Childhood trauma and use of analgesics in adolescence and young adulthood

Thesis for the degree of Philosophiae Doctor

by

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If we don't stand up for children, then we don't stand for much.

Marian Wright Edelman

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List of papers included in thesis

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II. Baumann-Larsen M, Zwart JA, Dyb G, Wentzel-Larsen T, Stangeland H, Storheim K, Stensland SØ. 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. Psychiatry Res. 2023 Aug 1;327:115400. doi: 10.1016/j.psychres.2023.115400. Epub ahead of print. PMID: 37574601.

III. Baumann-Larsen M, Storheim K, Stangeland H, Zwart JA, Wentzel-Larsen T, Skurtveit S, Dyb G, Stensland SØ. Childhood trauma and the use of opioids and other prescription analgesics in adolescence and young adulthood. The HUNT Study. Accepted for publishing in PAIN (November 7, 2023).

Acronyms and abbreviations

ACE	Adverse Childhood Experiences
ACC	Anterior cingular cortex
CI	Confidence Interval
CNS	Central Nervous System
DSM	Diagnostic and Statistical Manual of Mental Disorders
GABA	Gamma-aminobutyric acid
HUNT4	The 4th wave of The HUNT Study for adults
IASP	International Association for the Study of Pain
ICD-11	International Statistical Classification of Diseases and Related Health Problems, eleventh revision
IRR	Incidence Rate Ratio
ISTSS	International Society for Traumatic Stress Studies
NIPH	The Norwegian Institute of Public Health
NorPD	The Norwegian Prescription Database
NSAIDs	Non-steroid anti-inflammatory drugs
OTCA	Over-the-counter analgesics
OR	Odds Ratio
PAG	Periaqueductal grey
PTE	Potentially Traumatic Event
PTSD	Posttraumatic Stress Disorder
PTSS	Posttraumatic Stress Symptoms
SCL-5	Hopkins Symptom Checklist, five items
The HUNT Study	The Trøndelag Health Study (Helseundersøkelsen i Trøndelag)
UCLA	University of California, Los Angeles
UCLA PTSD-RI	UCLA Posttraumatic Stress Disorder Reaction Index
WHO	World Health Organization
Young-HUNT3	The 3rd wave of The HUNT Study for adolescents
Young-HUNT4	The 4th wave of The HUNT Study for adolescents

Summary

Analgesics are commonly used among young people. Although over-the-counter analgesics (OTCA) are considered safe to use within recommended doses for otherwise healthy young individuals, adolescents and young adults commonly report a frequency of use that is associated with medication overuse headache and chronification of pain. The same population of young people who use of OTCA frequently, appear to be at risk of receiving opioids and other prescription analgesics, due to many shared risk factors for frequent use of OTCA and prescription analgesics, including pain conditions, mental health problems, female sex and a lower socioeconomic status.

Exposure to childhood trauma is associated with pain conditions and mental health problems in adolescence and young adulthood. Having a lower socioeconomic status is associated with a higher risk of exposure to childhood trauma. In this thesis we aimed to examine whether childhood trauma exposure represents an underlying, early risk factor for more frequent use of OTCA and for receiving prescription analgesics in adolescence and young adulthood. Further, we aimed to investigate whether interpersonal trauma, the subtype of trauma representing exposure of an individual to intentional harm by another person, such as physical violence, sexual abuse and bullying, was especially strongly associated with analgesics use. This subtype of trauma exposure has generally been found to be more strongly associated with negative health outcomes in prior studies. We also examined whether a higher cumulative load of trauma exposure was more strongly associated with more frequent analgesics use compared to a lower cumulative exposure. In addition, we assessed the possible importance of pain and psychological symptoms for associations between childhood trauma exposure and use of analgesics.

We used survey data from three different waves of a large population-based cohort study (The HUNT Study) linked to registry data on individual prescriptions from the Norwegian Prescription Database (NorPD) to answer our research questions. Exposure to childhood trauma, socioeconomic status, pubertal development, and somatic and psychological symptoms were assessed in adolescence (Young-HUNT3 and -4). To investigate the relation of childhood trauma to use of OTCA in adolescence, we used cross-sectional data from Young-HUNT4 (2017-2019), where adolescents reported their frequency of OTCA use to treat headache and musculoskeletal pain. To prospectively investigate the relation of childhood trauma to use of OTCA in young adulthood, we used data on exposure to childhood trauma and background variables from Young-HUNT3 (2006-2008), collected when participants were aged 13 to 19 years, and data on frequency of OTCA use to treat

headache and musculoskeletal pain from HUNT4 (2017-2019), collected when the same participants were young adults (aged 20 to 32 years). To prospectively investigate the relation of childhood trauma to receiving prescription analgesics in adolescence and young adulthood, we used data from Young-HUNT3 (2006-2008) linked to individual prescription data from NorPD from 2004-2021. We examined prescriptions of opioids and the nonopioid analgesics paracetamol, NSAIDs and gabapentinoids. Prescriptions received in adolescence and young adulthood were analyzed separately.

We found significant and consistent associations between exposure to a wide range of childhood trauma and use of OTCA to treat headache and musculoskeletal pain in adolescence and young adulthood. We also found significant associations between exposure to childhood trauma and receiving more prescription analgesics in adolescence and young adulthood. We observed a tendency of stronger associations for trauma types representing interpersonal trauma, although all trauma types analyzed were associated with more frequent use of analgesics. Exposure to more than one trauma type was particularly strongly associated with using more OTCA and receiving more prescription analgesics in both adolescence and young adulthood. Symptoms present in adolescence, including weekly headaches and musculoskeletal pain, psychological distress, and posttraumatic stress symptoms, were found to be relevant for the associations between childhood trauma exposure and analgesics use.

A heightened risk of pain, posttraumatic stress disorder and other mental health disorders among young people exposed to childhood trauma may contribute to the observed associations between childhood trauma and frequent analgesics use. Findings from this thesis highlight childhood trauma exposure as an environmental factor that could potentially contribute to explain associations between socioeconomic status and chronic pain conditions, mental health disorders and use of analgesics.

Our findings indicate that individuals exposed to childhood trauma are at increased risk of pursuing and receiving pain treatment that might represent further risk for future adverse health outcomes, considering that frequent use of analgesics is a risk factor for onset, exacerbation, and maintenance of chronic pain. In the case of opioids, there is also a high risk of misuse and dependence, and this risk may be especially high in individuals exposed to childhood trauma. We found that pain and psychological symptoms present in adolescence were relevant for the associations. This finding emphasizes the importance of

optimal management of such early symptoms, to help young individuals escape adverse health trajectories.

The more frequent use of analgesics among trauma-exposed young individuals and the increased risk among the same individuals of detrimental outcomes following opioid prescriptions found in prior studies, can be accounted for clinically by assessing childhood trauma exposure when young people seek help with pain management. Trauma-exposed young people constitute a group that is known to refrain from seeking help for psychosocial problems despite high needs, and their contact with health care providers for help with pain management may represent a first opportunity for trauma-exposed individuals to receive trauma-specific care.

Sammendrag (Norwegian summary)

Smertestillende legemidler brukes hyppig av ungdommer og unge voksne. Reseptfrie smertestillende legemidler betraktes som trygge å bruke innenfor anbefalte doseringer blant ellers friske, unge mennesker. Undersøkelser har vist at mange unge bruker slike legemidler med en hyppighet som gir risiko for kronisk smerte og forverring av smertetilstander. Ettersom risikofaktorer for hyppig bruk av smertestillende legemidler i stor grad overlapper for reseptfrie og reseptbelagte smertestillende, kan unge individer som bruker reseptfrie smertestillende legemidler hyppig, også ha økt risiko for å motta smertestillende legemidler, inkludert opioider, på resept.

Kroniske smerter, psykiske lidelser og lavere sosioøkonomisk status inngår blant risikofaktorene for hyppig bruk av både reseptfrie og reseptbelagte smertestillende legemidler. Traumatiske barndomshendelser er assosiert med kroniske smerter blant ungdom og unge voksne. Slike hendelser er også forbundet med psykiske lidelser som debuterer i ung alder. Lavere sosioøkonomisk status er assosiert med forhøyet risiko for å oppleve traumatiske barndomshendelser.

I denne avhandlingen undersøkte vi hvorvidt eksponering for traumatiske barndomshendelser kan være en risikofaktor for hyppigere bruk av reseptfrie smertestillende legemidler og for å motta reseptbelagte smertestillende legemidler i ung alder. Vi undersøkte interpersonlige traumer og andre traumetyper. Interpersonlige traumer kjennetegnes av at den traumatiske hendelsen ble påført individet av en annen person, slik som fysisk vold, seksuelle overgrep og mobbing. Denne typen hendelser har generelt vist seg å være sterkere forbundet med ugunstige helseutfall senere i livet enn andre typer av traumatiske hendelser. En av våre hypoteser var at denne typen traumatiske hendelser ville være spesielt sterkt assosiert med bruk av smertestillende, da det er funnet i tidligere studier at denne traumetypen er sterkest assosiert med ugunstige helseutfall. Vi undersøkte også hvorvidt en høyere kumulativ eksponering for traumatiske barndomshendelser påvirker senere bruk av smertestillende legemidler, og hvorvidt smerte og psykiske symptomer i ungdomstiden var av betydning for sammenhengene.

Vi brukte data fra tre bølger av den store, populasjonsbaserte Helseundersøkelsen i Trøndelag (HUNT) koblet mot data for individuelle resepter på smertestillende medisiner fra Reseptregisteret (NorPD) for å undersøke problemstillingene. Selvrapportert informasjon om eksponering for traumatiske barndomshendelser, sosioøkonomisk status,

pubertetsutvikling og somatiske og psykologiske symptomer ble hentet fra ungdomsundersøkelsene ung-HUNT3 (2006-2008) og ung-HUNT4 (2017-2019).

Vi undersøkte relasjonen mellom traumatiske barndomshendelser og bruksfrekvens av reseptfrie smertestillende medisiner blant ungdom i alderen 13 til 19 år i en tverrsnittsstudie basert på selvrapporterte data fra ung-HUNT4 (2017-2019). For å undersøke en mulig prospektiv sammenheng mellom traumatiske barndomshendelser og bruk av reseptfrie smertestillende i ung voksen alder, brukte vi data om eksponering fra ung-HUNT3 (2006-2008), rapportert da deltakerne var 13 til 19 år gamle og data om bruksfrekvens av smertestillende fra HUNT4 (2017-2019), da de samme deltakerne var blitt unge voksne (20 til 32 år). For å undersøke en mulig prospektiv sammenheng mellom traumatiske barndomshendelser og reseptbelagte smertestillende medisiner, brukte vi data fra ung-HUNT3 koblet mot data fra NorPD for alle resepter på smertestillende medisiner deltakerne mottok i tidsrommet 2004 til 2021. Vi undersøkte resepter for opioider, paracetamol, NSAIDs og gabapentinoider i separate analyser. Resepter mottatt som ungdom og som ung voksen ble analysert hver for seg.

Vi fant klare sammenhenger mellom det å ha opplevd traumatiske barndomshendelser og hyppigere bruk av reseptfrie smertestillende mot hodepine og muskel- og skjelettsmerte som ungdom og ung voksen. Vi så også en sammenheng mellom eksponering for traumatiske barndomshendelser og høyere forskrivingsrate av reseptbelagte smertestillende medisiner av alle typer. Sammenhengene var mest markert for resepter mottatt som ung voksen. Det var en tendens til sterkere sammenhenger for interpersonlig vold, men vi fant at alle typer av traumatiske hendelser var assosiert med hyppigere bruk av smertestillende medisiner. Det å være utsatt for mer enn én type av traumatiske barndomshendelser var spesielt sterkt forbundet med å bruke mer reseptfrie smertestillende medisiner og å motta flere reseptbelagte smertestillende medisiner, både i ungdomstiden og som ung voksen. Symptomer deltakerne rapporterte som ungdommer, inkludert ukentlig hodepine og ukentlige muskel- og skjelettsmerter, samt psykiske symptomer, inkludert symptomer på posttraumatisk stress, var av betydning for sammenhengene mellom traumatiske barndomshendelser og hyppigere bruk av smertestillende medisiner både for ungdommer og unge voksne.

En høyere forekomst av kroniske smerter, posttraumatisk stress og andre psykiske helseplager blant unge utsatt for traumatiske barndomshendelser, kan medvirke til den observerte assosiasjonen mellom traumatiske barndomshendelser og senere bruk av

smertestillende. Våre funn peker også mot traumatiske barndomshendelser som en miljøpåvirkning som kan bidra til å forklare assosiasjoner funnet i tidligere studier mellom sosioøkonomisk status og kroniske smerter, psykiske helseplager og bruk av smertestillende.

Helseplager som debuterer i ung alder, kan vedvare resten av livet. Den økte risikoen for helseplager i voksen alder er godt dokumentert for både smerter og psykiske plager som debuterer i ungdomstiden. Våre funn vedrørende betydningen av smerter og psykiske plager i ungdomstiden for bruk av smertestillende som ungdom og ung voksen stemmer overens med dette. Sammen med tidligere funn, understreker våre resultater viktigheten av å tilby unge mennesker som søker hjelp for smerter og psykiske helseplager behandling som kan redusere deres risiko for langvarige helseplager.

Unge mennesker som har vært utsatt for traumatiske barndomshendelser ser ut til å ha forhøyet risiko for å få tidlige helseplager, som smerter og psykiske plager, med mulige livsvarige helsekonsekvenser, inkludert hyppig bruk av smertestillende legemidler. Bruk av opioider medfører også en betydelig risiko for misbruk og avhengighet, og denne risikoen kan være spesielt høy blant personer som har vært utsatt for traumatiske barndomshendelser. For å dra klinisk nytte av kunnskapen om den forhøyde risikoen for hyppig bruk av smertestillende blant unge utsatt for traumatiske barndomshendelser, må man legge til rette for at informasjon om slike hendelser kommer frem i situasjoner der unge mennesker søker hjelp for sine smertetilstander. Dette kan for eksempel skje gjennom at man rutinemessig spør unge smertepasienter om slike traumatiske barndomshendelser. Vi vet fra tidligere studier at personer som har vært utsatt for traumatiske barndomshendelser ofte unnlater å søke hjelp for psykososiale plager, til tross for at behovet kan være betydelig. Kontakt med helsevesenet for hjelp med smertetilstander kan representere en mulighet til å fange opp personer med behov for målrettet traumebehandling.

1. Introduction

1.1 The use of analgesics among adolescents and young adults

Analgesics are commonly used by adolescents and young adults (1, 2). Use of over-the-counter analgesics (OTCA) appears to be increasing in the general population across nations, and this trend is also observed for adolescents and young adults (1, 3-5). Additionally, analgesics are commonly prescribed to adolescents and young adults by medical professionals (6-8), and for certain analgesics, there is a noticeable trend of rising prescriptions to young individuals that cannot be solely attributed to an increase in the prevalence of pain conditions in this age group (9).

Generally, nonopioid analgesics such as paracetamol and NSAIDs are considered safe to use within recommended doses for otherwise healthy, young people. While these medications are widely available for purchase without a prescription in most countries, and young people report having easy access to OTCA (10), long-term, frequent use of OTCA is not without health risk. The frequent OTCA use observed among young people put them at risk for developing medication overuse headache and can contribute to the onset, maintenance, and exacerbation of chronic pain (11-13). The potential for medication poisonings is also a concern. High intake of paracetamol causes the majority of medication poisonings among young people. Such poisonings are often unintentional, and they have increased during the past decades (14, 15).

The benefit of using analgesics for long-term pain management among young people is not well documented for any type of analgesic, and evidence is particularly scarce for adolescents (16-19). It is increasingly emphasized in guidelines for management of chronic non-cancer pain for all age groups that nonpharmacological treatment modalities should always be included in the approach to pain management (20, 21). For certain chronic pain diagnoses that occur in pediatric populations, such as migraines and juvenile rheumatoid arthritis, intermittent analgesics use will in many cases be necessary, and such use is within recommendations in treatment guidelines (22-24).

For opioids, the potential for misuse, overdoses and dependence presents a challenge for clinicians in weighing benefits and risks of prescriptions, and such decisions must be made considering the individual pain patient. Generally, prescriptions to young individuals outside of palliative care or situations requiring hospital admission should be restrictive, and the decision to prescribe opioids should always be made bearing in mind that even short-term treatment is associated with a heightened risk of future opioid misuse (25, 26).

Recent guidelines emphasize the lack of evidence of superior effectiveness compared to nonopioid analgesics for most types of pain (27).

Due to the risks associated with frequent analgesics use and the potential of certain analgesics for adverse pain related outcomes, toxicity, misuse and dependence, the trend of frequent and increasing analgesics use among young people is an important public health concern. Behavioral patterns are established at an early age, and it is important to identify early predictors of frequent analgesics use in order to develop effective measures to counteract the trend of frequent and increasing use among young individuals.

1.1.2 Access to analgesics

1.1.2.1 Norwegian health services

In Norway, residents are automatically enrolled in the public healthcare system, which covers both primary and specialist care (28). Access to specialist care, including hospital treatment, requires a referral, while primary care services can be accessed without a referral. Health care costs are governmentally subsidized to maintain affordable rates (28). The public healthcare system also employs a cost limit for medical expenses. Once this limit is reached, further consultations and medication on reimbursed prescriptions (described in more detail below) are covered in their entirety by the government (29). For individuals under the age of 16, medications on a reimbursed prescription are dispensed free of charge, irrespective of total health care expenses. Individuals living in low-income households can apply for reimbursement of all health care expenses.

1.1.2.2 Regulations of over-the-counter and prescription analgesics

Among analgesics, NSAIDs and paracetamol are available without a prescription. The prices of such over-the-counter analgesics (OTCA) are not subject to regulation in Norway. Generally, these drugs are widely available at a low cost, due to several competing products in the market. OTCA are sold at the grocery store as well as in pharmacies. There is an age limit of 18 years for purchasing analgesics at the grocery store, for purchase in pharmacies there is no age limit. Young people generally report that they have easy access to OTCA (10, 30).

The prices of prescription drugs are regulated in Norway, and they have a fixed maximum cost. Obtaining paracetamol and NSAIDs through a prescription can be more affordable than buying the same medication over the counter. Prescription formulations of NSAIDs

and paracetamol may also contain higher dosages per tablet. Opioids and gabapentinoids are only available through a prescription in Norway.

Analgesics can be prescribed on a reimbursed prescription to individuals suffering from chronic non-cancer pain. Certain criteria apply for such prescriptions, including severity of the pain condition and the use of validated tools in diagnostics, severity assessment, function, and treatment effect. Only 2% of the entire population in Norway received analgesics on a reimbursed prescription for chronic non-cancer pain in 2010, corresponding to about 10% of individuals diagnosed with chronic pain at the time (31).

1.1.3 Risk factors for frequent use of analgesics among young people

There are several shared risk factors for frequent analgesics use across subtypes of analgesics. Treatment for cancer and severe injuries or other conditions requiring hospital admission will often require pain relief, and analgesics use for these indications are outside of the scope of this thesis. Palliative care will not be discussed, and analgesics use in critical care will only be discussed in relation to their potential to increase risk of long-term use.

1.1.3.1 Chronic and recurrent pain

Pain is defined by the International Association for the Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage (32). Chronic pain is often defined as pain that persists or recurs for more than 3 months (33). The experience of pain, and particularly recurrent pain and pain in multiple sites, is an important predictor for analgesics use among adolescents and adults (15, 34-37), and such complaints are substantial among young people, as outlined below.

Recurrent pain is prevalent among adolescents, and prevalence is observed to increase throughout adolescence (38). A recent study across several countries and regions found a mean proportion of 44.2% of adolescents reporting weekly recurrent pain (39). A prior study found that among 37.3% adolescents with recurrent pain, 5.1% reported moderate to severe pain that substantially impacting their daily life (40).

Individuals who endure recurrent pain in adolescence are at increased risk of experiencing chronic pain later in life (41, 42). Pain in multiple sites (43) and psychosocial difficulties (43-45) appear to increase risk of adolescent pain persisting into adulthood (43, 46). Psychological comorbidity and pain in multiple sites are associated with increased pain-related disability (47, 48), and higher disability may be a risk factor for persisting pain.

A recent review and meta-analysis found that 11.6% of young adults worldwide could be considered to have chronic pain, defined as pain lasting for at least three months (49). A scoping review found prevalence rates for young adults ranging from 5% to 30% for chronic pain, depending on the sample and the chronic pain definition used (42). The latter review also assessed factors associated with chronic pain in young adults and found that the most consistent associated factors were female sex, familial chronic pain, and experiencing recurrent pain in childhood.

The individual cost of pain substantially impacting daily life and debuting at a young age is enormous. In addition to suffering, recurrent pain can potentially result in daily practical challenges and reduced school and work participation, as well as reduced ability to participate in sports and other leisure activities (40, 50-52). Pain conditions debuting at a young age may lead to lost opportunities and reduced financial resources (53) and are associated with several negative health outcomes (54, 55), including prescription opioid misuse (56). In addition to the individual cost to those affected, chronic or recurrent pain conditions in adolescence and young adulthood represent a substantial burden on societies in terms of productivity loss and health service costs (57).

Given the considerable public health implications of pain conditions in young individuals, the treatment approach to such conditions is of great importance. Treatment that may prevent the progression from acute to chronic pain or produce recovery from chronic pain conditions would be of paramount importance in a public health perspective. Unfortunately, no treatment modalities are well documented to improve pain outcomes in chronic non-cancer pain among adolescents (16-19, 58, 59), however a multidisciplinary individualized approach is considered the gold standard (60). This is generally recommended also for treatment of chronic pain in adults (20).

1.1.3.2 Psychological symptoms and mental health problems

Mental health problems commonly cooccur with chronic pain conditions in young people (61-64). A prior study on a Norwegian general adolescent population found that symptoms of anxiety and depression were strongly associated with musculoskeletal pain (48). Comorbid mental health disorders have been found to be risk factors for using more analgesics among young people with chronic pain (63, 65). A study on adolescents and young adults found that patients with chronic non-cancer pain and comorbid mental health disorders were significantly more likely to receive prescription opioids than pain patients without such comorbidity. Mental health comorbidity was particularly predictive of chronic opioid use (65). Similar patterns are observed for OTCA, where symptoms of psychological

distress are associated with frequent OTCA use among adolescents and young adults (3, 66). Comorbid mental health disorders or a high load of psychological distress may contribute to a reduced ability to adhere to nonpharmacological treatment approaches to chronic pain, as such treatment approaches may be perceived to demand more from the young patient than analgesics use (60). Psychological factors may also be relevant for overall treatment response in multidisciplinary approaches to chronic pain management (67), and a study on pain rehabilitation in children found that higher anxiety levels were associated with a poorer treatment response (68). This could be due to anxiety-related challenges with treatment compliance; however, the lack of treatment response could also be interpreted as an indication that even the current best treatment approach to chronic and recurrent pain in children could potentially be lacking effective components needed to treat the subgroup also suffering from anxiety.

1.1.3.3 Socioeconomic status

Both abovementioned risk factors for using more analgesics (chronic pain and mental health problems) are more common among young individuals with a lower socioeconomic status (67, 69-71), however, a recent study on Norwegian adults found that socioeconomic status was strongly associated with long-term opioid use also after adjustment for pain and mental health diagnoses (72). A study on adolescents and young adults found that lower socioeconomic status in childhood was associated with higher risk of receiving long-term opioid treatment (73). A study on adults with new onset back pain, found that a lower neighborhood socioeconomic status was associated with receiving opioid treatment that was not according to guidelines (74). A lower socioeconomic status is also linked to frequent use of OTCA among young adults (75), particularly in the presence of cooccurring high perceived stress.

Challenges associated with a lower socioeconomic status, such as living in a single-parent household or facing financial instability may contribute to complicate adherence to certain treatment modalities for pain (60). Chronic pain also further negatively impacts functioning and financial resources of families (60), possibly affecting treatment adherence of young individuals.

1.1.3.4 Gender

Several prior studies on adolescents and adults have found that females use more analgesics than males (2, 9, 66). The sex difference becomes noticeable around the onset of puberty and increases during adolescence. It remains evident throughout young adulthood

(9). The possible reasons for the sex difference in analgesics use are not well described, however, prevalences of chronic pain conditions and mental health problems are higher among young females and could be important for the observation (42, 48, 69). Like analgesics use, prevalence of pain conditions are observed to increase among girls throughout adolescence (48). Sex differences in pain perception and effect of analgesics may also be relevant for this finding (76, 77).

1.1.3.5 Childhood trauma

Childhood trauma exposure is associated with several risk factors for frequent analgesics use among young people. Childhood trauma is defined slightly differently in DSM-5 (78) and ICD-11 (79), and a statement that encompasses important components of each of them, and that is also in compliance with the WHO definition of violence (80), could be that childhood trauma is exposure, before adulthood, to an extremely threatening event, experienced directly, by a loved one, or witnessed, that either results in or has high likelihood of resulting in injury, death, psychological harm, maldevelopment or deprivation. Prior studies have found an association between childhood trauma and chronic pain later in life (81-86), however, most studies have assessed childhood trauma exposure retrospectively. Retrospective reporting of childhood trauma in adulthood relies on the ability to remember the potentially traumatic events and is vulnerable to recall bias (87, 88). The reliability of retrospective reporting may also vary between trauma types (89). Existing results from prospective studies on the relation of childhood trauma and chronic pain are conflicting (86, 90, 91). Childhood trauma is also strongly associated with a spectrum of mental health disorders and psychological symptoms, including posttraumatic stress symptoms (92). Socioeconomic factors are relevant for risk of childhood trauma exposure, and a lower socioeconomic status is associated with frequent analgesics use even when accounting for chronic pain and mental health disorders, as outlined above.
In addition to the association of childhood trauma exposure with risk factors for analgesics use, the traumatic event may in itself be a cause of injury requiring pain relief. Childhood trauma exposure is also associated with risk behavior and more frequent injuries (93, 94). Due to all these priorly acknowledged associations, childhood trauma exposure may represent a potent risk factor for more frequent analgesics use among young people. Studies on the subject, where childhood trauma has been assessed retrospectively, suggests an association between childhood trauma and frequent use of analgesics, including opioids (95, 96). Prospective studies on the impact of childhood trauma on risk of receiving prescription analgesics in adolescence and young adulthood are lacking.

1.2 Analgesics: Mechanisms of action, risks and recommendations

1.2.1 Nonopioid analgesics

Paracetamol

Paracetamol is commonly used by children and young adults for its analgesic and antipyretic effect and is generally available without a prescription (97). The mechanism of action of paracetamol is not completely understood, however, it appears to inhibit cyclooxygenase in the brain selectively (97, 98). Paracetamol is liver toxic in excessive doses, and overdoses can be fatal (98, 99). Surviving a paracetamol overdose can lead to lasting liver damage (99). In individuals with impaired liver function, paracetamol can cause liver damage even within recommended doses. Few studies have examined the efficacy and harms of paracetamol in pain management in adolescents, and there is no conclusive evidence regarding this (17). The benefit of paracetamol in chronic pain management in adults is uncertain (20), with evidence of no effect compared to placebo for some conditions (100).

