for psychological distress (Strand et al., 2003). Cronbach’s alpha for the five items was 0.83.

2.2. Statistical procedures

Descriptive data on sociodemographics, exposure to interpersonal violence and other PTE and symptomatology as reported in adolescence (Young-HUNT3, 2006–2008) were stratified by frequencies of *Use of OTCA to treat musculoskeletal pain* and *Use of OTCA to treat headache* in young adulthood (HUNT4, 2017–2019). Population characteristics were also presented by sex. Categorical variables were described with counts and percentages, continuous variables were described with mean and standard deviation. The half rule was used to handle missing values (Fairclough, 2010), meaning that participants who answered at least half of the questions were used to calculate the mean scores and sum scores included in the analyses. In compliance with validation studies, SCL-5 (*Psychological distress*) was calculated for participants who responded to at least three of the five items (Strand et al., 2003). Spearman’s Rank Correlation was used to measure strength and direction of correlations for different types of PTEs.

Ordinal logistic regression analyses were used to estimate the strength of the associations between types of childhood exposure to PTEs, as reported in Young-HUNT3 (2006–2008), including *Physical violence*, *Witness to violence*, *Bullying*, *Sexual abuse*, *Severe illness or death of close person*, *Other potentially traumatic event*, and on young adulthood *Use of OTCA to treat musculoskeletal pain* and *Use of OTCA to treat headache*, as reported in HUNT4 a decade later (2017–2019). Each type of trauma was assessed by separate complete case analyses. Additionally, separate analyses were used to estimate the potential cumulative impact of exposure to increasing number of types of interpersonal violence in adolescence (*Interpersonal violence, number of types*) on OTCA use in young adulthood. In Model 1, all analyses were adjusted for age and sex (Tolin and Foa, 2006). In Model 2, analyses were additionally adjusted for adolescent *Household structure* and *Family economy* (Ahlborg et al., 2017; Kirkeby et al., 2014; Turner et al., 2007). Variables measuring pain (*Frequent musculoskeletal pain* and *Frequent headaches*) were added in Model 3, whereas, in Model 4, variables measuring psychological symptoms (*Posttraumatic stress symptoms* and *Psychological distress*) were added. All ordinal logistic regression analyses were tested with Brant tests (Brant, 1990), and analyses for which the assumption of

proportional odds was violated were examined by comparing the odds ratios for each group comparison in the ordinal logistic regression analyses. Logistic regression analyses where frequent OTCA use ($\geq 1-3$ times week) versus “never/rarely” served as the dichotomous outcome were run in cases of violation of the assumption of proportional odds. As the importance of PTEs for daily use was not assessed in the logistic regression analyses combining weekly and daily use, we conducted logistic regression sensitivity analyses comparing daily use to using never/rarely. Sensitivity analyses were conducted for Model 1–4 as outlined above. To examine the possible role of pain and psychological symptoms as mediators for an association of PTE exposure to more frequent OTCA use, mediation analyses were conducted for selected exposure-outcome relationships. E-values were computed for the relationships to indicate the amount of unmeasured confounding needed to explain away a mediation effect (Smith and VanderWeele, 2019). Analyses were conducted using Stata version 16 and R version 4.2.3, utilizing the R package CMAverse (Shi et al., 2021) for causal mediation analysis.

3. Results

As young adults, 17.5% of the 1742 females and 10.4% of males were frequent users of OTCA to treat musculoskeletal pain (Table 1 and Supplementary Table 2), while 28.2% of females and 24.3% males were frequent users of OTCA to treat headaches. The proportion of participants reporting exposure to PTEs in adolescence was higher among adults using OTCA frequently. Among the young adults using OTCA almost daily, about a third had reported childhood exposure to one or more interpersonal PTEs as adolescents over a decade earlier, as compared to about 15% of the young adults who never or rarely use OTCA. The group of young adults using OTCA frequently reported a higher load of pain and psychological symptoms in adolescence

compared to young adults who never or rarely used OTCA. Young adults using OTCA almost daily were 2–4 times more likely to have experienced frequent musculoskeletal pain and headaches and to have used OTCA frequently in adolescence. They also reported 2 times higher average pain-related disability in adolescence.

Spearman’s rank correlation coefficient was weak (< 0.39) for all correlations except for a moderate (0.41) correlation for exposure to physical violence and witnessing violence (Supplementary Table 3).

