*Stage 2 Manuscript*

# *Title:* Does childhood adversity alter opioid drug reward? A conceptual replication in outpatients before surgery

***Short title: opioid drug reward after childhood adversity***

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Words: 4539

Figures: 2

Tables: 2

# Abstract

**Introduction:** Opioid analgesic treatment during surgery entails risk of persistent use.Experiences of childhood adversity have been shown to increase opioid reward in preclinical models, a finding recently extended to healthy humans. We tested whether childhood adversity similarly increased opioid reward, operationalised as drug-induced feeling good and drug liking, in outpatients receiving opioids on the operating table.

**Methods:**This observational study recruited patients entering a Norwegian hospital for an outpatient surgical procedure. An opioid intravenous opioid analgesic (remifentanil [Minto model, effect site concentration: 5ng/ml], or oxycodone [5mg]) was administered in the minutes before general anaesthesia. Verbal numerical ratings of feeling good and anxious were collected 1 minute before, and 1-3 minutes after opioid infusion. Ratings of drug liking, disliking, and feeling high were also collected after infusion. Patients (n = 151) completed measures of childhood adversity at a later date.

**Results:** Regression analyses revealed a modest yet significant negative association between childhood adversity and post-opioid *liking* (*b* = -0.06, *p* = 0.046) but no significant effect on *feeling good* (*b* = 0.01, *p* = 0.690) after the pre-operative opioid dose. Exploratory analyses showed that more childhood adversity was significantly associated with higher reports of anxiety, depression, loneliness, and pain catastrophising, however not with alcohol or other drug use, or with any other subjective drug effects.

**Discussion:** Ratings of feeling good and drug liking of medically prescribed opioids given before surgery were not higher after childhood adversity, and previous findings were not conceptually replicated. The discrepancy between current and prior results may be due to the context and stress related to the impending surgery, the short duration of drug exposure, and the relatively limited levels of high childhood adversity in the current sample compared to the original study. Exploratory analysis was consistent with the possibility of a nonlinear relationship between positive opioid effects and childhood adversity scores. Future research should assess the link between childhood adversity, subjective effects, and use of the prescribed opioids after surgery.

***Keywords:*** Childhood trauma; childhood adversity; opioids; pleasure; liking; subjective effects; reward; analgesics; surgery; oxycodone; remifentanil.

# Introduction

Experiences of childhood adversity (such as abuse, neglect, and household dysfunction) are prevalent among people with opioid use disorders (OUD) (1, 2). Several mechanisms may underlie this link, including the use of opioids to cope with dysregulated emotion processing (3), heightened pain sensitivity (4), increased stress vulnerability (5), and greater impulsivity (6) after childhood adversity. Another important mechanism contributing to this link may be an increased sensitivity to opioid reward. In the context of childhood adversity, neurodevelopmental changes to reward and motivation networks may contribute to heightened reward responses to drugs such as opioids, leading to a greater risk of abuse and addiction (7).

Preclinical research supports neurobiological changes in reward networks in animals exposed to early adversity, paired with altered drug responses (8-10). Rodents exposed to maternal separation or limited bedding and nesting as infants (both models of early adversity in animals) demonstrated: greater self-administration of opioids, conditioned place-preference for opioid-paired areas (8), resistance to extinction of opioid-seeking behaviours, and faster reinstatement of opioid seeking-behaviours when exposed to cues (9). This effect has been shown to be stronger for opioids over other drugs such as stimulants or alcohol, indicating an opioid-specific preference after experiences of early adversity (10). There are several potential mechanisms to help explain this heightened reward response after early adversity. Panksepp (11) proposed that opioid drugs mimic the pleasure experienced from caring social bonds by binding to the mu-opioid attachment circuitry, and that exposure to adverse social factors (such as isolation) may increase the desirability of opioids. Accordingly, this may be one explanation for an enhanced pleasure response to opioids among those with limited early experiences of caring social bonds in childhood. However, support for this theory has scarcely been translated from preclinical findings to humans.

A recent translational study measured reward responses to morphine in people with and without experiences of childhood adversity (12). Using a placebo-controlled, double-blind opioid administration design, this study examined subjective and behavioural responses to an intramuscular dose of morphine (0.15 mg/kg) in healthy participants with either severe or no history of childhood abuse and neglect. Individuals with severe childhood adversity rated the effects of morphine as more likeable, felt more euphoric, and reported greater wanting for more drug from 15 minutes after the morphine administration. The childhood adversity group also rated less disliking, nausea and dizziness from 90 minutes after the dose compared with the non-adversity group. However, behavioural indices of reward from a progressive ratio paradigm where participants could work for hypothetical rewards (money or more morphine) did not significantly differ between the two groups. These results represent important initial evidence that childhood adversity could enhance the risk of opioid misuse via increased drug reward in humans.

Opioid analgesics such as morphine are critical medicines that are administered to millions of people every year. Rates of persistent use after surgical treatment in the USA are 5-10% (13, 14). Known risk factors of persistent opioid use after surgery include conditions such as depression, anxiety and chronic pain (15), which are also more frequent in people who experienced childhood adversity. In this study we examined whether childhood adversity increases positive effects of opioids given in a medical context.Positive drug effects are considered a sign of higher abuse liability (16). As replication and generalisation are critical components of the scientific method, it is essential to understand whether the previous findings are generalisable to naturalistic contexts where opioids are frequently administered.

