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Use of analgesics in the general population

Trends, persistence, high-risk use and associations with pain sensitivity

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The photo shows the blooming of a willow tree (Norwegian: selje).

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SUMMARY

Background

Analgesics are commonly used drugs but we are lacking knowledge of trends, persistence, high-risk use and the association with pain sensitivity at a population-level.

Purpose

To describe the use of analgesics, particularly persistent analgesic use, in a general population (30+ years), including change over time, contraindications and drug interactions, risk factors, and associations with pain sensitivity.

Methods

The Tromsø Study, including Tromsø 5 (2001-02, *n* = 8,030) and Tromsø 6 (2007-08, *n* = 12, 981), with the latter further linked with the Norwegian Prescription Database (2004-13).

Main results

The age-adjusted prevalence of analgesic use increased from 53.7% to 59.6% in women and from 29.1% to 36.7% in men between 2001 and 2008, due to an increase in the use of non-prescription analgesics. Several areas of potential high-risk use of analgesics were identified. The prevalence of persistent prescription analgesic use was 4.3% in general and 10.2% among those reporting chronic pain, while the incidence rate was 21.2 per 1,000 person-years; risk factors were chronic pain, increasing age, female sex, lower education level and most likely lower levels of physical activity. Analgesic use was associated with increased pain sensitivity; regular opioid users were more pain sensitive than regular users of non-opioid analgesics. Increased pain sensitivity was a risk factor for future persistent analgesic in the crude analysis.

Conclusions

The use of analgesics increased from 2001 to 2008. The extent of use of non-steroidal anti-inflammatory drugs in the presence of chronic kidney disease, gastrointestinal ulcers, cardiovascular disease and interacting drugs increasing the bleeding risk was a particular cause for concern. The prevalence of persistent analgesic use was relatively low, also among those reporting chronic pain, perhaps indicative of limited effectiveness. Analgesic use is associated with increased pain sensitivity but the potential causal mechanisms are unclear.

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S.D.G.

ABBREVIATIONS

ACE – angiotensin converting enzyme

ASA – acetylsalisylic acid, aspirin

ATC – Anatomical Therapeutic Chemical classification system

AT II – angiotensin II

CKD – chronic kidney disease

CKD-EPI – Chronic Kidney Disease Epidemiology collaboration

CNS – central nervous system

COX – cyclooxygenase

CPT – cold pressor test

CVD – cardiovascular disease

DAG – directed acyclic graph

DDD – defined daily dose

EGFR – estimated glomerular filtration rate

GI – gastrointestinal

IASP – International Association for the Study of Pain

MAR – missing at random

MCAR – missing completely at random

MNAR – missing not at random

NANSAID – non-aspirin NSAID

NorPD – the Norwegian Prescription Database

NRS – numerical rating scale

NSAID – non-steroidal anti-inflammatory drug

OR – odds ratio

OTC – non-prescription, "over-the-counter"

PDC – proportion-of-days-covered

PIN – personal identification number

Rx – prescription

SCORE - Systematic Coronary Risk Evaluation

SSRI – selective serotonin reuptake inhibitor

LIST OF PAPERS

I. Samuelsen PJ, Slørdal L, Mathisen UD, Eggen AE. Analgesic use in a Norwegian general population: change over time and high-risk use - The Tromsø Study. *BMC Pharmacol Toxicol* 2015; **16**: 16. DOI: 10.1186/s40360-015-0016-y

II. Samuelsen P-J, Svendsen K, Wilsgaard T, Stubhaug A, Nielsen CS, Eggen AE. Persistent analgesic use and the association with chronic pain and other risk factors in the population—a longitudinal study from the Tromsø Study and the Norwegian Prescription Database. *Eur J Clin Pharmacol* 2016; Epub ahead of print (12 Apr 2016). DOI: 10.1007/s00228-016-2056-7

III. Samuelsen PJ, Nielsen CS, Wilsgaard T, Stubhaug A, Svendsen K, Eggen AE. Pain sensitivity as risk factor for analgesic use in 10,486 adults: The Tromsø Study. Manuscript submitted for publication.

1 BACKGROUND

1.1 WHAT THIS DISSERTATION IS ABOUT

This dissertation is about the use of analgesics, i.e. painkillers, in the general adult (30+ years) population. The purpose is to describe how and why analgesics are used, with a special focus on long-term or *persistent* use. The dissertation consists of three papers, all using data from the Tromsø Study, conducted in Tromsø, Norway. In the first paper we present a general overview of analgesic use, including both non-prescription (OTC) analgesics and prescription (Rx) analgesics. It provides data on the change in use between 2001-02 and 2007-08, in addition to prevalence of use in high-risk groups, i.e., in the presence of contraindications or potential drug interactions. In the second paper, we narrow the focus to persistent analgesic use. We link the Tromsø Study to the Norwegian Prescription Database (NorPD) and develop a definition of persistent analgesic use. We use this definition to estimate the prevalence, incidence rate and the association with risk factors, particularly chronic pain and different aspects of chronic pain. In the third and final paper, using the definitions developed in the first two papers, we focus on a particular potential risk factor for analgesic use: increased pain sensitivity. Increased pain sensitivity may both be a risk factor for analgesic use and a consequence of analgesic use. We try to address if pain sensitivity can explain analgesic use, in relation to pain mechanisms and the effectiveness of analgesics.