Results from the ordinal logistic regression analyses showed consistent, significant associations between the six types of childhood PTE and more frequent use of OTCA to treat musculoskeletal pain in young adulthood (Table 2, model 1). The associations were particularly strong for childhood exposure to direct interpersonal violence. Analysis for *Interpersonal violence, number of types* showed that risk of more frequent use of OTCA gradually increased from no exposure, through one type to two or more types of direct interpersonal violence, indicating a dose-response relationship. Adjustment for family structure and economy had little effect on the associations (model 2). All associations were attenuated when adjusting for adolescent musculoskeletal pain and headache (model 3). When adding general and posttraumatic psychological symptoms to the model (model 4), only bullying remained significantly associated with more frequent OTCA use for musculoskeletal pain.

In estimating the relationship between childhood exposure to PTE and *Use of OTCA to treat headache* in young adulthood, the assumption of proportional odds was violated according to the Brant test for several of the models (as detailed in Table 3). In these cases, logistic regression analyses were used rather than ordinal logistic regressions. Although results of these analyses were less salient, childhood exposure to bullying, witnessing violence and severe illness or death of someone close were significantly related to heightened risk OTCA use for

Table 1

Sociodemographic characteristics, trauma exposure and symptoms in adolescence (young-HUNT3, 2006–2008) stratified by use of over-the-counter analgesics in young adulthood (HUNT 4, 2017–2019).

	Use of OTCA to treat headaches			Use of OTCA to treat musculoskeletal pain		
	Never/rarely	1–3 times/week	≥ 4 times/week	Never/rarely	1–3 times/week	≥ 4 times/week
All participants	2133 (73.3%)	699 (24.0%)	79 (2.7%)	2457 (85.4%)	323 (11.2%)	97 (3.4%)
Females	1163 (67.7%)	491 (24.4%)	65 (3.8%)	1406 (82.5%)	223 (13.1%)	75 (4.4%)
Males	970 (75.7%)	298 (23.2%)	14 (1.1%)	1051 (89.6%)	100 (8.5%)	22 (1.9%)
Age young-HUNT3, mean	16.0 (SD 1.77)	16.0 (SD 1.76)	15.9 (SD 1.77)	16.0 (SD 1.76)	16.0 (SD 1.79)	16.1 (SD 1.81)
Age HUNT4, mean	27.1 (SD 1.96)	27.0 (SD 1.89)	26.9 (SD 1.71)	27.1 (SD 1.95)	27.0 (SD 1.87)	27.1 (SD 1.89)
Socioeconomic factors						
Family economy below average	173 (8.6%)	54 (8.2%)	10 (13.7%)	199 (8.6%)	26 (8.7%)	7 (8.05%)
Household structure, living with both parents	1234 (58.4%)	387 (56.3%)	36 (46.8%)	1442 (59.3%)	153 (48.6%)	50 (51.6%)
Direct interpersonal violence						
Bullying	137 (6.7%)	52 (7.9%)	13 (17.6%)	155 (6.6%)	32 (10.5%)	12 (13.2%)
Physical violence	172 (8.4%)	56 (8.5%)	11 (14.9%)	194 (8.2%)	32 (10.5%)	11 (12.1%)
Sexual abuse	99 (4.8%)	40 (6.0%)	8 (10.8%)	111 (4.7%)	24 (7.9%)	8 (8.8%)
By peer	77 (3.8%)	28 (4.2%)	5 (6.8%)	84 (3.6%)	17 (5.6%)	6 (6.6%)
By adult	46 (2.2%)	17 (2.6%)	5 (6.8%)	54 (2.3%)	8 (2.6%)	3 (3.3%)
Direct interpersonal violence, number of types						
No events	1743 (85.0%)	562 (84.5%)	51 (68.9%)	2020 (85.5%)	242 (79.3%)	67 (73.6%)
1 type	226 (11.0%)	67 (10.1%)	16 (21.6%)	248 (10.5%)	41 (13.4%)	17 (18.7%)
2 or more types	82 (4.0%)	36 (5.4%)	7 (9.5%)	94 (4.0%)	22 (7.2%)	7 (7.7%)
Other potentially traumatic events						
Witness to violence	416 (20.3%)	150 (22.6%)	12 (16.2%)	471 (19.9%)	82 (26.8%)	15 (16.7%)
Disease or death of someone close	1467 (71.3%)	526 (78.7%)	59 (79.7%)	1713 (72.3%)	235 (76.3%)	76 (82.6%)
Severe accident, disaster or other traumatic event	613 (29.8%)	205 (30.8%)	29 (39.2%)	692 (29.2%)	111 (36.3%)	31 (34.1%)
Symptoms						
Posttraumatic stress, sum score (0–3), mean	0.74 (SD 0.96)	0.86 (SD 1.00)	1.25 (SD 1.20)	0.73 (SD 0.95)	1.21 (SD 1.06)	1.06 (SD 1.16)
Psychological distress, SCL-5, mean score (1–4)	1.47 (SD 0.53)	1.59 (SD 0.55)	1.80 (SD 0.75)	1.48 (SD 0.52)	1.69 (SD 0.61)	1.62 (SD 0.60)
Psychological distress above cutoff (SCL-5 > 2.0)	251 (12.0%)	103 (15.0%)	21 (27.6%)	283 (11.7%)	71 (22.4%)	17 (17.7%)
Frequent musculoskeletal pain	656 (31.0%)	293 (42.7%)	38 (49.4%)	780 (32.1%)	143 (44.8%)	55 (57.3%)
Pain in 1 site	312 (14.8%)	126 (18.4%)	10 (13.0%)	375 (15.4%)	54 (16.9%)	18 (18.8%)
Pain in 2 sites	180 (8.5%)	93 (13.6%)	14 (18.2%)	223 (9.2%)	44 (13.8%)	16 (16.7%)
Pain in 3–8 sites	164 (7.8%)	74 (10.8%)	14 (18.2%)	182 (7.5%)	45 (14.1%)	21 (21.9%)
Frequent headaches	126 (6.3%)	88 (13.3%)	21 (27.3%)	168 (7.2%)	45 (14.6%)	17 (18.1%)
Disability Index (0–5), mean	1.10 (SD 1.31)	1.50 (SD 1.45)	2.15 (SD 1.63)	1.12 (SD 1.31)	1.73 (SD 1.53)	2.15 (SD 1.66)
OTCA ≥ 2 days/week in young-HUNT3	152 (7.2%)	127 (18.7%)	23 (29.9%)	211 (8.8%)	58 (18.2%)	29 (31.2%)