NSAIDs

Non-steroid anti-inflammatory drugs, NSAIDs, are frequently used by young people for their analgesic and antipyretic effect (101). NSAIDs are generally available without a prescription, although some subtypes and formulations may only be available upon prescription. They inhibit the enzyme cyclooxygenase, that is involved in processes causing inflammation, pain and fever (102). Adverse effects of NSAIDs are related to gastrointestinal, renal and coagulation systems (103, 104), and even in healthy young people, frequent use can cause gastrointestinal symptoms (105). Young people with normal renal function and without cardiovascular risk factors are not at risk for renal failure or cardiovascular disease with use of NSAIDs within recommended doses. NSAIDs are found to be effective in the management of acute pain for certain conditions (106, 107). The usefulness in chronic pain conditions remain less certain (107). The efficacy and harm of NSAIDs in the treatment of pain among adolescents is not well documented (18, 101).

Gabapentinoids

The gabapentinoids pregabalin and gabapentin are antiepileptics and analgesics. As analgesics, gabapentinoids are mainly used to treat neuropathic pain, a subtype of chronic pain related to nerve damage (33). In Norway pregabalin is also approved for use in the treatment of generalized anxiety disorder. The analgesic effect of gabapentinoids is caused

by decreased release of excitatory neurotransmitters at synapses, and recent evidence suggests gabapentinoids could have an effect on the proposed neurobiological mechanisms involved in central sensitization, a mechanism that can be involved in chronic pain (108-110). Pregabalin is associated with increased risk of suicidal behavior, unintentional overdose, injuries, and road traffic incidents in young people (111).
In later years pregabalin's potential for abuse and addiction has been increasingly recognized (112-115), and it is a controlled drug in most countries. In Norway, pregabalin was introduced in 2004 and has been a controlled drug since 2018. Overall, there is little evidence supporting the use of gabapentinoids in the treatment of chronic pain in children (19), however, gabapentinoids appear to be effective in the treatment of fibromyalgia in adults (116), in addition to neuropathic pain.

1.2.2 Opioid analgesics

Opioids exert their analgesic effect on specific opioid receptors, interacting with the endogenous opioid system which is normally constantly adjusting between pain and reward in communicating areas of the brain (117). The opioid system interacts with stress response regulation and emotional responses, as well as processes involved in learning and memory (118, 119). Opioid analgesics has an analgesic, and euphoric, effect on the user. Prolonged exposure to opioids results in tolerance for both the euphoric and the analgesic effect (120). In cases of opioid dependence, the experience of euphoria and analgesia is diminished, and opioids become necessary to prevent symptoms of withdrawal.

The enormous potential of opioids for misuse and dependence is now well-known. Starting in the 1980's, opioids were increasingly prescribed to chronic pain patients in the US, resulting in increasing prevalence of opioid use disorder and high numbers of opioid overdoses (120). Opioid prescriptions for acute pain increased in the same time period, and such short-term prescriptions were found to function as a gateway in to long-term prescribing among young people (121). Within about a decade, the detrimental effect of widespread use of opioids to treat chronic pain was recognized as a public health concern (121). In the US and Canada, the phenomenon of increasing prescription rates of opioids and related adverse outcomes was termed an epidemic, and measures were made to reduce prescription rates (120). Similar prescription trends for opioids have been observed in Europe, however, rates of overdoses involving prescription opioids have remained low (122).

The benefits versus risks of opioids in pain management is continuously debated, and guidelines and recommendations appear to become increasingly reluctant to recommend opioid use in the management of acute and chronic non-cancer pain (21, 27). Guidelines emphasize that opioids are in most cases not documented to be superior to nonopioid analgesics or placebo, and it is increasingly difficult to justify offering a treatment that carries such high risk of future misuse and dependence. For adolescents, evidence of efficacy and harm of opioids in management of chronic pain is scarce (16).

Opioids remain important for alleviating the severe pain following surgical procedures and injuries involving extensive tissue damage (27), however, even short term opioid use is associated with later long-term opioid use and opioid misuse among young people (25, 26, 123, 124), and opioid stewardship is recommended also in these settings (27, 125). Opioids also remain important in palliative care for all age groups.

1.3 Chronic and recurrent pain

1.3.1 Definitions and subtypes

While acute pain may be a crucial que for survival and an important facilitator of tissue healing, chronic pain serves no obvious purpose. Generally, pain that persists beyond the expected healing period of an acute injury, is considered to represent chronic pain. Pain persevering after 3 months is often used as a definition of chronic pain, including in ICD-11 (33, 79). Chronic pain is increasingly acknowledged as a disease in its own right with its specific predisposing factors and pathological alterations in the peripheral and central nervous systems (126, 127).

Starting a few decades back, research and clinical practice has evolved from a condition-specific approach to chronic pain conditions to an acknowledgement of common processes underlying several conditions previously considered discrete chronic pain disorders, such as chronic low back pain and headaches (126). This view of chronic pain also aligns with the biopsychosocial model for chronic pain, which was introduced by psychiatrist George Engel in 1977 (128), and is considered to be relevant for all chronic pain conditions (129). The biopsychosocial model emphasizes the importance of considering the dynamic interaction of biological, psychological, and social factors underlying the clinical presentation of all chronic pain conditions (20, 129).

Although many of the same mechanisms can be manifest across different pain conditions, chronic pain is not a uniform phenomenon. Rather, the underlying causes and effectiveness

of treatment modalities can differ substantially between patients suffering from chronic pain (20). The pain definition stated in the beginning of this section, acknowledges that pain can occur without an initial identifiable tissue damage, which will be the case for a substantial proportion of individuals with a diagnosis of chronic pain. Three main categories of chronic pain mechanisms are considered to encompass the majority of chronic pain conditions: nociceptive, neuropathic and nociplastic pain (20).

Nociceptive pain is pain related to the well-established mechanisms of pain signaling related to inflammation and tissue damage, and is considered to be the most common form of chronic pain, encompassing prevalent disease groups related to degenerative processes, traumatic injury and visceral pathology (20). These conditions are classified as chronic secondary pain in ICD-11 (33).

Neuropathic pain is related to nerve damage (33). This type of pain is often associated with altered sensation in the corresponding area, and there may also be other neurological findings related to the affected structure (130). About one fifth of chronic pain patients will sort in this category, which encompasses diabetic neuropathy and postherpetic neuralgia, as well as radiculopathy. Neuropathic pain is classified as chronic secondary pain in ICD-11 (33).

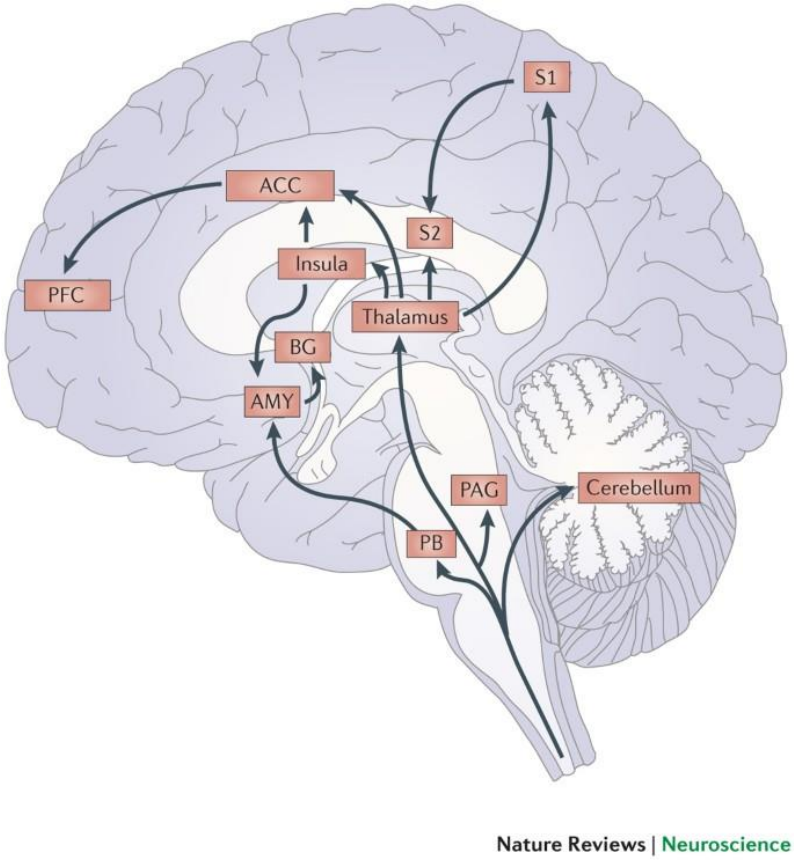
Nociplastic pain is pain without an identifiable primary cause(20). This types of pain is classified as chronic primary pain in ICD-11(79). This type of pain is considered to be caused by alterations in pain signaling systems and is present in the absence of evident damage to tissues or structures of the somatosensory system (33). Alterations in pain signaling associated with chronic primary pain have been observed at multiple levels in the nervous system and involve amplified processing or decreased inhibition of pain signals (131). Chronic primary pain conditions have previously often been referred to as functional pain syndromes, however, increasing knowledge about the underlying pathological processes causing chronic primary pain has warranted a more specific term for this category. Although several nociplastic mechanisms have been outlined, the category chronic primary pain will still clinically encompass all pain conditions where we do not know of a neuropathic or nociceptive primary pain mechanism. These conditions would priorly have been considered idiopathic or functional.

It is argued that pain classification should be considered in a continuum where a large proportion of patients will not be easily categorized as one distinct subtype (20).

1.3.2 Neurobiology of pain and chronic pain

Pain signaling involves a complex processing system. The typical ascending pain pathway activated by a noxious stimulus, such as tissue damage, will begin with the excitation of a peripheral, first-order, nociceptive neuron. These neurons synapse with second-order neurons in the spinal dorsal horn. The second-order neuron relays the signal to the periaqueductal gray (PAG) in the midbrain and to the thalamus in the central nervous system (CNS). From thalamus, the signal is transmitted to the somatosensory cortex, prefrontal cortex, anterior cingular cortex (ACC), amygdala and nucleus accumbens.

Figure 1. CNS structures of importance for nociception



Bushnell et al. 2013 (132). Reprinted with permission obtained through RightsLink.

Figure 1. Nociceptive information enters the brain from the spinal cord. Nociceptive information from the thalamus is projected to the insula, anterior cingulate cortex (ACC), primary somatosensory cortex (S1) and secondary somatosensory cortex (S2). Information from the amygdala (AMY) is projected to the basal ganglia (BG). PAG, periaqueductal grey; PB, parabrachial nucleus; PFC, prefrontal cortex. Text adapted from Bushnell et al. 2013.

The pain signal is not simply transmitted from peripheral nociceptors to the CNS, pain signaling is also continuously modulated by a parallel system from the CNS to the periphery. The descending modulatory systems is coordinated by the PAG, which is under descending control by the prefrontal cortex (133). Output from the PAG alters pain transmission in the dorsal horn through the rostral ventromedial medulla to facilitate or inhibit signal transmission.

The prefrontal cortex is involved in emotional and cognitive processing of pain, and the prefrontal cortex is important for reducing fear driven behaviors in response to subcortical pain signaling. Reduced activity and volume of the prefrontal cortex has been found to be associated with persisting pain in preclinical studies (134). The prefrontal cortex receives input from hippocampus, the anterior cingulate cortex (ACC), and the amygdala, in addition to the thalamus.

The amygdala is involved with emotional processing, and its activation in pain states suggests its role in the affective aspects of pain perception. The amygdala both receives signals from and sends signals to the prefrontal cortex. In response to persistent nociceptive stimuli, amygdala connections are upregulated, and amygdala volume is increased. This is considered to be of relevance for the negative affect associated with chronic pain (133).

The hippocampus regulates the hypothalamic–pituitary–adrenal axis and is important in learning and memory. The hippocampus sends signals to the prefrontal cortex, and changes in the hippocampus have been reported in chronic pain conditions (135).

The anterior cingulate cortex (ACC) incorporates the nociceptive input from thalamus with affective and motivational information from the amygdala, nucleus accumbens and prefrontal cortex. ACC also interacts directly with pain circuits in PAG and is considered to have a crucial role in pain processing and modulation (136). Alterations in ACC activity are associated with persistent pain (136).

Cortical and affective information is integrated in the nucleus accumbens, which is involved with encoding the importance of pain signals and selecting the appropriate behavioral response. Changes in nucleus accumbens circuitry and connectivity are associated with pain chronification (135).

CNS structures of particular interest in the context of chronic pain are summarized in Table 1.

Opioid receptors are present in all supraspinal pain processing sites as well as the dorsal root ganglion and the dorsal horn. Opioids activate inhibitory gamma-aminobutyric acid (GABA) supraspinal neurons. Opioid activity also triggers the dopaminergic network of the PAG, participating in descending inhibition. Thus, the overall effect of endogenous opioids is an inhibition of pain signaling (117). Endogenous opioids are important in placebo analgesia (133). Reduced availability of opioid receptors, due to decreased receptor expression, is considered to contribute to the development of chronic pain (135).

Central and peripheral neuroinflammation have been proposed as important components of persisting pain (137). Activation of glial cells leads to the release of proinflammatory cytokines, that are powerful neuromodulators and have the potential to induce hyperalgesia and allodynia. Sustained high levels of proinflammatory cytokines in the CNS could be involved in widespread chronic pain via central sensitization.

In summary, chronic pain is associated with many pathological alterations in pain signaling, including structural and functional changes involving central and peripheral signaling (135). While there is a somatotopic, mechanical aspect to nociception, there are always cognitive and emotional components as well, once again emphasizing the relevance of the biopsychosocial model for pain.

Table 1. CNS structures particularly relevant for chronic pain.

Brain region	Function and relevance for chronic pain
Medial prefrontal cortex	Decision making, self-control, regulation of emotion, processing of risk and fear, and regulation of amygdala activity
Amygdala	Memory modulation, decision-making, reward, emotional responses
Periaqueductal gray	Autonomic function, motivated behavior, response to threatening stimuli, primary control center for descending pain modulation
Anterior cingulate cortex	Attention allocation, reward anticipation, decision-making, ethics and moral, impulse control, registration of physical pain
Hippocampus	Consolidation of memories, emotion, navigation, spatial orientation, learning
Nucleus accumbens	Cognitive processing of motivation, aversion, reward, reinforcement learning, significant in addiction

Adapted from Yang et al. 2019 (135)

1.4 Childhood trauma

The definition of childhood trauma is worded differently in DSM-5 and ICD-11. In DSM-5, childhood trauma is defined as exposure to death, serious injury, or sexual violence, actual or threatened, experienced directly, by a loved one, or witnessed, before reaching adulthood (78). Witnessing does not include witnessing such events through electronic media, television, movies, or pictures.

In ICD-11, trauma is defined as exposure to an event or situation (either short- or long-lasting) of an extremely threatening or horrific nature (79). Such events include, but are not limited to, directly experiencing natural or human-made disasters, combat, serious accidents, torture, sexual violence, terrorism, assault or acute, life-threatening illness, witnessing the threatened or actual injury or death of others in a sudden, unexpected, or violent manner, and learning about the sudden, unexpected or violent death of a loved one.

Violence is defined by The World Health Organization as the intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community, that either results in or has a high likelihood of resulting in injury, death, psychological harm, maldevelopment or deprivation (138).

A statement to define childhood trauma that encompasses important components of the DSM-5 and the ICD-11 definitions and that is in compliance with the WHO definition of violence, could be the following: childhood trauma is exposure, before adulthood, to an extremely threatening event, experienced directly, by a loved one, or witnessed, that either results in or has high likelihood of resulting in injury, death, psychological harm, maldevelopment or deprivation.

The numbers of children exposed to potentially traumatic events are substantial across nations, and several studies have found that a majority of children have been exposed to a potentially traumatic event (139-142).

Trauma literature commonly distinguishes between interpersonal and non-interpersonal trauma types (143). Interpersonal trauma types are characterized by intentional harm being inflicted upon the victim by another person (143). Physical violence, sexual abuse, and witnessing such events, all sort in this category. Acts of terrorism and war will also sort as interpersonal trauma (143). Bullying victimization has not traditionally been included in trauma research, however, a recent review concludes that this type of victimization should be regarded interpersonal trauma, considering the pathology related to childhood bullying

(144). This is also in line with the WHO definition of interpersonal violence (138). Interpersonal trauma types have generally been found to be more closely linked to trauma-related pathology throughout childhood and adulthood than other trauma types (139, 142, 145, 146).

Non-interpersonal trauma are events that can be considered unintentional, such as accidents, disasters, severe illness affecting oneself or a close one, or the sudden loss of a loved one (143). Some of these events are fairly common exposures among children, such as the sudden loss of a loved one (139, 140) and accidents and injuries (143, 147).

Although childhood trauma exposure is prevalent in all societies and circumstances, certain individual characteristics and environments may entail a higher risk for trauma exposure. Generally, older children experience more traumatic events than younger children (143). Girls are more likely to be exposed to sexual abuse than boys (147), while boys are more likely to experience physical violence and accidents than girls (143). Preexisting behavior disorder increases the risk of trauma exposure (139). Young individuals with disabilities are more likely to be victims of abuse and bullying than peers without disabilities. Girls with intellectual disabilities have the highest risk (147). At the family level, lower socioeconomic status, family dysfunction and household structures other than growing up with both parents, have been found to be associated with an increased risk of exposure to childhood trauma (139, 140, 148). Environmental factors at the community and national level can further increase risk, including factors like neighborhood crime rates and elevated national conflict levels (143).

Studies assessing cumulative trauma exposure, have found considerable overlap of different types of trauma exposures, including interpersonal and non-interpersonal trauma within individuals (146, 149-151). A higher cumulative trauma exposure is associated with more severe impact on future health compared to a lower cumulative trauma exposure (149, 150, 152), this is also evident in studies on adverse childhood events (ACE) (153-155). All such events may not be defined as childhood trauma, however, there appears to be considerable overlap in associated pathology, also for adverse childhood events not normally included in childhood trauma assessments (156).

1.4.1 Consequences of trauma exposure

The potency of childhood trauma exposure as a pathogen in many disease processes is increasingly acknowledged across a wide spectrum of diagnoses involving most organ systems (82, 152, 155, 157-159). While the relation of childhood trauma to a wide range of

mental health disorders is well established, the relation of childhood trauma to somatic conditions has also received increasing attention in research over the past few decades (143). The relationships between trauma, posttraumatic stress symptoms, mental health disorders, and somatic health conditions are complex, with extensive comorbidity, and the potential of several trauma-related adverse health and functional outcomes reciprocally affecting each other (82, 142). Neurobiological, social, behavioral, and psychological factors are considered to be important for the extensive impact of childhood trauma on future health (160).

1.4.1.1 Mental health disorders

In addition to posttraumatic stress disorder (PTSD), there is extensive evidence of a relation of childhood to depression, anxiety, and externalizing behavior problems (143).

PTSD is diagnosed by the same criteria as adults in children over six years in DSM-5, utilizing a four-factor model of symptoms: reexperiencing the trauma, avoidance of trauma-related stimuli, negative alterations in cognition and mood, and hyperarousal and reactivity (143). For children younger than six years of age, there is a separate set of criteria, taking into account the different symptom presentation in younger children (161). ICD-11 uses three core criteria for PTSD, that are largely overlapping with DSM-5 criteria, except for the factor negative alterations in cognition and mood, that is not included in ICD-11 criteria. It is estimated that about 16% of all children exposed to trauma develop PTSD (145), and rates are higher following interpersonal trauma than non-interpersonal trauma (139, 145).

Depression has been shown to frequently cooccur with PTSD, and increased rates of depression has been observed in trauma-exposed youth (146, 162). Symptoms of anxiety have also been shown to frequently co-occur with PTSD in trauma-exposed youth (146), and it is debated whether this should be conceptualized as a distinct form of psychopathology in patients with PTSD (143).

While PTSD, depression and anxiety are all considered internalizing problems, trauma-exposed children may also exhibit externalizing behavior problems (143). Childhood trauma has been found to be associated with oppositional behavior, conduct problems and symptoms of attention-deficit/hyperactivity disorder in childhood, and in adolescence, childhood interpersonal trauma has been found to be associated with risk behavior (143).

1.4.1.2 Physical health problems

While pediatric physical health problems have received less attention than mental health problems in research on consequences of childhood trauma exposure, several pediatric physical conditions have been found to be associated with childhood trauma, including sleep disturbances, overweight, and pain (143, 163). Among adults, childhood trauma has been found to be associated with a range of adverse physical health outcomes, including diabetes, cancer, respiratory disease and cardiovascular disease (153, 164). As in pediatric populations, childhood trauma exposure and PTSD has also been found to be associated with pain conditions in adults (82, 86, 165).

1.4.1.3 Repeated traumatization

Exposure to one traumatic event increases the risk of exposure to another. The risk is observed to be particularly increased after initial exposure to interpersonal trauma, and the increased risk persists into adulthood (166-168). Studies assessing cumulative trauma exposure, have found considerable overlap of different types of trauma exposures, including interpersonal and non-interpersonal trauma within individuals (146, 149-151). The individual and environmental factors associated with increased risk of exposure to childhood trauma mentioned above, could contribute to the observed risk of repeated traumatization. In addition, trauma exposure is associated with outcomes that could put young individuals in situations with increased risk of trauma exposure, including several forms of risk behavior (169)

1.5 Adolescent and young adult health

1.5. 1 Transitioning from childhood to adulthood

Adolescence is a stage of rapid physical, neurocognitive and psychosocial development. It represents the beginning of the transition from childhood to adulthood, and is a formative developmental stage (147). During adolescence, puberty represents a phase of particularly rapid somatic growth and brain development, as well as sexual maturation and attainment of reproductive capacity. Prevalence of pain conditions are observed to increase throughout adolescence, and puberty and pubertal timing appears to affect risk of pain in adolescence (170, 171). Puberty and pubertal timing are also observed to affects risk of exposure to potentially traumatic events among girls (172).

Young adulthood is the developmental stage following adolescence. There is no consensus on the exact age group included in the term, however the age span from 18 to 25 years is

normally included, and the term sometimes extends to individuals in their 30's (173). Young adulthood is a stage of continued psychosocial and biological development, and the dramatic spurt in brain development that begun in adolescence is completed within young adulthood (173). Young adulthood also represents many transitions and new responsibilities, including changes in the health care services offered and the responsibility of managing one's own health, including pain conditions.

1.5.2 Window of opportunity

Chronic pain and mental health disorders are among the largest causes of morbidity in adolescence, and for a number of individuals, this represents the onset of a trajectory of increased morbidity throughout young adulthood and beyond (147). The influence of the family decreases, while important determinants for future health, such as peer relations and school environment are established (174). Adolescence is an important phase for establishing behavioral patterns and coping strategies (147), and unmet health needs in adolescence have been observed to negatively affect adult health outcomes (175). It has been suggested that health service transition programs targeted at emerging adults with pain could benefit young individuals as they enter adulthood (49).

Adolescence and young adulthood may be seen as a window of opportunity for establishing beneficial behavioral patterns and for guiding individuals towards trajectories that are likely to benefit their health throughout life (147, 176). Interventions targeted at young individuals at increased risk of adverse health outcomes, could substantially improve public health.

2. Aims of the thesis

The overall aim of the thesis was to investigate how exposure to childhood trauma relates to use of analgesics among adolescents and young adults outside of palliative and critical care. A broad range of potentially traumatic events were included, as well as relevant symptoms in the context of analgesics use, including chronic pain and symptoms of posttraumatic stress and general psychological distress. In addition to specific research question for each paper as listed below, we examined the potential impact of a higher cumulative load of interpersonal trauma and other trauma types.

The following research questions were addressed in the three papers:

Paper I

Is childhood trauma related to use of over-the-counter analgesics (OTCA) in adolescence, and can frequency of OTCA use be explained by frequency of pain?

Paper II

Is childhood trauma related to use of OTCA in young adulthood, and is symptomatology in the form of pain and psychological symptoms emerging in adolescence of importance for a potential relation?

Paper III

Is childhood trauma related to use of prescription opioid and nonopioid analgesics in adolescence and young adulthood? Are pain and psychological symptoms emerging in adolescence related to prescription rates for analgesics in adolescence and young adulthood among trauma-exposed individuals?

3. Methods

3.1 Data sources

3.1.1 The HUNT Study

The Trøndelag Health Study (The HUNT Study) is a large population-based study consisting of a survey, an interview, and physical measurements (177). The HUNT Study has been conducted in several waves. This thesis utilized data from Young-HUNT3 (2006-2008, n=8199), Young-HUNT4 (2017-2019, n=8066) and HUNT4 (2017-2019). As of 2019, the HUNT Study includes a metropolitan area due to an expansion of the study region, however, the data used in this thesis is limited to the participants of Young-HUNT3 and -4, residing in the region formerly known as Nord-Trøndelag at the time of participation. This geographical region in Norway is characterized by low immigration and is without large metropolitan areas (177).

Figure 2. Map of Norway, showing the region of Nord-Trøndelag (in orange).

Image: KF-bok, snl.no. «Nord-Trøndelag - tidligere fylke»

Participation in the HUNT Study was voluntary. 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 consent includes agreement to linkage of individual study data to registry data and can be withdrawn at any time. The surveys have been approved by the Regional Committee for Medical Research Ethics and the Data Inspectorate of Norway.