1.2 HISTORY OF ANALGESIC USE

People have used painkillers, e.g., in the form of extracts, dry leaves/bark, in traditional medicine for centuries. Most of the analgesics that are in use today are natural occurring substances or synthetic substances based on the chemical structure and/or the pharmacological properties of the original natural compounds. Myrtle leaves have been used for rheumatic and back pain as far back as 1500 BC, while at the time of Hippocrates (400 BC) people were recommended to chew bark from the willow tree to treat fever or pain.[1,2] Likewise, extracts from the opium poppy have been used as analgesics for thousands of years.[3(p515)] Different plants from the genera *Salix*, including the willow tree, and *Spiraea* have been used to remedy fever, inflammation and pain.[2] In Norway, including the northern parts of the country, the willow tree is widely abundant, giving reason to believe that the analgesic properties where known also in this part of the world. Willow bark contains salicin which is metabolized *in vivo* into salicylic acid.[2] After the discovery of salicin, salicylic acid became the chemical

precursor of acetylsalisylic acid (ASA), known as aspirin ("Acetyl Spiraea") – a drug still in use today.[1] ASA later lead to the discovery and development of the widely used non-steroidal anti-inflammatory drugs (NSAIDs), with ibuprofen being marketed in 1969.[1]

Another plant of immense importance is *Papaver somniferum* (literally: poppy bringing sleep) – the opium poppy. Natural compounds originating from the opium poppy have been known since ancient times to give effects like euphoria, analgesia, sleep (hence the name of the poppy) and to stop diarrhea.[3(p515)] The chemical structure of the archetypical opioid, morphine (named after the Greek god of sleep, *Morpheus*), was determined in 1902, leading to the development of a range of synthetic and semi-synthetic opioids.[3(p515)]

In an attempt to find a remedy against worms, the antipyretic effects of acetanilide (later called "antifebrin") was discovered by serendipity in 1884.[4] This led to the synthesis of phenacetin. Phenacetin, ASA, and, additionally, phenazone, became the first fully synthetic analgesics – and early "block-busters".[4] Due to limiting side effects of phenacetin, an active metabolite of phenacetin named paracetamol (or acetaminophen in the USA) was developed. Paracetamol was marketed and supplanted phenacetin in the 1950s.[4]

1.3 DEFINITION OF ANALGESICS

1.3.1 Analgesics

Analgesics (painkillers, pain relievers) are, according to the Medical Subject Heading, defined as "compounds capable of relieving pain without the loss of consciousness".[5] The word *analgesic* comes from *analgesia*, literally meaning "painlessness" (from Greek *an-* "not" + *algein* "feel pain").[6] The analgesics may also possess *antipyretic*, i.e., fever-reducing, or anti-inflammatory (historically called *antiphlogistic*) actions.

In this dissertation, classical analgesics are defined as NSAIDs, opioids or drugs belonging to the Anatomical Therapeutic Chemical classification system (ATC, whocc.no)[7] group N02B ("other analgesics and antipyretics"), including paracetamol, ASA and phenazone-caffeine. Drugs used in pain management but with other primary indications, e.g., antiepileptics and antidepressants, are often termed atypical or adjuvant analgesics or co-analgesics.

1.3.2 Non-steroidal anti-inflammatory drugs

NSAIDs are drugs that inhibit the cyclo-oxygenase (COX) enzyme, producing anti-inflammatory, anti-pyretic and analgesic effects.[3(p320)] The chemical structures are not based upon the steroid structure, hence the name "non-steroidal". ASA may be considered as the

mother-NSAID, but is often kept separate from other NSAIDs due to its slight difference in pharmacology and dual indication, i.e., use as an anticoagulant and cardio-protective agent. Sometimes the term "non-aspirin NSAID" (NANSAID) is used to make a distinction between ASA and other NSAIDs.[8] The COX-2 inhibitors, or "coxibs" belong among the NSAIDs but are sometimes kept distinct from other ("traditional") NSAIDs in the literature.[3(p317)] Glucosamine was approved as a drug in Europe in 2003 and included in the same ATC group as the NSAIDs, M01A. However, according to a widely cited systematic review from 2010, glucosamine is ineffective in reducing joint pain in osteoarthritis of the knee or hip.[9] Furthermore, a prescription registry study shows that use of glucosamine do not reduce the use of analgesics, which provides indirect evidence of lack of clinical effect.[10] Glucosamine is therefore, and due to the different pharmacodynamic properties, often excluded in studies on NSAIDs.[11-13] In this dissertation, NSAIDs are defined as all drugs in the ATC group M01A, which includes both "traditional" NSAIDs and COX-2 inhibitors but not ASA, excluding glucosamine. The topical NSAIDs in M02A were thus not included.

1.3.3 Other analgesics and antipyretics

The ATC group N02B, "other analgesics and antipyretics", includes paracetamol, ASA and phenazone-caffeine in Norway (the cannabinoid Sativex® has recently been marketed). The use in this group is highly dominated by paracetamol. Paracetamol is an analgesic with antipyretic effect but weak anti-inflammatory action. Paracetamol is sometimes classified as an NSAID, like in a reference book in pharmacology,[3(p324)] but is commonly not regarded as an NSAID due to the lack of anti-inflammatory effect and a different adverse effects profile. "Other analgesics and antipyretics" are defined as all drugs belonging to the ATC group N02B. Unless otherwise stated, we define paracetamol as belonging to ATC group N02B, while paracetamol-codeine is classified as an opioid (N02A).

1.3.4 Opioids

Opioids are defined as "any substance, whether endogenous or synthetic, that produces morphine-like effects that are blocked by antagonists such as naloxone".[3(p517)] The term "opiates" actually means natural occurring substances from the opium poppy, and therefore includes, among others, morphine and the cough suppressant noscapine, with the latter having no analgesic action. Furthermore, an opioid may be fully synthetic and not naturally occurring, e.g., pethidine. However, the term "opiates" is sometimes used interchangeably with "opioids" in the literature. In this dissertation, opioids are defined as any drug belonging to the ATC group N02A. Codeine alone (R05DA04) is not included, due to its main use as a

cough suppressant and low use in general.[14] Opioids mainly used in the treatment of opioid-addiction (N07BC) are also not included.

