INTRODUCTION

Chronic musculoskeletal pain is highly prevalent in the general population and the leading cause of years lived with disability worldwide (GBD 2017 Disease and Injury Incidence and Prevalence Collaborator, 2018; Hurwitz et al., 2018; Murray et al., 2012). Accordingly, it is the main cause of early retirement and loss of productive life years in the workforce compared with other non-communicable diseases (Bevan, 2015).

Chronic widespread pain (CWP) has a stronger negative impact on work participation, quality of life, and physical and mental health than localized or regional chronic pain (Bevan, 2015; Lacey et al., 2014; Paananen et al., 2011). Considering the vast impact of chronic musculoskeletal pain on individual well-being and public health, it is desirable to re-focus health care from curative to preventive (Briggs et al., 2018). This requires insight into modifiable risk factors to inform the development of preventive interventions.
Prospective studies have shown that indicators of poor sleep quality, such as insomnia, number of insomnia symptoms and sleeplessness are associated with increased risk of chronic musculoskeletal pain and CWP (Mork & Nilsen, 2012; Skarpsno, Mork, et al., 2019; Skarpsno, Nilsen, et al., 2019; Uhlig et al., 2018). However, these studies have assessed sleep quality at one time point and have not considered long-term variations (Afoulou et al., 2018). Sleep quality may vary throughout the life course (Gadie et al., 2017; Li et al., 2018), and it is conceivable therefore to examine if changes in sleep quality over a 10-year period are associated with risk of any chronic musculoskeletal pain. The aim of the current study was to examine if changes in sleep quality over a 10-year period influenced the risk of chronic musculoskeletal pain and CWP.

2 | METHODS

2.1 | Study population

All inhabitants aged 20 years or older in Nord-Trøndelag County, Norway, were invited to participate in four health surveys (the HUNT Study): first in 1984–1986 (HUNT1); then in 1995–1997 (HUNT2); and 2006–2008 (HUNT3); and last in 2017–2019 (HUNT4). Information about chronic musculoskeletal pain was not collected at HUNT1, and the current study is therefore based on data from the three last surveys. Information on lifestyle and health-related factors was collected by questionnaires and clinical examination. Further information regarding the HUNT Study can be found at http://www.ntnu.edu/hunt.

In 1995–1997, 65,237 (69.5%) people participated, whereas 50,807 (54.1%) and 56,078 (54%) participated in 2006–2008 and 2017–2019, respectively. In the current study, we selected the 25,909 participants who participated in 1995–1997, 2006–2008 and 2017–2019. Of these, 6,033 persons reported no chronic pain in 1995–1997 and 2006–2008, and responded to the pain question in 2017–2019. To improve efficiency and reduce potential bias due to missing data, a simulation-based multiple imputation procedure was used to replace missing observations on sleep quality (n = 605, 10%) in 1995–1997 and 2006–2008.

The study was approved by the Regional Committee for Ethics in Medical Research (project no. 2014/612 REK midt). The study was carried out according to the Declaration of Helsinki.

2.2 | Sleep quality in the 1995–1997 and 2006–2008 surveys

Sleep quality in 1995–1997 was assessed by the following three questions: (1) “How often do you suffer from sleeplessness?”, (2) “Have you had problems falling asleep during the last month?”, and (3) “During the last month, did you ever wake up too early, not being able to fall asleep again?”. Question 1 had the response options: “never, or just a few times a year”, “1–2 times a month”, “approximately once a week” and “more than once a week”, whereas questions 2 and 3 had the response options: “never”, “occasionally”, “often” and “almost every night”. Participants were classified as having “poor sleep” if they answered “more than once a week” on question 1, or “often/almost every night” on questions 2 and/or 3; otherwise, they were classified as reporting “good sleep”.

Sleep quality in 2006–2008 was assessed by the following three questions: (1) “How often during the last 3 months have you had difficulty falling asleep at night?”, (2) “How often during the last 3 months have you woken up repeatedly during the night?”, and (3) “How often during the last 3 months have you woken too early and couldn’t get back to sleep?”, with each question having three response options: “never/seldom”, “sometimes” and “several times a week”. Participants were classified as having “poor sleep” if they answered “several times a week” on at least one of the questions; otherwise they were classified as reporting “good sleep”.