We aimed to conceptually replicate the findings from the previous study (12) in generally healthy patients undergoing outpatient surgery. In this observational study, patients were given an intravenous dose of either remifentanil or oxycodone as part of routine care prior to being anaesthetised. Both drugs are opioid agonists that are fast-acting and primarily stimulate the µ-opioid receptor subtype and are frequently used both pre- and post-operatively to provide quick and effective pain relief. Patients were asked to give verbal numerical ratings of how good and how anxious they felt immediately before and one minute after opioid infusion, as well as to rate their liking of the effects, disliking of the effects, and feeling high between one and three minutes after. Patients later completed additional state and trait measures. Our primary hypotheses were that patients with greater childhood adversity (higher trauma) would 1) exhibit a larger mood boost (*feeling good*), and 2) express greater *liking* of the drug effects after the opioid administration, conceptually replicating the previous findings. The *feeling high* translation was not deemed as a positive drug effect in a Norwegian population (17), and we did not expect any effect of childhood adversity on *disliking* or *feeling high*. Since anxiety is typically higher in people with childhood trauma and opioid use disorder (18), and anxiety relief has been cited as a motivator for continued opioid use (19), we also explored the links between childhood trauma and anxiety pre- and post-drug. Identifying relationships between childhood adversity and opioid drug effects in this pre-operative surgery population has implications for pain management in patients at higher risk of persistent use due to childhood adversity.

# 2.0 Methods

## 2.1 Participants and procedure

This was an observational study of subjective opioid drug effects in day surgery patients who received a pre-operative opioid analgesic, as part of routine care. The study was part of a broader research project (17, 20) (see Figure 1 for an overall timeline) that recruited 269 generally healthy patients (defined in line with the American Society of Anaesthesiologists’ Physical Status Classification System, ASA I-II (21)) admitted for outpatient surgery at Kongsberg Hospital in Norway between April 2018 to June 2021. Outpatient surgeries were typically minor abdominal, minor gynaecological, minor orthopaedic, otorhinolaryngological, or colorectal surgeries. For recruitment, patients were sent a letter ~two weeks prior to the procedure with information about their upcoming surgery, in addition to the study information sheet, consent form, and some routine clinical questions. All patients provided informed written consent on the morning before the surgery. The study protocol was approved by the internal review board (data protection officer) at Kongsberg Hospital.

Of the initial sample, 220 (82%) were then successfully recontacted by phone and/or email between August 2021 and February 2022 (between 4-40 months after the surgery) and agreed to complete the relevant outcomes for this study. A total of 155 (71%) patients completed these additional questionnaires, which was the final sample size for this study. Patients were asked to provide additional consent, and subsequently received the questionnaires either electronically by email, or hardcopy by post (depending on the patient’s preference). The email contained a link to the electronic questionnaire form using the University of Oslo’s online data collection software (*Nettskjema)*, and responses were automatically stored in on the University of Oslo’s secure data storage server *TSD*. Hardcopy questionnaires were received and completed by post and registered manually by one of the hospital research personnel. If patients had not completed the questionnaires within one week, they were sent reminders by email. In the rare case of repeated responses, the earliest complete response was used for the analyses. Cases where the patients responded with the same answer for all questions were considered invalid and excluded from analyses. The follow-up data collection was approved by the Regional Ethics Committee (Rek Sør-Øst D: 198224).



*Figure 1.* Study procedure in the context of the broader research project. T – timepoint for data collection. T4 is in grayscale to indicate that outcomes were collected but are not included within the current study. CTQ – childhood trauma questionnaire, SES – socio-economic status.

**2.2 Opioid administration and subjective effects**

As part of routine care for the surgical procedure, patients were given an intravenous opioid analgesic three to five minutes before being administered the general anaesthetic. Patients were informed by the medical personnel that they would be given medication for pain and for sleep while on the operating table. The opioid analgesic was either remifentanil (n=157, 59%; Minto model, effect site concentration; 5 ng/ml; surgeries conducted Jan 2018-May 2019), or oxycodone (n=112, 41%; 5 mg; surgeries conducted Nov 2019-June 2021). Both opioids led to comparable subjective intoxication, as reported in the broader research trial (17). Immediately prior to opioid administration, patients were asked by the medical personnel to verbally rate their mood for: (i) how good they felt; and (ii) how anxious they felt, on a scale from 0 (not at all) - 10 (very much) (*pre-drug scores*). At precisely one minute following the opioid dose, patients were asked to rate their mood again (i-ii), in addition to the subjective opioid effects on a scale from 0-10 for: (iii) how high they felt; (iv) how much they liked any of the effects of the drug; (v) how much they disliked the effects. These ratings took between one and three minutes to complete. The drug effect items are from the Drug Effect Questionnaire (DEQ; 22), a measure frequently used for psychopharmacological research exploring acute drug effects. All patient responses were recorded by pen and paper by the medical personnel.

## 2.3 Other measures

The primary predictor for childhood adversity was a history of childhood abuse and neglect, which was measured by the Childhood Trauma Questionnaire (CTQ; 23). The CTQ is a 28-item measure of experiences of abuse and/or neglect in childhood across five subcategories: emotional and physical abuse, emotional and physical neglect, and sexual abuse. Responses are made on a 5-point Likert-scale (1 - never true, 5 - very often true), where the total severity score across all subscales is calculated. Another exploratory measure of childhood adversity was the MacArthur Scale of Subjective Social Status in childhood (MSSS; 24), a measure of childhood socioeconomic status (SES) where patients were asked to rate their family’s SES compared to the rest of the Norwegian society when they were young, on a one item scale (0 – low, 10 – high). The families with the highest income, education and most respected jobs were located at the top of the scale, and the families with either no or the lowest ranged education, jobs, and income at the bottom of the scale.

Choice of other exploratory measures were guided by previous research linking adversity with substance use and mental health. This included an assessment of problematic substance use by the both the Alcohol Use Disorders Identification Test (AUDIT; 25) and the Drug Use Disorders Identification Test (DUDIT; 26), which comprise of 10-11 items answered by either 5-point (0 – never, 4 – almost daily) or 3-point (0 – no, 4 – yes, this year) Likert scales. Mental health was measured by the 14-item Hospital Anxiety and Depression scale (HADS; 27) (4-point Likert response scale: 0 – not at all, 3 – all the time), and loneliness was measured with the Three Item Loneliness Scale (T-ILS; 28) (3-point Likert scale; 1 - hardly ever, 3 - often). Mindfulness was measured by the 15-item Five Facet Mindfulness Questionnaire (FFMQ; 29) (5-point Likert scale, 1 – never, 5 – very often). Pain catastrophising was measured by the 13-item Pain Catastrophizing Scale (PCS; 30), (5-point Likert scale, 0 – not at all, 4 – all the time). Total scores were computed for all exploratory outcomes. Demographic data such as *age* (years), *sex* (male, female), and *weight* (kg), were collected, in addition to *opioid type* (oxycodone, remifentanil), and *surgery type* (categorical and dummy coded).