1.4 PAIN

1.4.1 Definition of pain

The word "pain" stems from the Latin word *poena* meaning "penalty", cf. "penal code" or "penal institution".[6] The International Association for the Study of Pain (IASP) defines pain as:

> *"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."*[15]

This definition does not connect pain exclusively to tissue damage or a pathophysiological cause, as pain is a subjective experience that may also occur in the absence of such damage.[3(p509),15] Pain is thus not only related to the physiological transduction of a noxious stimulus but also has a strong emotional (affective) component as well as involvement of cognitive processes in the brain.[3(p509),16]

Pain is a biological warning sign but when it chronifies and "outlives its usefulness as a warning system" pain becomes a debilitating disease in its own right.[16,17] Chronic pain has been defined as pain persisting beyond the normal time of healing.[18] However, IASP has allowed for flexibility in the definition of chronic pain, both in respect of the duration, e.g., one month, three months, six months, or conditions where "healing" has not occurred, e.g., rheumatoid arthritis, or recurring pain, e.g., migraine. Chronic pain has also been suggested to be "a persistent pain that is not amenable, as a rule, (…) to the routine methods of pain control such as nonnarcotic analgesics".[18]

1.4.2 Pain mechanisms

Nociception refers to the "the neural process of encoding noxious stimuli",[15] and includes the molecular mechanisms by which primary sensory neurons detect these stimuli.[16] The concept of nociception is important for the understanding of pain but pain does not equal nociception.[3(p509)] Briefly and simplified, a noxious stimulus, either mechanical, chemical or thermal, activates nociceptors, i.e., nerve endings of nociceptive afferent neurons projecting from the dorsal horn of the spinal cord, with further transmission of the signal to the brain (Figure 1). Nociceptive afferent neurons are broadly classified into fast conducting, partly myelinated Aδ-fibers, where activation produces a sharp, well-localized "first pain", while the

second class consists of slow-conducting, unmyelinated C-fibers, which gives rise to a dull, diffuse and burning "second pain" upon activation.[3(p509),16] Tissue injury also results in inflammation and a release of a range of chemicals ("the inflammatory soup") from neighboring cells, which either activate the nerve terminals directly or enhance the sensitivity of the nociceptor.[3(p509),16] Sensitization of peripheral nerve terminals, i.e., lowering of the activation thresholds, is mediated by, among others, prostaglandins and bradykinin.[3(p510),16] The nociceptive afferent neurons also contain neuropeptides, particularly substance P and calcitonin gene-related peptide, which facilitates the production of the inflammatory soup causing neurogenic inflammation.[3(p509),16] In addition to peripheral sensitization, central sensitization occurs when there is an "increased responsiveness of spinal cord "pain" transmission neurons", where activation of non-nociceptive primary sensory fibers also produces pain.[16] Peripheral sensitization in addition to central facilitation of the transmission in the dorsal horn, i.e., "wind-up", where repeated stimuli lead to an increasing amplitude of synaptic potentials, can produce the clinical condition hyperalgesia. [3(p510)] Hyperalgesia is present when a stimulus that normally causes pain, produces *increased* pain.[15] The brain controls the impulse transmission in the dorsal horn through a process termed descending inhibitory control. Inputs from many parts of the brain control the "nociceptive gate" in the dorsal horn through the periaqueductal grey of the midbrain. Important transmitters in this regard are serotonin and the enkephalins, while another pathway involves noradrenaline.[3(pp510-11)]