The information on sleep quality from 1995–1997 and 2006–2008 was then used to categorize the participants into one of four groups: (1) “good sleep at both surveys”; (2) “changed from poor to good sleep”; (3) “changed from good to poor sleep”; and (4) “poor sleep at both surveys”. We used the term “poor sleep” as our definitions do not fulfill the insomnia diagnosis criteria according to the current classification system (Riemann et al., 2017). However, the nighttime insomnia symptoms at the second survey can be used to define nocturnal sleep disruption according to the classification system (Riemann et al., 2017), and further categorize people into subtypes of insomnia (e.g. sleep-onset latency-insomnia, wake after sleep onset-insomnia, and early morning awakenings insomnia; Bjørøy et al., 2020).

2.3 | Chronic musculoskeletal pain in 1995–1997, 2006–2008 and 2017–2019

Questions on chronic musculoskeletal pain were adopted from the Standardized Nordic Questionnaire (Kuorinka et al., 1987), which has been shown to have acceptable reliability and validity (Descatha et al., 2007; Palmer et al., 1999). In 1995–1997 and 2006–2008, all
participants were asked “During the last year, have you had pain and/or stiffness in your muscles and joints that lasted for at least three consecutive months?”; with the response options “no” and “yes”. Participants who answered “yes” on this question in 1995–1997 and 2006–2008 were excluded from the study, i.e. our study sample comprised people without chronic musculoskeletal pain in both 1995–1997 and 2006–2008.

At follow-up (2017–2019), all participants were asked “During the last year, have you had pain in your muscles and joints that lasted for at least three consecutive months?”. Participants were defined to have any chronic pain if they answered “yes” to this question. Further, participants answering “yes” were asked to indicate the affected body area(s), including neck, shoulders, upper back, elbows, low back, hips, wrists/hand, knees, and ankles/feet. They were also asked “Have you been suffering from pain in both left and right sides of the body?”. Those who reported chronic pain in the axial skeleton (neck, upper back, or low back), above (shoulders, elbows, wrists/ fingers) and below (hips, knees, calf, ankle/feet) the waist, and in the left and right sides of the body were considered to have CWP (Wolfe et al., 1990). The reliability of any chronic pain and CWP shows kappa values of 0.63 (95% confidence interval [CI]: 0.53–0.73) and 0.48 (95% CI: 0.38–0.64), respectively; Hagen et al., 2011). Preliminary data from HUNT4 indicate somewhat better kappa values (Hagen et al., 2019).

2.4 Possible confounders

All potential confounders were assessed at the second measurement point (2006–2008), except for: (a) education that was obtained in 1995–1997 as this information was not collected in 2006–2008; and (b) changes in body weight between the two first surveys. Educational level was categorized into “primary school”, “high school”, “college ≤ 4 years” and “college > 4 years”. Standardized measurements of height (to the nearest centimetre) and weight (to the nearest half kilogram) obtained at the clinical examinations in 2006–2008 were used to calculate body mass index (BMI) as weight divided by the square of height (kg m$^{-2}$; World Health Organization, 1995). Relative change in body weight was calculated as percentage change from 1995–1997 to 2006–2008. Leisure time physical activity was obtained from questions about frequency, duration and intensity, and participants were classified as “inactive”, “below recommended” or “recommended and above” according to public recommendations for physical activity at baseline (Haskell et al., 2007). These questions have been validated against direct measurements of maximal oxygen uptake and accelerometer-derived activity, and found to perform well (Kurtze et al., 2008). Shift work was assessed by the question: “Do you work shifts, at night, or on call?”, with two response options “no” and “yes”. Alcohol consumption was assessed by the four-item CAGE (Cut down, Annoyed, Guilty, Eye-opener) screening questionnaire using a cut-off score ≥ 2 to indicate possible alcohol abuse (Ewing, 1984). We then divided alcohol problems into three categories (“no alcohol problem [no symptom]”; “possible alcohol problem [one symptom]”; and “possible alcohol abuse [≥ 2 symptoms]”). Smoking status was divided into five categories (“never smoked”; “former smoker”; “current low-intensity smoker [< 10 cigarettes per day]”; “medium-intensity smoker [10–19 cigarettes per day]”; and “high-intensity smokers [20 or more cigarettes per day]”). Symptoms of anxiety and depression were assessed by the Hospital Anxiety and Depression Scale (HADS) with a cut-off score of ≥ 8 on both anxiety and depression (Bjelland et al., 2002). Symptoms were then divided into four categories (“no anxiety or depression”; “anxiety”; “depression”; and “anxiety and depression”). To assess comorbid conditions, participants were asked if they have or have had heart disease, lung diseases, diabetes, or cancer. We then classified people into “no” and “yes” (at least one comorbid condition). The presence of sleep apnea and restless legs was assessed by the question: “How often during the last 3 months have you stopped breathing and/or had tingling in legs during sleep or in relation to sleep”, with the response options “never/seldom”, “sometimes” and “several times a week”. Acute pain and/or stiffness in muscles or joints were assessed by the question: “During the last month, have you experienced pain and/or stiffness in your muscles and joints?” with the response options “no” and “yes”. In 2006–2008, pain during the last month was assessed by the question: “Have you experienced intense bodily pain the last month?”, and categorized into “no/very weak”, “weak/moderate”, and “strong/very strong”. Self-reported use of pain medication was assessed in both 1995–1997 and 2006–2008.