Table 2

The association of exposure to potentially traumatic events reported in childhood (Young-HUNT3, 2006–2008) with use of over-the-counter analgesics to treat musculoskeletal pain in young adulthood (HUNT4, 2017–2019), by type of event and number of types of direct interpersonal violence.

	n	Model 1 ^a (sex and age) (n = 2750–2768)		N	Model 2 ^{a,b} (background)(n = 2636–2648)		Model 3 ^{a,b,c} (somatic symptoms) (n = 2478–2488)		n	Model 4 ^{a,b,c} (psychological symptoms) (n = 1570–1576)		
		OR (95% CI)	p-value		OR (95% CI)	p-value	OR (95% CI)	p-value		OR (95% CI)	p-value	
Direct exposure to interpersonal violence												
by type												
Bullying	2750	1.84 (1.29, 2.63)	0.001	2636	1.84 (1.28, 2.66)	0.001	2478	1.56 (1.06, 2.31)	0.025	1574	1.53 (1.01, 2.31)	0.044
Sexual abuse	2758	1.61 (1.07, 2.42)	0.023	2643	1.70 (1.12, 2.57)	0.013	2484	1.38 (0.89, 2.14)	0.148	1574	1.15 (0.72, 1.85)	0.553
Physical violence	2757	1.50 (1.05, 2.14)	0.024	2640	1.53 (1.07, 2.19)	0.021	2481	1.27 (0.86, 1.87)	0.230	1570	1.08 (0.72, 1.63)	0.707
by number of types												
1 type of direct interpersonal violence	2758	1.60 (1.17, 2.18)	0.003	2643	1.63 (1.18, 2.24)	0.003	2484	1.48 (1.05, 2.07)	0.024	1574	1.35 (0.94, 1.95)	0.104
≥2 types of direct interpersonal violence	2758	2.05 (1.33, 3.16)	0.001	2643	2.12 (1.37, 3.30)	0.001	2484	1.66 (1.03, 2.68)	0.036	1574	1.48 (0.89, 2.48)	0.132
Exposure to other potentially traumatic events, by type												
Witness to violence	2758	1.42 (1.10, 1.85)	0.007	2641	1.40 (1.07, 1.84)	0.013	2482	1.27 (0.96, 1.68)	0.100	1572	1.19 (0.87, 1.63)	0.277
Severe illness or death of someone close	2768	1.30 (1.01, 1.68)	0.042	2648	1.38 (1.06, 1.80)	0.018	2488	1.26 (0.95, 1.65)	0.106	1576	1.37 (0.78, 2.38)	0.271
Severe accident, disaster or other traumatic event	2765	1.34 (1.07, 1.68)	0.010	2648	1.40 (1.11, 1.76)	0.005	2488	1.31 (1.03, 1.67)	0.029	1576	1.14 (0.85, 1.53)	0.380