**2.4 Analyses**

Data were analysed using R v4.1.1 (31). Normality of residuals were assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Bootstrapping using random sampling with replacement (5000 iterations) was used if any of the two tests were significant (*p<*.01 for the Shapiro-Wilk and *p<*.05 for the Kolmogorov-Smirnov). The threshold for the Shapiro-Wilk test was adjusted due to overestimates of non-normality in samples when n>50 (32). Outliers (defined as responses >3 standard deviations from the mean) for the CTQ scores were assessed using boxplots. Some extreme values were expected as there is typically a reduction in variation in CTQ scores for the moderate-severe range, however these were retained and reported. Extreme values were not expected for drug effect outcomes as these were bounded between 0 and 10 (11-point integers). Patients with a post-drug rating for a given outcome and a CTQ score were included in that analysis. Missing values were treated as missing. The alpha criterion for significance was p<.05 and p-values were corrected for multiple testing using the Holm-Bonferroni correction.

### 2.4.1 Primary analyses

Multiple linear regressions were conducted to assess whether the primary predictor variable for childhood adversity (CTQ score) was significantly positively associated with *feeling good* (H1), and *drug liking* (H2). Analyses adjusted for demographic variables (*age*, *sex*), *weight*, *opioid type*, and *surgery type*. The analyses for feeling good were adjusted for the pre-drug ratings by entering pre-drug responses as predictors in the regression, as this was also measured before as well as after opioid administration. The regression equation for these analyses were:

*Ŷi = β0 + β1CTQi + β2Agei + β3Sexi + β4Opioidi + β5Weighti + β6Surgeryi + β7Pre-drug scorei + ϵi* ,

where Ŷ is post*-*drug score. *Surgery type* was categorical and dummy coded, where a regression coefficient was obtained for each level of the variable. Pre-drug scores in the regression equation were only relevant for *feeling good*.

The findings were interpreted as a full conceptual replication if both H1 and H2 were confirmed by a significant positive association between CTQ score and post-drug *feeling good* and *drug liking*, or a partial conceptual replication if one of the two were significant. Regression coefficients (betas) were interpreted for effect size. For non-significant findings or significant associations in the opposite direction than hypothesised, we concluded that the conceptual replication was unsuccessful. Because the study was only powered to detect small-medium effect sizes, any null effect was not interpreted as support for no effect. Primary analyses were preregistered as a peer-reviewed, published registered report (33; link https://osf.io/7ymts). The data has not been made publicly available due to the sensitive nature regarding health and adversity. The conditions of our ethical approval, and the constraints of Norwegian law, prevent sharing of the data supporting this research with any individual outside the author team.

***2.4.2 Exploratory analyses***

*Subgroup analyses comparing high childhood adversity with none for ‘feeling good’ and ‘feeling anxious’*

The previous study limited recruitment to two groups of participants (people with CTQ scores in the ‘none’ category, and people with a ‘severe’ CTQ score on at least one subscale) which were then compared statistically. In contrast, the current preregistered linear regression tested for a cumulative effect of CTQ, with a linear increase or decrease in positive drug effects with higher CTQ scores. We therefore explored (i) the number of patients in this dataset that would qualify for inclusion in the previous study (scoring ‘none’ across all subscales or ‘severe’ on one or more subscales), and (2) whether they showed a similar pattern of drug responses as in the original study. We first visually inspected outcomes in the three subgroups: ‘none’, ‘low-moderate’ on >1 subscale, and ‘severe’ on >1 subscale. We then used mixed ANOVAs to statistically compare change from ‘pre’ and ‘post’ responses between the ‘none’ and ‘severe’ groups for the two repeated-measures items *feeling good* and *anxious*.

*Childhood adversity and other subjective drug effects*

Other opioid-induced drug effects (*disliking* and *feeling high)* were analysed as outcomes using linear regression models that adjusted for the same variables as the primary analyses. The ‘mediation’ package in R was used to conduct a mediated regression analysis for *feeling anxious*, since childhood adversity was expected to be associated with higher *pre-opioid anxiety*, and in turn be associated with a greater reduction in *post-opioid anxiety.* The *feel effects* responsewas dichotomous (yes/no) and analysed using a logistic regression with the same predictors.

*Associations with mental health, alcohol and other drug use, and related constructs*

Other exploratory analyses included Pearson’s correlations to assess associations between the predictors and outcomes with: Socioeconomic status, alcohol and other drug use, mental health, and loneliness. Spearman’s Rho correlations were used for non-parametric data. Any group-based analyses were conducted using analyses of variance (ANOVA). The alpha level for exploratory analyses was not corrected for multiple testing as they were considered hypothesis-generating (34).

## 2.5 Level of bias and control

As a registered prospective analysis, we designated a Level 2 bias control because the wider dataset (n = 269) was acquired and partially observed as part of the broader research project (17). However, the main predictor, CTQ scores, and the exploratory variables, were not accessed or observed prior to in-principle acceptance, nor did any of the authors know which individuals made up the subset of participants (n = 155, 71%) that provided data for the current analysis. Steps to reduce bias included: (i) the submission of the pre-specified analysis script to provide transparency on the analytical plan and contingencies before this data was observed; (ii) using the Holm-Bonferroni alpha correction on the confirmatory tests; (iii) ensuring the lead authors of the manuscript responsible for analysis had limited exposure to the data that was already accessed as part of the broader research project.