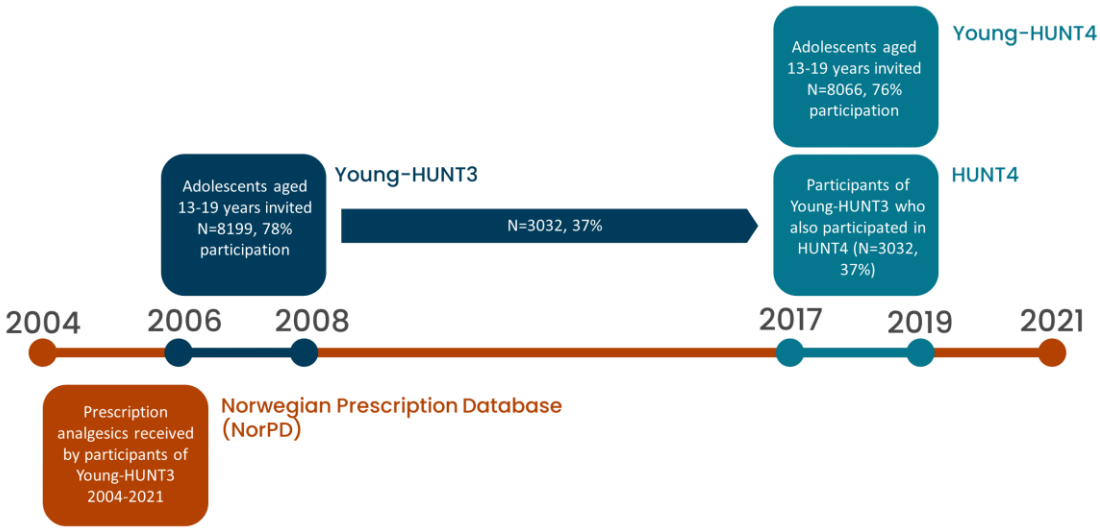
Data utilized in this thesis on exposure to childhood trauma, experiencing headache, musculoskeletal pain, pain-related disability, and psychological symptoms including symptoms of posttraumatic stress were all collected in Young-HUNT3 and -4 when participants were aged 13-19 years. Data on background factors including pubertal development, household structure and family economy was also collected in Young-HUNT3 and -4. Data on young adult use of OTCA was collected in HUNT4, and data from HUNT4 was utilized only for participants also taking part in Young-HUNT3 (n=3032).

In Young-HUNT3 (2006-2008) the full cohort of 10 464 adolescents (aged 13-19 years) living in the region of Norway formerly called Nord-Trøndelag were invited to participate. The participation rate in Young-HUNT3 was 78% (n=8 199). Most adolescents completed the self-administered questionnaire during school hours. Adolescents in vocational training and adolescents not in school were invited to participate in settings relevant to their daily activities.

In Young-HUNT4 (2017-2019) the full cohort of 10 608 adolescents (aged 13-19 years) living in the region of Norway formerly called Nord-Trøndelag were invited. The participation rate was 76% (n=8066). Most adolescents completed the survey during school hours; however, measures were made to increase participation of adolescents not in school. Youth representatives were involved in planning the survey, and adolescents in pilot schools gave feedback to optimize conduction of the full survey.

In HUNT4 (2017- 2019), all adult inhabitants of the region of Norway formerly called Nord-Trøndelag were invited to participate, as well as participants in previous waves of the survey who had moved out of the region. Among the participants in Young-HUNT3, 37% also participated in HUNT4 (n=3032).

Figure 3. Timeline of data sources



Attrition in The HUNT Study

While overall participation rate in Young-HUNT3 was high (78%), participation was lower among adolescents in vocational training (33%, n=128) and adolescents not enrolled in education (23%, n=115), although they were invited and given opportunity to participate. In Young-HUNT4 additional measures were made to recruit participants among adolescents in vocational training and adolescents not in education. It was arranged for adolescents in vocational training to participate on planned gatherings, and adolescents who were not in education were invited to participate on their meetings with the follow-up service. While the participation rate was slightly higher among adolescents in vocational training (40%, n=237) compared to Young-HUNT3, the participation rate for adolescents not enrolled in education was still low (10%, n=42), and participation rates were lower than for adolescents in school (76%) for both groups.

Among participants in Young-HUNT3, more females than males also participated in HUNT4. Participation in HUNT4 was observed to be lower among individuals reporting exposure to interpersonal trauma, a lower family economy, not living with both parents, and suffering from chronic pain in Young-HUNT3.

3.1.2 The Norwegian Prescription Database

We utilized data from the Norwegian Prescription Database (NorPD) for paper III of this thesis. NorPD is an electronic registry which has obtained data on all filled prescriptions from all pharmacies in Norway from 2004 onwards. Patient identifiers, date of dispensing and an Anatomical Therapeutic Chemical (ATC) code identifying the specific drug (178) is registered with each filled prescription (179). In Norway, opioids and gabapentinoids are not available for purchase without a prescription, and prescription data from the NorPD therefore contain information on all dispensing of these drugs in Norway outside of a hospital setting. For Paracetamol and NSAIDs the situation is different, as some medications within these analgesics groups can be obtained without a prescription. Medications administered during hospital admissions and at institutions are not registered in NorPD.

We linked data from the Young-HUNT3 Study (2006-2008) to data from the Norwegian Prescription Database (NorPD). This linkage enabled tracking of individual prescriptions for opioid and nonopioid analgesics for the participants from 2004 to 2021. Table 2 shows an overview of study designs and data sources for the three papers included in this thesis.

Table 2. Study design and data sources

	Paper I	Paper II	Paper III
Design	Cross-sectional	Longitudinal, prospective	Longitudinal, prospective
Outcome measure	Frequency of OTCA use to treat i) headaches and ii) musculoskeletal pain	Frequency of OTCA use to treat i) headaches and ii) musculoskeletal pain	Analgesics prescriptions in adolescence and young adulthood
Data source	Young-HUNT4 (2017-2019)	Young-HUNT3 (2006-2008) → HUNT4 (2017-2019)	Young-HUNT3 (2006-2008) → NorPD (2004-2021)
Participants	n=8066	n=3032	n=8199
Type of data	Self-report	Self-report	Self-report and registry data

3.2 Measures

Exposure to childhood trauma, socioeconomic factors and psychological and somatic symptoms were measured in Young-HUNT4 (2017-2019) for paper I and in Young-HUNT3 (2006-2008) for paper II and III. Participants were adolescents (age 13-19 years) when these surveys were conducted. The corresponding measures utilized in papers I-III, derived from Young-HUNT3 and -4 are very similar, although with slight variations in the underlying questions between the two Young-HUNT surveys. This is detailed in the description of the items below. An overview of all measures utilized in analyses and their status as exposure, covariate or dependent in the three papers is shown in Table 3.

Table 3. Overview of variables used in analyses in papers I-III

Variable	Paper I	Paper II	Paper III
Frequency of OTCA use in adolescence			
to treat musculoskeletal pain	D		
to treat headache	D		
Frequency of OTCA use in adulthood			
to treat musculoskeletal pain		D	
to treat headache		D	
Number of prescriptions in adolescence			
Opioids			D
Paracetamol			D
NSAIDs			D
Gabapentinoids			D
Number of prescriptions in young adulthood			
Opioids			D
Paracetamol			D
NSAIDs			D
Gabapentinoids			D
Childhood interpersonal trauma			
Bullying	E	E	E
Sexual abuse	E	E	E
Physical violence	E	E	E
Witnessing violence	E	E	E
Other childhood trauma			
Severe disease or death of someone close	E	E	E
Accidents, disasters, other traumatic events	E	E	E
Cumulative scores for childhood trauma			
Interpersonal trauma	E		
Direct interpersonal trauma		E	E
Other trauma including indirect violence			E
Other trauma not including indirect violence	E		
Background variables			
Sex	C	C	C, E**
Age	C	C	C, E**
Family economy	C	C	C, E**
Household structure	C	C	C, E**
Pubertal development	C		C, E**
Adolescent symptoms			
Weekly headaches	C	C	E*
Weekly musculoskeletal pain	C	C	E*
Juvenile idiopathic arthritis	C		
Psychological distress		C	E*
Posttraumatic stress		C	E*

E: Exposure variable
C: Covariate
D: Dependent variable
*Exposure variable for the subsample exposed to trauma
**Exposure variable in analyses for assessment of the relation of background factors to the outcomes

3.2.1 Background: Sociodemographics

Age, sex, and pubertal development.

Data on age and sex is obtained by The HUNT Study from the Norwegian National Population Registry, these variables are included in the data from The HUNT Study. Pubertal development stage was assessed using a four-item version of a validated pubertal development scale (180). Girls and boys were asked to rate their growth spurt and body hair on a four-point rating scale from 1="has not begun" to 4="development completed". The same rating scale was used when asking boys to rate their extent of voice change and facial hair and when asking girls to rate breast development. Girls also reported on whether they had reached menarche, where premenarchal stage was rated 1 and postmenarchal stage was rated 4. A mean pubertal development score ranging 1 to 4 was computed.

Socioeconomic status

Questions about participants' household structure and perceived family economy were used to assess socioeconomic status. We grouped participants into those living with both their parents, including adoptive parents, and those living in other types of households (139). For the measure on family economy, participants were grouped into those perceiving their family economy as below that of their peers and those perceiving their family economy as about the same or better than that of their peers.

3.2.2 Childhood trauma exposure

Childhood trauma exposure was assessed in both Young-HUNT3 and Young-HUNT4 in a brief lifetime childhood trauma screen derived from the UCLA Stress Disorder Reaction Index, part I (181), adapted to a Norwegian context (Table 4). The adaptation consisted of the omission of specific questions concerning events that would be rare occurrences in the study population, including gun violence and acts of war, and the inclusion of a question on bullying in Young-HUNT3, in compliance with the WHO definition of interpersonal violence (80). The trauma screen included an open question on threatening and frightening experiences in both waves, ensuring that individuals could report on all types of potentially traumatic events.

While the UCLA PTSD Index, Part I, is a validated instrument (182), it has not been validated in Norwegian. The development of the Norwegian version was meticulously focused on maintaining high quality standards in a Norwegian setting. The Norwegian

version has been used in prior studies to investigate associations between childhood trauma and health outcomes (183-185).

All events were listed under the question "Did you ever experience any of these events?". In Young-HUNT3, the items on interpersonal trauma (physical violence, sexual abuse and bullying) were all assessed in the trauma screen, while in Young-HUNT4 bullying was assessed separately in four questions specifically assessing different types of bullying. While the measure from Young-HUNT3 used in paper 2 and 3 will only capture physical bullying and threats, the measure from Young-HUNT4 utilized in paper I encompasses a broader spectrum of exposure to bullying, including social exclusion, verbal bullying and cyberbullying. Participants responded to the questions on bullying in Young-HUNT4 by the frequency of which the bullying had occurred, and participants reporting weekly or more frequent exposure for the past 6 months were labeled as being bullied. This contrasts with the measure in Young-HUNT3, where any exposure at any point in time before participation would result in the participant being labeled as exposure to bullying.

Cumulative Childhood Trauma Exposure

We assessed cumulative childhood trauma exposure in all papers. While it is generally agreed upon that cumulative trauma exposure is relevant in the context of investigating the impact of childhood trauma on health, no system for grouping of trauma types is established (186).

In paper I, we assessed all types of interpersonal trauma (bullying, sexual abuse, physical violence and witnessing violence) in a cumulative variable ranging from 0 to ≥2, and other trauma types (severe illness or death and accidents, disasters, and other trauma) in a different cumulative variable ranging from 0 to 2.

In paper II, we assessed direct interpersonal trauma (bullying, sexual abuse and physical violence) cumulatively, in a variable ranging from 0 to ≥2.

In paper III, we assessed direct interpersonal trauma (bullying, sexual abuse and physical violence) in a cumulative variable ranging from 0 to ≥2, and other trauma types, including witnessing violence in addition to severe illness or death and accidents, disasters, and other trauma in a separate cumulative variable ranging from 0 to 3.

Table 4. Operational definition of childhood trauma exposure

Measure	Survey question	Operationalization	Questions derived from
Exposure to interpersonal trauma	Young-HUNT3 and -4 *Have you ever experienced any of these events?*	In Young-HUNT3, participants could answer i) never, ii) yes, in my life or iii) yes, the last year. Participants answering "yes"(ii/iii) were labeled exposed. In Young-HUNT4, participants could answer i)never, ii) yes, once, or iii) yes, more than once. Participants answering "yes" (ii/iii) were labeled exposed.	UCLA PTSD Reaction Index for DSM IV, part I (181)
Physical violence	been subjected to violence (beaten/injured)		
Witness to violence	seen someone else being subjected to violence		
Sexual abuse	been subjected to an unpleasant sexual act by a peer been subjected to an unpleasant sexual act by an adult		
Bullying	Young-HUNT3 *Have you ever experienced any of these events?* been threatened or physically harassed by fellow students at school over a period of time Young-HUNT4 *How many times has this happened to you the last 6 months?* i)I have been made fun of, teased, or called names ii)I have been hit, kicked, attacked, or had my hair pulled III)I have been excluded, not allowed to participate iv)I have received unpleasant messages or photos by phone or online	In Young-HUNT3, participants could answer i) never, ii) yes, in my life, or iii) yes, the last year. Participants answering yes were labeled exposed. In Young-HUNT4, participants could answer never, 1-3 times per month, once per week, 2-4 times per week and almost daily. Participants reporting weekly or more frequent bullying were labeled exposed.	In compliance with the WHO definition of interpersonal violence (80)
Exposure to other trauma	Young-HUNT3 and -4 *Have you ever experienced any of these events?*	In Young-HUNT3, participants could answer i) never, ii) yes, in my life or iii) yes, the last year. Participants answering yes were labeled exposed. In Young-HUNT4, participants could answer i)never, ii) yes, once, or iii) yes, more than once. Participants answering yes were labeled exposed.	UCLA PTSD Reaction Index for DSM IV, part I (182)
Severe illness or death of someone close	you or someone in your family was seriously ill the death of someone close to you		
Disaster, serious accident or other traumatic event	a disaster (fire, hurricane or similar) a serious accident (e.g., serious car accident) other experience that was very frightening, dangerous or violent *Only Young-HUNT3* painful or frightening hospital treatment for a disease or an accident		

3.2.3 Pain and pain-related measures

Musculoskeletal pain was assessed by asking about frequency of pain in several sites for the past three months. This method of assessing musculoskeletal pain among adolescents has been extensively used in prior studies (64, 187, 188). The instrument used in Young-HUNT3 and -4 were based on an instrument developed by Mikkelsen et al (189). There were some minor differences in the sites assessed between Young-HUNT3 and Young-HUNT4, this is detailed in Table 5. We counted the sites from which participants reported weekly or more frequent pain. This pain frequency has been used for assessment of musculoskeletal pain in adolescents in prior studies (48, 190).

Recurring headache for the past year was assessed in a headache interview that has been validated in a Norwegian adolescent population (191). Participants were asked about headache characteristics in order to assess type of headache (migraine, tension type headache or other headache), and further they were asked about headache frequency for each subtype, as detailed in Table 2. Participants reporting weekly headaches of any subtype were labeled as having headache.

In Young-HUNT4, participants were asked if they had received a diagnosis of juvenile idiopathic arthritis from a doctor. Participants responding “yes”, were classified as having Juvenile Idiopathic Arthritis.

Pain-related disability was assessed based on survey questions in Young-HUNT3 and -4 using an established disability index (189) containing five statements. Participants were asked to indicate whether the statements were a true or false description of their disability caused by pain. The statements were used to compute a sum score ranging 0-5. The survey statements differed from the original instrument in that there were two statements assessing the impact of pain on sleep. These measures were combined to give a maximum of 1 point in the sum score, in compliance with the original instrument and previous assessments (48). This measure was used to describe pain-related disability among adolescents in paper I and II.

OTCA use in adolescence, reported in Young-HUNT3, was used as a descriptive measure in paper II, where OTCA use in young adulthood, reported in HUNT4, was the outcome measure. Participants reported frequency of use: never, ≤1 day per week, 2 days per week, 3 days per week, or ≥4 days per week, to treat back pain, other musculoskeletal pain, headache, and stomachache. As it was not possible to use weekly OTCA use as a cutoff for this measure, participants who reported using OTCA two or more days per week were

considered to use OTCA frequently. The proportion using OTCA two or more days per week was reported for descriptive purposes.

3.2.5 General psychological distress and posttraumatic stress symptoms

Symptoms of general psychological distress were assessed in Young-HUNT3 by using a validated short version of the Hopkins Symptoms Checklist (SCL-5) (192), as detailed in Table 2. The SCL-5 has been validated in adolescents aged 16 to 19 years (192). This measure was used to assess general psychological symptoms in paper II and III. The mean score (ranging from 1.0 to 4.0) was used for regression analysis, while a score >2.0 was used as a cutoff for experiencing psychological distress for descriptive purposes, in compliance with the validation study.

Symptoms of posttraumatic stress were assessed by three questions in Young-HUNT3, as detailed in Table 2. This measure was used in paper II and III. Questions were derived from UCLA PTSD reaction index, part III. The full version of UCLA PTSD-RI has been used to assess symptoms of posttraumatic stress among Norwegian adolescents in several prior publications and exhibits a Cronbach's alpha of 0.89 (193), although Norwegian validation studies have not been conducted. The three questions used in Young-HUNT3 were carefully selected in a collaboration between The Norwegian Centre for Violence and Traumatic Stress Studies and the authors of the original instrument, with the aim of capturing participants suffering from posttraumatic stress symptoms in an epidemiological study allowing for only a few questions.

Table 5. Operational definition of symptoms in adolescence.

Symptom	Survey questions	Operationalization	Questions derived from
Posttraumatic stress symptoms	Young-HUNT3 i)I have upsetting thoughts, pictures or sounds of what happened come into my mind when I do not want them to ii)When something reminds me of what happened I get very afraid, upset or sad iii)I try not to talk about, think about or have feelings about what happened	Questions were answered with yes/no and scored yes=1 and no=0, resulting in a sum score ranging 0-3	UCLA PTSD Reaction Index for DSM IV, part III (181)
Psychological distress, SCL-5	Young-HUNT3 *Experienced for the past 14 days:* i) feeling fearful ii) nervousness or shakiness inside iii) feeling hopeless about the future iv) feeling blue v) worrying about things too much	Participants rated to which extent they were bothered by each item, ranging from 1 – "not bothered" to 4 "very bothered", resulting in a mean score ranging 1-4	Hopkins Symptoms Checklist (SCL-5) (192)
Headache, weekly	Young-HUNT3 and -4, interview *Reoccurring headaches past 12 months:* i)Migraine ii)Tension type headache iii)Other headache	Headache frequency was assessed for each type, 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". Any headache weekly or more frequently was scored 1, less frequent headaches were scored 0, resulting in a measure for weekly headache yes/no, scored 1/0	Validated headache interview (191)
Musculoskeletal pain, weekly, number of sites	Young-HUNT3 *How often during the past 3 months have you experienced any of these complaints?* Neck or shoulder pain Chest pain Upper back pain Lower back pain Pain in left arm Pain in right arm Pain in left leg Pain in right leg Young-HUNT4 *How often during the past 3 months have you experienced any of these complaints?* Jaw pain Neck or shoulder pain Chest pain Upper back pain Lower back pain Pain in arms Pain in legs	Response alternatives were "never/rarely", "monthly", "weekly", "several times per week", "almost daily" in both Young-HUNT3 and -4. Weekly or more frequent pain was scored 1, less frequent pain was scored 0, resulting in a sum score for number of pain sites ranging 0-≥3.	Assessment instrument by Mikkelson et al. (189)

3.2.6 Outcome measures: use of over-the-counter and prescription analgesics

Use of over-the-counter analgesics in adolescence (paper I).

In Young-HUNT4, participants reported their use of over-the-counter-analgesics (OTCA) to treat headache and musculoskeletal pain for the last 3 months.

The survey question was worded: "How often during the last 3 months have you used non-prescription medication to treat the following complaints? (medication not prescribed by a doctor, for instance bought at a pharmacy or grocery store) for i) headache and ii) muscle or joint pain". Response alternatives were "never/rarely" = 0, "1-3 days per month" = 1, "1-3 days per week" = 2, "4-6 days per week" = 3 and "daily" = 4. The frequency categories "4-6 days/week" and "daily" were combined in one group, and participants were grouped into using never/rarely, monthly, weekly, or daily, giving a range of 0-3 for frequency (13, 194). A similar measure has been used priorly to assess frequency of OTCA use in adults (2). Frequency of use of over-the-counter analgesics for the two indications (headaches and musculoskeletal pain) served as separate outcomes in ordinal logistic regression analyses.

Use of over-the-counter analgesics in young adulthood (paper II)

In HUNT4, participants reported their use of over-the-counter analgesics to treat headache and musculoskeletal pain for the last month. The survey question was worded "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". The frequency categories "4-6 times/week" and "daily" were combined in one group (2, 13, 194), and participants were grouped into using never/rarely, weekly and daily. Frequency of use of over-the-counter analgesics for the two indications (musculoskeletal pain and headaches) served as separate outcomes in ordinal logistic regression analyses.

Prescription analgesics received in adolescence and young adulthood (paper III)

Prescriptions of opioids (ATC group N02A) and the nonopioid analgesics paracetamol (ATC group N02BE), gabapentinoids (N03AX12 and N03AX16) and NSAIDs (non-steroid anti-inflammatory drugs, ATC group M01A) were assessed. Analgesics received in adolescence and in young adulthood were analyzed separately. Counts of all prescriptions of opioid and nonopioid analgesics filled by the participants in Young-HUNT3 as adolescents (age 13-19 years) and young adults (age 20-32) within the time period 2004-2021 served as outcome measures. Number of follow-up years within each developmental stage was accounted for,

as this would vary between individuals. The count measure for each developmental stage was chosen due to prior findings that receiving analgesics prescriptions is not common within this age group in this population, and it is likely that very few will meet criteria previously used to define persistent use (195, 196). Prescriptions with a reimbursement code indicating palliative care (-90) were excluded (197, 198), as use on this indication was outside of the scope of this thesis.

3.3 Statistics

In papers I and II, descriptive data were presented stratified by frequency of OTCA use in adolescence (paper I) and young adulthood (paper II), and by sex. In paper III, descriptive data were presented by opioid prescriptions and by sex. Categorical variables were described with counts and percentages, while continuous variables were described with mean and standard deviation (SD).

In paper I, self-reported frequency of use of OTCA for headaches and musculoskeletal pain in adolescence served as separate outcomes in ordinal logistic regression analyses. The impact of exposure to the different childhood trauma types, as well as the impact of exposure to multiple types of interpersonal trauma and other trauma types were assessed in separate complete case analyses using ordinal logistic regression. The assumption of proportional odds was tested with Brant test for all ordinal regression analyses. In Model 1, analyses were adjusted solely for the background factors age, sex, pubertal development, family economy and household structure. Adjustments for weekly headaches, number of sites of weekly musculoskeletal pain and juvenile idiopathic arthritis, were added in Model 2.

In paper II, self-reported frequency of use of OTCA for headaches and musculoskeletal pain in young adulthood served as separate outcomes in ordinal logistic regression analyses. The impact of exposure to different childhood trauma types and to multiple types of interpersonal trauma were assessed in separate complete case analyses using ordinal logistic regression. The assumption of proportional odds was tested with Brant test for all ordinal regression analyses. In Model 1, analyses were adjusted for sex and age. In Model 2, the socioeconomic factors household structure and family economy were added. In Model 3, weekly headaches and number of sites of weekly musculoskeletal pain in adolescence was additionally adjusted for. In Model 4, psychological distress and posttraumatic stress in adolescence was additionally adjusted for. Mediation analyses were conducted for the relation of childhood interpersonal trauma to OTCA use for musculoskeletal pain in young

adulthood. To indicate the amount of unmeasured confounding needed to explain a possible mediation effect, E-values were computed.

In paper III, prescriptions of the analgesics NSAIDs, paracetamol, gabapentinoids, and opioids, filled in adolescence (13-19 years) and young adulthood (20-32 years) served as separate outcomes in zero-inflated negative binomial regression analyses. The impact of exposure to different trauma types were assessed in separate complete case analyses. Exposure to multiple types of childhood trauma was assessed in one complete case analysis including interpersonal trauma and other trauma types. The associations of symptoms reported in adolescence to analgesics prescriptions in adolescence and young adulthood were assessed in separate analyses for the subsample reporting exposure to childhood trauma. All analyses were adjusted for the background factors age, sex, family economy and household structure. Analyses for analgesics prescriptions filled in adolescence were additionally adjusted for pubertal development. Unadjusted analyses were conducted for the relation of background factors to the outcome. Follow-up time variation was accounted for by offsetting for number of years of follow-up. Results were presented as incidence rate ratios (IRR), which may be interpreted as ratios between rates per year.

Across all papers, the half-rule was used to handle missing data, meaning that mean scores and sum scores were computed for participants answering at least half of the questions used for score calculation (199). Regression analyses were conducted using Stata version 16 in paper I and II and Stata version 17 in paper III. R version 4.2.3 with the R package CMAverse (200) was utilized for causal mediation analyses in paper II. R version 4.2.2 with the R package data.table (201) was utilized for aggregating prescription data in paper III.

3.4 Ethics

This thesis is a part of the Killing Pain Study, which was preregistered through ClinicalTrials.gov, registration number NCT04336605. The Killing Pain Study was approved by the Norwegian Regional Committee for Medical Research Ethics (2017/2229). As mentioned in the methods section, The HUNT Study has also been approved by the Norwegian Regional Committee for Medical Research Ethics, as well as the Data Inspectorate of Norway, and 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 consent to participate in The HUNT Study can be withdrawn at any time.

Considering the extent of sensitive data used in this project, it is important that the anonymity of participants is never compromised. The linking of data from The HUNT Study and the Norwegian Prescription Database was conducted by the Norwegian Institute of public health (NIPH). Data were received encrypted and were decrypted only on a safe server dedicated to sensitive data. The data were only accessible to researchers involved in the Killing Pain project.

Young-HUNT survey questions used in this thesis include sensitive questions on childhood experiences. Adolescents may have experienced these and other questions as uncomfortable to respond to. The well-being of individual children should not be compromised in research for the greater benefit of all children (202). The potential impact of Young-HUNT survey questions on adolescent's well-being was acknowledged. To address this and to become aware of reactions to survey questions, all participants were given the opportunity to talk privately with a nurse after participation.

It is an important ethical principle when conducting research in a vulnerable group that the same group should benefit from the knowledge derived from the research (202). This has been an important guiding principle in the process of deciding on specific research questions in this thesis. The research conducted needs to be important and relevant for young people, and it should reveal and communicate important health findings so that they can impact future directions and decisions to the benefit of young individuals.

User involvement is increasingly acknowledged as crucial in all decision-making in most research projects, from defining the most relevant research questions to the interpretation and dissemination of results (203). In this thesis, a user involvement project was planned in collaboration with The Change Factory, a foundation that collects and reports experiences that young people have with the Norwegian health services and school system. While two workshops with youth representatives were conducted in the early phase of the project, the intended collaboration could not proceed as planned, as The Change Factory unfortunately had to pause their activities due to concerns regarding their work environment. External investigation of the concerns led to the termination of the collaboration between The Change Factory and The Norwegian Directorate for Children, Youth and Family Affairs, and as a result, the decision was made to also terminate the planned user involvement collaboration in the Killing Pain Study. While establishing a new user involvement collaboration for this thesis has proven to be challenging, our commitment remains. The perspectives shared by youth representatives who took part in the initial workshops

influence our approach to interpreting our findings and our considerations of their potential implications within the context of adolescent health and the health services provided to young people.