Trauma types were assessed by separate ordinal logistic regression analyses. Direct interpersonal violence encompasses bullying, sexual abuse and physical violence.

^dModel 4 is additionally adjusted for posttraumatic stress and general psychological symptoms.

^a Models 1–4 are all adjusted for sex and age, pubertal development, household structure and family economy.

^b Models 2–4 are additionally adjusted for the background factors household structure and family economy.

^c Models 3–4 are additionally adjusted for frequent headaches and musculoskeletal pain.

headache in young adulthood. Analysis for *Interpersonal violence, number of types* showed that risk of more frequent use of OTCA gradually increased from no exposure, through one type to two or more types of direct interpersonal violence, indicating a dose-response relationship. Adjusting for pain and psychological symptoms in adolescence attenuated the associations.

Sensitivity analyses comparing daily use to using never/rarely showed strong and cumulative associations for direct interpersonal violence with daily use of OTCA to treat headache (Supplementary Table 4). The association was not significant for sexual abuse, however sexual abuse and daily use of OTCA to treat headache were both infrequent in this population (Table 1).

Mediation analyses for the relation of exposure to sexual abuse, bullying and physical violence to OTCA use for musculoskeletal pain, modeling headache, musculoskeletal pain and psychological distress as possible mediators, showed significant mediated effects and no significant direct effect (Supplementary Table 5). The E-values for the mediated risk ratios indicated that substantial unmeasured confounding was needed to explain the pure natural indirect effect while less unmeasured confounding was needed to explain away the total natural indirect effect.

4. Discussion

The significantly increased risk of frequent use of OTCA among young adults exposed to potentially traumatic events (PTE) in childhood shown in this prospective population study is a novel finding. The

strongest associations were found between direct interpersonal events and more frequent use of OTCA to treat musculoskeletal pain, and between direct interpersonal events and daily use of OTCA to treat headaches. The cumulative effect of trauma appears to be important within this relationship, as results indicated a dose-response relationship between childhood exposure to direct interpersonal violence and more frequent use of OTCA in young adulthood. Adding pain and psychological symptoms in adolescence to the models consistently attenuated the associations between traumatic events and higher frequency use of OTCA, indicating that the higher level of somatic and psychological symptoms experienced by adolescents exposed to traumatic events explains, to some extent, their use of OTCA a decade later. Mediation analysis for the relation of exposure to direct interpersonal violence to OTCA use for musculoskeletal pain supports the possible role of pain and psychological symptoms as mediators.

It is well established that traumatic childhood events can have a long-term impact on health, including a wide spectrum of psychological and somatic symptoms in adulthood (Hughes et al., 2021; Norman et al., 2012). The increased risk of poor physical health in adulthood after childhood abuse has been found to be of the same magnitude as poor psychological outcomes and to have the largest effect sizes for neurological and musculoskeletal conditions (Wegman and Stetler, 2009). However, the existing evidence for stressful childhood events as a risk factor for adult chronic pain is inconsistent. Although several adult studies have found that retrospectively assessed traumatic childhood events are strongly associated with pain conditions in adulthood (Brown et al., 2018; Davis et al., 2005; Sachs-Ericsson et al., 2017), there is little

Table 3

The association of exposure to potentially traumatic events reported in childhood (Young-HUNT3, 2006–2008) with use of over-the-counter analgesics to treat headaches in young adulthood (HUNT4, 2017–2019), by type of event and number of types of direct interpersonal violence.