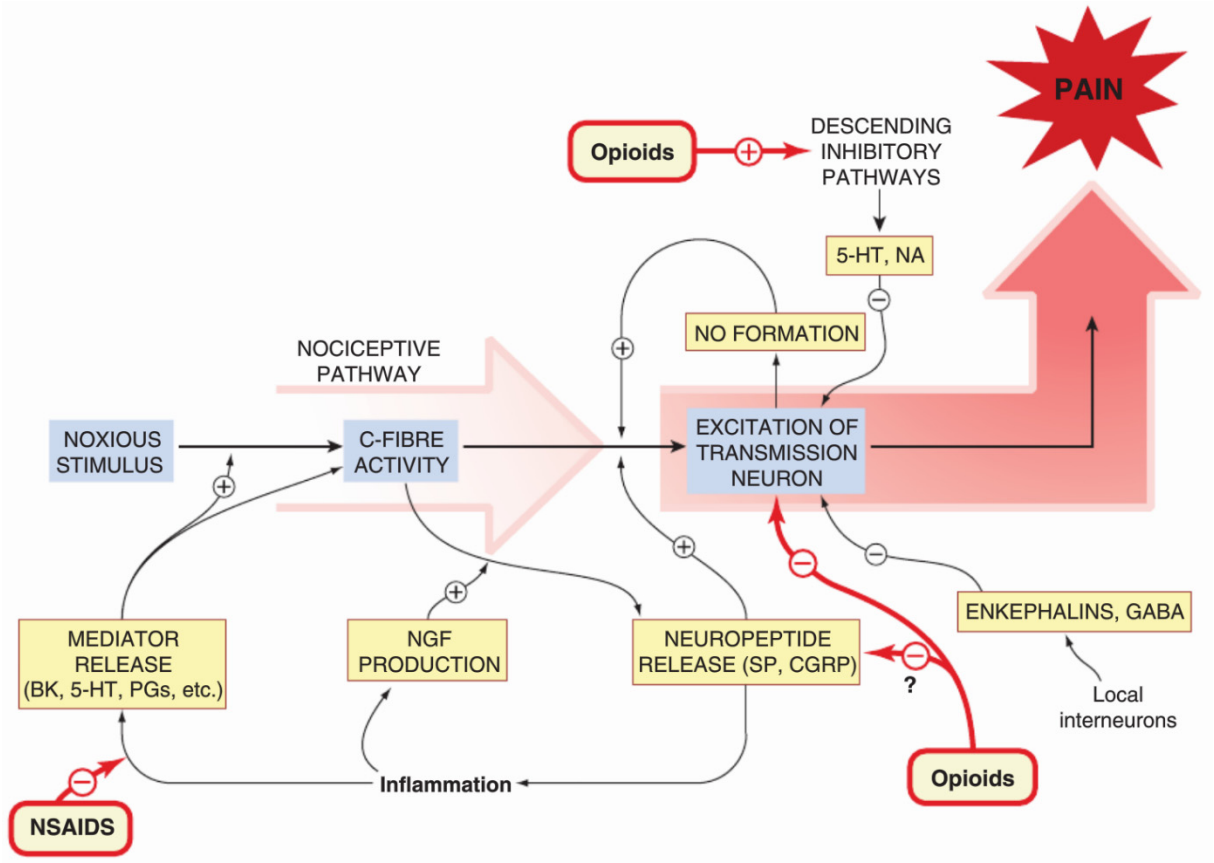

Figure 1 Nociception and mechanism of action of analgesics. A noxious stimulus activates nociceptors (here: C-fibers), with cell bodies located in the dorsal horn of the spinal cord. Injury results in inflammation with the release of several mediators ("the inflammatory soup"), including prostaglandins, which sensitizes the nociceptor or activates them directly. The signal travels from the dorsal horn to the brain, while the pain is inhibited through the descending inhibitory pathways. NSAIDs mainly inhibit the production of the pro-inflammatory prostaglandins peripherally but also have central action. Opioids act centrally by reinforcing the descending inhibitory pathways and peripherally by inhibiting the excitation of nociceptive nerve terminals. 5-HT: serotonin, BK: bradykinin, CGRP: calcitonin gene-related peptide, GABA: gamma-amino butyric acid, NA: noradrenaline, NGF: nerve growth factor, NO: nitric oxide, NSAID: non-steroidal anti-inflammatory drug, PG: prostaglandin, SP: substance P. *Reproduced with permission from Rang et al.*[3]

1.4.3 Experimental pain

The large differences in reported pain among patients with the same clinical condition, i.e., disease or trauma, may reflect individual differences in pain sensitivity.[19] Pain sensitivity is not clearly defined in the literature but can only be appraised in controlled, experimental pain settings, e.g., by measurement of pain threshold or pain tolerance.[19] Pain threshold is defined as "the minimum intensity of a stimulus that is perceived as painful", while pain tolerance is defined as "the maximum intensity of a pain-producing stimulus that a subject is willing to accept in a given situation".[15] The aforementioned pain definition does not tie pain to a

stimulus.[15] However, experimental pain models measure the psychophysical response toward a nociceptive stimulus, i.e., a proxy measure of pain.[17] For example, the cold pressor test (CPT) used in this dissertation, involves submerging of the hand in cold water. This stimulus activates peripheral nociceptors as well as central pain systems to produce a tonic, deep, dull aching pain.[20]

1.5 MECHANISM OF ACTION OF ANALGESICS

1.5.1 Non-steroidal anti-inflammatory drugs

The NSAIDs bind to the COX enzymes and inhibit the production of pro-inflammatory prostaglandins from arachidonic acid.[16] Prostaglandins, particularly PGE_2, are not by themselves pain evoking substances but they play a central role in inflammation and peripheral sensitization of the nociceptors (Figure 1).[16] NSAIDs also have a central action, possible through central inhibition of prostaglandin release in the spinal cord.[3(p321)] The COX enzyme exists in two important isoforms, COX-1 and COX-2. The COX-1 enzyme is constitutively expressed in different cells and tissues, including the gastric endothelium, kidney and platelets, while the COX-2 enzyme is induced by inflammation.[21]

1.5.2 Paracetamol

Well over a century after its discovery, the mechanism of action of paracetamol is still largely unknown. Paracetamol has analgesic and antipyretic actions but no or only weak anti-inflammatory activity.[3(p324)] One hypothesis, although questioned in recent years, is that paracetamol is an inhibitor of a third isoform of the COX enzyme, COX-3, present in the central nervous system (CNS),[3(p324),4,21] while it may also have other effects in the CNS, on the COX-2 enzyme, or on transient receptor potential (Trp) channels.[3(pp324,526)]

1.5.3 Opioids

The binding of opioids (agonists) to opioid receptors, particularly μ receptors, produces antinociception and analgesia. Opioids also reduce the affective component of pain.[3(pp518-9)] For a long time the role of the opioid receptors in the body was not clear, as no endogenous ligand was found. However, later it was discovered that the body has its own opioids, the enkephalins, which bind the opioid receptor. The enkephalins belong to a larger family of endogenous opioids called endorphins.[3(p517)] The periaqueductal grey in the midbrain and the substantia gelatinosa in the dorsal horn of the spinal cord are rich in opioid receptors.[3(pp510-1)] The opioids produce their analgesic effect both at the supraspinal and spinal level, through

activation of the descending inhibitory pathways and inhibition of transmission through the dorsal horn, i.e., a "closing" of the nociceptive gate (Figure 1).[3(pp511,519)] Additionally, the opioids seem to have peripheral action by inhibiting excitation of nociceptive nerve terminals.[3(p519)]