# 3.0 Results

## 3.1 Sample descriptives

Patients were aged 48 years on average (SD = 14.0), 52% were female, and self-reported socioeconomic status was relatively high *(*M *=* 7.0, SD = 1.2; maximum of 10) (Table 1). The most common surgical procedure was abdominal surgery (n = 66, 44%), followed by minor gynaecological surgery (n = 32, 21%). Remifentanil was the pre-operative opioid analgesic delivered in 55% of the patients, and oxycodone for the remaining 45%. Overall, 80% of the patients reported that they felt the effect of the opioid when asked one minute after injection. For the five CTQ subscales, 11% of patients scored in the severe range for one or more subscale, which was most commonly emotional abuse (6%), while 52% scored in the none range across all five subscales. A subset of patients reported anxiety (15% scored as mild or higher), depression (<2% scored as mild or higher), risky alcohol use (10%) and other risky drug use (6%). Of the originally reported 155 patients, 4 (3%) were identified as duplicate cases, leading to a final sample of 151 patients.

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| **Table 1.** SampleDescriptives for Patients (n = 151) Involved in This Study. |
|  | **N** | **%** | **M** | **SD** |  | **Range** |
| **Mdn** | **Min.** | **Max.** |
| **Demographics** |  |  |  |  |  |  |  |
| Age (years) | 151 | 100 | 47.9 | 14.0 | 48.0 | 17.0 | 81.0 |
| Sex (n) |  |  |  |  |  |  |  |
| *Female* | 78 | 52 |  |  |  |  |  |
| *Male* | 73 | 48 |  |  |  |  |  |
| Weight (kg) | 151 | 100 | 81.2 | 15.2 | 80.0 | 50.0 | 125.0 |
| Socioeconomic status (0-10) |  |  |  |  |  |  |  |
| *Childhood* | 139 | 92 | 5.5 | 1.6 | 6.0 | 2.0 | 10.0 |
| *Current (adulthood)* | 140 | 93 | 7.0 | 1.2 | 7.0 | 4.0 | 10.0 |
| **Surgery information** |  |  |  |  |  |  |  |
| Surgery type (n) |  |  |  |  |  |  |  |
|  *Colorectal* | 26 | 17 |  |  |  |  |  |
|  *Minor gynecological* | 32 | 21 |  |  |  |  |  |
|  *Otorhinolaryngological* | 3 | 2 |  |  |  |  |  |
|  *Minor orthopedic* | 14 | 9 |  |  |  |  |  |
|  *Minor abdominal* | 66 | 44 |  |  |  |  |  |
|  *Other* | 10 | 7 |  |  |  |  |  |
| Opioid type |  |  |  |  |  |  |  |
|  *Remifentanil*  | 83 | 55 |  |  |  |  |  |
|  *Oxycodone* | 68 | 45 |  |  |  |  |  |
| Felt opioid effects (1 – 3 minutes after) |  |  |  |  |  |  |  |
| *Yes* | 68 | 80 |  |  |  |  |  |
| *No* | 17 | 20 |  |  |  |  |  |
| **Childhood trauma**  |  |  |  |  |  |  |
| CTQ total (25-125) | 143 | 95 | 33.1 | 9.8 | 30.0 | 25.0 | 72.0 |
| Missing data for > 2 items (n)*Refused to complete CTQ* | 83 | 52 |  |  |  |  |  |
| CTQ total severity cut-offs (n) |  |  |  |  |  |  |  |
|  *None (<41)* | 120 | 84 |  |  |  |  |  |
|  *Low (41 – 55)* | 16 | 11 |  |  |  |  |  |
|  *Moderate (56 – 72)* | 7 | 5 |  |  |  |  |  |
|  *Severe (>72)* | 0 | 0 |  |  |  |  |  |
| CTQ severe on >1 subscale (n) | 15 | 11 |  |  |  |  |  |
|  *Physical abuse* | 1 | 1 |  |  |  |  |  |
|  *Physical neglect* | 4 | 3 |  |  |  |  |  |
|  *Emotional abuse* | 8 | 6 |  |  |  |  |  |
|  *Emotional neglect* | 5 | 4 |  |  |  |  |  |
|  *Sexual abuse* | 4 | 3 |  |  |  |  |  |
|  CTQ low-moderate on >1 subscale (n) | 52 | 36 |  |  |  |  |  |
| CTQ none for all subscales (n) | 76 | 53 |  |  |  |  |  |
| CTQ subtypes mean score (5-25) |  |  |  |  |  |  |  |
|  *Physical abuse* | 142 | 94 | 5.4 | 1.3 | 5.0 | 5.0 | 15.0 |
|  *Physical neglect* | 141 | 93 | 6.3 | 2.1 | 5.0 | 5.0 | 16.0 |
|  *Emotional abuse* | 139 | 92 | 7.1 | 3.4 | 5.0 | 5.0 | 19.0 |
|  *Emotional neglect* | 140 | 93 | 8.7 | 3.8 | 8.0 | 5.0 | 20.0 |
|  *Sexual abuse* | 141 | 93 | 5.7 | 2.7 | 5.0 | 5.0 | 25.0 |
| **Alcohol and other drug use** |  |  |  |  |  |
| AUDIT total (0-40) | 136 | 90 | 3.8 | 2.6 | 4.0 | 0.0 | 14.0 |
| AUDIT severity cut-offs (n) |  |  |  |  |  |  |  |
|  *Low risk (0-7)* | 123 | 90 |  |  |  |  |  |
|  *Increased risk (*>*7)* | 13 | 10 |  |  |  |  |  |
| DUDIT total (0-44) | 131 | 87 | 0.3 | 1.1 | 0.0 | 0.0 | 8.0 |
| DUDIT severity cut-offs |  |  |  |  |  |  |  |
|  *Low risk (0-1)* | 123 | 94 |  |  |  |  |  |
|  *Increased risk (*>*2)* | 8 | 6 |  |  |  |  |  |
| **Mental health and related variables** |  |  |  |  |  |  |
| HADS anxiety total (0-21) | 146 | 97 | 4.8 | 3.6 | 4.0 | 0.0 | 16.0 |
| HADS anxiety cut-offs (n) |  |  |  |  |  |  |  |
|  *Normal (<8)* | 119 | 85 |  |  |  |  |  |
|  *Mild (8-10)* | 8 | 6 |  |  |  |  |  |
|  *Moderate (11-15)* | 12 | 9 |  |  |  |  |  |
|  *High (>15)* | 1 | 1 |  |  |  |  |  |
| HADS depression total (0-21) | 144 | 95 | 2.5 | 2.4 | 2.0 | 0.0 | 11.0 |
| HADS depression cut-offs (n) |  |  |  |  |  |  |  |
|  *Normal (<8)* | 138 | 98 |  |  |  |  |  |
|  *Mild (8-10)* | 1 | 1 |  |  |  |  |  |
|  *Moderate (11-15)* | 1 | 1 |  |  |  |  |  |
|  *High (>15)* | 0 | 0 |  |  |  |  |  |
| FFMQ mindfulness total (15-75) | 133 | 88 | 51.2 | 6.7 | 51.0 | 35.0 | 68.0 |
| Pain catastrophising total (0-52) | 143 | 95 | 6.2 | 7.1 | 4.0 | 0.0 | 30.0 |
| T-ILS Loneliness total (3-9) | 138 | 91 | 4.2 | 1.5 | 4.0 | 3.0 | 9.0 |
| *Notes*. M – mean, SD – standard deviation, Mdn – Median. Patients with more than 10% items missing for a subscale were excluded from the total score calculation. The CTQ total score was calculated for 25 items, as three items in this scale measure ‘deminimalisation’ and is not included in the total or subscale scores for abuse and neglect.  |