4. Summary of results

4.1 Prevalence of childhood trauma exposure

The proportion exposed to bullying was similar in In Young-HUNT3 (8.1%) and in Young-HUNT4 (8.3%) (Table 6). In terms of sexual abuse, 5.5% were exposed in Young-HUNT3 and 8.6% were exposed in Young-HUNT4. More girls than boys were exposed to sexual abuse in both waves, and the reports of sexual abuse among girls increased from 8.1% in Young-HUNT3 to 14.5% in Young-HUNT4, while reports among boys were similar in the two waves. The proportion of participants exposed to physical violence was 10.1% in Young-HUNT3 and 8.6% in Young-HUNT4. Witnessing violence was a more common experience than direct interpersonal trauma in both waves, and the proportion of participants who reported having witnessed violence was observed to decrease from Young-HUNT3 (23.2%) to Young-HUNT4 (15.0%). Exposure to disasters, accidents and other traumatic events was experienced by about 30% of participants in both waves. Death or severe illness of someone close or own severe illness was the most common childhood trauma exposure in both waves, experienced by 73.4% in Young-HUNT3 and 80.7% in Young-HUNT4. Overlap of trauma exposure in Young-HUNT3 was assessed in paper III, and was found to be considerable, with a substantial group reporting high exposure to both interpersonal trauma and other trauma. An assessment of the overlap of trauma exposure in Young-HUNT4 shows a similar pattern, with 45.3% of participants reporting exposure to two or more types of direct interpersonal trauma also reporting exposure to all three types of other trauma (Table 7).

Table 6. Trauma exposure in Young-HUNT3 and -4 by gender

	Young-HUNT3 (2006-2008)				Young-HUNT4 (2017-2019)			
	N	All N (%)	Girls N (%)	Boys N (%)	N	All N (%)	Girls N (%)	Boys N (%)
Bullying	7803	628 (8.1)	296 (7.5)	332 (8.7)	7818	652 (8.3)	347 (8.7)	305 (8.0)
Physical violence	7809	789 (10.1)	304 (7.6)	485 (12.7)	7799	667 (8.6)	319 (8.0)	348 (9.1)
Sexual abuse	7829	430 (5.5)	324 (8.1)	106 (2.8)	7796	662 (8.5)	578 (14.5)	84 (2.2)
Witness to violence	7812	1810 (23.2)	722 (18.1)	1088 (28.4)	7777	1169 (15.0)	456 (11.5)	713 (18.8)
Severe disease or death	7848	5757 (73.4)	3064 (76.6)	2693 (70.0)	7830	6317 (80.7)	3310 (82.5)	3007 (78.7)
Disasters, accidents, other	7848	2481 (31.6)	1304 (32.6)	1177 (30.6)	7814	2514 (32.2)	1330 (33.2)	1184 (31.1)

Table 7. Overlap of exposure to direct interpersonal trauma and other trauma types in childhood, reported in Young-HUNT4

	Interpersonal trauma, number of types			
Other trauma, number of types	**0 n/%**	**1 n/%**	**≥2 n/%**	**Total n/%**
0	1130 (18.0)	80 (6.6)	7 (2.0)	1217 (15.6)
1	3383 (54.0)	446 (37.0)	55 (15.8)	3884 (49.7)
2	1480 (23.6)	447 (37.1)	129 (37.0)	2056 (26.3)
3	275 (4.4)	233 (19.3)	158 (45.3)	666 (8.5)
Total	6268 (100)	1206 (100)	349 (100)	7823 (100)

4.2 Main results, paper I

In this paper, we investigated the cross-sectional relationship between childhood trauma exposure reported in adolescence and frequency of use of over-the-counter analgesics for headaches and musculoskeletal pain in adolescence. We found that weekly or more frequent use of over-the-counter analgesics was common among adolescents participating in Young-HUNT4 (2017-2019). About 10% of participants reported weekly or more frequent use of OTCA to treat headache and 4% reported using OTCA to treat musculoskeletal pain weekly or more frequently.

Ordinal logistic regression analyses showed that childhood trauma exposure was significantly and consistently associated with higher frequency use of OTCA to treat headache and musculoskeletal pain. Associations for bullying, physical violence and sexual

abuse were particularly strong, and a dose-response relationship between trauma exposure and OTCA use was observed for all trauma types analyzed. Attenuation of associations was observed after adjustment for weekly headache and musculoskeletal pain, although associations remained significant for the majority of trauma types.

4.3 Main results, paper II

In this paper, we prospectively investigated the relationship between childhood trauma and frequency of use of over-the-counter analgesics for headaches and musculoskeletal pain in young adulthood. We also investigated the possible importance of pain and psychological symptoms experienced in adolescence for this relationship. Exposure to childhood trauma, as well as psychological distress, posttraumatic stress, weekly headaches, and weekly musculoskeletal pain were assessed in adolescence (13-19 years, Young-HUNT3), while use of OTCA to treat headache and musculoskeletal pain was assessed in young adulthood (22-32 years, HUNT4). Weekly or more frequent use of OTCA to treat headache in young adulthood was reported by 26.7% of participants, while weekly or more frequent use of OTCA to treat musculoskeletal pain was reported by 14.6% of participants. Among young adults who reported weekly or daily OTCA use in HUNT4, a large proportion also reported using OTCA two or more days per week when they participated in Young-HUNT3 as adolescents.

Ordinal logistic regression analyses showed that childhood trauma exposure was significantly and consistently associated with higher frequency use of OTCA to treat headache and musculoskeletal pain in young adulthood. A dose response relationship was observed for events representing interpersonal trauma. Attenuation of associations was observed after adjustment for weekly headaches, weekly musculoskeletal pain, and psychological symptoms, including posttraumatic stress, as reported in adolescence. Mediation analyses for the relationship between trauma types representing interpersonal trauma and use of OTCA for musculoskeletal pain indicated that chronic pain and psychological distress serve as mediators in the relationship between childhood trauma and use of OTCA.

4.4 Main results, paper III

In this paper, we prospectively investigated the relationship between childhood trauma and use of prescription analgesics in adolescence and young adulthood. Exposure to childhood trauma, as well as psychological distress, posttraumatic stress, headaches, and

musculoskeletal pain were assessed in adolescence (13-19 years, Young-HUNT3). Survey data from Young-HUNT3 was linked to prescription data for analgesics from the Norwegian Prescription Database (NorPD, 2004-2021). NSAIDs were the analgesic group most frequently prescribed to adolescents, and about two in five participants received prescriptions for NSAIDs in adolescence. About one in ten received opioids in adolescence. NSAIDs remained the analgesic group most frequently received in young adulthood, and about two in three participants received an NSAID as a young adult. About two in five participants received opioids in young adulthood. Among participants who received opioids in adolescence, 59.7% also received opioids in young adulthood.

Zero inflated negative binomial regression analyses showed that childhood trauma exposure was significantly and consistently associated with receiving more opioid and nonopioid prescription analgesics in adolescence and young adulthood. A particularly strong association was observed for exposure to multiple trauma types, and this was evident both for interpersonal trauma and other trauma types.

4.5 Childhood interpersonal trauma and other trauma

In paper I, we found that the childhood trauma types bullying and sexual abuse were most strongly associated with more frequent use of OTCA to treat headache, and that bullying and sexual violence were most strongly associated with more frequent OTCA use to treat musculoskeletal pain. These trauma types remained among the trauma types most strongly associated with more frequent analgesics use after adjustment for pain. In paper II, the associations for exposure to direct interpersonal trauma to OTCA use for musculoskeletal pain in young adulthood were consistently stronger than for other trauma types. For OTCA use to treat headaches in young adulthood, this was less evident in the main analyses, however for daily use of OTCA to treat headaches, we observed a similar trend. In paper III, we also found the highest effect measures (ORs, IRRs) for the associations of direct interpersonal trauma to prescription analgesics.

We did not conduct analyses to assess whether associations for childhood trauma types representing direct interpersonal trauma were significantly stronger than other trauma types.

4.6 Cumulative childhood trauma

In paper I, we assessed the association of cumulative childhood trauma exposure to interpersonal trauma and other trauma types with the frequency of OTCA use to treat headaches and musculoskeletal pain in adolescence. We found that the odds ratio (OR) was higher for one interpersonal trauma exposure compared to no exposure and further increased with exposure to two or more trauma types, indicating a dose-response relationship. A similar trend was observed for other trauma types. In paper II, cumulative childhood trauma exposure was assessed only for interpersonal trauma, and we observed a similar trend as in paper I. In paper III, cumulative exposures to direct interpersonal trauma and to other trauma types were assessed in the same zero-inflated negative binomial analysis. We observed a dose-response relationship for interpersonal trauma and other trauma types, most prominent in young adulthood.

4.7 Pain, pain-related disability and psychological symptoms

In paper I, we observed an attenuation of the associations between childhood trauma and OTCA use when adjusting for weekly headaches and number of sites of weekly musculoskeletal pain. In paper II, we also observed an attenuation of effect when adjusting for headaches and musculoskeletal pain. Adjustment for psychological symptoms, including posttraumatic stress symptoms, further attenuated the associations in paper II. Additionally in paper II, we ran mediation analyses for the relation of trauma types representing direct interpersonal trauma to use of OTCA in young adulthood, with results indicating that weekly headaches and musculoskeletal pain, along with psychological distress, were mediators for this relationship. In paper III, we observed that weekly headaches and weekly musculoskeletal pain and a higher score for psychological distress and posttraumatic stress were all associated with higher prescription rates for analgesics in the subsample reporting exposure to childhood trauma. Weekly headaches and weekly musculoskeletal pain were associated with higher prescription rates for opioids and all nonopioid analgesics in adolescence, while posttraumatic stress symptoms were only significantly associated with higher prescription rates for NSAIDs and gabapentinoids in adolescence. Psychological distress was not significantly associated with higher prescription rates for analgesics in adolescence. In adulthood, weekly headaches, weekly musculoskeletal pain, psychological distress, and posttraumatic symptoms were all significantly associated with higher prescription rates for opioid and nonopioid analgesics.

Pain-related disability was presented descriptively in paper I and paper II and was observed to correspond closely with OTCA use in both adolescence and young adulthood.

5. Discussion

5.1 Discussion of findings

5.1.1 Novelty of main findings

In this thesis we found that young people exposed to childhood trauma use more analgesics in adolescence and young adulthood. While the relation of bullying to use of OTCA had been investigated in prior studies (204, 205), our finding in paper I that this association was evident across a wide range of trauma types, is a novel finding. The significant association between childhood trauma reported in adolescence and use of OTCA in young adulthood is a novel finding in a prospective study. To our knowledge this relationship has not been assessed in prior studies. In paper III, we found that childhood trauma was significantly associated with higher prescription rates of opioid and nonopioid prescription analgesics throughout adolescence and young adulthood. To our knowledge, this is the first prospective study assessing the relation of childhood trauma to opioid and nonopioid analgesics prescriptions in young individuals, although studies assessing childhood trauma retrospectively have indicated a relation for both nonopioid prescription analgesics and opioids (96, 206).

5.1.2 Analgesics use across adolescence and young adulthood

In paper II, we observed that many of the participants who reported frequent (two or more times per week) use of OTCA in adolescence also used OTCA at least once weekly in young adulthood. This indicates that for a substantial group, the frequent OTCA use observed in young adulthood, was established at an early age. In paper III, we found that the majority of individuals who received opioids in adolescence, also received opioids in young adulthood, indicating that receiving opioids early could be predictive of future opioid use. The group receiving opioids throughout adolescence and young adulthood also received more nonopioid prescription analgesics of all types in both adolescence and young adulthood. This was evident in adolescence and became more prominent in young adulthood. Taken together, these descriptive findings suggest that a trajectory of frequent analgesics use of both OTCA and prescription analgesics is established already in adolescence, and that it results in substantial differences in use in young adulthood. These findings align with prior findings that medication use patterns are established at an early age (207), and that

receiving opioid prescriptions in adolescence is associated with increased opioid use in adulthood (208). Our findings indicate that young individuals exposed to childhood trauma are at increased risk of entering such a trajectory of frequent analgesics use, that is evident across analgesics groups.

5.1.3 Childhood interpersonal trauma and cumulative trauma exposure

While we did observe a tendency of higher effect estimates (ORs, IRRs) for childhood interpersonal trauma compared to other trauma types, the most striking finding throughout our papers, was that all types of childhood trauma were related to later use of analgesics. It is a concern with several trauma screening instruments that they do not allow for differentiation between more severe and less severe events (209), and this is the case also for the trauma measure used in this thesis. Each trauma type is described in terms that could include events ranging from low to high severity. While this means the instrument exhibits low specificity in terms of capturing only the events that were in fact experienced as traumatic, the instrument also exhibits high sensitivity, meaning that it is likely that the events of interest will be captured by the trauma measure. The classification of both severe and less severe events as "exposed to childhood trauma", likely attenuates the associations, as we must assume that some of the events reported have a low potential for causing trauma-related health consequences. More nuanced trauma measures facilitating differentiation of events based on severity would be useful to further investigate if there are subtypes or severities of trauma exposure that are particularly strongly associated with analgesics use.

We assessed cumulative childhood trauma exposure for both interpersonal trauma and other trauma types in paper I and III, and for interpersonal trauma in paper II. Interpersonal trauma types are known to commonly overlap (210), and there is a tradition of assessing the cumulative exposure to interpersonal trauma types (149, 150, 183, 186). A higher cumulative exposure to interpersonal trauma has been found to be more strongly associated with adverse health outcomes, supporting the rationale for assessing this trauma type cumulatively (149, 150, 183). The operationalization of cumulative exposure to interpersonal trauma varies across studies, and a recent review concluded on the need for a consensus in the field on a construct that is agreed upon in the research community (186). There is also evidence of a cumulative effect of childhood trauma exposure across interpersonal and other trauma types (142, 151), suggesting the value of considering the cumulative effect also for other trauma types and even of a collapsed cumulative measure

including all childhood trauma exposure, regardless of subtypes (142, 152). In hindsight, we acknowledge that it could have been useful to assess the cumulative exposure to other trauma types also in paper II.

The cumulative scores for exposure to childhood interpersonal trauma and other trauma types added nuances to the trauma measures and captured some of the variety in trauma-related outcomes between individuals that were all considered exposed. A dose-response relationship for childhood trauma exposure and frequency of analgesics use in adolescence and young adulthood was observed in all three papers. The pattern of dose-response was evident for both interpersonal trauma and other trauma types. The consistency of this finding and the agreement with previous findings on the importance of cumulative trauma exposure for future health outcomes (81, 149, 152, 211), highlights the importance of considering all types of childhood trauma exposures when investigating relations between childhood trauma exposure and future health outcomes.

5.1.4 Childhood trauma and pain

Our finding that young individuals exposed to childhood trauma use more analgesics, may be due to a higher symptom load of pain. Adjusting for pain attenuated the associations between exposure to childhood trauma and use of OTCA in adolescence and young adulthood, indicating the importance of pain symptoms for the relation. Our finding that adolescent pain was associated with higher prescription rates in adolescence and young adulthood in the subsample reporting childhood trauma exposure in paper III also supports this. The association between childhood trauma and pain has been indicated in prior studies (81, 86, 184, 212-214). A longitudinal study found that hospitalization following a traffic accident and maternal death in childhood were both associated with chronic widespread pain in adulthood, as were factors that are known to be associated with an increased risk of childhood trauma exposure, including growing up in financial hardship and having resided in institutional care (86). A study retrospectively assessing childhood exposure to bullying and maltreatment, including sexual abuse and physical violence, in a general population sample, found significant associations between childhood bullying and maltreatment and adult pain (81). Significant associations between childhood trauma exposure and persistent weekly and daily migraines and tension type headaches was found in a study assessing headaches four to five months after exposure to terror in the form of a mass shooting (212), indicating that pain may be an early symptom after trauma exposure. Cross-sectional findings in a general population of adolescents have

indicated the same, showing an association between childhood interpersonal trauma and persistent headaches in adolescence (184, 185).

The biopsychosocial approach to pain offers an integrative view of biological, psychological and social mechanisms in the development and maintenance of pain, and several factors that are generally considered to be relevant in a biopsychosocial approach to pain could contribute to explain a higher symptom load of pain among trauma-exposed individuals (215). Some mechanisms that could contribute to increased pain among trauma-exposed individuals will be outlined in the following sections.

5.1.4.1 Trauma reactions and pain

Trauma reactions such as hypervigilance and avoidance may be relevant for the associations of childhood trauma with pain conditions found in prior studies (216). It has been observed that a reaction pattern similar to that characterizing posttraumatic stress, activated in response to pain, is a pattern associated with poorer pain outcomes (216). The interpretation of pain as a threat even when acute injury or illness is ruled out is thought to be a mechanism by which stress exacerbates pain (217), and such a response is sometimes termed pain catastrophizing. Pain catastrophizing is a description of an observed phenomenon where the patients subjective experience of pain, including severity and perceived pain-related threat, exceeds what would be expected given the observable characteristics of the pain condition, and involves rumination and perceived helplessness (218). An initial appraisal of pain as a threat can induce guarding behaviors often termed as avoidant behavior. Avoidant behavior is considered to contribute to the maintenance of pain and is associated with prolonged pain and increased disability (218, 219). Overuse of analgesics is a behavioral pattern considered to be a form of avoidant pain behavior, as it produces immediate pain relief, although it does not improve the long-term functional impairment associated with pain (220). A study on adolescents suffering from chronic pain found that catastrophizing was higher among trauma-exposed individuals than among non-exposed (221), indicating that pain catastrophizing may be a mechanism by which risk of chronic pain is increased among trauma-exposed individuals.

The relationships between trauma exposure, PTSD and chronic pain has been examined in several studies, and a leading view is that chronic pain and PTSD may both be considered to be reactive disorders in response to trauma exposure (222). Pain may also serve as a trauma reminder (223), evoking trauma reactions and psychological distress, that are again considered relevant for maintaining pain conditions (224).

Sleep disturbances are common among individuals exposed to childhood trauma (158), and sleep disturbances are considered to be a possible contributor to the co-occurrence of trauma exposure and chronic pain among adolescents (225). Sleep has also been found to be important for the relation between PTSD and chronic pain in adolescents (226), and it is considered to have a role in the transition from acute to chronic pain (227).

5.1.4.2 Mental health disorders, childhood trauma and pain

Mental health disorders are a common comorbidity of chronic pain (228-230), and childhood trauma is strongly associated with multiple mental health disorders (155, 231, 232). A mutual maintenance between mental health disorders and chronic pain conditions is considered to be an important mechanism (228, 233). The higher prevalence of mental health disorders among individuals exposed to childhood trauma compared to their non-exposed peers, may put them at risk of pain chronification due to the potential mutual maintenance of mental health disorders and chronic pain conditions.

Recent twin studies indicate that the comorbidity between mental health disorders and chronic pain is caused by common underlying factors (234, 235). These factors could be genetic or environmental, and genetic and environmental factors may interact to produce the clinical picture of comorbidity of chronic pain and mental health disorders often observed. Childhood trauma exposure as a risk factor for both chronic pain and mental health disorders fits with this model.

Mental health disorders are also associated with increased pain-related disability (62). We observed that disability index corresponded closely with analgesics use in paper I and paper II, and a higher pain related disability due to mental health comorbidity could be relevant for the observed associations between childhood trauma exposure and more frequent analgesics use.

5.1.4.3 Neurobiology of childhood trauma and pain

Childhood trauma is related to structural and functional neurobiological changes that may be relevant for pain perception (82, 214, 236, 237). Childhood trauma exposure affects individuals during a phase when brain development is not completed. This timing may be highly relevant for the observed consequences of childhood trauma exposure (82). Alterations in the processes of threat detection and fear processing, reward circuits and somatosensory mechanisms are all observed to be vulnerable to change following childhood trauma exposure, and these changes may contribute to alterations in pain

perception (82). There is considerable overlap of brain regions that appear to be vulnerable to childhood trauma and regions that are important for pain perception and pain chronification, including the prefrontal cortex, hippocampus, and amygdala (135, 237-240). Among functional changes, HPA axis dysfunction (237, 241-244) and proinflammatory changes, including microglia activation (237, 242, 244), are considered possible contributors to the higher prevalence of chronic pain observed among individuals exposed to childhood trauma. The specific timing of exposure to stressful events within neurobiologically important developmental periods throughout childhood may be of importance for the resulting neurobiological changes (240, 245).

Neurobiological changes are also relevant for the psychological symptoms described in the previous section, and there is considerable overlap between neurobiological changes associated with chronic pain and neurobiological changes associated with psychological symptoms (82, 230). The similar neurobiological alterations observed in mental health disorders and chronic pain are considered important for understanding the comorbidity of these conditions (230).

5.1.4 Childhood trauma and pain management

Analgesics have a limited role in the recommended treatment approaches for chronic pain in young individuals. A multidisciplinary approach targeting psychological, social, as well as biological contributors to chronic pain are recommended (21). While we did not investigate whether participants received other types of pain treatment than analgesics, prior studies have found that adolescents suffering from chronic pain often do not receive the recommended multidisciplinary care (60). Mental health comorbidity and trauma reactions may complicate pain management among individuals exposed to childhood trauma, by affecting the ability to adhere to other treatment options (246). Psychological symptoms may also increase risk of poorer treatment outcomes (246). Taken together, mental health comorbidities and other trauma-related symptoms could contribute to a treatment approach relying more heavily on analgesics.

The association of childhood trauma with a lower socioeconomic status could also be relevant for the observed more frequent use of analgesics among trauma-exposed individuals. Analgesics are easily available and affordable. They do not require the economical or practical resources of attending a session of cognitive or physical therapy, including parental support and resources. In this thesis, the socioeconomic factors family economy and household structure were adjusted for.

Prior studies have found that a lower socioeconomic status is associated with long-term opioid prescriptions after adjustment for pain and mental health disorders (72). Our finding that childhood trauma was associated with use of OTCA and receiving prescription analgesics after adjustment for socioeconomic factors, could indicate that childhood trauma may be a driving force behind the association between socioeconomic status and analgesics use observed in prior studies.

5.1.5 Help seeking after childhood trauma and importance of trauma assessment

In spite of high needs, individuals exposed to childhood trauma often refrain from seeking help for psychosocial health problems (247, 248). A coping strategy relying on self-management has been observed to represent a barrier for help seeking (247). Other barriers may be directly related to the traumatic event, including avoidance of the trauma memory and difficulties trusting others (248). In this thesis, the finding that individuals exposed to childhood trauma used OTCA more frequently, could represent a self-management strategy. In contrast, the finding that individuals exposed to childhood trauma received prescription analgesics at higher rates than their unexposed peers, involves contact with health care services. Awareness of the association between childhood trauma and pain in young individuals could be applied clinically by using such settings as an opportunity for childhood trauma assessment. This could be particularly important in assessments of the risks and benefits of opioid prescriptions. Our findings indicate that young individuals exposed to childhood trauma may be at increased risk of belonging to the patient group still subject to high-risk prescription practices for opioids. Such practices involve the prescription of long-acting drugs, higher doses, and longer treatment duration, and still appear to be common in populations of young people where overall prescription rates are decreasing (6, 249). High-risk prescription practices could be particularly detrimental for individuals exposed to childhood trauma, as there are indications of increased risk of opioid misuse and dependence among trauma-exposed individuals (250, 251). Such a pattern of adverse selection of high-risk patients into high-risk opioid treatment has been observed in prior studies (252).

5.2 Methodological considerations

5.2.1 Study design

In paper I, for the assessment of the relation of childhood trauma to frequency of use of over-the-counter analgesics, a cross-sectional design was utilized, where exposure and

outcome was measured at the same time. The exposure to childhood trauma may have occurred at any point in time throughout childhood before participation in The HUNT Study. Events may have happened well before participation; however, it is not possible for us to know whether the use of OTCA or the trauma came first. While we have a theoretically founded hypothesis of the direction of the associations, the design does not allow for causal assumptions. What we did show in paper I, was that there is in fact an association between childhood trauma and more frequent use of OTCA in adolescence.

In paper II and III, a prospective design was utilized. In paper II, we assessed exposure to childhood trauma in adolescence, while the outcome, frequency of OTCA use, was assessed in young adulthood. This establishes a timeline where childhood trauma is reported before the young adult OTCA use. While we found that young adults who reported childhood trauma did use OTCA more frequently in young adulthood, we can still not conclude that this is causal. As with all observational studies, the association could be the result of residual confounding, described in more detail below. Although not enough to conclude on causation, the temporal sequence of events where exposure is measured before outcome, aligns with a possible causal relationship.

In paper III, we assessed childhood trauma in adolescence, when participants were aged 13-19 years, while outcome data (number of filled prescriptions), were collected continuously throughout adolescence and young adulthood. As in paper II, this design is not enough to establish causality, however, the temporal sequence of events aligns with a possible causal relation. As in paper II, we cannot rule out that the observed association is caused by residual confounding.

An experimental design is of course not an alternative when investigating health consequences of childhood trauma. It could be argued that a prospective design where childhood trauma is reported while participants are still in childhood, is among our best available designs for examining this topic.

5.2.2 Random errors

Random errors are inevitable in most research due to variation in measurements, introducing imprecision to measures and results (253). Random errors can obscure an actual association and dilute results (254).

Data collection through questionnaires and interviews, are subject to random errors, due to variations in reporting (253). Utilizing validated instruments exhibiting good psychometric

properties reduces random errors in these types of data collection (253). In our papers, several validated measures are used, although not all measures have been validated, and not all validations have been conducted in Norwegian. We utilized self-reported survey measures as exposure and outcome in paper I and II, and as exposure in paper III. While the measure for childhood trauma exposure has been validated (182), it has not been validated in Norwegian. The self-reported outcome measures on frequency of OTCA use utilized in papers I and II have not been validated, however, similar measures have been used in prior studies investigating frequency of OTCA use (2, 66). Data on use of OTCA in this population will necessarily rely on self-report, as the utilization of such medication is not registered. Our adjustment variables also rely on self-report measures (family economy, household structure, pubertal development, pain, and psychological symptoms). We can assume that these measures introduce random errors in our studies.

Random errors are accounted for in statistical theory and they are handled by calculating the uncertainty surrounding the measures of interest (255). Generally, a larger sample will diminish the impact of random errors and increase precision of effect estimates (254). In the papers included in this thesis, we had the benefit of large sample sizes (paper I: n=8066, paper II: n=2947, paper III: n=8199), increasing precision of estimates.

5.2.3 Systematic Errors

Generally more problematic than random errors, systematic errors can introduce bias (255). Systematic errors cannot be helped by increasing the sample size, and it is important to assess all potential sources of systematic errors in epidemiological studies, in order to account for them if possible (254).