	n	Model 1 ^a (sex and age) (n = 2790–2799)		N	Model 2 ^{a,b} (background) (n = 2667–2679)		n	Model 3 ^{a,b,c} (somatic symptoms) (n = 2507–2517)		n	Model 4 ^{a,b,c} (psychological symptoms) (n = 1587–1593)	
		OR (95% CI)	p-value		OR (95% CI)	p-value		OR (95% CI)	p-value		OR (95% CI)	p-value
Direct exposure to interpersonal violence by type												
Bullying	2790	*1.41 (1.03, 1.93)	0.031	2667	*1.40 (1.02, 1.94)	0.040	2507	1.40 (1.00, 1.97)	0.052	1591	1.35 (0.94, 1.94)	0.108
Sexual abuse	2789	1.25 (0.87, 1.79)	0.227	2674	1.23 (0.85, 1.77)	0.276	2513	1.10 (0.75, 1.62)	0.625	1591	1.03 (0.68, 1.56)	0.885
Physical violence	2789	*1.25 (0.92, 1.69)	0.148	2671	1.23 (0.90, 1.68)	0.191	2510	1.02 (0.73, 1.43)	0.906	1587	0.91 (0.64, 1.30)	0.608
by number of types												
1 type of direct interpersonal violence	2790	*1.09 (0.83, 1.43)	0.545	2674	*1.05 (0.79, 1.39)	0.755	2513	*0.96 (0.71, 1.29)	0.771	1591	*0.90 (0.65, 1.23)	0.502
≥2 types of direct interpersonal violence	2790	*1.55 (1.05, 2.27)	0.027	2674	*1.55 (1.05, 2.31)	0.029	2513	*1.39 (0.91, 2.12)	0.131	1591	*1.27 (0.80, 2.00)	0.309
Exposure to other potentially traumatic events, by type												
Witness to violence	2790	1.28 (1.04, 1.58)	0.022	2672	1.28 (1.03, 1.59)	0.025	2511	*1.19 (0.95, 1.51)	0.135	1589	*1.07 (0.82, 1.39)	0.622
Severe illness or death of someone close	2799	1.45 (1.18, 1.78)	<0.001	2679	1.44 (1.17, 1.78)	0.001	2517	1.44 (1.15, 1.79)	0.001	1593	1.32 (0.87, 2.03)	0.188
Severe accident, disaster or other traumatic event	2797	1.11 (0.93, 1.33)	0.253	2679	1.12 (0.93, 1.35)	0.242	2517	1.01 (0.82, 1.23)	0.935	1593	0.83 (0.66, 1.06)	0.142

Trauma types were assessed by separate ordinal logistic regression analyses. Direct interpersonal violence encompasses bullying, sexual abuse and physical violence. ^dModel 4 is additionally adjusted for posttraumatic stress and general psychological symptoms.

^a Models 1–4 are all adjusted for sex and age, pubertal development, household structure and family economy.

^b Models 2–4 are additionally adjusted for the background factors household structure and family economy.

^c Models 3–4 are additionally adjusted for frequent headaches and musculoskeletal pain.

^{*} The assumption of proportional odds was not met for this comparison, therefore odds ratio from logistic regression for using OTCA to treat headaches never/rarely ($n = 2133$) vs at least one time per week ($n = 778$) is reported for this exposure variable in this model.

prospective research assessing trauma in childhood and chronic pain in the same individuals as they reach adulthood, and existing results are conflicting (Jones et al., 2009; Raphael et al., 2004; Raphael and Widom, 2011).

Research on potential underlying biological mechanisms link early life stress to dysfunctional adaptations in pain physiology (Burke et al., 2017). Trauma reactions such as sleep disturbances, hypervigilance and avoidance are symptoms that are also considered risk factors for maintenance and exacerbation of pain conditions (Nelson et al., 2017). The increased risk appears to be partly related to (mal)adaptive coping mechanisms, such as disengagement or avoidance strategies (Nelson et al., 2022). Coping mechanisms linking traumatic events and pain may also be relevant for the approach to OTCA use.

Emerging evidence on the effects of OTCA indicate that some of these medications may alleviate psychological symptoms (Köhler-Forsberg et al., 2019; Ratner et al., 2018). Such an effect could help to explain frequent use among trauma-exposed adolescents and young adults experiencing a high load of psychological symptoms, often in combination with pain.