2.5 Statistical analyses

A modified Poisson regression model was used to estimate risk ratios (RR) for any chronic musculoskeletal pain and for CWP at follow-up (2017–2019) associated with the four categories of sleep quality. Those who reported good sleep at both baseline surveys (1995–1997 and 2006–2008) served as the reference category. The precision of the RRs was assessed by 95% CIs using robust variance estimation. All associations were adjusted for age, sex, education, BMI, relative change in body weight, leisure time physical activity, and smoking status. We imputed missing data on covariates (20 imputations). The predictors in the imputation model were all the variables used in the main analysis (including the outcome variables any chronic musculoskeletal pain and CWP), as well as mental health, other comorbid conditions, shift work, alcohol consumption, and other sleep disorders.

We conducted a series of supplementary analyses to assess the robustness of the results. First, because there is a considerable overlap, but unclear temporal effects, between sleep quality and comorbid conditions such as psychiatric illness and medical conditions (Alvaro et al., 2013; Katz & McHorney, 1998; Taylor et al., 2007), we included adjustment for anxiety and/or depression and other comorbid conditions (heart disease, lung diseases, diabetes, cancer) in separate models as they could induce collider bias. Second, both sleep apnea and restless leg syndrome are associated with chronic pain (Hoogwout et al., 2015; Tentindo et al., 2018), and we therefore
repeated the main analysis excluding people with these specific sleep disorders. Third, to assess possible reverse causation, i.e. that existing musculoskeletal pain that was not captured by the questionnaire had already caused poor sleep at the time of participation, we repeated the main analysis: (1) excluding those who reported physical pain during the last month in 1995–1997 and 2006–2008; and (2) reported regular use of pain medication in 1995–1997 and 2006–2008.

All statistical analyses were performed using Stata for Windows, version 16.0 (StataCorp LP).

3 | RESULTS

Overall, among the 6,033 participants without chronic musculoskeletal pain at baseline, 34.3% (2,067) reported any chronic musculoskeletal pain at follow-up in 2017–2019, whereas 5.2% (314) reported CWP. Table 1 shows the baseline characteristics of the study sample stratified by the four categories of long-term sleep quality.

Table 2 shows the association between sleep quality in 1995–1997 and 2006–2008, respectively, and risk of chronic musculoskeletal pain at follow-up in 2017–2019. Participants who reported poor sleep in 1995–1997 had a RR of 1.24 (95% CI: 1.12–1.40) for any chronic pain and 1.56 (95% CI: 1.12–2.17) for CWP, compared with participants with good sleep quality. Similar associations were found for participants who reported poor sleep in 2006–2008, with RRs of 1.28 (95% CI: 1.18–1.40) for any chronic pain and 1.75 (95% CI: 1.36–2.26) for CWP.