5.2.3.1 Selection bias

All surveys can be biased by systematic differences between those participating and those choosing not to participate. For this reason, it is of interest to compare participants with nonparticipants if possible. In The HUNT Study, this has been assessed quite thoroughly among participants in the adult surveys (177, 256), and this assessment is directly relevant for our paper II, where the outcome is a measure from the adult HUNT4 Study. It has generally been found that nonparticipation is associated with more negative health outcomes (177, 256). As we know that childhood trauma is associated with several adverse health outcomes, this could be relevant for our study, as trauma-exposed individuals with trauma-related poorer health could be overrepresented among nonparticipants.

In our paper II, we examined differences in Young-HUNT3 measures between participants and nonparticipants in HUNT4. We observed that the proportion reporting exposure to childhood trauma was higher among nonparticipants. Factors found to be associated with more frequent use of OTCA in adulthood, including family economy below average and not living with both parents, as well as pain conditions and psychological distress, were also generally more common among Young-HUNT3 participants who were nonparticipants in HUNT4. Selective attrition among individuals exposed to childhood trauma, displaying early signs of declining health during adolescence, may attenuate our effect estimates in paper II.

The original pattern of attrition in Young-HUNT3 is also relevant for paper II, as well as for paper III. While the overall high participation rate in Young-HUNT3 (78%, n=8199) is a strength, the participation was lower among adolescents in vocational training (33%) and adolescents outside of the education system (23%) (257), as described in the methods section. These groups were underrepresented also in Young-HUNT4 with 40% and 10% participation compared to 76% participation among adolescents in school. This is relevant for our paper I, relying on data from this wave. While the groups of adolescents in vocational training and outside of the school system are small, the selective attrition in these groups could introduce bias. The group of adolescents outside of the education system is at increased risk of adverse health outcomes, and dropping out of school is associated with background factors associated with more frequent analgesics use and higher exposure to childhood trauma, including a lower socioeconomic status (258, 259). It is possible that the exposures and outcomes we are investigating is overrepresented among nonparticipants, and this could possibly attenuate effect estimates across all papers.

5.2.3.2 Information bias

If data collection is systematically different between groups, so that key variables are measured or classified differently between groups, this can introduce information bias (255). Responses to questionnaires and interview questions can be subject to such bias, as described in detail below.

Recall bias is a type of information bias where past events are reported systematically different between groups of interest (254). This is relevant for all papers in this thesis. Although exposure to childhood trauma was reported while participants were still in adolescence, these events may have occurred several years before, which introduces the potential for recall bias in reporting. The accuracy of memory could be influenced by the

event itself or by morbidity resulting from the event, and other reactions to the event. Generally, it has been found that adult retrospective reporting of childhood trauma is subject to underreporting of events of interest, and false positive reports are uncommon (87). The same trend is observed in adolescent reports (260). Stress and mental health disorders have been shown to be relevant for whether events are reported retrospectively by adults (261). Psychological factors have also shown to be relevant for consistency of reports in adolescence (262). Discrepancies between adolescent reports and adult retrospective reports of childhood trauma have been observed (263), and developmental stage, memory, cognition, and emotional state are possible contributors to the observed difference.

Social desirability bias. The tendency to report what is socially acceptable and desirable despite this not being the individual's subjectively perceived true report, is commonly observed and is named social desirability bias (264). Sensitive subjects where the true report is not in agreement with social expectations will be particularly vulnerable to such bias, and there is some evidence that sensitive events, such as sexual abuse, may be more subject to underreporting than other traumatic events when reported in adolescence and adulthood (89, 260).

Confounding. A confounder is a factor that influences both the exposure and the outcome, and adjustment for relevant confounders is essential in observational studies to avoid biased results (254). We have adjusted for known confounders in our analyses, however, there may still be residual confounding. There could be residual confounding due to known confounders not being adequately adjusted for or due to unknown confounders not adjusted for.

In paper I, we adjusted all ordinal logistic regression analyses for pubertal development, age, sex, family economy and household structure. These factors may influence both exposure to childhood trauma and analgesics use in adolescence. In paper II, we adjusted all ordinal logistic regression analyses for age, sex, family economy and household structure, as these factors may influence both exposure to childhood trauma and analgesics use in young adulthood. In paper III, we adjusted for the same background variables as in paper I (pubertal development, age, sex, family economy and household structure) in analyses for analgesics prescriptions received in adolescence. For analyses for analgesics prescriptions received in young adulthood, we adjusted for the same background variables as in paper II (age, sex, family economy and household structure).

5.2.4 External validity

In this thesis, we propose several mechanisms, including neurobiological, psychological and socio-behavioral, that may contribute to explain the associations we have found between childhood trauma and analgesics use in adolescence and young adulthood. While these mechanisms may have the potential to be relatively universal, the actual causal relationships for the observed more frequent use of analgesics among trauma-exposed remain uncertain. Qualities of the study population or the community or regulation of health services could be relevant. The HUNT Study is conducted in a geographical region that does not include large cities and has a limited immigrant population. Except for this, the region is considered to be representative of Norway. The availability of over-the-counter medication and regulations of prescriptions vary between nations, and this may be relevant for the generalizability of our findings outside of a Norwegian context. The availability of other health services could affect analgesics use, and the approach to childhood trauma in health services could impact the associations observed in our study. It is possible that our results are only generalizable to populations that are similar to the Norwegian with respect to health care structure, approach to childhood trauma within health services, and availability of analgesics among young people. Nevertheless, our results are consistent with patterns observed in populations with health care systems different from the Norwegian model, suggesting that the relationships observed in this thesis may be transferable to other populations.

6. Conclusions and implications

The main finding of this thesis is the more frequent use of analgesics among young people who have been exposed to childhood trauma compared to their unexposed peers, which was evident throughout adolescence and young adulthood. The association was observed across trauma types and analgesics groups, and a dose-response relationship was revealed for both interpersonal trauma and other trauma types. We have described some of the mechanisms that may be relevant to this association, including an increased symptom burden of pain and psychological symptoms. An increased symptom burden of pain could encompass more severe, long-lasting, or more disabling pain.

The more frequent use of OTCA among young individuals exposed to childhood trauma, may reflect a strategy for coping with pain, possibly exacerbated by psychological symptoms. The individuals who frequently use OTCA may not have sought medical help for pain relief. For prescription analgesics, the observed higher prescription rates among

trauma-exposed individuals reflect not only an individual coping strategy but also the help offered to young individuals who turn to health services to relieve their pain.

Our observation that individuals who received opioid prescriptions in adolescence tended to continue to do so in young adulthood, underscores the importance of exercising great caution when prescribing opioids to young people. The same cohort of young individuals also received more nonopioid analgesics throughout adolescence and young adulthood. This finding in a population where opioid prescribing practices are conservative and prescription rates for opioids to young people are low, can be seen as indicative of the symptom burden that this cohort is struggling with and the lack of alternative effective treatment options that are available or considered relevant.

Adolescence is a sensitive stage of development in which the course for future health may be set (147). Interventions to help guide individuals towards more favorable health trajectories in adolescence, may impact their health throughout adulthood (265). Effective early pain interventions could therefore represent a major advance for public health, considering the significant contribution of chronic pain to the overall health burden and the related risk of frequent use of analgesics, including opioids.

6.1 Clinical Implications

Given the high prevalence of childhood trauma and chronic pain conditions in young people, it could be argued that a general trauma-informed approach to pain management in young people is warranted. This could help in the early identification of young people who are at particularly high risk of falling into unfavorable trajectories of persistent pain and frequent use of pain medication. A trauma-informed approach to pain management could also be a first opportunity for traumatized individuals to receive trauma-specific treatment. Because the processes underlying trauma-related psychological symptoms and pain appear to largely overlap, a treatment that is considered effective for other trauma-related symptoms may also be effective in treating pain. One clinical approach to investigate this might be to assess and monitor pain in addition to the more established posttraumatic symptoms when providing trauma-specific treatment.

6.2 Implications for future research

The results of this study justify future research on the potential impact of a trauma-informed approach to pain management on trajectories of pain and analgesic use in young people.

It could be hypothesized that the provision of trauma-specific care could contribute to help trauma-exposed young people escape a trajectory of persisting pain and frequent use of analgesics. Further research into the potential benefits of trauma-specific treatment on pain outcomes in individuals who have been exposed to childhood trauma may prove essential in a public health perspective.

There are few prospective studies on the association between trauma exposure in childhood and chronic pain in adolescence and adulthood. Future prospective studies on risk factors for chronic pain could benefit from evaluating childhood trauma exposure as a potential risk factor.

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Exposure to traumatic events and use of over-the-counter analgesics in adolescents: cross-sectional findings from the Young-HUNT study

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ABSTRACT

Objective Frequent and increasing use of over-the-counter analgesics (OTCA) among adolescents is a public health concern. Prior research indicates that adolescents exposed to traumatic events may be at increased risk of suffering from headaches and musculoskeletal pain. In this study, we assessed the association between trauma exposure and use of OTCA for headaches and musculoskeletal pain.

Design A cross-sectional population study among adolescents, self-reported data on trauma exposure, pain and use of OTCA.

Setting and participants All 10 608 adolescents aged 13–19 years in a region of Norway were invited in this school-based survey, participation rate was 76%.

Outcome measure Frequency of OTCA use for headache and musculoskeletal pain served as separate outcomes in ordinal logistic regression analyses.

Results Trauma exposure was significantly and consistently related to higher frequency use of OTCA for headache and musculoskeletal pain, of which associations for bullying (OR 1.79, 95% CI 1.50 to 2.12, and OR 2.12, 95% CI 1.70 to 2.66), physical violence (OR 1.49, 95% CI 1.25 to 1.78 and OR 1.83, 95% CI 1.45 to 2.32) and sexual abuse (OR 1.83, 95% CI 1.55 to 2.18 and OR 1.53, 95% CI 1.18 to 1.90) were particularly strong. A dose–response relationship was found between interpersonal violence and OTCA use for headache (OR 1.46, 95% CI 1.29 to 1.66 for one type and OR 1.81, 95% CI 1.53 to 2.14 for two or more types) and musculoskeletal pain (OR 1.61, 95% CI 1.91 to 3.00 for one type and OR 2.39, 95% CI 1.91 to 3.00 for two or more types). The associations remained significant after adjustment for pain, although an attenuation in strength was observed.

Conclusion Trauma exposed adolescents use OTCA for headaches and musculoskeletal pain more frequently than those not exposed. The higher frequency of pain conditions among trauma exposed only partially explained their more frequent OTCA use, indicating an increased risk relating to features beyond frequency of pain.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first study exploring the relation of trauma exposure to use of over-the-counter analgesics in a representative adolescent population.
⇒ The general participation rate was high.
⇒ Participation rate was lower among adolescents not enrolled in school.
⇒ The study is cross-sectional and does not allow for causal assumptions.
⇒ Trauma-specific treatment was not assessed.

INTRODUCTION

Over-the-counter analgesics (OTCA) are commonly used among adolescents,[1–4] and use appears to have increased over the past decades.[1] In studies on adolescents, it is consistently found that girls use more pain medication than boys, and that analgesic use increases from early to late adolescence.[1 5] Pubertal development plays a part in this sudden increase and discrepancy in use between the sexes.[6 7] Socioeconomic factors appear to be related to use, and largely it has been found that lower socioeconomic status is associated with using more OTCA.[8 9]

Frequent use of OTCA poses a risk of unwanted health outcomes. In an adolescent population, the most important known somatic health risk is medication overuse headache,[10 11] although it should be noted that the efficacy and safety of common non-prescription analgesics such as ibuprofen and paracetamol is not well examined in adolescents.[12] It is also a concern that medication use in adolescence may prevent development of more favourable coping strategies, as studies have shown that adolescents establish habits of medication use that they carry with them into adulthood.[13] Further, adolescents who frequently use pain medication, smoke more and drink more alcohol than peers who do not use such medication.[14] For these reasons, the highly prevalent and frequent use of OTCA among adolescents may constitute a present and future public health concern.

Headache and musculoskeletal pain are among the worldwide leading causes of morbidity in children and adolescents.[15 16] The recommended management of chronic pain in adolescents involves use of analgesics only after an individual assessment of the patient and with the shortest possible duration.[17 18] For migraine headaches, it is recommended that analgesics are used for acute attacks.[19] There seems to be a discrepancy between these restrictive guideline recommendations and actual use.

Findings from cross-sectional and qualitative studies indicate a relationship between bullying and more frequent use of analgesics among adolescents.[20 21] Bullying is a form of interpersonal violence, the subgroup of traumatic events that includes direct or indirect exposure to physical, sexual or psychological violence and neglect.[22] Interpersonal violence and other traumatic events are common stressful exposures in a youth population,[23 24] and interpersonal violence has been found to be related to chronic pain conditions in adolescents.[25–27]

The impact of trauma exposure as risk factor for frequent use of OTCA remains to be explored. The main purpose of the present study was to assess the association between trauma exposure and use of OTCA for headaches and musculoskeletal pain among adolescents.

METHODS

The study is based on cross-sectional data from the population-based survey Young-HUNT4.[28] Among the complete cohort of 10 608 invited adolescents (aged 13–19 years) living in the region formerly called Nord-Trøndelag in Norway, 8066 (76%) participated in the Young-HUNT4 between 2017 and 2019. Most adolescents completed the survey during school hours as an electronic questionnaire including questions assessing OTCA use for headache and musculoskeletal pain, frequency of headaches and musculoskeletal pain and trauma exposure. Adolescents in apprentice positions were invited to participate in Young-HUNT4 on apprentice gatherings. They were informed about the survey and how to participate in advance of these gatherings. Adolescents not enrolled in school were invited to participate through the follow-up service for adolescents not enrolled in school, a service that is regularly in contact with these adolescents. Although measures were made to recruit participants outside of school, participation rate was lower among apprentices (40%, n=237) and adolescents not enrolled in school (10%, n=42).

Patient and public involvement

Youth representatives were involved in planning the survey, and adolescents in pilot schools gave feedback to optimise conduction of the full survey.

Measures

Data on age and sex were obtained from the Norwegian National Population Registry. Pubertal development stage was assessed using a four-item version of the pubertal development scale by Carskadon and Acebo.[29] The participants were asked two questions regarding members of their household(s) and time spent in different households, and were categorised as 'living with both parents' or 'living in other type of household'. The adolescents were asked whether they perceived their family's economy as below average, average or above average and were grouped into 'family economy average or better' and 'family economy below average'.

Use of OTCA for headaches and musculoskeletal pain

Self-reported use of OTCA for (i) headache and (ii) musculoskeletal pain served as two separate outcomes. Participants were asked 'How often during the last 3 months have you used non-prescription medication to treat the following complaints? (medication not prescribed by a doctor, for instance bought at a pharmacy or grocery store) for (i) headache and (ii) muscle or joint pain'. Response alternatives were 'never/rarely'=0, '1–3 days per month'=1, '1–3 days per week'=2, '4–6 days per week'=3 and 'daily'=4. We combined the frequency categories '4–6 days/week' and 'daily' into one group, giving a range of 0–3 for frequency.[10 11] A similar question has previously been used for the purpose of assessing frequency of use of OTCA in adults.[30]

Exposure to traumatic events

Bullying

The participants were asked to report the frequency of being exposed to four types of bullying for the past 6 months. Questions were derived from validated questionnaires.[31 32] Participants were asked the introductory question 'How many times has this happened to you the last 6 months?' and then assessed the four statements 'I have been made fun of, teased, called names', 'I have been hit, kicked, attacked, got my hair pulled', 'I have been excluded, not allowed to participate' and 'I have received unpleasant messages or photos by phone or online' by how often it had occurred. Response alternatives were 'never', '1–3 times per month', 'once per week', '2–4 times per week' and 'almost daily'. Responders reporting bullying weekly or more frequently were categorised as being bullied.

Lifetime trauma screen

Exposure to *physical violence*, *sexual abuse* and *other traumatic events* was assessed by a brief lifetime trauma screen, derived from the UCLA Stress Disorder Reaction Index, part I,[33] adapted to a Norwegian context. All events were listed under the question 'Did you ever experience any of these events?'. Response alternatives were 'never', 'once' and 'more than once' for all items, and participants responding 'once' or 'more than once' were labelled exposed.

Physical violence

Lifetime exposure to physical violence was measured by two items worded 'subjected to violence (beaten/harmed) by someone close to you' and 'subjected to

violence (beaten/harmed) by others'. Participants were also asked if they had 'seen someone else being subjected to violence', this question was used to define the item *witness to violence*.

Sexual abuse

Lifetime exposure to sexual abuse was measured by two items worded 'subjected to unpleasant sexual act by a peer' and 'subjected to unpleasant sexual act by an adult', and reports of any exposure were categorised as *sexual abuse*.

Other traumatic events

The participants were asked about lifetime occurrence of five other traumatic events, these items were worded: 'that you or someone in your family were seriously ill', 'the death of someone close to you', 'a disaster (fire, hurricane or similar)', 'a serious accident (eg, serious car accident)', 'another experience that was very frightening, dangerous or violent'. These questions were used to define the two items *severe illness or death of close person* and *accident, disaster or other potentially traumatic event*.

Number of types of trauma exposure

Two separate sum scores (ranging 0 to ≥2) for (i) *interpersonal violence* (bullying, physical violence, witness to violence and sexual abuse, ranging 0–4) and (ii) *other traumatic events* (illness/death and accident/disaster/other), were calculated for each individual.

Musculoskeletal pain, headache and juvenile idiopathic arthritis

Musculoskeletal pain

Participants were asked 'How often during the past 3 months have you experienced any of these complaints?'. The complaints in question were pain in seven locations (jaw, neck, chest, upper back, lower back, arms and legs). Response alternatives were 'never/rarely', 'monthly', 'weekly', 'several times per week', 'almost daily'. The questions are based on an instrument developed to assess musculoskeletal pain in adolescents.[34] We counted all sites from which participants reported weekly or more frequent pain, in compliance with measures of chronic multisite musculoskeletal pain in adolescents from other studies.[3 35 36] For regression analysis, we grouped responders based on number of pain sites: 0, 1, 2 and 3 or more sites.

Headache

The interview part of the survey included a validated headache interview.[37] Participants were asked if they had experienced headaches for the past 12 months, and if they had experienced reoccurring headaches for 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 were coded 1 for headache, whereas participants reporting less frequent or no headaches were coded 0.[10 11]

Juvenile idiopathic arthritis

Participants reporting that they had received a diagnosis of juvenile idiopathic arthritis (JIA) from a doctor were classified as having JIA.

Pain-related disability

Level of pain-related disability was measured using a six-item version of the Mikkelsson *et al* disability index.[34] In the questionnaire, six specific complaints were stated, and the adolescents were asked to assess if the statement was a true or false description of their disability due to pain. The complaints stated 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 kilometre', 'due to pain, I have problems with physical education classes', 'pain limits my leisure activities'. One point was given for each affirmative answer to the questions on impairment of function due to pain. The two questions about sleep were combined to give one point for affirmative answer to either or both questions, in compliance with the original index ranging from 0 to 5. Cronbach's alpha for the six items was 0.74.

Statistical procedures

Descriptive data were presented stratified by frequency of OTCA use and by sex. Categorical variables were described with counts and percentages, while continuous variables were described with mean and SD. Half-rule was used to handle missing, meaning that for mean scores, participants answering at least half of the questions used to calculate the score, were included in the analysis. Self-reported frequency of use of OTCA for (i) headaches and (ii) musculoskeletal pain served as separate outcomes in ordinal logistic regression analyses. The impact of exposure to the five categories of potentially traumatic events, as well as the impact of number of types of (i) exposure to interpersonal violence and (ii) exposure to other traumatic events were assessed in separate ordinal logistic regression analyses. All analyses were adjusted for the predefined background factors age,[2] sex,[38] pubertal development,[39] socioeconomic status[8 40] and household structure,[9 41 42] and conducted as complete case analyses. In model 1, analyses were adjusted for background factors only. Indications for OTCA use, including variables of headache and musculoskeletal pain frequency and JIA, were added in model 2, in order to account for pain. All ordinal logistic regression analyses were tested with Brant test. Outcome variables for which the assumption of proportional odds was violated according to Brant test, were examined by comparing the ORs for each group comparison in the ordinal logistic regression. Analyses were conducted using Stata V.16.

Table 1 Sociodemographic characteristics, trauma exposure and symptoms in adolescence stratified by frequency of use of over-the-counter analgesics to treat headache

		Total	Never	Monthly	Weekly	Daily
	N	N (%)/mean (SD)	N (%)/mean (SD)	N (%)/mean (SD)	N (%)/mean (SD)	N (%)/mean (SD)
All participants	7829	7829 (100)	4739 (60.5)	2326 (29.7)	577 (7.4)	187 (2.4)
Female		3989 (51.0)	2032 (42.9)	1374 (59.1)	435 (75.4)	148 (79.1)
Male		3840 (49.1)	2707 (57.1)	952 (40.9)	142 (24.6)	39 (20.9)
Age	7829	16.1 (1.8)	15.9 (1.8)	16.3 (1.7)	16.6 (1.6)	16.5 (1.7)
Family economy	7757					
Average or better		7145 (92.1)	4395 (93.6)	2108 (91.3)	488 (85.8)	154 (83.7)
Below average		612 (7.9)	301 (6.4)	200 (8.7)	81 (14.2)	30 (16.3)
Household	7256					
Living with both parents		4290 (59.1)	2706 (61.3)	1253 (58.4)	259 (49.2)	72 (42.4)
Other type of household		2966 (40.9)	1707 (38.7)	894 (41.6)	267 (50.8)	98 (57.7)
Pubertal development score	7390	3.1 (0.7)	3.0 (0.7)	3.2 (0.6)	3.3 (0.6)	3.3 (0.6)
Exposure to traumatic event						
Bullying	7686	641 (8.3)	322 (6.9)	206 (9.0)	75 (13.2)	38 (20.5)
Physical violence	7668	658 (8.6)	342 (7.4)	196 (8.6)	84 (15.0)	36 (19.8)
Sexual abuse	7665	655 (8.6)	263 (5.7)	236 (10.3)	108 (19.3)	48 (26.4)
Witness to violence	7650	1150 (15.0)	647 (14.0)	344 (15.1)	108 (19.4)	51 (28.3)
Illness/death of someone close	7689	6219 (80.9)	3636 (78.2)	1950 (85.0)	481 (85.4)	152 (82.2)
Disaster/accident/other	7681	2477 (32.3)	1325 (28.6)	808 (35.2)	262 (46.6)	82 (44.8)
Interpersonal violence, number of types	7718					
0		5592 (72.5)	3548 (76.1)	1619 (70.4)	334 (58.4)	91 (49.2)
1		1421 (18.4)	769 (16.5)	458 (19.9)	145 (25.4)	49 (26.5)
≥2		705 (9.1)	344 (7.4)	223 (9.7)	93 (16.3)	45 (24.3)
Weekly or more frequent headache	7259	1129 (15.6)	264 (6.0)	407 (18.9)	327 (62.2)	131 (77.1)
Musculoskeletal pain, number of sites	7745					
0		4685 (60.5)	3223 (68.8)	1241 (53.8)	179 (31.4)	42 (22.7)
1		1320 (17.0)	735 (15.7)	460 (20.0)	95 (16.6)	30 (16.2)
2		719 (9.3)	347 (7.4)	274 (11.9)	71 (12.4)	27 (14.6)
≥3		1021 (13.2)	379 (8.1)	330 (14.3)	226 (39.6)	86 (46.5)
Disability index, mean	6278	1.3 (1.4)	1.0 (1.3)	1.3 (1.4)	2.1 (1.6)	2.5 (1.5)

RESULTS

Close to 10% of all the 8066 adolescents in the study reported at least weekly use of OTCA for headache (table 1), while about 4% reported weekly OTCA use for musculoskeletal pain (table 2). Overall, girls reported weekly use of OTCA for headaches or musculoskeletal pain about three times more frequently than boys. About 8.5% reported exposure to each type of direct interpersonal violence (bullying, sexual abuse and physical violence), while 15% reported having witnessed violence. 9% reported exposure to two or more interpersonal events. The proportion of adolescents exposed to traumatic events increased with increasing frequency of OTCA use, this trend was particularly pronounced for interpersonal violence (bullying, sexual abuse, physical violence and witnessing violence), and for experiencing two or more interpersonal events. Almost 40% of adolescents reported musculoskeletal pain in at least one location weekly or more often, while 15.5% reported weekly headaches. Females reported such symptoms 2–3 times more often than males (online supplemental table 1). Disability index was higher with higher frequencies of OTCA use (tables 1 and 2). Missing data for variables of interest were in the range of 1.5%–7.0%.

Ordinal logistic regression for frequency of use of OTCA for headache by type of trauma, showed a significant association with all the types of traumatic events that were analysed (table 3, model 1). The strongest associations were found for bullying and sexual abuse. Following adjustment for headache and musculoskeletal

Table 2 Sociodemographic characteristics, trauma exposure and symptoms in adolescence stratified by frequency of use of over-the-counter analgesics to treat musculoskeletal pain

		Total	Never	Monthly	Weekly	Daily
	N	N (%)/mean SD	N (%)/mean (SD)	N (%)/mean (SD)	N (%)/mean (SD)	N (%)/mean (SD)
All participants	7776		6902 (88.8)	586 (7.5)	173 (2.2)	115 (1.5)
Female		3954 (50.9)	3372 (48.9)	377 (64.3)	119 (68.8)	86 (74.8)
Male		3822 (49.2)	3530 (51.1)	209 (35.7)	54 (31.2)	29 (25.2)
Age	7776	16.1 (1.8)	16.1 (1.8)	16.4 (1.8)	16.5 (1.8)	16.2 (1.8)
Family economy	7705					
Average or better		7096 (92)	6336 (92.6)	519 (90.0)	145 (84.3)	96 (85.0)
Below average		609 (7.9)	507 (7.4)	58 (10.1)	27 (15.7)	17 (15.0)
Household	7210					
Living with both parents		4266 (59.2)	3825 (59.8)	304 (55.6)	94 (59.5)	43 (41.0)
Other type of household		2944 (40.8)	2575 (40.2)	243 (44.4)	64 (40.5)	62 (59.1)
Pubertal development score	7503	3.1 (0.66)	3.1 (0.66)	3.2 (0.62)	3.2 (0.61)	3.3 (0.63)
Exposure to traumatic event						
Bullying	7641	637 (8.3)	509 (7.5)	78 (13.4)	29 (17.1)	21 (18.3)
Physical violence	7629	654 (8.6)	536 (7.9)	65 (11.3)	28 (16.7)	25 (22.3)
Sexual abuse	7625	650 (8.5)	518 (7.7)	80 (13.9)	25 (14.9)	27 (23.9)
Witness to violence	7610	1140 (15.0)	962 (14.2)	109 (19.0)	37 (22.3)	32 (28.3)
Illness/death of someone close	7642	6180 (80.9)	5436 (80.2)	488 (84.3)	155 (91.7)	101 (88.6)
Disaster/accident/other	7640	2467 (32.3)	2101 (31.0)	233 (40.2)	82 (48.5)	51 (44.7)
Interpersonal violence, number of types	7671					
0		5563 (72.5)	5045 (74.2)	364 (62.4)	98 (57.7)	56 (48.7)
1		1407 (18.3)	1202 (17.7)	138 (23.7)	39 (22.9)	28 (24.4)
≥2		701 (9.1)	556 (8.2)	81 (13.9)	33 (19.4)	31 (27.0)
Weekly or more frequent headache	7213	1116 (15.5)	876 (78.5)	128 (11.5)	67 (6.0)	45 (4.0)
Musculoskeletal pain, number of sites	7708					
0		4664 (60.5)	4429 (64.7)	200 (34.4)	27 (15.9)	8 (7.1)
1		1316 (17.1)	1137 (16.6)	132 (22.7)	28 (16.5)	19 (16.8)
2		716 (9.3)	587 (8.6)	89 (15.3)	25 (14.7)	15 (13.3)
≥3		1012 (13.1)	690 (10.1)	161 (27.7)	90 (52.9)	71 (62.8)
Disability index, mean	6247	1.3 (1.4)	1.1 (1.4)	1.8 (1.5)	2.6 (1.5)	3.0 (1.5)

pain frequency and JIA (model 2) all trauma types except for physical violence remained significantly associated with OTCA use, although an attenuation in strength was observed. Ordinal logistic regression for frequency of use of OTCA for headache by number of types of interpersonal violence, showed a trend of increasing strength of association with increasing number of types (table 3, model 1). The strength of the associations was attenuated with adjustment for headache, musculoskeletal pain and JIA (model 2). Ordinal logistic regressions for frequency of use of OTCA for headache by number of types of other traumatic events showed similar results (online supplemental table 2).