1.6 BENEFITS AND RISKS OF ANALGESIC USE

1.6.1 Effectiveness and efficacy of analgesics

The opioids have been most extensively studied and also show the most positive evidence in a large number of clinical or experimental pain settings, followed by the NSAIDs.[17] Perhaps surprisingly, the NSAIDs show an equivocal evidence of efficacy in inflammatory arthritis.[17] A recent network meta-analysis concludes that diclofenac is the most effective NSAID in osteoarthritis, while treatment with paracetamol alone is ineffective.[22] Recent systematic reviews show a limited or unproven effectiveness/efficacy of long-term analgesic use or use in chronic pain: the evidence of long-term opioid use in chronic pain is insufficient,[23,24] the evidence of efficacy of paracetamol in chronic pain is limited,[25] the effectiveness of long-term opioid therapy of chronic low back pain is unproven,[26] while NSAIDs show only a small effect with low level of evidence in chronic back pain.[27] This is further supported by epidemiological evidence showing that around two thirds of chronic pain patients using prescription analgesics report that their prescription analgesics are inadequate to control the pain,[28] while around 90% of opioid users with chronic pain still report moderate, severe or very severe pain.[29] However, Moore et al. argue that most analgesics work well but only in a minority of patients, and that the choice of treatment should be based on the individual's response to treatment and not the reported average response in the population.[30]

1.6.2 Risks of analgesic use

The potential benefits of analgesic use must be weighed against the risks. Analgesics, and in particular the opioids and NSAIDs, are associated with several potential serious adverse effects and drug interactions. Briefly, NSAID use increases the risk of cardiovascular disease (CVD), including myocardial infarction and stroke, heart failure, kidney failure and gastrointestinal bleeding.[31-35] Although the adverse effects of NSAIDs seem to be a group effect, individual differences between the substances exist, depending on the degree of selectivity of COX-1 or COX-2. Gastrointestinal adverse effects are most strongly associated with COX-1 selective NSAIDs, including naproxen, although all NSAIDs, including COX-2 inhibitors, increase the risk of upper gastrointestinal complications.[31] The risk of CVD is

particularly associated with the COX-2 inhibitors, but diclofenac is comparable in terms of risk, while naproxen is associated with the lowest relative risk.[31,34] Regarding analgesic doses of NSAIDs there seems to be a plateau for the effectiveness, while the risk of adverse effects generally increases with dose without any ceiling effect.[36] NSAIDs are furthermore associated with a range of drug interactions, with the most noteworthy potential pharmacodynamic interactions involving angiotensin converting enzyme (ACE) inhibitors/angiotensin II (AT II) antagonists (renal insufficiency), other antihypertensives (antagonized effect), anticoagulants (bleeding), and selective serotonin reuptake inhibitors (SSRIs) and oral glucocorticoids (bleeding).[37(pp249-53),38]

Common, important adverse effects of the opioids include respiratory depression, nausea, vomiting and constipation. Opioid use may lead to tolerance development, physical and psychological dependence, as well as opioid-induced hyperalgesia (OIH; more in section 1.14).[3(pp519-23),37(pp5-6)] Concurrent use of opioids with other CNS depressant drugs, e.g., benzodiazepines, increases the risk of accidents, e.g., falls or car accidents, sedation and respiratory depression.[39]

Paracetamol is considered acceptable safe in recommended doses. However, among individuals with hepatic dysfunction therapeutic doses may lead to aggravated dysfunction and possible hepatic failure. Supratherapeutic doses of paracetamol are hepatotoxic and may cause severe liver injury.[37(pp200-19)] Paracetamol use is furthermore linked to possibly increased blood pressure and risk of CVD.[37(pp200-19),40]

1.7 LITERATURE SEARCH

The literature search was conducted mainly in PubMed, with additional searches in Embase and Google Scholar (final search date January 30, 2016). As the literature on analgesics is extensive, I have chosen to limit the following literature review mainly to pharmacoepidemiological studies on analgesic use in a general, predominantly adult population and/or with topics similar to this dissertation. This is presented in tables (Table 1-3) or in relevant text, while selected studies published after the planning of this research project (autumn 2012) are discussed in relationship to the results in the discussion section.

1.8 SALES OF ANALGESICS

The sales of analgesics has had an increasing trend over the last decades in the Nordic countries[41-45] but also in other Western countries.[46,47] Denmark has historically had the highest sales of the Nordic countries and is still on the top today, while Norway has been (1988) and still is at the bottom.[41,43] Between 2002 and 2006 the sales of opioids increased in the Nordic countries (except Sweden),[48] while opioid consumption in Denmark increased with more than 600% from 1984 to 2002.[29] While Denmark has had a decline in analgesic sales over the last 10 years (2005-13), the sales has increased in the other Nordic countries (2005-14).[43] Selected events that may have affected the availability and sales in Norway over the last decades is shown in Figure 2.