Table 3 shows the association between long-term change in sleep quality and the risk of chronic musculoskeletal pain. Compared with participants who reported good sleep at both surveys (crude absolute risk: 32.4%), the RRs for any chronic pain were: 1.20 (95% CI: 1.02–1.41) for those who changed from poor to good sleep; 1.25 (95% CI: 1.12–1.39) for those who changed from good to poor sleep; and 1.41 (95% CI: 1.21–1.63) for those who reported long-term poor sleep, respectively. The corresponding RRs for CWP were 1.35 (95% CI: 0.82–2.23), 1.55 (95% CI: 1.14–2.12) and 2.09 (95% CI: 1.38–3.17), respectively.

3.1 | Supplementary analyses

Additional adjustments for anxiety and/or depression and comorbid conditions or exclusion of people with possible sleep apnea or restless legs syndrome.
restless legs syndrome had negligible influence on the estimated RRs (showing ~4%–10% reduction in risk compared with the main analysis). Moreover, analyses that assessed possible reverse causation showed similar estimates as in the main analysis. However, we observed somewhat stronger associations when we excluded people who reported pain the last month in both 1995–1997 and 2006–2008, i.e. a 10%–30% increased risk among those who reported long-term poor sleep quality.

### TABLE 2
Risk of any chronic musculoskeletal pain and CWP at follow-up in 2017–2019 associated with sleep quality in 1995–1997 and 2006–2008

| Pain outcomes and sleep quality in 1995–1997 and 2006–2008 | No. of persons | No. of cases | Crude absolute risk (%) | Age-adjusted, RR<sup>a</sup> | Multi-adjusted, RR<sup>b</sup> (95% CI)<sup>b</sup> |
|-----------------------------------------------------------|----------------|--------------|--------------------------|-----------------------------|--------------------------------------------------|
| Any chronic pain                                          |                |              |                          |                             |                                                  |
| Sleep quality in 1995–1997                                 |                |              |                          |                             |                                                  |
| Good sleep                                                | 5,482          | 1,833        | 33.4                     | 1.00                        | Reference                                       |
| Poor sleep                                                | 551            | 234          | 42.5                     | 1.28                        | 1.24 (1.12–1.40)                                 |
| Sleep quality in 2006–2008                                |                |              |                          |                             |                                                  |
| Good sleep                                                | 5,109          | 1,676        | 32.8                     | 1.00                        | Reference                                       |
| Poor sleep                                                | 924            | 391          | 42.3                     | 1.31                        | 1.28 (1.18–1.40)                                 |
| CWP                                                       |                |              |                          |                             |                                                  |
| Sleep quality in 1995–1997                                 |                |              |                          |                             |                                                  |
| Good sleep                                                | 5,482          | 273          | 5.0                      | 1.00                        | Reference                                       |
| Poor sleep                                                | 551            | 41           | 7.4                      | 1.64                        | 1.56 (1.12–2.17)                                 |
| Sleep quality in 2006–2008                                |                |              |                          |                             |                                                  |
| Good sleep                                                | 5,109          | 238          | 4.7                      | 1.00                        | Reference                                       |
| Poor sleep                                                | 924            | 76           | 8.2                      | 1.86                        | 1.75 (1.36–2.26)                                 |

CI, confidence interval; CWP, chronic widespread pain; RR, risk ratio.

<sup>a</sup>Adjusted for age (continuous).

<sup>b</sup>Adjusted for age (continuous), sex (women, men), education (primary school, high school, college ≤ 4 years, college > 4 years), BMI (continuous), relative change in body weight (continuous), leisure time physical activity (inactive, low, moderate-to-high) and smoking (never smoked, former smoker, current low-intensity smoker [< 10 cigarettes per day], medium-intensity smoker [10–19 cigarettes per day] and high-intensity smokers [20 or more cigarettes per day]).

### TABLE 3
Risk of any chronic musculoskeletal pain and CWP at follow-up in 2017–2019 associated with change in sleep quality from 1995–1997 to 2006–2008