Ordinal logistic regression for frequency of use of OTCA for musculoskeletal pain by type of trauma, showed a significant association with all the types of potentially traumatic experiences that were analysed (table 4, model 1). The association was particularly strong for bullying. When adding pain to the model (model 2); bullying, witnessing violence and other potentially traumatic experiences, including disasters and serious accidents remained significantly associated with the outcome, although the strength of association was attenuated. Ordinal logistic regression for frequency of use of OTCA for musculoskeletal pain by number of types of interpersonal violence, showed a trend of increasing strength of association with increasing number of types (table 4, model 1). The associations were attenuated when adding pain (model 2) to the model, although still significant. Ordinal logistic regressions for frequency of use of OTCA for musculoskeletal pain by

Table 3 Ordinal logistic regression analyses for outcome (i), frequency of use of over-the-counter analgesics to treat headache, by type of event and number of types of interpersonal violence

	Model 1*			Model 2*†		
	n	OR (95% CI)	P value	n	OR (95% CI)	P value
Exposure to potentially traumatic events, by type						
Bullying	6818	1.79 (1.50 to 2.12)	<0.001	6679	1.31 (1.09 to 1.57)	0.004
Sexual abuse	6806	1.83 (1.55 to 2.18)	<0.001	6669	1.37 (1.15 to 1.64)	0.001
Physical violence	6807	1.49 (1.25 to 1.78)	<0.001	6671	1.12 (0.93 to 1.34)	0.248
Witness to violence	6792	1.35 (1.18 to 1.55)	<0.001	6656	1.16 (1.00 to 1.34)	0.046
Severe illness or death of someone close	6814	1.36 (1.19 to 1.55)	<0.001	6672	1.27 (1.11 to 1.46)	0.001
Severe accident, disaster or other potentially traumatic event	6813	1.48 (1.33 to 1.64)	<0.001	6675	1.23 (1.10 to 1.37)	<0.001
Exposure to interpersonal violence, number of types						
1 type of interpersonal violence	6830	1.46 (1.29 to 1.66)	<0.001	6689	1.25 (1.10 to 1.43)	0.001
≥2 types of interpersonal violence	6830	1.81 (1.53 to 2.14)	<0.001	6689	1.26 (1.01 to 1.51)	0.010

*Models 1 and 2 are ordinal logistic regression models estimating odds for a higher frequency of use of over-the-counter analgesics for headache. Each trauma type was assessed by separate complete case analysis. Both models are adjusted for background factors: sex, age, pubertal development, household and family economy.
†Ordinal logistic regression model adjusted for headache, musculoskeletal pain and juvenile idiopathic arthritis in addition to background factors.

number of types of other traumatic events showed similar results (online supplemental table 3).

DISCUSSION

This population study shows a strong and consistent relationship between trauma exposure and higher frequency use of OTCA for headache and musculoskeletal pain among adolescents. The strongest associations were found for bullying, physical violence and sexual abuse. Overall, with increasing trauma exposure, we observed higher use of OTCA, indicating a dose–response relationship. The associations remained significant after adjustment for headache and musculoskeletal pain frequency and JIA, although an attenuation in strength was observed. Thus, the higher frequency of pain conditions among trauma-exposed only partially explained their more frequent use of OTCA. The finding indicates that trauma-exposed adolescents may be at particular risk

Table 4 Ordinal logistic regression analyses for outcome (ii), frequency of use of over-the-counter analgesics to treat musculoskeletal pain, by type of event and number of types of interpersonal violence

	Model 1*			Model 2*†		
	n	OR (95% CI)	P value	n	OR (95% CI)	P value
Exposure to potentially traumatic events, by type						
Bullying	6778	2.12 (1.70 to 2.66)	<0.001	6655	1.43 (1.12 to 1.82)	0.004
Sexual abuse	6768	1.53 (1.18 to 1.90)	<0.001	6645	1.05 (0.82 to 1.35)	0.698
Physical violence	6771	1.83 (1.45 to 2.32)	<0.001	6647	1.29 (1.00 to 1.66)	0.051
Witness to violence	6755	1.71 (1.40 to 2.07)	<0.001	6632	1.40 (1.13 to 1.72)	0.002
Severe illness or death of someone close	6773	1.35 (1.09 to 1.67)	0.006	6648	1.17 (0.93 to 1.46)	0.183
Severe accident, disaster or other traumatic event	6775	1.57 (1.34 to 1.83)	<0.001	6651	1.22 (1.03 to 1.44)	0.020
Exposure to interpersonal violence, number of types						
1 type of interpersonal violence	6789	1.61 (1.34 to 1.94)	<0.001	6665	1.31 (1.07 to 1.60)	0.008
≥2 types of interpersonal violence	6789	2.39 (1.91 to 3.00)	<0.001	6665	1.52 (1.20 to 1.94)	0.001

*Models 1 and 2 are ordinal logistic regression models estimating odds for a higher frequency of use of over-the-counter analgesics for musculoskeletal pain. Each trauma type was assessed by separate complete case analysis. Both models are adjusted for background factors: sex, age, pubertal development, household and family economy.
†Ordinal logistic regression model adjusted for headache, musculoskeletal pain and juvenile idiopathic arthritis in addition to background factors.

of using OTCA, relating to features beyond frequency of pain.

Close to 10% of the adolescents in our study reported using OTCA for headache weekly or daily and 3.5% reported use for musculoskeletal pain weekly or daily. These findings comply with previous studies showing that a substantial subgroup of adolescents use OTCA frequently.[2 4 10] Such weekly use will generally represent overuse and may have negative health effects.[11 43]

In this study, all events with potential to induce a long-lasting stress response were included, and 83.1% of participants reported life-time exposure to at least one potentially traumatic event. Studies with a similar approach have shown a similarly high prevalence.[24 44 45] Different types of trauma have been found to impact future health differently, with interpersonal violence being particularly detrimental.[24 44 46] In compliance with this, we found that bullying, physical violence and sexual abuse were the types of trauma most strongly associated with higher frequency use of OTCA. Not only type of traumatic event, but also number of types of trauma exposure has been shown to be relevant for future health.[45 47] The observed dose–response relationship between number of types of both interpersonal violence and other traumatic events and higher frequency use of OTCA in this study is in compliance with this.

Our results indicate that the higher use of OTCA by adolescents exposed to traumatic events could only partially be explained by the higher frequency of headaches and musculoskeletal pain experienced by this group. However, the adolescents using OTCA frequently did report higher level of disability due to pain than adolescents using OTCA less frequently, possibly relating to higher pain severity. Thus, there is a possibility that the more frequent use of OTCA among adolescents exposed to trauma relates to this group running increased risk of experiencing a combination of higher frequency and severity of pain. Findings from neurobiological studies could lend some evidence to such a potential explanation, as pathophysiological (mal)adaptations are considered to contribute to increased pain among young people exposed to trauma, including dysregulation of stress response systems such as the hypothalamic–pituitary–adrenal axis[48 49] and central sensitisation, where pain receptors of the central nervous system become sensitive to normally subthreshold stimuli.[50]

In addition to biological factors linking traumatic events and pain, experiencing traumatic events in childhood is related to the later development of a wide spectrum of psychopathology.[42 51–54] The mechanisms involved may overlap with mechanisms increasing risk of chronic pain,[51 55] including catastrophising, negative pain appraisal, depression and anxiety.[49] Recent studies have found that adolescents also report using OTCA as an aid in stressful situations and that frequency of use is associated with reporting higher symptom load for psychological distress.[2 4 56] In terms of depression and anxiety, these conditions have been found to be associated with using OTCA more frequently also after adjusting for pain.[4] There is also an overlap between social factors related to trauma and to chronic pain, including a less favourable family environment and poorer peer relational skills.[49] Thus, it is plausible that physiological and psychological trauma reactions and related social problems may contribute to more frequent use of OTCA among trauma-exposed adolescents. As such, overlapping treatment opportunities for trauma and chronic pain could favourably impact both psychological distress, chronic pain and OTCA use.[57]

Total sales of analgesics that are also available over-the-counter, are increasing rapidly,[58] perhaps reflecting an increasing inclination to alleviate complaints by use of pain medication. Such overarching societal trends may be relevant for the association between traumatic events and use of OTCA, as the adolescents exposed to trauma may be a group at increased risk, due to the factors described above. Adolescents exposed to interpersonal trauma and other multiple traumatic events may represent a marginalised group left with few options for coping with stress and pain.[41 59] Lack of other options could explain a higher tendency to use easily accessible OTCA.[2 60]

STRENGTHS AND LIMITATIONS

Strengths of this study were the large sample size and high participation rate, the use of a questionnaire derived from validated instruments and questions allowing for a thorough assessment of exposures and symptoms. The relationship between exposure to traumatic events and higher frequency use of OTCA shown in this study on a representative youth population in Norway, is likely to be transferrable to other adolescent populations with high availability of OTCA.

A limitation of this study is that the cross-sectional design does not allow for causal assumptions based on our analyses. The response rate among the small group of adolescents not enrolled in school was low, which may introduce a selection bias and possibly a slight underestimation of the associations, due to under-representation of a group of adolescents at increased risk.[61] Sample weights were not available for this survey. It is possible that well-calculated sample weights could improve the accuracy of our estimates. Health problems and use of OTCA were measured across various time frames, ranging from 3 to 12 months. Despite the variation, all of these measures use a time frame of ≥3 months, in coherence with current definitions of more persistent or chronic symptomatology or use.[62] It is also a limitation that exposure to bullying was assessed for the previous 6 months as opposed to lifetime exposure for the remaining items.

We did not have data on trauma-specific or other treatment, which hindered assessment of whether OTCA were used in combination with treatment.

CONCLUSION AND IMPLICATIONS

This representative population study shows higher frequency use of OTCA among adolescents exposed to traumatic events, which may increase the health burden of exposed adolescents. Findings from this study indicate that trauma-exposed adolescents may be at particular risk of using OTCA, relating to features beyond frequency of pain. The increased risk of frequent OTCA use could relate to pain severity, possibly related to potentially malleable post-traumatic stress reactions. Future studies on OTCA use in adolescence should assess trauma exposure as a potential risk factor. Longitudinal studies to examine if there is a long-term risk of frequent analgesics use after exposure to childhood trauma are needed. Further, we need studies that assess the impact of trauma-specific treatment on OTCA use after trauma, as there are some indications of overlapping treatment opportunities for trauma and chronic pain.

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Contributors SØS applied for funding and for data. All the authors contributed substantially to the study conception and design. TW-L and MB-L conducted the statistical analyses, all authors contributed in interpretation of data. MB-L drafted the work and SØS, KS, TW-L GD and J-AZ revised it critically for important intellectual content. MB-L is responsible for the overall content as guarantor. All authors have given their approval for the publication of this manuscript and agree to be accountable for all aspects of the work to ensure that the questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval Participation in the study was voluntary. Inclusion in Young-HUNT 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 (REK, reference number 2017/2229). The Young-HUNT studies have been approved by REK and the Data Inspectorate of Norway.

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Data availability statement The dataset analysed belongs to a third party, the Trøndelag Health Study (HUNT study). The authors of the current manuscript have been granted permission to analyse the data after obtaining the necessary Norwegian permits. Research groups that wish to analyse data from the HUNT study may apply to the HUNT Research Centre 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).

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Supplementary tables

Supplementary table 1. Sociodemographic factors, use of over-the-counter analgesics, trauma exposure and symptoms

	N	All	Female	Male
		N(%)/mean(SD)	N(%)/mean(SD)	N(%)/mean(SD)
All participants (percent)	8066	8066	4106 (50.9)	3960 (49.1)
Age and development				
Age, mean	8066	16.1 (1.8)	16.1 (1.8)	16.1 (1.8)
Pubertal development score (1-4), mean	7503	3.1 (0.7)	3.3 (0.6)	2.9 (0.7)
Socioeconomic factors				
Economy below average	7947	629 (7.9)	375 (9.2)	254 (6.5)
Not living with both parents	7461	3040 (40.8)	1610 (41.5)	1430 (39.9)
OTCA for headache	7829			
Never/rarely		4739 (60.5)	2032 (50.9)	2707 (70.5)
Monthly		2326 (29.7)	1374 (34.4)	952 (24.8)
Weekly		577 (7.4)	435 (10.9)	142 (3.7)
Daily (4-7 days/week)		187 (2.4)	148 (3.7)	39 (1.0)
OTCA for musculoskeletal pain	7776			
Never/rarely		6902 (88.8)	3372 (85.3)	3530 (92.4)
Monthly		586 (7.5)	377 (9.5)	209 (5.5)
Weekly		173 (2.2)	119 (3.0)	54 (1.4)
Daily (4-7 days/week)		115 (1.5)	86 (2.2)	29 (0.8)
Interpersonal violence, by type				
Bullying weekly	7818	652 (8.3)	347 (8.7)	305 (8.0)
Physical violence	7799	667 (8.6)	319 (8.0)	348 (9.1)
Sexual abuse	7796	662 (8.5)	578 (14.5)	84 (2.2)
Witness to violence	7777	1169 (15.0)	456 (11.5)	713 (18.8)
Interpersonal violence, number of types	7858			
No event		5700 (72.5)	2903 (72.1)	2797 (73.0)
1 type of event		1441 (18.3)	730 (18.1)	711 (18.6)
≥2 types of events		717 (9.1)	393 (9.8)	324 (8.5)
Other traumatic events, by type				
Illness self or family, death of close person	7830	6317 (80.7)	3310 (82.5)	3007 (78.7)
Severe accident, disaster or other trauma	7814	2514 (32.2)	1330 (33.2)	1184 (31.1)
Symptoms				
Musculoskeletal pain in any site, at least weekly	7868	3105 (39.5)	1896 (47.2)	1209 (31.3)
Pain in 1 site		1336 (17.0)	726 (18.1)	610 (15.8)
Pain in 2 sites		730 (9.3)	451 (11.2)	279 (7.2)
Pain in 3-7 sites		1039 (13.2)	719 (17.9)	320 (8.3)
Headache weekly or more often	7464	1151 (15.4)	905 (23.3)	246 (6.9)
Any disability due to pain (disability index ≥1)	6561	3711 (56.6)	2276 (63.5)	1435 (48.2)

Supplementary Table 2. Ordinal logistic regression analyses for outcome 1, frequency of use of over-the-counter medication to treat headache, by number of types of other events

		Model 1[a]			Model 2 [a b]	
	n	**OR (CI)**	**p-value**	**n**	**OR (95% CI)**	**p-value**
Exposure to other potentially traumatic events, number of types	6818			6676		
1 type of other event		1.23 (1.06, 1.42)	0.006		1.21 (1.04, 1.41)	0.013
2 types of other events		1.80 (1.53, 2.10)	<0.001		1.47 (1.25, 1.74)	<0.001

[a]Models 1 and 2 are ordinal logistic regression models estimating odds for a higher frequency of use of over-the-counter analgesics to treat headache. Both models are adjusted for background factors: sex, age, pubertal development, household and family economy.

[b]Ordinal logistic regression model adjusted for headache, musculoskeletal pain and Juvenile Idiopathic Arthritis in addition to background factors.

Supplementary Table 3. Ordinal logistic regression analyses for outcome 2, frequency of use of over-the-counter medication to treat musculoskeletal pain, by number of types of other events

		Model 1[a]			Model 2 [a b]	
	n	**OR (CI)**	**p-value**	**n**	**OR (95% CI)**	**p-value**
Exposure to other potentially traumatic events, number of types	6777			6652		
1 type of other event		1.36 (1.06, 1.75)	0.017		1.28 (0.99, 1.67)	0.064
2 types of other events		1.96 (1.51, 2.54)	<0.001		1.43 (1.08, 1.88)	0.012

[a]Models 1 and 2 are ordinal logistic regression models estimating odds for a higher frequency of use of over-the-counter analgesics to treat musculoskeletal pain. Both models are adjusted for background factors: sex, age, pubertal development, household and family economy.

[b]Ordinal logistic regression model adjusted for headache, musculoskeletal pain and Juvenile Idiopathic Arthritis in addition to background factors.

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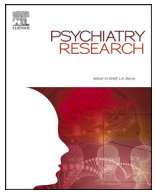

Killing pain? A prospective population-based study on trauma exposure in childhood as predictor for frequent use of over-the-counter analgesics in young adulthood. The HUNT study

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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

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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 (Mikkelsson 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 Mikkelsson 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 (≥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 (SD1.95)	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.

		Model 1[a] (sex and age) (n = 2750–2768)			Model 2[a,b] (background)(n = 2636–2648)			Model 3[a,b,c] (somatic symptoms) (n = 2478–2488)			Model 4[a,b,c] (psychological symptoms) (n = 1570–1576)	
	n	OR (95% CI)	p-value	N	OR (95% CI)	p-value	n	OR (95% CI)	p-value	n	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.
[d]Model 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.

		Model 1[a] (sex and age) (n = 2790–2799)			Model 2[a,b] (background) (n = 2667–2679)			Model 3[a,b,c] (somatic symptoms) (n = 2507–2517)			Model 4[a,b,c] (psychological symptoms) (n = 1587–1593)	
	n	OR (95% CI)	p-value	N	OR (95% CI)	p-value	n	OR (95% CI)	p-value	n	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.
[d]Model 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 underrepresented (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 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

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2023.115400.

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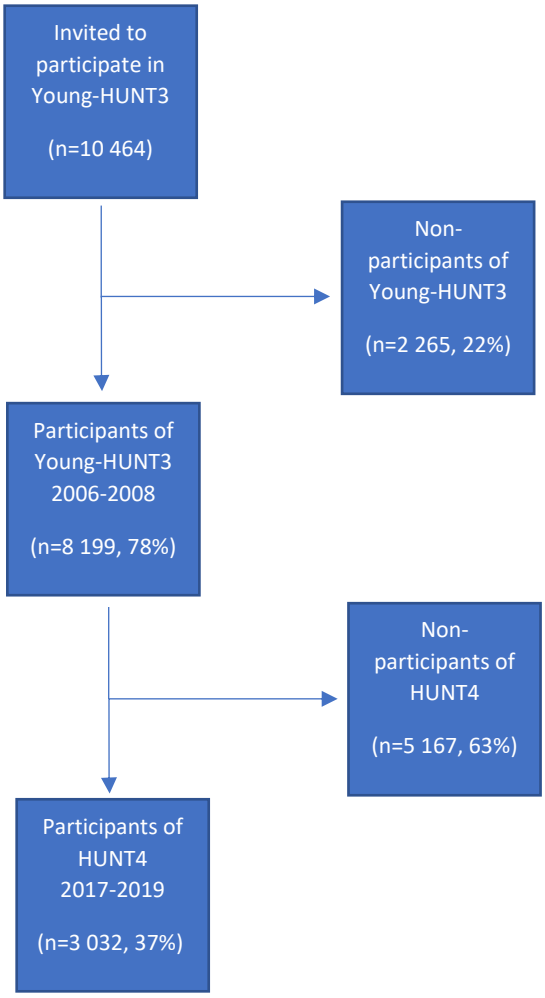
Supplementary Figure 1.



Participation flowchart. Young-HUNT3 (2006-2008) was conducted in a school setting. The survey part of HUNT4 (2019-2019) was conducted as a population survey where participants could respond by mail or online. Participants of previous waves of the HUNT Study who had moved out of the region were also invited to participate in HUNT4.

Supplementary Table 1. Measures used in ordinal logistic regression analyses to assess exposure to PTEs and symptoms experienced in adolescence

Measure	Items from Young-HUNT 3 included in measure	Questions derived from
Exposure to PTE representing direct interpersonal violence	*Experienced at any point in time before the survey:*	
Physical violence	been subjected to violence (beaten/injured)	UCLA PTSD Reaction Index for DSM IV, part I (Steinberg et al., 2004)
Bullying	been threatened or physically harassed by fellow students at school over a period of time	In compliance with the WHO definition of interpersonal violence (Krug et al., 2002)
Sexual abuse	subjected to an unpleasant sexual act by a peer	UCLA PTSD Reaction Index for DSM IV, part I
	subjected to an unpleasant sexual act by an adult	UCLA PTSD Reaction Index for DSM IV, part I
Exposure to other PTE	*Experienced at any point in time before the survey:*	
Witness to violence	seen someone else being subjected to violence	UCLA PTSD Reaction Index for DSM IV, part I
Severe illness or death of someone close	someone in your family was seriously ill	UCLA PTSD Reaction Index for DSM IV, part I
	the death of someone close to you	UCLA PTSD Reaction Index for DSM IV, part I
Other potentially traumatic event	a disaster (fire, hurricane or similar)	UCLA PTSD Reaction Index for DSM IV, part I
	a serious accident (e.g., serious car accident)	UCLA PTSD Reaction Index for DSM IV, part I
	painful or frightening hospital treatment for a disease or an accident	UCLA PTSD Reaction Index for DSM IV, part I
	other experience that was very frightening, dangerous or violent	UCLA PTSD Reaction Index for DSM IV, part I
Posttraumatic stress symptoms		
	I have upsetting thoughts, pictures or sounds of what happened come into my mind when I do not want them to	UCLA PTSD Index for DSM IV, part III (Steinberg et al., 2004)
	When something reminds me of what happened I get very afraid, upset or sad	UCLA PTSD Index for DSM IV, part III
	I try not to talk about, think about or have feelings about what happened	UCLA PTSD Index for DSM IV, part III
Psychological distress, SCL-5	*Experienced for the past 14 days:*	Hopkins Symptoms Checklist (SCL-5) (Strand et al., 2003)
	i) feeling fearful	
	ii) nervousness or shakiness inside	
	iii) feeling hopeless about the future	
	iv) feeling blue	
	v) worrying about things too much	
Headache, weekly	*Reoccuring headaches past 12 months:*	Validated headache interview (Zwart et al., 2003)
	Weekly migraine	
	Weekly tension type headache	
	Weekly other headache	
Musculoskeletal pain, number of sites	*Weekly pain for the past 3 months in:*	Assessment instrument by Mikkelson et al. (Mikkelsson et al., 1997)
	Neck or shoulders	
	Chest	
	Upper back	
	Lower back	
	Left arm	
	Right arm	
	Left leg	
	Right leg	

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Supplementary Table 2. Sociodemographic factors, traumatic exposures, symptoms and use of over-the-counter analgesics by sex.

	N	All	Female	Male
		N(%)/mean(SD)	N(%)/mean(SD)	N(%)/mean(SD)
All participants (percent)	2947	2947 (100)	1742 (59.1)	1205 (40.9)
Age Young-HUNT3, mean	2947	16.0 (1.77)	16.0 (1.80)	16.0 (1.72)
Age HUNT4, mean	2947	27.1 (1.94)	27.1 (1.94)	27.0 (1.94)
Socioeconomic factors				
Family economy below average	2766	239 (8.6)	146 (8.8)	93 (8.4)
Household structure, living with both parents	2947	1678 (57.6)	984 (57.3)	694 (58.0)
OTCA for headaches, young adult	2911			
Never/rarely		2133 (73.3)	1163 (67.7)	970 (81.4)
1-3 times per week		699 (24.0)	491 (28.6)	208 (17.5)
More than 4 times per week		79 (2.7)	65 (3.8)	14 (1.2)
OTCA for musculoskeletal pain, young adult	2877			
Never/rarely		2457 (85.4)	1406 (82.5)	1051 (89.6)
1-3 times per week		323 (11.2)	223 (13.1)	100 (8.5)
More than 4 times per week		97 (3.4)	75 (4.4)	22 (1.9)
Direct interpersonal violence				
Bullying	2815	203 (7.2)	113 (6.7)	90 (8.0)
Physical violence	2822	240 (8.5)	109 (6.5)	131 (11.5)
Sexual abuse	2823	148 (5.2)	121 (7.2)	27 (2.4)
By peer	2819	110 (3.9)	85 (5.1)	25 (2.2)
By adult	2747	69 (2.5)	53 (3.2)	16 (1.4)
Other potentially traumatic events				
Witness to violence	2823	586 (20.8)	275 (16.3)	311 (27.4)
Disease or death of someone close	2833	2073 (73.2)	1278 (75.6)	795 (69.6)
Severe accident, disaster or other traumatic event	2830	859 (30.4)	523 (31.0)	336 (29.5)
Direct interpersonal violence, number of types	2823			
No event		2388 (84.6)	1439 (85.2)	949 (83.8)
1 type of event		309 (11.0)	178 (10.5)	131 (11.6)
2 or more types of events		126 (4.5)	73 (4.3)	53 (4.7)
Symptoms				
Posttraumatic stress, sum score (0-3)	1886	0.8 (0.99)	1.0 (1.04)	0.5 (0.81)
Psychological distress, SCL-5, mean score (1-4)	2893	1.51 (0.54)	1.61 (0.58)	1.35 (0.45)
Psychological distress above cutoff (SCL-5> 2.0)	2893	380 (13.1)	306 (17.8)	74 (6.3)
Frequent musculoskeletal pain	2930	1010 (34.5)	675 (39.0)	335 (27.9)
Pain in 1 site		454 (15.6)	296 (17.2)	158 (13.3)
Pain in 2 sites		292 (10.0)	193 (11.2)	99 (8.3)
Pain in 3-8 sites		256 (8.8)	184 (10.7)	72 (6.1)
Frequent headaches	2793	238 (8.5)	190 (11.5)	48 (4.2)
Disability Index (0-5)	2165	1.2 (1.38)	1.4 (1.43)	1.0 (1.25)

Supplementary Table 3.