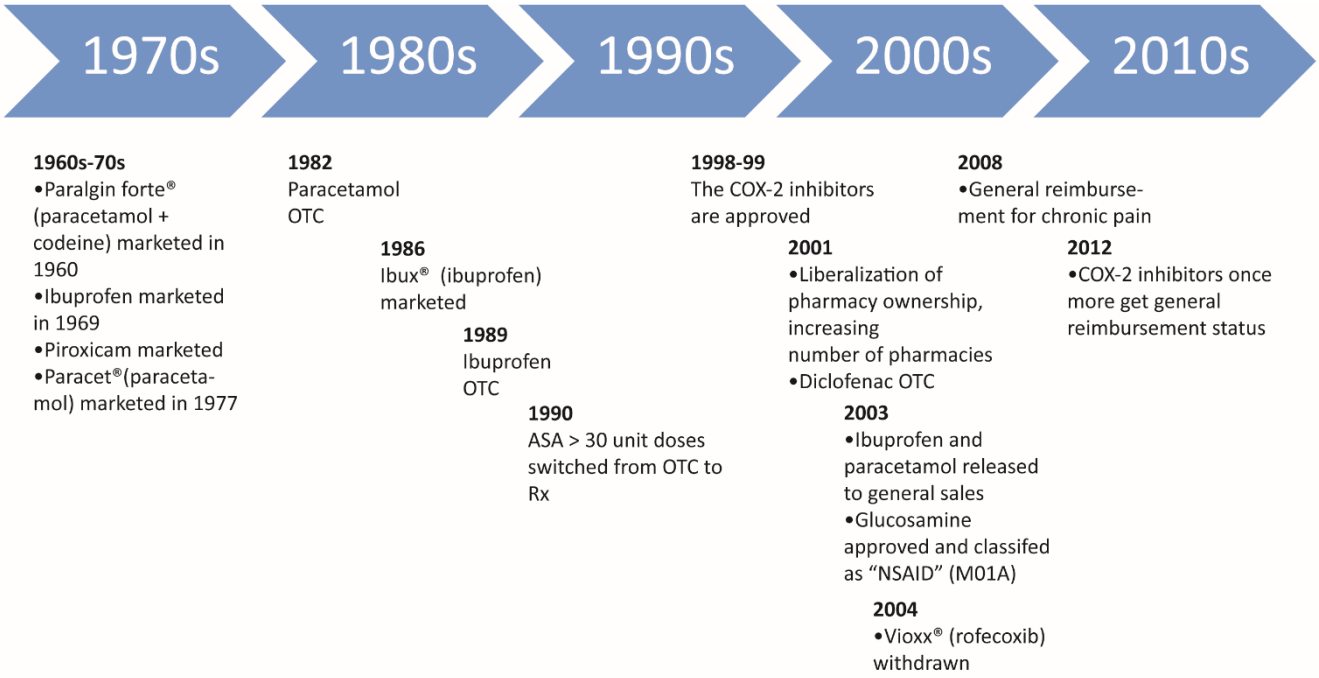

Figure 2 Time line of important events in relationship to analgesic use in Norway. ASA: acetylsalicylic acid, COX-2 inhibitors: cyclooxygenase 2 inhibitors or coxibs, NSAIDs: non-steroidal anti-inflammatory drugs, OTC: non-prescription, Rx: prescription, *Sources: Hawkey[1], weifa.no and personal communication, Solveig Sakshaug, Norwegian Institute of Public Health.*

The defined daily dose (DDD) is "the assumed average maintenance dose per day for a drug used for its main indication in adults".[7] The total sales of analgesics in Norway was around 100 DDD/1,000/day in 2014.[45] This suggests that, on average, approximately 10% of the population uses one DDD of an analgesic per day. The consumption statistics are useful for monitoring overall trends in drug use in the population and for comparison between countries. However, the consumption statistics provide a measure of drugs sold and may deviate from recommended dose, prescribed daily dose or actual use.[7] Furthermore, the consumption

statistics provide aggregated data and not individual data. For example, an increase in sales of analgesics may be due to increased prevalence, more intensive treatment, or a combination of both, or changes in stockpiling/amount discarded. Finally, sales statistics, not being individual-level data, cannot provide insight into risk factors or subgroups.

1.9 PREVALENCE OF ANALGESIC USE

As shown in Tables 1-3, the definition of analgesic use and the composition of the study population, e.g., the age- and sex-distribution, vary largely between different studies. This makes a direct comparison of prevalence measures between different studies challenging. Nevertheless, Nordic studies with comparable definitions of use and based on data from the end of the 80s[49-51] and the mid-90s[52] report a prevalence of 28-42% among women and 13-27% among men; the prevalence of OTC use is higher than Rx use (30-37% vs. 12-13% among women).[53,54] Paulose-Ram et al. report a prevalence of prescription analgesic use of 9% and OTC analgesic use of 87% in the USA (data from ~1990),[55], suggesting large differences in analgesic use between the Nordic countries and the USA. A Scottish study reports a prevalence of OTC analgesic use of 37% in 2002.[56]

1.10 TRENDS IN ANALGESIC USE

The number of prescription analgesic users in Denmark increased by 10% from 2002 to 2004[42], the prevalence of prescription NSAID use in Denmark and Finland increased slightly from 1997 to the early 2000s,[11,57] while the prevalence of opioid use in Norway increased by 9% in 2004-07.[58] The one-year period prevalence of prescription analgesic use (including glucosamine) in Norway was slightly higher in 2012 compared to 2004 (23.4% vs. 22.9%).[59(search:Mar8'16)] In all, these studies on individual analgesic groups and the sales statistics suggest an increasing use of analgesics (at least in the Nordic countries). However, there is a paucity of studies on the overall trend in analgesic use, which also include the use of OTC analgesics.

Table 1: Pharmacoepidemiological studies of prevalence and trends in analgesic use in the general population