| Pain outcomes and change in sleep quality from 1995–1997 to 2006–2008 | No. of persons | No. of cases | Crude absolute risk (%) | Age-adjusted, RR<sup>a</sup> | Multi-adjusted, RR<sup>b</sup> (95% CI)<sup>b</sup> |
|-----------------------------------------------------------------------|----------------|--------------|--------------------------|-----------------------------|--------------------------------------------------|
| Any chronic pain                                                       |                |              |                          |                             |                                                  |
| Remained good sleep                                                    | 4,792          | 1,555        | 32.4                     | 1.00                        | Reference                                       |
| Poor sleep to good sleep                                               | 274            | 107          | 39.1                     | 1.22                        | 1.20 (1.02–1.41)                                 |
| Good sleep to poor sleep                                               | 707            | 286          | 40.5                     | 1.26                        | 1.25 (1.12–1.39)                                 |
| Remained poor sleep                                                    | 260            | 119          | 45.8                     | 1.41                        | 1.41 (1.21–1.63)                                 |
| CWP                                                                    |                |              |                          |                             |                                                  |
| Remained good sleep                                                    | 4,792          | 223          | 4.7                      | 1.00                        | Reference                                       |
| Poor sleep to good sleep                                               | 274            | 17           | 6.2                      | 1.45                        | 1.35 (0.82–2.23)                                 |
| Good sleep to poor sleep                                               | 707            | 51           | 7.2                      | 1.66                        | 1.55 (1.14–2.12)                                 |
| Remained poor sleep                                                    | 260            | 23           | 8.8                      | 2.16                        | 2.09 (1.38–3.17)                                 |

CI, confidence interval; CWP, chronic widespread pain; RR, risk ratio.

<sup>a</sup>Adjusted for age (continuous).

<sup>b</sup>Adjusted for age (continuous), sex (women, men), education (primary school, high school, college ≤ 4 years, college > 4 years), BMI (continuous), relative change in body weight (continuous), leisure time physical activity (inactive, low, moderate-to-high), and smoking (never smoked, former smoker, current low-intensity smoker [< 10 cigarettes per day], medium-intensity smoker [10–19 cigarettes per day] and high-intensity smokers [20 or more cigarettes per day]).
The results of the current study show that people who reported poor sleep over a ~10-year period have an increased risk of any chronic musculoskeletal pain, and in particular CWP, compared with people who reported good sleep over the same period. The causal effect of improving sleep quality cannot be firmly established, but people who changed from poor to good sleep quality had 5%–20% lower relative risk of chronic pain than people who changed from good to poor sleep quality. In sum, these findings suggest that prolonged exposure to poor sleep is a major risk factor for chronic musculoskeletal pain, and especially CWP.

Few studies have investigated the influence of long-term changes in sleep quality on the risk of chronic musculoskeletal pain. One study found that increased insomnia symptoms over a ~4-year period increased the risk of back pain by about 40% among working adults (Agmon & Armon, 2014). Another study found that persistence of poor sleep over a ~6-year period is associated with a twofold increased risk of work disability due to a low back diagnosis (Ropponen et al., 2013). The current study expands on these findings by showing that people who reported poor sleep over a ~10-year period had close to 41% increased risk of any chronic pain and more than twofold increased risk of CWP, compared with people who remained good sleep. The increased risk remained after adjustments for concurrent changes in body weight between the two first surveys (i.e. a possible marker of change in health status). Furthermore, supplementary analyses with additional adjustments for anxiety, depression and other comorbid conditions as well as exclusion of people with possible sleep apnea or restless legs syndrome had negligible influence on the risk estimates. In sum, our study suggests that long-term poor sleep quality is an important risk factor for any chronic musculoskeletal pain and CWP, and that preventing or reducing sleep problems may have the potential of reducing the risk of chronic pain. The underlying mechanisms for the effect of long-term poor sleep quality on risk of chronic musculoskeletal pain and CWP might be related to a complex interplay between neurobiological changes, immune responses, and altered cognitive and emotional pain processing (Finan et al., 2017; Haack et al., 2020; Irwin et al., 2016; Tiede et al., 2010; Whibley et al., 2019). For instance, there may exist a link between severity of poor sleep and low-graded inflammation (Irwin et al., 2016), and dysregulation of pro-inflammatory markers can induce changes in peripheral and central pain processing (Wieseler-Frank et al., 2005) that are involved in the development of chronic pain states (Zhang & An, 2007). It is also possible that insufficient sleep quality exaggerates the sensation of pain by causing significant mood disruption (Whibley et al., 2019) or weakens the ability to disengage from painful stimuli (Tiede et al., 2010).