A key element in our findings is that symptoms in adolescence may help to explain adult use of OTCA. The young adults in this study who used OTCA frequently also reported higher disability and OTCA use in adolescence as compared to their peers. This indicates that clinically important complaints after childhood PTEs can emerge early on and could be important targets for early interventions. The finding is in line with studies showing that shared environmental factors, such as

exposure to PTEs, may be important for the co-occurrence of anxiety, depression and pain conditions among adolescents (Khan et al., 2020). Childhood PTEs are known to be associated with lifestyle factors considered as risk factors for pain and psychological symptoms, such as a higher BMI and lower physical activity level (Abrahamyan et al., 2023; De Rubeis et al., 2023; Zhang et al., 2023).

4.1. Strengths and limitations

The prospective design is a strength of this study. Unfortunately, a large proportion was lost to follow-up, however the high participation rate in the adolescent part of the survey made it possible to describe differences between study participants and those lost to follow-up (Supplementary Table 6). The questions in the survey were derived from validated instruments and allowed for a thorough assessment of exposures and symptoms. The relationship between exposure to traumatic events in adolescence and more frequent use of OTCA in young adulthood shown in this study is likely to be transferrable to other populations with high availability of OTCA.

It is a limitation that we could not conduct ordinal logistic regression for all PTEs for *Use of OTCA to treat headaches*. Dichotomizing the outcome variable to perform logistic regression in these analyses resulted in a rougher estimate of the importance of childhood PTEs for later OTCA use. Sensitivity analyses specifically examining the relationship between PTEs and almost daily use of OTCA were conducted to identify associations that were lost when dichotomizing the outcome in the main analyses.

Some participants may have experienced traumatic events while still in adolescence, but after the adolescent survey was conducted. They would then be misclassified as unexposed. This type of misclassification could lead to an underestimation of the true associations.

The small group of adolescents not in school ($n = 493$) was under-represented (23% participation) in the adolescent survey, possibly introducing a selection bias (Holmen et al., 2014). More males than females were lost to follow-up, and females generally reported using OTCA more frequently than males. Apart from this, we see that factors observed to be more common among the group of young adults using OTCA frequently (traumatic events, family economy below average, not living with both parents, frequent adolescent use of OTCA), are also more common in the lost to follow-up group. These differences may introduce a selection bias, and it is likely that this would lead to an underestimation of the true associations. The differences are also consistent with previous findings that non-participation is associated with poorer health outcomes (Langhammer et al., 2012).

5. Conclusion and implications

This study found that adolescents exposed to PTEs, and especially to direct interpersonal violence, use OTCA more frequently as young adults. A higher burden of exposure was associated with a particularly high and gradually increasing risk of frequent OTCA use. The increased risk was related to a higher symptom load of adolescent psychological complaints and pain, and the early manifestation of symptoms related to adult overuse of OTCA after childhood PTEs, emphasizes the need to address these symptoms early on. It also points to the importance of identifying their underlying causes, including specifically assessing exposure to interpersonal violence and other PTEs. A general societal trend of increasingly using medication to alleviate symptoms may put young adults exposed to childhood PTEs at particularly increased risk of overuse.

Data sharing statement

The data set analyzed belongs to a third party, the Trøndelag Health Study (HUNT Study). The authors of the current manuscript have been granted permission to analyze the data after obtaining the necessary Norwegian permits. Research groups that wish to analyze data from the HUNT study may apply to the HUNT organization to get access to the data. HUNT databank online provides a complete overview of the research variables (<https://hunt-db.medisin.ntnu.no/hunt-db/variablelist>).

Trial registration

The study is part of the Killing Pain project that was pre-registered through [ClinicalTrials.gov](https://clinicaltrials.gov) on April 7th, 2020. Registration number NCT04336605; <https://clinicaltrials.gov/ct2/show/record/NCT04336605>.

Author statement

Synne Øien Stensland applied for funding and for data. All the authors contributed substantially to the study conception and design. Tore Wentzel-Larsen and Monica Baumann-Larsen conducted the statistical analyses, all authors contributed in interpretation of data. Monica Baumann-Larsen drafted the work and Synne Øien Stensland, John-Anker Zwart, Kjersti Storheim, Grete Dyb, Helle Stangeland, and Tore Wentzel-Larsen revised it critically for important intellectual content. All authors have read the manuscript and given their approval for the submission of this manuscript to Psychiatry Research.

Declaration of Competing Interest

All authors declare that they have no conflicts of interest.

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Supplementary materials

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