Author #1	Year	Title	Definition	Population	Prevalence	Selected findings
Ahonen R	1991	Use of analgesics in a rural Finnish population. [ABSTRACT][60]	RX: Current OTC: Use last week	Finnish farmers (*n* = 12,056)	NA	Risk factors: Pain, chronic morbidity, frequent use of physician service, psychoneurotic symptoms, female sex
Ahonen R	1991	Consumption of analgesics and anti-inflammatory drugs in the Nordic countries between 1978-1988.[41]	N02/M01 (OTC/Rx) Sales in DDD/1,000/day	The total populations in the Nordic countries		Increased 15-42% 1978-88 Lowest consumption in Norway (1988: 61 DDD/1,000/day)
Eggen AE	1993	The Tromso study: frequency and predicting factors of analgesic drug use in a free-living population (12-56 years).[50]	OTC/Rx Use last two weeks	Age 12-56 years (*n* = 19,137)	W: 28% M: 13%	Risk factors: Headache, infections, depression/sleeplessness
Eggen AE	1994	Use of codeine analgesics in a general population. A Norwegian study of moderately strong analgesics.[61]	Codeine (Rx) One-year period prevalence	Age 10-99 years (*n* = 5,306)	W: 9% M: 7%	
Antonov K	1996	Use of analgesics in Sweden - the importance of sociodemographic factors, physical fitness, health and health-related factors, and working conditions.[49]	OTC/Rx Use last two weeks	Age 16+ years (*n* = 13,295)	Total: 35% W: 42% M: 27%	Risk factors: Decreasing age (in multiple regression), female sex, lifestyle, sleeping problems, health care utilization
Eggen AE	1996	The use of controlled analgesics in a general population (15-59 years)- the influence of age, gender, morbidity, lifestyle and sociodemographic factors.[62]	Opioids (Rx) One-year period prevalence	Age 15-59 years (*n* = 18,781)	W: 10% M: 8%	Risk factors: Poor self-reported health, headache, previous use of analgesics/psychotropics, low education level, daily smoking
Furu K	1997	Legal drug use in a general population: Association with gender, morbidity, health care utilization, and lifestyle characteristics.[51]	OTC/Rx Use last two weeks	Age 20-59 years (*n* = 15,986)	W: 32% M: 17%	
Antonov KI	1998	Prescription and nonprescription analgesic use in Sweden.[53]	OTC/Rx Use last two weeks	Age 18-84 years (*n* = 11,996)	W, Rx: 12% W, OTC: 30% M, Rx: 7% M, OTC: 20%	Risk factors: Headache, musculoskeletal pain, poor self-reported health (Rx), smoking, alcohol use (W), poor physical function (Rx)
Furu K	2001	Validity of questions in the use of specific drug-groups in health surveys.[54]	OTC/Rx Use last two weeks	Age 20-79 years (*n* = 6,702)	W, Rx: 13% W, OTC: 37% M, Rx: 8% M, OTC: 20%	30% of Rx users were daily users
Curhan GC	2002	Frequency of use of acetaminophen, nonsteroidal anti-inflammatory drugs, and aspirin in US women.[63]	Paracetamol/ASA/NSAIDs (OTC/Rx) Regular medication past two years	Women, aged 33-77 years (*n* = 179,987)	Paracetamol: >20% NSAIDs: 42% ≤51 years	
Isacson D	2002	Epidemiology of analgesic use: a gender perspective.[52]	OTC/Rx Use last two weeks	Age 20-84 years (*n* = 5,404)	W: 35% M: 21%	Risk factors (of sex difference): Different types of pain and ache, pain severity

Table 1: Pharmacoepidemiological studies of prevalence and trends in analgesic use in the general population (cont.)

Author #1	Year	Title	Definition	Population	Prevalence	Selected findings
Paulose-Ram R	2003	Prescription and non-prescription analgesic use among the US adult population: results from the third National health and nutrition examination survey (NHANES III).[55]	OTC/Rx Use last month	Age 17+ years (*n* = 20,050)	W, Rx: 11% W, OTC: 81% M, Rx: 7% M, OTC: 71%	↑ Women OTC: ↓ Age Rx: ↑ Age
Motola D	2004	Pattern of NSAID use in the Italian general population: a questionnaire-based survey.[64]	NSAIDs (OTC/Rx) Use last week Chronic use: Daily or frequent use > 6 months	Age 18+ years (*n* = 2,738)	23% Chronic use: 4%	↓ Age Risk factors: Female sex, unspecified pain, musculoskeletal disorder Chronic use: Cardiovascular diseases, nervous system disorders
Diener HC	2005	Per-capita consumption of analgesics: a nine-country survey over 20 years.[46]	Sales in "standardized units" N02B			Generally increased 1986-2005 but large variations between countries (Sweden on top)
Rosenzweig M	2006	[The use of analgesics in Denmark, 2000-2004].[42]	Opioids/N02B/NSAIDs (OTC/Rx)	Total Danish population	2002-04: 10% increase in Rx users	Increase in RX sales, not OTC
Fosbøl EL	2008	The pattern of use of non-steroidal anti-inflammatory drugs (NSAIDs) from 1997 to 2005: a nationwide study on 4.6 million people.[11]	NSAIDs (Rx)	Age 10+ years	1997-2005: 15% → 17%	Risk factors: Female sex, increasing age, rheumatic disease, other analgesics
Garcia del Pozo J	2008	Trends in the consumption of opioid analgesics in Spain. Higher increases as fentanyl replaces morphine.[47]	Opioids (reimbursed Rx) Sales in DDD/1,000/day	Total population of Spain		1992-2006: 14-fold increase in sales
Hamunen K	2009	Trends in opioid consumption in the Nordic countries 2002-2006.[48]	Opioids Sales in DDD/1,000/day	The total populations in the Nordic countries		Increase, except Sweden
Fredheim OM	2010	Increasing use of opioids from 2004 to 2007 - pharmacoepidemiological data from a complete national prescription database in Norway.[58]	Opioids (Rx) One-year period prevalence	Total Norwegian population	2007:10% (2.8% of those for cancer pain)	4% of chronic non-cancer pain patients >400 DDDs/year 2004-07: 9% increase
Mijatovic V	2011	Consumption of non-steroidal anti-inflammatory drugs in Serbia: a comparison with Croatia and Denmark during 2005-2008.[65]	NSAIDs (Rx) Sales in DDD/1,000/day	Total populations of Serbia, Croatia and Denmark		Large differences between countries Decrease/stable
Duong M	2014	Usage patterns of 'over-the-counter' vs. prescription-strength nonsteroidal anti-inflammatory drugs in France.[13]	NSAIDs Reimbursed dispensings (includes OTC)	Age 10+ years, salaried workers (*n* = 526,108)	2009-10: ≈20% (OTC/Rx)	OTC users younger than Rx users OTC users more often female than Rx users Chronic comorbidities: 19% of OTC users 28% of Rx users

Table 1: Pharmacoepidemiological studies of prevalence and trends in analgesic use in the general population (cont.)