In contrast to previous studies looking into the impact of increased sleep problems on chronic pain, we assessed the effect of both long-term improvement and worsening in sleep quality. Compared with people who reported long-term good sleep quality, the risk of any chronic musculoskeletal pain and CWP was 25% and 55% greater among those who changed from good to poor sleep. In comparison, changing from poor to good sleep was associated with a somewhat lower relative risk of any chronic pain (20%) and CWP (35%). Although it should be acknowledged that our data cannot confirm any causal link or effect of improved sleep quality, these results are encouraging because they indicate that improving the sleep quality among people with poor sleep reduces the risk of chronic musculoskeletal pain. The possible causal link between insomnia and chronic pain is supported by a recent study using genetic variants for insomnia as an instrumental variable (Broberg et al., 2021) and by experimental evidence showing that sleep disruption over several nights heightens pain perception (Haack & Mullington, 2005). However, to fully understand the relationship between long-term changes in poor sleep quality and risk of chronic musculoskeletal pain, more research is needed to assess the impact of other sleep characteristics, including sleep duration, different measures of sleep quality, and circadian preferences. Additionally, future studies should assess trajectories of sleep characteristics or use approaches that may mitigate key sources of bias (e.g. reverse causation and residual confounding).

The strengths of the current study include the large study sample, the prospective design among people without a history of chronic musculoskeletal pain, assessment of long-term changes in sleep quality, and detailed information on possible confounders. However, our definition of sleep quality is not aligned with established frameworks for classification of sleep disorders, for example, the International Classification of Sleep Disorders (American Academy of Sleep Medicine, 2014), which hampers a clinical interpretation of our findings. Moreover, sleep quality was assessed by different questions in 1995–1997 and 2006–2008, and we had no information about variations in sleep quality between the surveys, nor which factors that are likely to influence the possible variations in sleep quality. Although we conducted a sensitivity analysis excluding people with self-reported sleep apnea, there may be differences between subjective and objective measures of obstructive events (Nam et al., 2016). Our definition of CWP did not include information about symptom severity, and is therefore not aligned with the current classification scheme (Wolfe et al., 2010). Moreover, due to the small number of CWP cases at follow-up we could not stratify our analyses by gender, age or other potential effect modifiers. It should also be noted that the participants had to take part in three consecutive surveys during approximately two decades, and it is possible that they constitute a particularly healthy cohort. Thus, we cannot rule out whether this may have underestimated our findings. Moreover, we cannot exclude the possibility that our findings are influenced by reverse causation. However, we observed similar associations when we excluded people reporting use of pain medication or physical pain the last month at the two first surveys. Finally, although we adjusted for several lifestyle and health-related factors, residual confounding due to unknown or unmeasured factors (e.g. genetic or familial factors) influencing both sleep and chronic pain cannot be excluded (Beaulieu-Bonneau et al., 2007; Lier et al., 2014; Stein et al., 2018).
In conclusion, long-term poor sleep quality is associated with increased risk of any chronic musculoskeletal pain and CWP. Although the causal effect of improving sleep quality cannot be established, our data showed that people who changed from poor to good sleep quality had 5%–20% lower relative risk of chronic musculoskeletal pain than people who changed from good to poor sleep quality. Preventing sleep problems and promoting good sleep quality throughout adulthood may therefore have the potential to reduce the incidence of chronic musculoskeletal pain.

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CONFLICT OF INTERESTS
No conflicts of interest declared.

AUTHOR CONTRIBUTIONS
ESS, TILN, KH and PJM designed the study. ESS analysed the data. ESS, TILN, KH and PJM interpreted the data. ESS and PJM drafted the manuscript. ESS, TILN, KH and PJM revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript. All authors declare that they accept full responsibility for the conduct of the study, had access to the data and controlled the decision to publish.

DATA AVAILABILITY STATEMENT
This study used data from the HUNT Study (https://www.ntnu.edu/hunt). Any research group with a Principal Investigator affiliated with a Norwegian research institute can apply for access to use data from the HUNT Study. This means that researchers from non-Norwegian countries must have a collaboration partner in Norway to be able to use data from the HUNT Study. Each project needs to be approved by the HUNT Data Access Committee, Regional Medical Ethical Committee, in some cases also the Data Inspectorate. Due to participant confidentiality, participant data are not publicly available.

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