## 3.2 Childhood adversity and post-drug feeling good and liking (hypotheses 1-2)

In the tests of the preregistered hypotheses, regression analyses indicated a modest yet significant effect of childhood adversity on post-opioid *liking* (*b* = -0.06, 95%CIs [-0.11 – -0.01], *p* = 0.046; Holm-Bonferroni corrected, Table 2), indicating a negative association between total CTQ score and liking (Figure 2) when adjusting for opioid type, age, sex, weight, and operation category. As the CTQ total score is the sum of 25 items answered on a 1 to 5-point Likert scale (range 25-125), an average 1 Likert unit increase across all items would equate to a 25-point increase in the CTQ total score. Thus, for each average 1 Likert unit increase on the CTQ, we would expect a decrease in 1.5 numeric rating scale (NRS) units of *liking.* The regression analyses also showed a significant effect of surgery type, with patients undergoing minor gynaecological surgery reporting significantly less *liking* than patients undergoing minor abdominal surgeries (*b* = -2.28, 95%CIs [-3.91 – -0.64], *p* = .014).

For post-opioid *feeling good,* there was no significant effect of CTQ score (0.25 NRS units of change in *feel good*, per average increase in 1 Likert unit of the CTQ; *b* = 0.01, 95%CIs [- 0.03 – 0.04], *p* = 0.690; Holm-Bonferroni corrected, Table 2). The only significant predictor for post-opioid *feeling good* was pre-opioid *feeling good* (0.71 NRS units of change in post-opioid *feel good*, per average increase in 1 NRS unit of *pre-opioid* *feel good*; *b* = 0.71, 95%CIs [0.55 – 0.87], *p* <.001). Residuals for *feeling good* regression deviated from normality, however bootstrapped estimates did not differ significantly from the original model. No other predictors were significantly associated with the two outcomes. Both regression outcomes are presented in Figure 2.

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| **Table 2.** *Regression Model Estimates for Post-Drug Liking and Feeling Good.* |
|  | **Like effects** | **Feel good** | **Feel good: bootstrapped** |
| **Predictors** | B | β | 95% CIs | p | B | β | 95% CIs | p | B | 95% CIs | p |
| CTQ score | -0.06 | -0.20 | -0.11 – -0.01 | **.046a** | 0.01 | 0.03 | -0.03 – 0.04 | .690a | 0.01 | -0.03 - 0.04 | .670 |
| Age | 0.03 | 0.15 | -0.01 – 0.07 | .097 | -0.02 | -0.10 | -0.04 – 0.01 | .177 | -0.02 | -0.04 - 0.01 | .134 |
| Sex | -0.43 | -0.07 | -1.70 – 0.84 | .502 | -0.01 | -0.01 | -0.79 – 0.76 | .971 | -0.02 | -0.77 - 0.70 | .967 |
| Weight | 0.00 | 0.01 | -0.03 – 0.04 | .889 | -0.02 | -0.13 | -0.04 – 0.00 | .074 | -0.02 | -0.04 - 0.00 | .090 |
| Opioid type | -0.12 | -0.02 | -1.23 – 0.99 | .831 | 0.47 | 0.10 | -0.21 – 1.16 | .175 | 0.51 | -0.20 – 1.20 | .139 |
| Surgery type |  |  |  |  |  |  |  |  |  |  |  |
| *Colorectal* | 0.42 | 0.06 | -0.99 – 1.83 | .556 | 0.50 | 0.09 | -0.39 – 1.40 | .268 | 0.50 | -0.32 – 1.26 | .205 |
| *Minor* *gynaecological* | -2.28 | -0.33 | -3.91 – -0.64 | **.014a** | -0.46 | -0.08 | -1.48 – 0.56 | .372 | -0.45 | -1.39 – 0.54 | .351 |
| *Otorhinolaryngological* | 0.83 | 0.03 | -3.31 – 4.96 | .693 | -0.92 | -0.06 | -3.08 – 1.24 | .401 | - | -2.81 – 0.46 | - |
| *Minor orthopaedic* | -0.50 | -0.05 | -2.40 – 1.41 | .606 | 0.22 | 0.03 | -0.89 – 1.33 | .697 | 0.24 | -0.94 – 1.34 | .662 |
| *Other* | -1.11 | -0.09 | -3.35 – 1.14 | .332 | -0.39 | -0.04 | -1.73 – 0.95 | .567 | -0.41 | -1.81 – 1.10 | .567 |
| Feel good pre-drug |  |  |  |  | 0.71 | 0.61 | 0.55 – 0.87 | **<.001\*\*\*** | 0.71 | 0.57 – 0.85 | **<.001\*\*\*** |
| Observations | 134 | 141 |  |
| R2 / R2 adjusted | 0.153 / 0.084 | 0.447 / 0.400 |
| *Note*. Significant p-values are bolded in text, B – Beta estimate, β – standardised beta estimate. a Adjusted for multiple comparisons using the Holm-Bonferroni correction (35). Uncorrected p-value for liking p = 0.031. Surgery type was dummy coded and "minor abdominal" was used as the reference category, as this surgery type comprised of the largest proportion of surgeries. |