Spearman's rank correlation coefficient for the relationship between different types of trauma exposures

	1	2	3	4	5	6
1 Bullying	1.00					
2 Sexual abuse	0.22, p<.001	1.00				
3 Physical violence	0.29, p<.001	0.27, p<.001	1.00			
4 Witnessing violence	0.21, p<.001	0.16, p<.001	0.41, p<.001	1.00		
5 Severe illness or death of someone close	0.09, p<.001	0.04, p=0.018	0.10, p<.001	0.13, p<.001	1.00	
6 Disaster, accident or other trauma	0.19, p<.001	0.15, p<.001	0.26, p<.001	0.29, p<.001	0.21, p<.001	1.00

Supplementary Table 4.

Logistic regression analyses for outcome ii), frequency of use of over-the-counter analgesics to treat headaches, 0 = using never/rarely for the past month, 1= using ≥4 times per week for the past month, by type of event and number of types of direct interpersonal violence.

	Model 1[a]		Model 2[a b]		Model 3[a b c]		Model 4[a b c]	
	OR (95CI)	**p-value**	**OR (95CI)**	**p-value**	**OR (95CI)**	**p-value**	**OR (95CI)**	**p-value**
Exposure to direct interpersonal violence								
By type								
Bullying	3.31 (1.76, 6.24)	<0.001	3.09 (1.58, 6.05)	0.001	2.71 (1.30, 5.67)	0.008	2.79 (1.25, 6.21)	0.012
Sexual abuse	2.00 (0.92, 4.32)	0.080	1.74 (0.76, 3.96)	0.189	1.30 (0.52, 3.24)	0.574	1.17 (0.43, 3.18)	0.754
Physical violence	2.49 (1.27, 4.91)	0.008	1.92 (0.92, 4.03)	0.084	1.26 (0.54, 2.96)	0.595	1.09 (0.44, 2.69)	0.856
By number of types								
1 type of interpersonal violence	2.67 (1.48, 4.80)	0.001	2.54 (1.38, 4.68)	0.003	2.22 (1.16, 4.24)	0.016	1.72 (0.84, 3.54)	0.141
≥2 types of interpersonal violence	3.22 (1.40, 7.42)	0.006	2.64 (1.07, 6.51)	0.089	1.89 (0.68, 5.26)	0.224	0.77 (0.28, 2.14)	0.618
Exposure to other types of traumatic events								
Witness to violence	0.99 (0.52, 1.89)	0.982	0.80 (0.40, 1.62)	0.539	0.48 (0.21, 1.09)	0.079	0.36 (0.14, 0.90)	0.029
Severe illness or death of someone close	1.51 (0.84, 2.69)	0.165	1.32 (0.74, 2.38)	0.349	1.28 (0.70, 2.37)	0.422	1.80 (0.41, 7.97)	0.437
Severe accident, disaster or other potentially traumatic event	1.54 (0.95, 2.49)	0.080	1.45 (0.88, 2.41)	0.148	1.16 (0.68, 2.00)	0.582	0.88 (0.46, 1.68)	0.695

Trauma types were assessed by separate analyses.

[a] Models 1-4 are all adjusted for sex and age

[b] Models 2-4 are additionally adjusted for the background factors household structure and family economy

[c] Models 3-4 are additionally adjusted for headaches and musculoskeletal pain.

[d] Model 4 is additionally adjusted for posttraumatic stress and psychological distress.

Supplementary table 5.

Mediation analyses for the relation of exposure to direct interpersonal violence to OTCA use due to musculoskeletal pain in young adulthood (daily use vs weekly or monthly use) with weekly headaches, musculoskeletal pain and psychological distress (SCL-5) as potential mediators.

	Estimate	CI	p-value	E-value	E-value lower
Sexual abuse					
Controlled direct effect	1.19	0.38-2.52	0.797	1.67	-
Pure natural direct effect	1.24	0.71-2.11	0.385	1.78	-
Total natural direct effect	1.25	0.79-2.08	0.294	1.81	-
Pure natural indirect effect	1.33	1.20-1.52	<0.001	1.98	1.68
Total natural indirect effect	1.34	1.03-1.90	0.032	2.02	1.20
Total effect	1.66	1.05-2.77	0.031	2.70	1.28
Bullying					
Controlled direct effect	1.71	0.81-3.01	0.159	2.81	-
Pure natural direct effect	1.50	0.99-2.22	0.055	2.36	-
Total natural direct effect	1.37	0.96-2.00	0.083	2.08	-
Pure natural indirect effect	1.34	1.20-1.52	<0.001	2.01	1.69
Total natural indirect effect	1.22	1.01-1.58	0.040	1.74	1.12
Total effect	1.83	1.30-2.66	0.002	3.06	1.92
Physical violence					
Controlled direct effect	1.71	0.81-3.01	0.159	2.81	-
Pure natural direct effect	1.50	0.99-2.22	0.055	2.36	-
Total natural direct effect	1.37	0.96-2.00	0.083	2.08	-
Pure natural indirect effect	1.34	1.20-1.52	<0.001	2.01	1.69
Total natural indirect effect	1.22	1.01-1.58	0.040	1.74	1.12
Total effect	1.83	1.30-2.66	0.002	3.06	1.92

The E-value for a risk RR ratio is computed as $RR + \sqrt{RR(RR-1)}$, and indicates the amount of unmeasured confounding that is needed to explain away the relationship. E-values for the confidence bound closest to 1 is computed when the confidence interval does not cross 1.

Supplementary Table 6. Distribution of background factors and exposure to traumatic events by sex in young-HUNT3 among participants and non-participants in HUNT4.

		Participants of both Young-HUNT3 and HUNT4				Participants of Young-HUNT3 and not HUNT4		
	n	All	Female	Male	N	All	Female	Male
		N(%) mean(SD)	N(%) mean(SD)	N(%) mean(SD)		N(%) mean(SD)	N(%) mean(SD)	N(%) mean(SD)
All participants (percent)	2947	2947	1742 (59.1)	1205 (40.9)	5167	5167	2327 (45.0)	2840 (55.0)
Age young-HUNT3, mean	2947	16.0 (1.77)	16.0 (1.80)	16.0 (1.72)	5167	15.8 (1.72)	15.8 (1.72)	15.8 (SD 1.72)
Socioeconomic factors								
Family economy below average	2766	239 (8.6)	146 (8.8)	93 (8.4)	4789	461 (9.6)	247 (11.2)	214 (8.3)
Household structure, living with both parents	2947	1678 (57.6)	984 (57.3)	694 (58.0)	5092	2607 (51.2)	1171 (50.9)	1436 (51.5)
Direct interpersonal violence								
Bullying	2815	203 (7.2)	113 (6.7)	90 (8.0)	4906	414 (8.4)	176 (7.9)	238 (8.9)
Physical violence	2822	240 (8.5)	109 (6.5)	131 (11.5)	4904	541 (11.0)	192 (8.6)	349 (13.1)
Sexual abuse	2823	148 (5.2)	121 (7.2)	27 (2.4)	4924	272 (5.5)	194 (8.6)	78 (2.9)
By peer	2819	110 (3.9)	85 (5.1)	25 (2.2)	4916	201 (4.1)	133 (5.9)	68 (2.5)
By adult	2747	69 (2.5)	53 (3.2)	16 (1.4)	4916	146 (3.0)	94 (4.2)	52 (1.9)
Other potentially traumatic events								
Witness to violence	2823	586 (20.8)	275 (16.3)	311 (27.4)	4907	1208 (24.6)	440 (19.6)	768 (28.8)
Disease or death of someone close	2833	2073 (73.2)	1278 (75.6)	795 (69.6)	4933	3623 (73.4)	1738 (77.1)	1885 (70.3)
Severe accident, disaster or other traumatic event	2830	859 (30.4)	523 (31.0)	336 (29.5)	4935	1592 (32.3)	760 (33.8)	832 (31.0)
Direct interpersonal violence, number of types	2823				4914			
No event		2388 (84.6)	1439 (85.2)	949 (83.8)		4004 (81.5)	1837 (81.9)	2167 (81.1)
1 type of event		309 (11.0)	178 (10.5)	131 (11.6)		661 (13.5)	286 (12.8)	375 (14.0)
2 or more types of events		126 (4.5)	73 (4.3)	53 (4.7)		249 (5.1)	120 (5.4)	129 (4.8)
Frequent use of OTCA in adolescence (Young-HUNT3)	2888	305 (10.6)	242 (14.1)	63 (5.4)		583 (11.6)	391 (17.1)	192 (6.7)

III

Childhood trauma and the use of opioids and other prescription analgesics in adolescence and young adulthood. The HUNT Study.

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Abstract

Opioid and nonopioid analgesics are commonly prescribed to young people to alleviate pain. Even short-term prescriptions increase the risk of persistent use and future misuse of potent analgesics, such as opioids. Childhood trauma exposure has been found to be related to pain conditions and to using more prescription analgesics. This large, prospective cohort study aimed to investigate the association of a broad range of childhood trauma exposures with prescription rates for opioid and nonopioid analgesics in adolescence and young adulthood. Self-reported data on childhood trauma exposures from adolescents (aged 13-19 years) who participated in the Young-HUNT3 Study (2006-2008, n= 8199) were linked to data from the Norwegian Prescription Database (NorPD, 2004-2021). We found that exposure to childhood trauma was consistently associated with higher prescription rates for opioids throughout adolescence and young adulthood. The highest incidence rate ratio (IRR) in adolescence was observed for sexual abuse (IRR 1.63, confidence interval (CI) 1.19-2.23). In young adulthood, the highest IRR was observed for physical violence (2.66, CI 2.27-3.12). The same overall pattern was observed for nonopioid analgesics. The more frequent prescriptions of opioid and nonopioid analgesics to participants exposed to childhood trauma suggests a higher symptom load of pain causing them to seek professional help with pain relief. Receiving potent

analgesics is not without risk, and the likelihood of misuse may be elevated among trauma exposed individuals. A trauma-informed approach to pain could be vital for guiding clinicians to the most effective and least harmful treatment for each patient.

1. Introduction

Opioid and nonopioid analgesics are commonly prescribed to young individuals to alleviate pain in outpatient settings [17; 18; 74]. Receiving prescription analgesics implies seeking help for pain management, indicating the severity of the pain condition [26]. Even short-term prescriptions increase the risk of persistent use and future misuse of potent analgesics, such as opioids [1; 34; 35], and they should therefore be prescribed with great caution in all settings [22; 43]. Overall, more frequent use of both opioid and nonopioid analgesics is linked to female sex, low socioeconomic status, pain in multiple sites, and psychological distress [8; 13; 54; 62; 68; 69], with prescriptions increasing sharply from mid-adolescence [69]. Although evidence is sparse, retrospectively assessed childhood interpersonal trauma, including sexual abuse, emotional abuse, and exposure to physical violence, has been found to be associated with using more analgesics [6; 28; 64]. Recent results from a large, prospective study on the relation of childhood trauma to subsequent use of over-the-counter analgesics are consistent with these findings, with results indicating an increased risk of frequent use of over-the-counter analgesics among young adults exposed to childhood trauma [9]. Trauma types representing interpersonal violence, such as bullying, sexual abuse and physical violence, and particularly multiple types of such trauma, have been found to be especially strongly associated with frequent use of over-the-counter analgesics [8]. Such cumulative load may be of importance for the relation to analgesics use also for other trauma types [8]. Childhood trauma is associated with pain, often in combination with functional impairment as well as psychological distress, with the latter representing an independent risk factor for

chronic pain [3; 5; 15; 72]. Exposure to childhood trauma may therefore result in an increased risk of receiving prescription analgesics, including opioids.

There is a dearth of prospective studies on the relation of childhood trauma to prescription rates for analgesics in adolescence and young adulthood. Knowledge about the potential importance of childhood trauma exposure as a risk factor for receiving prescription analgesics may inform clinical approaches to pain management for this especially vulnerable group.

In this study, we aimed to investigate the relation of a broad range of childhood trauma exposures to risk of receiving prescriptions for opioid and nonopioid analgesics in adolescence and young adulthood. We further explored whether exposure to multiple trauma types would predict an especially high prescription rate.

2. Methods

2.1 Data sources

This large, prospective cohort study utilized self-reported data on childhood trauma exposures from adolescents (aged 13-19 years) who participated in the Young-HUNT3 Study (2006-2008) [38] linked to data from the Norwegian Prescription Database (NorPD) [27]. The linkage enabled tracking of individual prescriptions for opioid and nonopioid analgesics for the participants from 2004 to 2021. The Norwegian Institute of Public Health linked the data from the Young-HUNT3 and NorPD based on the unique personal identification number of each individual, ensuring high linkage quality [36]. Prescription data were linked for all 8199 participants, including participants who did not receive analgesics prescriptions within the follow-up period. The study was approved by the Norwegian Regional Committee for Medical Research Ethics (project ID: 2017/2229).

In Young-HUNT3 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=8 199). 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 consent to linkage of survey data to registry data was an integrated part of the consent to participate in The HUNT Study, as data from The HUNT Study are extensively used in linkage studies. Participants can withdraw their consent at any time. Individuals who withdraw consent to linkage are considered nonparticipants, and they are not included in participant counts. Most adolescents completed the self-administered questionnaire during school hours.

NorPD is an electronic registry which has obtained data on all filled prescriptions from all pharmacies in Norway since 2004 [27]. Each filled prescription is registered with patient identifiers and drug information, including the date of dispensing and an Anatomical Therapeutic Chemical (ATC) code identifying the specific drug [77]. All prescriptions filled at a pharmacy, whether issued in primary or specialist care, including hospitals and institutions, are registered. Medications directly dispensed from an institution's medication inventory are not registered.

2.2 Norwegian health services and prescription subsidy program

Residents of Norway are automatically enrolled in the public healthcare system, covering both primary and specialist care [66]. Specialist care, including hospital care, requires a referral, while primary care services do not. The costs of health services are subsidized by the government and maintained at an affordable rate.

Prescription medications are paid for by the recipient. Analgesics can be obtained on a reimbursed prescription for chronic pain, where the cost of medication is reduced to 39% of the total cost. To qualify, the patient must have chronic, severe pain that significantly reduces quality of life and function. Validated tools must be used to assess diagnosis, pain severity and treatment effect. Only 2% of the entire Norwegian population received an analgesic to

treat chronic pain on a reimbursed prescription in 2010, corresponding to about 10% of those with a diagnosis of chronic pain at the time [57].

There is a cost limit for all payments within the public health care system, including payment for consultations and reimbursed prescriptions. Once this limit is reached, further consultations and reimbursed prescriptions are free of charge. Individuals living in a low-income household can apply for reimbursement of health costs regardless of total health expenses. For individuals under the age of 16 years, medication on a reimbursed prescription will be dispensed for free, irrespective of total health expenses.

While prescription medication has a fixed maximum price, the pricing of non-prescription medication is not regulated in Norway. NSAIDs and paracetamol can be purchased over the counter, however, acquiring them through a prescription can be more affordable.

2.3 Measures

2.3.1 Sociodemographics in adolescence

Data on sex and age at the time of attendance in the Young-HUNT3 Study were obtained from the Norwegian National Population Registry. *Pubertal development* was assessed using a four-item version of the pubertal development scale by Carskadon and Acebo [14]. 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*.

2.3.2 Childhood trauma

Lifetime trauma screen. Childhood exposure to potentially traumatic events, termed *childhood trauma*, was assessed in adolescence by a lifetime trauma screen derived from the UCLA Posttraumatic Stress Disorder Reaction Index, part I [70; 71], adapted to a Norwegian context. All events were listed under the question "Did you ever experience any of these events?". Response alternatives were "never", "yes, last year" and "yes, in my life" for all items. Participants responding "yes, last year" and "yes, in my life" were labelled as exposed.

Direct interpersonal trauma. Items on exposure to direct interpersonal trauma included physical violence, bullying and sexual abuse. Participants were classified as exposed to *physical violence* if they responded affirmatively to the statement "been subjected to violence (beaten/injured)". Participants who answered "yes" to the statement "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: "subjected to an unpleasant sexual act by a peer" and "subjected to an unpleasant sexual act by an adult". Reports of exposure to either or both were categorized as *sexual abuse*. A sum score (range 0-3) of the three items assessing exposure to different types of direct interpersonal trauma was computed and labelled *Interpersonal trauma, number of types*. For regression analyses, scores of 2 and 3 were combined due to low counts.

Other trauma. Participants were asked if they had "seen someone else being subjected to violence", and responders answering affirmatively were classified as having been a *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*. Participants responding "yes" 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" or "other experience that was very frightening, dangerous or violent" were classified as exposed to *other potentially traumatic event*. A sum

score (range 0-3) of the three items assessing exposure to different types of other trauma was computed and labelled *other trauma, number of types*.

2.3.3 Chronic pain and psychological symptoms in adolescence. Posttraumatic stress symptoms, psychological distress, headaches and musculoskeletal pain were assessed in Young-HUNT3, these measures are detailed in Supplementary Table 1.

2.3.4 Opioid and nonopioid prescription analgesics

Counts of all prescriptions of opioid analgesics (ATC group N02A) and the nonopioid analgesics paracetamol (ATC group N02BE), gabapentinoids (N03AX12 and N03AX16) and NSAIDs (non-steroid anti-inflammatory drugs, ATC group M01A) filled by the participants as i) adolescents and ii) young adults in the time period 2004-2021 served as outcome measures. The number of filled prescriptions within each analgesic group were counted for each individual. Prescriptions in adolescence (age 13-19 years) and in young adulthood (age 20-32 years) were analyzed separately, accounting for number of follow-up years (e.g., an individual who was 13 years old in 2006 would have seven years of follow-up as an adolescent and nine years as a young adult, while an individual who was 19 years old in 2006 would have three years of follow-up as an adolescent and 13 years as a young adult). The count measure for each developmental stage was chosen based on the knowledge that prescription opioid use is relatively rare among adolescents and young adults and that very few will meet the criteria of previously used definitions for persistent use [31; 32]. Prescriptions with a reimbursement code indicating palliative care (-90) were excluded [48; 49].

2.4 Statistical procedures

Descriptive data on the adolescents' sociodemographics, exposure to childhood trauma and nonopioid analgesics prescriptions were presented stratified by the follow-up periods in which

the participants received opioid prescriptions, and 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, meaning that participants who answered at least half of the questions were used to calculate mean scores and sum scores. Number of types of exposure to other trauma types were presented by number of types of exposure to interpersonal trauma.

The number of prescriptions of opioids, paracetamol, NSAIDs and gabapentinoids filled in i) adolescence (age 13-19 years) and ii) young adulthood (age 20-32 years) served as separate outcomes in zero-inflated negative binomial regression analyses. Variation in follow-up time was accounted for by offsetting for log follow-up time, resulting in incidence rate ratios that may be interpreted as ratios between rates per year [24]. Exposure to each trauma type was assessed in separate complete case analyses, while number of trauma types was assessed in one complete case analysis including interpersonal trauma and other trauma types. For the subsample reporting trauma exposure, symptoms reported in adolescence were assessed in separate zero-inflated negative binomial regression analyses for the number of analgesics prescriptions filled in adolescence and young adulthood.

All the described analyses were adjusted for the variables age, sex, *household structure* and *family economy* as reported in adolescence [7; 46]. Analyses for prescription analgesics in adolescence were additionally adjusted for *pubertal development* [16; 47]. Separate and unadjusted zero-inflated negative binomial regression analyses were run to show the association of background variables to the outcomes. Statistical analyses were conducted using R version 4.2.2 and Stata version 17.0, with the R package data.table [23] for aggregating from data on individual prescriptions to number of prescriptions for participants, and Stata for estimation of zero-inflated negative binomial regression models.

3. Results

3.1 Sample descriptives

Girls and boys were evenly represented among participating adolescents in the Young-HUNT3 Study (50.3% females, n=4128). During the study period, about one in ten participants received opioid analgesics in adolescence and two in five received opioids in young adulthood (Table 1, Supplementary Table 2). Among nonopioids, NSAIDs were prescribed to the largest proportion of participants, both in adolescence (about two in five) and young adulthood (two in three), while paracetamol prescriptions were received by fewer participants than opioid prescriptions, both in adolescence and young adulthood. Very few participants received gabapentinoid prescriptions. Participants who received opioid prescriptions in both adolescence and young adulthood were overall more exposed to childhood trauma (Table 1). This cohort also received more nonopioid prescription analgesics in both developmental stages. As adolescents, participants in this cohort reported more psychological and somatic symptomatology, including posttraumatic stress, psychological distress, recurrent musculoskeletal pain, and headaches. Girls reported higher childhood exposure to sexual abuse and boys reported higher exposure to physical violence and witnessing violence (Supplementary Table 2). More females than males received opioid and nonopioid analgesics, both in adolescence and young adulthood, and girls reported more chronic pain and psychological symptoms than boys. There was considerable overlap of exposure to different trauma types, with a substantial subgroup reporting exposure to the maximum number of types for both interpersonal trauma and other trauma (Supplementary Table 3).

Table 1. Number and proportion of participants receiving opioid analgesics in adolescence and/or young adulthood by background factors, trauma and history of nonopioid analgesics

		All	No prescription opioids in adolescence or young adulthood	Prescription opioids in adolescence only	Prescription opioids in young adulthood only	Prescription opioids in adolescence and young adulthood
	n	n (%)/ mean (SD)	n (%)/ mean (SD)	n (%)/ mean (SD)	n (%)/ mean (SD)	n (%)/ mean (SD)
All participants	8199	8199	4314 (52.6)	378 (4.6)	2947 (35.9)	560 (6.8)
Females	4128	4128 (50.3)	1962 (47.5)	208 (5.04)	1601 (38.8)	357 (8.7)
Males	4071	4071 (49.7)	2352 (57.8)	170 (4.2)	1346 (33.1)	203 (5.0)
Age at Young-HUNT3, mean (min 12.7, max 20.9)	8199	15.9 (1.7)	15.8 (1.7)	15.6 (1.7)	16.0 (1.7)	16.0 (1.7)
Pubertal development score, mean (range 1-4)	7511	3.1 (0.7)	3.1 (0.7)	3.1 (0.6)	3.1 (0.7)	3.2 (0.6)
Socioeconomic factors						
Family economy below average	7636	708 (9.3)	351 (8.7)	27 (7.6)	266 (9.7)	64 (12.1)
Household, not living with both parents	8104	3776 (46.6)	1874 (43.9)	173 (46.3)	1433 (49.2)	296 (53.6)
Direct interpersonal trauma						
By type						
Bullying	7803	628 (8.1)	284 (6.9)	22 (6.0)	257 (9.2)	65 (12.0)
Physical violence	7809	789 (10.1)	340 (8.3)	29 (7.9)	340 (12.2)	80 (14.8)
Sexual abuse	7829	430 (5.5)	189 (4.6)	18 (4.9)	165 (5.9)	58 (10.7)
By number of types	7833					
No events		6464 (82.5)	3512 (85.1)	313 (84.6)	2226 (79.7)	413 (76.1)
1 type		987 (12.6)	457 (11.1)	48 (13.0)	407 (14.6)	75 (13.8)
≥ 2 types		382 (4.9)	158 (3.8)	9 (2.4)	160 (5.7)	55 (10.1)
Other trauma						
By type						
Witness to violence	7812	1810 (23.2)	869 (21.1)	82 (22.4)	692 (24.8)	167 (30.9)
Disease or death of someone close	7848	5757 (73.4)	2979 (72.0)	278 (75.1)	2073 (74.1)	427 (78.8)
Severe accident, disaster or other traumatic event	7848	2481 (31.6)	1168 (28.2)	115 (31.0)	959 (34.3)	239 (44.0)
By number of types	7863					
No events		1657 (21.1)	942 (22.7)	72 (19.4)	570 (20.3)	73 (13.4)
1 type		3307 (42.1)	1803 (43.5)	168 (45.3)	1133 (40.4)	203 (37.4)
2 types		1956 (24.9)	990 (23.9)	86 (23.2)	709 (25.3)	171 (31.5)
3 types		943 (12.0)	411 (9.9)	45 (12.1)	391 (14.0)	96 (17.7)
≥ 1 nonopioid prescriptions in adolescence	8199					
Paracetamol		646 (7.9)	193 (4.5)	89 (23.5)	215 (7.3)	149 (26.6)
NSAIDs		3196 (39.0)	1243 (28.8)	270 (71.4)	1234 (41.9)	449 (80.2)
Gabapentinoids		21 (0.3)	<5	<5	<5	9 (1.6)
≥ 1 nonopioid prescriptions in young adulthood	8199					
Paracetamol		2439 (29.8)	669 (15.5)	73 (19.3)	1370 (46.5)	327 (58.4)
NSAIDs		5472 (66.7)	2238 (51.9)	235 (62.2)	2491 (84.5)	508 (90.7)
Gabapentinoids		178 (2.2)	18 (0.4)	<5	108 (3.7)	47 (8.4)
Symptoms reported in adolescence						
Psychological distress (SCL-5, 1-4)	7961	1.50 (0.55)	1.46 (0.51)	1.49 (0.56)	1.54 (0.58)	1.64 (0.65)
Posttraumatic stress symptoms (0-3)	5016	0.82 (0.99)	0.73 (0.93)	0.82 (0.98)	0.90 (1.05)	1.00 (1.07)
Musculoskeletal pain, weekly	8035	2748 (34.2)	1190 (28.2)	139 (37.5)	1124 (38.9)	295 (53.5)
Headaches, weekly	7619	617 (8.10)	226 (5.6)	39 (11.1)	274 (10.0)	78 (15.1)

Table 2. Zero-inflated negative binomial regression analyses for number of prescriptions of analgesics in adolescence and young adulthood by background factors as reported in adolescence.