*Figure 2*. Overlay of scatter plot and regression line (with the shaded 95% confidence interval band) for the effect of childhood adversity on post-opioid a) *liking* of the effects and b) *feeling good*. There was a modest yet significant effect of childhood adversity (CTQ total score) on post-opioid *liking* (b = -0.06, *p* = 0.046) where an average 1 Likert unit increase across all of the CTQ items (rated on a 1-5 Likert scale) led to a significant -1.5 NRS unit decrease in *liking*. There were no significant effects of CTQ total score on *feeling good* (b = 0.01, *p* = 0.690). While the range of the CTQ total score is 25-125, the maximum score did not exceed 72 in this patient population. The red dotted vertical lines crossing the x-axis are to visually illustrate total scores with an average 1 Likert unit difference for the CTQ items (equivalent to a 25-point difference in the CTQ total score), starting from the lowest total score. The regression lines and respective models adjusted for age, sex, weight, opioid type, and surgery type. As these variables were mean-centred prior to plotting, the regression line reflect predicted *liking* and *feel good* averaged across gender, drug, age, and weight for an individual that is undergoing the most common surgery (minor abdominal surgery)

## 3.3 Exploratory subgroup analyses comparing high childhood adversity with none for ‘feeling good’ and ‘feeling anxious’

Seventy-two patients scored in the ‘none’ range for all CTQ subscales (50%); 56 patients scored in the ‘low’ and ‘moderate’ ranges on one or more subscales (39%); and 15 patients rated scored in the ‘severe’ range for at least one subscale (11%). After visual inspection of group means for subjective drug effects (Figure 2), we noted that none of the 15 patients with ‘severe’ CTQ scores reported a reduction in *feel good* after opioid injection, whereas the overall group mean was reduced by 0.4 points. While the positive mean change in *feeling good* scores for the severe group is consistent with the original study results, post-hoc exploratory ANOVA’s comparing the interaction between group (‘none’, ‘severe’) and time (pre, post) did not yield a significant interaction effect for *feeling good* (F(1,89) = 3.45, *p =* .067), nor any significant main effects. The ANOVA of anxiety ratings did not show any significant interaction effects (F(1,87) = 1.69, *p* = .202*)*.These were exploratory analyses that were not included in the registered report. Additional data and figures comparing these groups are available in SM2, including scatterplots where visual inspection did not indicate a clear linear or nonlinear pattern. SM2 also contains demographic variables between this and the previous sample, in addition to mean differences and confidence intervals for each of the drug effects.



**Figure 3.** Subjective opioid effects (feeling good, feeling anxious, and drug specific effects for liking, disliking, and feeling high post-opioid) stratified by group: (i) patients that scored in the ‘none’ category across all CTQ subscales (n = 76), (ii) patients that scored in the ‘low’ or ‘moderate’ category for one or more (denoted as ‘1+’ in the figure legend) of the CTQ subscales, but never in the severe category (n = 52), and (iii) patients that scored severe on one or more (1+) subscales (n = 15). Error bars represent standard errors.

## 3.4 Exploratory regressions for other subjective drug effects

For other subjective drug effects not relevant to the conceptual replication, exploratory regression models indicated no significant effects of childhood adversity on *feeling high* (-0.09 units of change in *feeling high*, per average increase in 1 Likert unit of the CTQ; *b* < -0.01, 95%CIs [-0.05 – 0.04], *p* = .87), *disliking* (0.1 units of change in *disliking*, per average increase of 1 Likert unit of the CTQ; *b* = 0.01, 95%CIs [- 0.04 – 0.06], *p* = .760), or *feel effects* (logistic regression; OR = 0.99, 95%CIs [0.93 – 1.07], *p* = .773) (full model estimates are in SM1). Childhood adversity was not significantly associated with greater pre*-* (*b* < 0.00, 95%CIs [-0.05 – 0.05], *p* = .965)or post-opioid *anxiety* (*b* = 0.03, 95%CIs [-0.02 – 0.07], *p* = .206).

## 3.5 Exploratory correlations with mental health, alcohol and other drug use, and related constructs

Table 3. displays the exploratory correlations between the main predictor (childhood adversity) and theoretically-related exploratory variables. CTQ score was negatively associated with childhood socioeconomic status (SES; rs = –0.30, *p*<.001), and to a lesser degree with adulthood SES (rs = -0.14, *p* = .12). CTQ was also associated with higher anxiety (rs = 0.29, *p* <.001), depression (rs = 0.26, *p* = .002), loneliness (rs = 0.20, *p* = .021), and pain catastrophising (rs = 0.23, *p* = .005). Other significant associations were also found between the exploratory variables and post-drug effects (Table 3.). Correlations between drug effects are reported in SM3.

|  |
| --- |
| **Table 3.** *Correlation Matrix for Exploratory Variables (Total Scores) with Post-Drug Effects.* |
|  | CTQ | Child SES | Adult SES | AUDIT alcohol | DUDIT drug | PCS Pain catastr. | TILS Lone-liness | HADS Anxiety | HADS Dep-ression | FFMQ Mindfulness |
| CTQ | — |  |  |  |  |  |  |  |  |  |
| Child SES | -.30\*\*\* | — |  |  |  |  |  |  |  |  |
| Adult SES | -.14 | .32b\*\*\* | — |  |  |  |  |  |  |  |
| AUDIT alcohol | .03 | .01 | -.04 | — |  |  |  |  |  |  |
| DUDIT drug | .12 | -.13 | -.06 | .13 | — |  |  |  |  |  |
| PCS Pain catastrophising | .23\*\* | -.23\*\* | -.06 | .06 | .13 | — |  |  |  |  |
| TILS Loneliness | .20\* | -.04 | -.17 | -.04 | .07 | .24\*\* | — |  |  |  |
| HADS Anxiety  | .29\*\*\* | -.11 | -.21\* | .09 | .09 | .41\*\*\* | .49\*\*\* | — |  |  |
| HADS Depression | .26\*\* | -.10 | -.12 | .04 | .02 | .26\*\* | .46\*\*\* | .49\*\*\* | — |  |
| FFMQ Mindfulness | -.09 | -.02b | .22b\* | -.06 | -.12 | -.21\* | -.29\*\*\* | -.28\*\* | -.21\* | — |
| **Post-drug effects** |
| Liking | -.23\*\* | -.04 | .04 | .05 | .01 | -.07 | -.25\*\* | -.18\* | -.19\* | .09 |
| Feel good | -.11 | -.06 | .26\*\* | -.04 | -.11 | -.11 | -.24\*\* | -.22\*\* | -.05 | .21 |
| Δ Feel good | -.05 | -.09b | .06b | .20\* | -.19\* | .05 | -.06 | .07 | .05 | .07 |
| Feeling high | -.02 | .15 | .08 | -.13 | .13 | -.02 | .03 | -.01 | -.12 | -.06 |
| Disliking | .10 | .17 | .00 | .06 | -.00 | -.02 | .19\* | .18\* | .11 | -.17 |
| Anxious | .17 | .04 | -.11 | .06 | -.00 | .10 | .21\* | .35\*\*\* | .15 | -.00 |
| Δ Anxious | .17\* | -.09b | .04b | .10 | .09 | -.08 | -.04 | -.04 | .05 | .11b |
| *Note.* b IndicatesPearsons correlation coefficient, all other coefficients are Spearman’s correlation coefficients. Δ indicates change from pre-drug score which was subtracted from post-drug score, where the positive correlation coefficient closer to 1 indicates (a) feeling more good and (b) feeling more anxious at post-opioid than pre-opioid, while 0 is no change, the correlation coefficients closer to –1 are (a) feeling less good and (b) less anxious post-opioid. PCS – Pain catastrophising scale; TILS – Three item loneliness scale; HADS – Hospital anxiety and depression scale. FFMQ - Five Facet Mindfulness Questionnaire; AUDIT – alcohol use disorder identification test; DUDIT – drug use disorder identification test; SES – socioeconomic status; CTQ – childhood trauma questionnaire. \* p<.05, \*\* p<.01, \*\*\* p<.001. |

# 4.0 Discussion

We aimed to conceptually replicate the findings of increased subjective pleasure and liking of opioids after childhood adversity (12) in patients administered an intravenous opioid before undergoing surgery. Our analyses did not support the hypothesis that cumulatively more experiences of childhood adversity would heighten ratings of drug liking and feeling good after opioid injection in day surgery patients on the operating table (N = 151). Rather, the findings indicated an inverse relationship: Patients with higher levels of childhood adversity reported significantly less liking of the effects. Exploratory subgroup analysis restricted to patients matching the groups included in the original study (‘none’ or ‘severe’ in at least one CTQ domain) showed a non-significant pattern of change in feeling good that was consistent with the original study, allowing for a non-linear effect of childhood adversity that should be examined with greater sample sizes. Childhood adversity scores were linearly associated with higher anxiety, depression, loneliness, and pain catastrophising, in line with previous literature (36-38), including the study we aimed to conceptually replicate (12).

There are many possible explanations for the lack of replication of the previously reported association between childhood adversity and positive opioid effects. Impending surgery is a stressful situation, whereas participants in the previous study volunteered for a drug experiment designed to limit stress. The pre-existing stress experienced as part of surgery may limit or alter the subjective effects of opioids, in line with the ‘state-dependent’ perspective of opioids on behaviour (39). Different psychological responses to the acute stress of surgery in patients with greater childhood adversities could have contributed to lower opioid liking e.g., an increased desire to remain in control. Note that the reported inverse effect on liking is modest, with a 0.6-point reduction in liking of the pre-surgical opioid injection per 10 percentage point increase in childhood adversity. Demographic differences between this patient sample and the prior study sample, such as older age and higher body weight (kg), may have contributed to different drug effects. The present data also deviate substantially from the original study in the timing of drug effects measures. Here, responses were given between 1-3 minutes after a substantial intravenous dose of remifentanil or oxycodone. In contrast, after intramuscular morphine or saline (placebo) in the previous study, greater positive effects were found after the first measure (at 15 minutes), whereas significantly reduced nausea and dizziness emerged after 90 minutes in people with childhood adversity. It is conceivable that the impact of childhood adversity on positive subjective effects may become more pronounced after a longer duration of time following the dose. In healthy people, a biphasic pattern has been described where initial positive responses to opioids are followed by increasing ratings of nausea, dizziness and higher disliking of the drug effects (e.g., 40, 41).

While this observational study had enough variation in childhood adversity to explore the research question, exploratory subgroup analyses were limited by the small number of patients that scored as severe on one or more subscales for childhood adversity. Mean differences and confidence intervals for post-opioid liking and feeling good were not comparable to the previous study. Curvilinear effects of childhood adversity have been reported for related areas of research, for example when assessing stress-related resilience: Primates exposed to some early adversity demonstrate greater indications of stress resilience compared to primates with either none or high levels of early adversity (42). Observational work in humans similarly report that children who experience some adversity demonstrate lower biological markers of stress reactivity than children with none or high adversity (43), and some adversity has been linked to better adult quality of life (44). A large amount of evidence supporting a ‘dose-like’ cumulative effect of childhood adversity for poor physical and mental health outcomes has also been reported however (45, 46).