		Opioids		**Nonopioid analgesics**			
		Opioids		Paracetamol		NSAIDs	
	n	**IRR (95%CI)**	**p-value**	**IRR (95%CI)**	**p-value**	**IRR (95%CI)**	**p-value**
Analgesics use in adolescence							
Age	8199	1.10 (1.05, 1.15)	<0.001	0.92 (0.87, 0.97)	<0.001	1.04 (1.01, 1.06)	0.002
Sex, female	8199	1.97 (1.69, 2.30)	<0.001	1.58 (1.31, 1.89)	<0.001	1.69 (1.56, 1.83)	<0.001
Pubertal development score	7511	1.42 (1.26, 1.60)	<0.001	0.95 (0,82, 1.09)	0.465	1.22 (1.15, 1.30)	<0.001
Family economy below average	7636	1.93 (1.51, 2.46)	<0.001	1.22 (0.89, 1.67)	0.225	1.10 (0.96, 1.27)	0.170
Household structure, not living with both parents	8104	1.30 (1.12, 1.52)	0.001	1.33 (1.11, 1.60)	0.002	1.01 (0.94, 1.10)	0.694
Analgesics use in young adulthood							
Age	8199	1.22 (1.19, 1.26)	<0.001	1.22 (1.19, 1.26)	<0.001	1.22 (1.20, 1.24)	<0.001
Sex, female	8199	1.71 (1.55, 1.89)	<0.001	2.22 (1.99, 2.47)	<0.001	1.50 (1.41, 1.60)	<0.001
Family economy below average	7636	2.13 (1.79, 2.52)	<0.001	1.56 (1.29, 1.89)	<0.001	1.29 (1.16, 1.449	<0.001
Household structure, not living with both parents	8104	1.77 (1.61, 1.95)	<0.001	1.43 (1.28, 1.60)	<0.001	1.21 (1.14, 1.29)	<0.001

Background factors were assessed in unadjusted, separate complete case analyses.

3.2 Results from regression analyses

Results from the regression analyses showed significant and consistent relationships between the broad range of childhood trauma exposures and higher prescription rates for opioid analgesics in both the shorter term, during adolescence, and the longer term, during young adulthood (Table 3). Patterns were similar for paracetamol and NSAIDs, although less distinct in adolescence than in young adulthood. Childhood trauma exposure was generally significantly related to higher prescription rates for NSAIDs in adolescence, whereas prescriptions for paracetamol were only significantly linked to prior exposure to *severe illness or death of someone close* and *severe accidents, disasters or other event* (Table 3). In young adulthood, childhood trauma was significantly associated with higher prescription rates for both NSAIDs and paracetamol (Table 3).

Exposure to more than one type of direct interpersonal trauma predicted particularly high prescription rates for both opioid and nonopioid analgesics across adolescence and young adulthood, suggesting a dose-response relationship (Table 3). A similar trend was observed for other trauma types (Table 3).

Table 3. Zero-inflated negative binomial regression analyses for number of prescriptions of analgesics in adolescence and young adulthood by type of traumatic events and number of types of direct interpersonal trauma and other trauma types

		Opioids		**Nonopioid analgesics**			
		Opioids		Paracetamol		NSAIDs	
	n	**IRR (95%CI)**	**p-value**	**IRR (95%CI)**	**p-value**	**IRR (95%CI)**	**p-value**
ADOLESCENCE (age 12-19)		n=938		n=646		n=3196	
Direct interpersonal trauma							
Bullying	7244	1.46 (1.10, 1.94)	0.009	1.33 (0.93, 1.89)	0.113	1.21 (1.04, 1.41)	0.013
Sexual abuse	7266	1.63 (1.19, 2.23)	0.002	1.08 (0.71, 1.65)	0.718	1.26 (1.06, 1.50)	0.011
Physical violence	7244	1.50 (1.17, 1.94)	0.002	1.07 (0.76, 1.50)	0.693	1.05 (0.91, 1.21)	0.510
Other trauma types							
Witness to violence	7245	1.17 (0.97, 1.41)	0.099	0.98 (0.77, 1.26)	0.902	1.04 (0.94, 1.15)	0.461
Severe illness or death of someone close	7269	1.37 (1.13, 1.66)	0.001	1.56 (1.23, 1.99)	<0.001	1.34 (1.21, 1.48)	<0.001
Severe accident, disaster or other traumatic event	7274	1.59 (1.35, 1.88)	<0.001	1.57 (1.28, 1.94)	<0.001	1.30 (1.19, 1.42)	<0.001
Direct interpersonal trauma, number of types							
1 type	7270	0.83 (0.64, 1.07)	0.141	0.70 (0.51, 0.97)	0.033	0.93 (0.81, 1.06)	0.248
≥2 types	7270	1.61 (1.13, 2.29)	0.008	1.22 (0.76, 1.95)	0.419	1.18 (0.97, 1.44)	0.106
Other trauma, number of types							
1 type	7270	1.24 (0.99, 1.56)	0.067	1.49 (1.13, 2.00)	0.005	1.27 (1.13, 1.42)	<0.001
2 types	7270	1.76 (1.37, 2.27)	<0.001	1.88 (1.38, 2.57)	<0.001	1.45 (1.28, 1.65)	<0.001
3 types	7270	1.63 (1.19, 2.22)	0.002	1.92 (1.29, 2.87)	0.001	1.48 (1.25, 1.74)	<0.001
YOUNG ADULTHOOD (age 20-32)		n=3507		n=2439		n=5472	
Direct interpersonal trauma							
Bullying	7455	1.72 (1.43, 2.06)	<0.001	2.20 (1.82, 2.67)	<0.001	1.49 (1.34, 1.66)	<0.001
Sexual abuse	7480	1.59 (1.28, 1.98)	<0.001	1.38 (1.10, 1.75)	0.006	1.24 (1.08, 1.41)	0.002
Physical violence	7460	2.66 (2.27, 3.12)	<0.001	1.95 (1.63, 2.32)	<0.001	1.32 (1.19, 1.46)	<0.001
Other trauma types							
Witness to violence	7461	1.96 (1.74, 2.21)	<0.001	1.51 (1.32, 1.72)	<0.001	1.20 (1.11, 1.29)	<0.001
Severe illness or death of someone close	7485	1.17 (1.04, 1.31)	0.008	1.39 (1.22, 1.58)	<0.001	1.21 (1.13, 1.30)	<0.001
Severe accident, disaster or other traumatic event	7490	1.69 (1.52, 1.88)	<0.001	1.62 (1.44, 1.82)	<0.001	1.24 (1.17, 1.33)	<0.001
Direct interpersonal trauma, number of types							
1 type	7484	1.40 (1.20, 1.64)	<0.001	1.35 (1.15, 1.60)	<0.001	1.23 (1.12, 1.36)	<0.001
≥2 types	7484	1.94 (1.53, 2.46)	<0.001	2.07 (1.61, 2.66)	<0.001	1.35 (1.16, 1.56)	<0.001
Other trauma, number of types							
1 type	7484	1.02 (0.89, 1.17)	0.761	1.26 (1.08, 1.47)	0.003	1.16 (1.06, 1.26)	0.001
2 types	7484	1.48 (1.27, 1.72)	<0.001	1.58 (1.33, 1.87)	<0.001	1.28 (1.16, 1.41)	<0.001
3 types	7484	1.82 (1.49, 2.21)	<0.001	1.84 (1.49, 2.27)	<0.001	1.33 (1.19, 1.50)	<0.001

Complete case analyses adjusted for age, sex, household structure, family economy as reported in adolescence. Analyses for prescriptions received in adolescence are additionally adjusted for pubertal development. Trauma types were assessed in separate analyses, while number of types were assessed in one analysis including interpersonal trauma and other trauma types. Number of participants included in analyses is the same for all analgesics, as data on filled prescriptions are available for all participants.

Among trauma-exposed participants, psychological and somatic symptoms, including posttraumatic stress, psychological distress, recurrent musculoskeletal pain, and headaches experienced in adolescence, were found to be significantly associated with higher prescription rates for opioids, paracetamol, and NSAIDs in young adulthood. Although less distinct, a similar trend was observed for prescriptions received in adolescence, most prominent for pain (Table 4). Prescriptions of gabapentinoids were limited in both adolescence and young adulthood, and results for gabapentinoids were less reliable (Supplementary Table 4). Background factors adjusted for were significantly related to the outcomes (Table 2).

Table 4. Zero-inflated negative binomial regression analyses for number of prescriptions of analgesics in adolescence and young adulthood by symptoms as reported in adolescence. Subsample analysis among participants exposed to childhood trauma.

		Opioids		**Nonopioid analgesics**			
		Opioids		Paracetamol		NSAIDs	
	n	**IRR (95%CI)**	**p-value**	**IRR (95%CI)**	**p-value**	**IRR (95%CI)**	**p-value**
Analgesics use in adolescence							
Psychological distress	5807	1.06 (0.91, 1.24)	0.460	1.07 (0.87, 1.30)	0.537	1.07 (0.98, 1.16)	0.128
Posttraumatic stress symptoms	4753	1.05 (0.95, 1.40)	0.338	1.11 (0.99, 1.25)	0.064	1.13 (1.07, 1.19)	<0.001
Musculoskeletal pain	5790	1.35 (1.24, 1.47)	<0.001	1.56 (1.42, 1.72)	<0.001	1.29 (1.24, 1.35)	<0.001
Headaches	5447	1.54 (1.15, 2.06)	0.003	1.91 (1.35, 2.70)	<0.001	1.86 (1.60, 2.17)	<0.001
Analgesics use in young adulthood							
Psychological distress	5954	1.48 (1.33, 1.64)	<0.001	1.26 (1.13, 1.42)	<0.001	1.17 (1.10, 1.25)	<0.001
Posttraumatic stress symptoms	4858	1.31 (1.23, 1.40)	<0.001	1.17 (1.09, 1.25)	<0.001	1.10 (1.06, 1.14)	<0.001
Musculoskeletal pain	5939	1.47 (1.39, 1.55)	<0.001	1.49 (1.40, 1.58)	<0.001	1.26 (1.22, 1.30)	<0.001
Headaches	5586	1.88 (1.54, 2.29)	<0.001	2.38 (1.94, 2.93)	<0.001	1.67 (1.48, 1.88)	<0.001

Complete case analyses adjusted for age, sex, household structure, family economy. Analyses for analgesics use in adolescence were additionally adjusted for pubertal development.

4. Discussion

To our knowledge, this is the first prospective study investigating the relationship between childhood trauma exposure and prescription rates for opioid and nonopioid analgesics in adolescence and young adulthood. Overall, we found that exposure to childhood trauma was consistently and significantly related to higher prescription rates for opioids throughout adolescence and young adulthood. Although somewhat less pronounced in adolescence, similar patterns were observed for nonopioid analgesics. A higher cumulative load of trauma

was linked to higher prescription rates for both opioid and nonopioid analgesics, suggesting a dose-response relationship.

Our finding that opioids are more commonly prescribed to adolescents and young adults exposed to childhood trauma is consistent with results from studies where childhood trauma exposure has been assessed retrospectively [6; 64]. Our results suggest that trauma-exposed young people may be overrepresented in the subgroup exposed to high-risk opioid prescription practices. Such practices, including the prescription of higher doses, longer duration and use of long-acting drugs, are still common in populations of young people where the overall prescription rate is decreasing [17; 61]. The risk of addiction and misuse may be higher among trauma-exposed individuals [19; 65; 76], and great caution is warranted when prescribing opioids to this group.

Socioeconomic factors increasing risk of trauma exposure, may also increase risk of receiving long-term opioid prescriptions [52]. Despite national variations in prescription practices, it is observed that patients with psychosocial problems receive more opioid prescriptions than individuals without such problems [13; 58; 62]. The current study was conducted in Norway, where prescription rates for opioids are generally low [32] and health care is accessible and affordable [66]. While this could mitigate the impact of socioeconomic differences in health, health care utilization still differs with socioeconomic status [33]. This could affect the health care received, including analgesics prescriptions. A recent study on adults in Norway found that socioeconomic factors remain strongly associated with long-term opioid use, also when accounting for pain conditions and mental health diagnoses [52]. Our finding that childhood trauma exposure was associated with higher analgesics prescription rates after adjustment for socioeconomic factors, could indicate that the higher prevalence of childhood trauma among children growing up with a lower socioeconomic status is a driving force behind the observed higher risk of long-term opioid use in this group.

The higher prescription rates for nonopioid analgesics among participants exposed to childhood trauma is consistent with previous findings from studies on adults where trauma has been assessed retrospectively [64]. The higher prescription rates for both opioid and nonopioid analgesics among trauma-exposed participants found in this study could indicate a higher symptom load of pain in this group, and we found that pain in adolescence was related to higher prescription rates throughout adolescence and young adulthood for trauma-exposed participants. There are indications that exposure to childhood trauma may increase risk of persistent pain, although most studies on the subject assess childhood trauma retrospectively [21; 63], possibly introducing bias [20; 45], and prospective findings are conflicting [42; 59; 60]. Trauma reactions such as sleep disturbances, hypervigilance and avoidance are symptoms considered to be relevant for the maintenance and exacerbation of pain conditions [7; 10; 37; 51; 53; 56], and our finding that posttraumatic stress symptoms were related to higher prescription rates in young adulthood among trauma-exposed participants aligns with this. Childhood interpersonal trauma is considered a predisposing factor for alterations in pain signaling leading to chronic pain [25]. Neurobiological findings indicate that early life stress contributes to alterations in pathways involved in pain signaling [10; 11; 50]. A higher cumulative load of stress and comorbidities may increase the risk of pain chronification [10], which supports our finding that exposure to multiple types of trauma was particularly predictive of a higher prescription rate. This finding also aligns with studies indicating that exposure to multiple types of interpersonal trauma is more predictive of future health outcomes than any individual trauma type [2; 12; 39]. Our finding that prescription rates for analgesics tended to be higher already in adolescence among trauma-exposed participants is consistent with previous findings that pain may present as an early symptom after trauma exposure [29; 73]. The higher prescription rates found for analgesics in young adulthood aligns with prior knowledge of the lasting detrimental effect of trauma on health, where

psychological and somatic comorbidities may increasingly add to the burden of coping with pain [4; 5; 10].

In addition to the mechanisms outlined above, linking trauma exposure to pain, exposure to childhood trauma is associated with risk behavior and more frequent injuries [30; 40; 55]. This may result in more encounters with health care services for acute pain management. The overlap of trauma exposure and a higher symptom load of pain is increasingly recognized [7; 29]. A trauma-informed approach to pain management could help identify the best treatment for each patient and may be particularly important for young people. This study showed that several young people exposed to childhood trauma turned to health care services for help with pain relief. This group often refrains from seeking psychosocial treatment regardless of high needs [67; 75], and the assessment of trauma exposure in young people seeking professional help with pain management could be the first step in providing trauma-specific health care to trauma-exposed individuals.

4.1 Strengths and limitations

The strengths of this study include the large sample size, prospective design and access to longitudinal prescription data for the participants over a time period of 18 years. The high participation rate in the adolescent survey and survey questions derived from validated instruments allowed for a thorough assessment of exposures. This study was conducted in a geographical region without metropolitan areas and with low immigration [38], however, previous studies have found similar rates of long-term opioid use regardless of such characteristics [58]. Although health care is highly accessible and affordable in Norway, the associations revealed in this study appear to conform with patterns found in populations with different health care systems [6; 7; 58; 64], and we therefore consider that these associations may be generalized to other populations. The universal mechanisms outlined above also supports the generalizability of results across populations with different prescription rates.

A limitation of our study is the lack of information regarding other treatments offered to these young people, which prevents us from making assumptions about the individual appropriateness of the prescribed analgesics.

Participants may have encountered traumatic events in adolescence after the completion of the adolescent survey, leading to them being misclassified as unexposed. This could lead to an underestimation of the true incidence rate ratio (IRR). The trauma measure used in this study relies on self-report and is a subjective measure. Reports from caregivers or health care providers would only capture events the adolescents had disclosed, and adolescents do not always tell adults about trauma exposure [41]. Alternative objective measures such as court records would not capture all the events of interest in this study. Considering the sensitivity of the subject, social desirability bias is a concern. Our findings may also be subject to recall bias, a systematic difference in reporting between groups.

The trauma measure used does not allow for distinction between exposures according to their degree of severity. While it is likely that relevant traumatic events are captured by the measures used, events with a low potential for causing trauma-related symptoms cannot be distinguished from events with a high potential for causing trauma-related symptoms.

It is also a limitation that although the UCLA PTSD Reaction Index is a validated instrument, it has not been validated in Norwegian.

The small group of adolescents not in school (n=493) were underrepresented among survey participants (23.3% participation). This may have led to a slight underestimation of the true IRR, as non-participation has generally been found to be associated with poorer health [44].

The significant associations of socioeconomic factors to higher prescription rates for NSAIDs and paracetamol (Table 2) could be confounded by the lower price of prescription medications compared to the same medication purchased over the counter.

Registry data from NorPD utilized in this article are on filled prescriptions. Thus, we do not know whether the medication was actually used after it was obtained from the pharmacy. Paracetamol and NSAIDs are also available without a prescription, and this may affect the prescription rates observed for these nonopioid analgesics. Medication received during hospital stays or in institutions are not registered in NorPD.

4.2 Conclusion and implications

The consistently and significantly higher prescription rates for opioid and nonopioid analgesics to participants exposed to childhood trauma likely reflects a higher symptom load of pain. Psychological symptoms debuting in adolescence may also be of importance for the observed higher prescription rates among trauma-exposed individuals. Among prescription analgesics, opioids may be particularly detrimental for trauma-exposed young people due to an elevated risk of misuse and addiction. A trauma-informed approach to pain may help guide clinicians to the most effective and least harmful treatment for each patient. This approach may also provide an opportunity to offer trauma-specific treatment to a group which often refrains from seeking psychosocial treatment.

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Unfortunately, we are not able to share the data analyzed in this study, as they belong to the third parties The Trøndelag Health Study and Norwegian Institute of Public Health (NorPD). The linked data set was generated for the Killing Pain project after obtaining necessary permits.

The authors report no conflicts of interest.

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Supplementary Table 1. Operational definition of symptoms in adolescence.

Symptom	Young-HUNT3 questions	Operationalization	Questions derived from
Posttraumatic stress symptoms	I have upsetting thoughts, pictures or sounds of what happened come into my mind when I do not want them to When something reminds me of what happened I get very afraid, upset or sad I try not to talk about, think about or have feelings about what happened	Questions were answered with yes/no and scored yes=1 and no=0, resulting in a sum score ranging 0-3	UCLA PTSD Reaction Index for DSM IV, part III (1) The items included in the Young-HUNT3 study were carefully selected in collaboration with authors of the original instrument.
Psychological distress, SCL-5	*Experienced for the past 14 days:* i) feeling fearful ii) nervousness or shakiness inside iii) feeling hopeless about the future iv) feeling blue v) worrying about things too much	Participants rated to which extent they were bothered by each item, ranging from 1 – "not bothered" to 4 "very bothered", resulting in a mean score ranging 1-4	Hopkins Symptoms Checklist (SCL-5) (2)
Headache, weekly	*Reoccurring headaches past 12 months:* Migraine Tension type headache Other headache	Headache frequency was assessed for each type, and any headache weekly or more frequently was scored 1, less frequent headaches were scored 0, resulting in a measure for weekly headache yes/no, scored 1/0	Validated headache interview (3)
Musculoskeletal pain, number of sites	*Pain for the past 3 months in:* Neck or shoulders Chest Upper back Lower back Left arm Right arm Left leg Right leg	Weekly or more frequent pain was scored 1, less frequent pain was scored 0, resulting in a sum score for number of pain sites ranging 0-≥3.	Assessment instrument by Mikkelson et al. (4)

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Supplementary Table 2. Sample descriptives and trauma exposures as reported in Young-HUNT3 (2006-2008) and the number receiving prescription opioid and nonopioid analgesics (NorPD, 2004-2021) in adolescence and young adulthood.

		All	**Females**	**Males**
	n	n (%)/mean (SD)	n (%)/mean (SD)	n (%)/mean (SD)
All participants	8199	8199	4128 (50.3)	4071 (49.7)
Age at Young-HUNT3, mean (min 12.7, max 20.9)	8199	15.9 (1.7)	15.9 (1.8)	15.9 (1.7)
Pubertal development score, mean (range 1-4)	7511	3.1 (0.7)	3.3 (0.6)	2.9 (0.7)
Socioeconomic factors				
Family economy below average	7636	708 (9.3)	399 (10.2)	309 (8.3)
Household, not living with both parents	8104	3776 (46.6)	1900 (46.5)	1876 (46.7)
Direct interpersonal trauma				
By type				
Bullying	7803	628 (8.1)	296 (7.5)	332 (8.7)
Physical violence	7809	789 (10.1)	304 (7.6)	485 (12.7)
Sexual abuse	7829	430 (5.5)	324 (8.1)	106 (2.8)
By number of types	7833			
No events		6464 (82.5)	3321 (83.2)	3143 (81.8)
1 type		987 (12.6)	475 (11.9)	512 (13.3)
≥ 2 types		382 (4.9)	196 (4.9)	186 (4.8)
Other trauma				
By type				
Witness to violence	7812	1810 (23.2)	722 (18.1)	1088 (28.4)
Disease or death of someone close	7848	5757 (73.4)	3064 (76.6)	2693 (70.0)
Severe accident, disaster or other traumatic event	7848	2481 (31.6)	1304 (32.6)	1177 (30.6)
By number of types	7863			
No events		1657 (21.1)	746 (18.6)	911 (23.6)
1 type		3307 (42.1)	1821 (45.5)	1486 (38.5)
2 types		1956 (24.9)	1048 (26.2)	908 (23.5)
3 types		943 (12.0)	391 (9.8)	552 (14.3)
≥ 1 analgesi**c** prescriptions in adolescence	8199			
Opioid analgesics		938 (11.4)	565 (13.7)	373 (9.2)
Nonopioid analgesics				
Paracetamol		646 (7.9)	378 (9.2)	268 (6.6)
NSAIDs		3196 (39.0)	1829 (44.3)	1367 (33.6)
Gabapentinoids		21 (0.3)	18 (0.4)	< 5
≥ 1 analgesic prescriptions in young adulthood	8199			
Opioid analgesics		3507 (42.8)	1958 (47.4)	1549 (38.1)
Nonopioid analgesics				
Paracetamol		2439 (29.8)	1414 (34.3)	1025 (25.2)
NSAIDs		5472 (66.7)	2935 (71.1)	2537 (62.3)
Gabapentinoids		178 (2.2)	114 (2.8)	64 (1.6)
Symptoms reported in adolescence				
Psychological distress (SCL-5, 1-4)	7961	1.50 (0.55)	1.65 (0.60)	1.35 (0.45)
Posttraumatic stress (0-3)	5016	0.82 (0.99)	1.04 (1.07)	0.56 (0.84)
Musculoskeletal pain, weekly	8035	2748 (34.2)	1671 (41.0)	1077 (27.2)
Headaches, weekly	7619	617 (8.10)	456 (11.9)	161 (4.25)

Supplementary Table 3. Overlap of exposure to direct interpersonal trauma and other trauma types.

	Interpersonal trauma, number of types			
Other trauma, number of types	**0 n/%**	**1 n/%**	**≥2 n/%**	**Total n/%**
0	1572 (24.3)	66 (6.7)	8 (2.1)	1646 (21.0)
1	2998 (46.4)	248 (25.1)	48(12.6)	3294 (42.1)
2	1461 (22.6)	367 (37.2)	123 (32.2)	1951 (24.9)
3	433 (6.7)	306 (31.0)	203 (53,1)	942 (12.0)
Total	6464 (100.0)	987 (100.0)	382 (100.0)	7833 (100.0)

Supplementary Table 4. Zero-inflated negative binomial regression analyses for number of prescriptions of gabapentinoids in adolescence and young adulthood by type of traumatic events, number of types of direct interpersonal trauma and other trauma types, background factors and adolescent symptoms.

	Gabapentinoid prescriptions					
	Adolescence n=21			Young adulthood n=178		
	n	**IRR (95%CI)**	**p-value**	**n**	**IRR (95%CI)**	**p-value**
Direct interpersonal trauma						
Bullying	7244	0.92 (0.04, 21.24)	0.957	7455	5.66 (2.08, 15.39)	0.001
Sexual abuse	7266	2.00 (0.16, 25.76)	0.595	7480	2.00 (0.55, 7.29)	0.292
Physical violence	7244	0.61 (0.03, 12.03)	0.747	7460	2.06 (0.81, 5.29)	0.131
Other trauma types						
Witness to violence	7245	0.12 (0.02, 0.91)	0.040	7461	1.25 (0.63, 2.51)	0.523
Severe illness or death of someone close	7269	2.18 (0.45, 10.61)	0.334	7485	1.10 (0.56, 2.15)	0.774
Severe accident, disaster or other traumatic event	7274	0.51 (0.11, 2.37)	0.391	7490	1.59 (0.84, 3.04)	0.157
Direct interpersonal trauma, number of types						
1 type	7270	3.79 (0.36, 40.3)	0.270	7484	2.02 (0.86, 4.76)	0.108
≥2 types	7270	1.87 (0.04, 91.01)	0.753	7484	6.04 (1.43, 25.48)	0.014
Other trauma, number of types						
1 type	7270	1.17 (0.12, 11.42)	0.894	7484	2.12 (0.96, 4.68)	0.063
2 types	7270	0.32 (0.03, 3.47)	0.345	7484	1.38 (0.57, 3.30)	0.474
3 types	7270	0.11 (0.01, 1.52)	0.099	7484	0.93 (0.30, 2.90)	0.899
Background factors						
Age	8199	0.85 (0.56, 1.57)	0.844	8199	1.31 (1.14, 1.51)	<0.001
Sex, female	8199	5.8 (1.65, 20.38)	0.006	8199	2.20 (1.27, 3.83)	0.005
Pubertal development score	7511	0.58 (0.19, 1.76)	0.334		-	
Family economy below average	7636	0.58 (0.10, 3.20)	0.529	7636	1.08 (0.40, 2.94)	0.875
Household, not living with both parents	8104	1.97 (0.49, 7.94)	0.343	8104	1.72 (0.98, 3.04)	0.060
Subsample analyses for participants exposed to childhood trauma						
Symptoms in adolescence						
Psychological distress	5807	0.65 (0.14, 3.07)	0.585	5954	1.49 (0.93, 2.36)	0.101
Posttraumatic stress symptoms	4753	3.27 (1.45, 7.36)	0.004	4858	1.26 (0.89, 1.80)	0.196
Musculoskeletal pain	5790	1.59 (0.75, 3.36)	0.223	5939	1.90 (1.32, 2.73)	0.001
Headaches	5447	4.25 (0.53, 33.96)	0.172	5586	1.52 (0.48, 4.84)	0.481

Trauma types and symptoms were assessed in separate analyses, while number of types were assessed in one analysis including interpersonal trauma and other trauma types. n is the same for all analgesics, as data on filled prescriptions are available for all participants. Analyses were run as complete case analyses adjusted for age, sex, household structure, and family economy. Analyses for prescriptions in adolescence were adjusted for pubertal development. Background factors were assessed in unadjusted, separate complete case analyses. Symptoms were analyzed only for the subsample reporting trauma exposure.

Errataliste

Navn kandidat: Monica Baumann-Larsen

Avhandlingstittel: Childhood trauma and use of analgesics in adolescence and young adulthood

Side	Linje	Original	Type av rettelse	Rettelse
102	5	Grete Dyb[2-3]	Korrektur	Grete Dyb[2,4]