Similar to the previous study, the current sample varied on other important characteristics associated with childhood adversity that may be relevant to subjective drug effects, including loneliness, socioeconomic status, and mental health, all of which are known risk factors associated with persistent opioid use (47-49). The findings support a linear relationship between childhood adversity scores and these health-related measures. Exploratory correlations indicated the potential importance of loneliness and anxiety on subjective opioid effects; future research should aim to better understand and address the impacts of these factors. The lack of significant association between childhood adversity with problematic alcohol and other drug use could be due to low levels of use overall in this patient sample. Scores for hazardous alcohol use using the AUDIT in the current sample were almost two points lower than the Norwegian general population-based sample for that age group (an average of 4.5 for people aged 36-55 (50)), however drug use scores by the DUDIT were in line with the Swedish findings from the general population (3% scoring >2) (26).

The study had several limitations. The limited number of patients with high levels of childhood adversity was expected given the sample size. The data provides important insights on the impact of lower and moderate levels of childhood adversity, with clinical relevance since patients exposed to opioids are more likely to have experienced lower levels of childhood adversity. The data may also reflect some selection bias where patients with more childhood adversity were less likely to respond. Furthermore, follow-up questionnaires for exploratory outcomes were collected later than the surgery and the state measures may not reflect the time of surgery. Lastly, this study only aimed to conceptually replicate the prior findings using subjective responses as an early indicator of risk for persistent use. Future research should assess the link between childhood adversity, subjective effects, and use of the prescribed opioids after surgery.

To conclude, this study did not conceptually replicate findings for increased subjective pleasure to opioids given before surgery in people with greater histories of childhood adversity. This study found some support for the inverse: that people with greater childhood adversity reported less liking of the opioid effects. This effect was predominantly driven by patients with lower to moderate levels of childhood adversity as there were limited numbers of patients with high levels; however, the effects of moderate childhood trauma are still important to understand given the greater prevalence of lower levels of adversity at a population level. Exploratory associations between childhood adversity and more loneliness, anxiety, pain catastrophising, and lower SES may support clinically targeting these as risk factors for persistent use, and help to curb the increase of prescribed opioid-related deaths in Norway (51) and internationally (52). Opioids are the cornerstone of surgical care, and understanding the specific early risk factors for persistent use is critical for developing more individualised and supportive approaches to prescribing opioid analgesics, while ensuring necessary pain treatment for all patients.

**Declarations of interests**

The authors of this article declare that they have no financial conflict of interest with the content of this article. **Funding**

This study was funded by grants awarded to SL as part of the broader research trial by the European Research Council under the EU Horizon 2020 research and innovation programme (grant no. 802885) and South-Eastern Norway Regional Health Authority (grant no. 2020087).

**CRediT statement**

ME, SL, MK, and MC conceptualised this study, while ME, SL, and GE conceptualised the broader research trial. MK, IMM, KB, and ENJ conducted the data curation. MC and MK conducted the formal analyses, supported by ME and MT. SL acquired the funding as part of the broader trial. MC and MKK completed data visualisation. MC, MK, ME and SL wrote the original draft. IMM, MT, KB, ENJ, and GE reviewed and edited.

**PCI-RR study design:**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Question** | **Hypothesis** | **Sampling plan** | **Analysis Plan** | **Rationale for deciding the test sensitivity**  | **Interpretation given different outcomes** | **Theory that could be shown wrong**  |
| Can we conceptually replicate the findings that childhood adversity results in altered subjective effects of opioids naturalistically in generally healthy patients undergoing day surgery? | After the administration of an opioid analgesic, patients with greater childhood adversity will report: Primary hypotheses: H1: A greater mood boost (feeling good), and H2: greater liking of the effects (conceptually replicating the previous study).We do not expect to find effects of adversity on disliking the opioid effects or feeling high. Anxiety relief will be examined in exploratory analyses. | The study is using existing data collected as part of a larger observational research project. This study recontacted patients to complete additional measures, including for childhood adversity. The sample size was therefore constrained to as many respondents for the additional measures of the original sample size, which was n = 155. A post-hoc power analysis with a sample size of 155 and a small – medium effect size (f2 = .05) indicated a power of 0.78, which is sufficient to explore the research question.  | Two separate linear regressions will be conducted with childhood trauma questionnaire (CTQ) total score as the predictor, and drug liking and feeling good as outcomes. The p-values for feeling good and liking will be corrected for multiple tests using the Holm-Bonferroni method. | The effect size and hypotheses were based on a recent study that compared responses to a dose of morphine in people with either severe or no childhood adversity. On a 100-pt scale, this study reported a mean difference of 17.99 (95% CI: 6.69, 29.30) and a medium effect size d = 0.65 for euphoria, and a mean difference of 14.67 (95% CI = 0.48, 28.87) and small-medium effect size d = 0.39 for liking. The current naturalistic study uses continuous variables and an alternative design, however a post-hoc power calculation using existing estimates of effect size indicates sufficient power for a small- medium effect.  | H1 will be accepted if CTQ is significantly positively associated with post-drug feeling good, and we will conclude that people with childhood adversity are more sensitive to the mood-enhancing effects of the drug in a medical pre-operative context.H2 will be accepted if CTQ is significantly positively associated with post-drug liking. We will conclude that people with childhood adversity are more sensitive to the subjectively pleasurable drug effects in a medical pre-operative context.We will consider the study as a full conceptual replication of the previous study if both H1 and H2 are significant, or a partial conceptual replication if only one is significant in the predicted direction. H1 and H2 will be rejected if we find no effect, or significant effects in the opposite direction. However, because the study sample size is limited and we are only powered to detect medium-large effects, we will not conclude this as support for the null effect, but rather that we are not powered to reliably detect smaller effects (f 2<.05).We will also interpret any findings in line with the different opioid drugs, doses, and route of administration, in addition to the amount of variation with CTQ scores, and study context (hospital vs research study).   | Existing theory indicates a heightened risk of opioid addiction after adversity via a sensitivity to subjectively pleasurable effects.  We are not powered to support the null hypothesis (that childhood adversity is not a risk factor for persistent use of medically prescribed opioids). In the case of null findings, we can only tentatively discuss the potential role of methodological differences, limited statistical power, or a non-linear effect of adversityWe will also broadly explore potential challenges in generalising laboratory-based research to naturalistic settings, which is important when considering these studies for policy.  |

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