Author #1	Year	Title	Definition	Population	Prevalence	Selected findings
Neutel CI	2014	Trends in prescription of strong opioids for 41-80 year old Norwegians, 2005-2010.[66]	Only strong opioids (Rx) One-year period prevalence	Age 41-80 years (whole population)	2005-10: 0.86% →1.33% (56% increase)	20% received more than one type of opioid annually DDD per prescription did not change substantially
Schmidt M	2014	Potential of prescription registries to capture individual-level use of aspirin and other nonsteroidal anti-inflammatory drugs in Denmark: trends in utilization 1999-2012.[12]	NSAIDs (OTC/Rx) One-year period prevalence Sales in DDD/1,000/day	Age 15+ years Total Danish population	1999-2004: 14% → 15% 2004-12: → 13%	↑ Women Use of coxibs almost ceased, while diclofenac use halved since 2008
Zin CS	2014	Changes in trends and pattern of strong opioid prescribing in primary care.[67]	Strong opioids (Rx) Annual number of prescriptions DDD/1,000/day	Age 18-107 years (*n* = 5,404)	2000-10: 0.18% → 0.92%	12% of prescriptions issued with or following cancer diagnosis Greater increase in number of prescriptions than users
Dale O	2015	Prevalence of use of non-prescription analgesics in the Norwegian HUNT3 population: Impact of gender, age, exercise and prescription of opioids.[68]	Paracetamol/NSAIDs/ASA (OTC) Use at least once a week in the last month	Age 20+ years (*n* = 41,204)	47% Paracetamol: 38% NSAIDs: 19% ASA: 8%	NSAIDs: ↓ Age ASA: ↑ Age Paracetamol: - Age Risk factors (daily use): Female sex, increasing age, low physical activity, headache, increasing pain intensity
Frenk SM	2015	Prescription opioid analgesic use among adults: United States, 1999-2012.[69]	Opioids (Rx) Past 30 days	Age 20+ years	1999-2006: 5% → 7%, thereafter stable to 2012	↑ Women
Ruscitto A	2015	Changes in opioid and other analgesic use 1995-2010: repeated cross-sectional analysis of dispensed prescribing for a large geographical population in Scotland.[70]	Any analgesic use (includes topical NSAIDs and gabapentinoids, Rx) Dispensed analgesic within 84 days preceding index date	Age 20+ years (*n* = 301,020 and *n* = 311,881)	1995-2010: 16% → 18% (RR = 1.09)	Paracetamol, opioids and gabapentinoids increased, the rest decreased 18-fold increase in strong opioids Use of multiple analgesic classes increased
Sarganas G	2015	Prevalence, trends, patterns and associations of analgesic use in Germany.[71]	ASA/Diclofenac/Ibuprofen/Paracetamol/Naproxen (OTC/Rx) Use last 7 days	Age 18-79 years (*n* = 7,099 and *n* = 7,091)	1998-2011: 19% → 21%	Increase due to OTC analgesics only: 10% → 12% Rx use remained constant Risk factors: Female sex, smoking, obesity with medium/high socioeconomic status (Rx), low physical activity level

M: men, NA: not applicable/not available, W: Women

Table 2 Pharmacoepidemiological studies of persistent or regular analgesic use in the general population

Author #1	Year	Title	Definition	Population	Prevalence	Selected findings
Helin-Salmivaara A	2003	Heavy users of non-steroidal anti-inflammatory drugs: a nationwide prescription database study in Finland.[57]	NSAIDs (Rx) Heavy use: ≥ 182 DDDs/year Reimbursed prescriptions only	All ages (*n* = 500,000)	1.5% in 2000 1997-2000: Relatively stable (18% → 19%)	Risk factors: Female sex, increasing age
Paulose-Ram R	2005	Frequent monthly use of selected non-prescription and prescription non-narcotic analgesics among U.S. adults.[8]	Non-opioids (OTC/Rx) Frequent use: Nearly every day for a month	Age 20+ years (*n* = 4,880)	14% (currently) 20% (lifetime)	↑ Age Use ≥ 1 year: 46% of NSAID users 63% of paracetamol users
Turunen JH	2005	Frequent analgesic use at population level: prevalence and patterns of use.[72]	OTC/Rx Frequent use: Daily or a few times a week	Age 15-74 years (*n* = 4,542)	Rx only: 9% OTC only: 9% Both OTC & Rx: 5%	Risk factors: Increasing age (slightly), not working, lower education level, chronic diseases, low mood, longer pain duration, more severe pain, more frequent pain
Eriksen J	2006	Critical issues on opioids in chronic non-cancer pain: an epidemiological[29]	Opioids Positive response to continuous or regular use	Age 20+ years (*n* = 10,066)	Non-opioids: 9% Opioids: 3%	Risk factors: Moderate/sever pain, poor self-reported health, unemployment, higher use of health care system
Hudson TJ	2008	Epidemiology of regular prescribed opioid use: results from a national, population-based survey.[73]	Opioids (Rx) Regular use: At least several times a week for a month or more	Age 20+ years (*n* = 7,909)	2%	No sex difference Risk factors: Painful condition (arthritis, chronic back problems, migraine/chronic headache), high pain interference, lower health status
Parsells Kelly J	2008	Prevalence and characteristics of opioid use in the US adult population.[74]	Opioids (Rx) Regular use: ≥ 5 days per week for ≥ 4 weeks	Age 18+ years (*n* = 19,150)	2%	Risk factors: Increasing age, female sex, lower education level One fifth of users used opioids regularly for ≥ 5 years
Von Korff M	2008	De facto long-term opioid therapy for noncancer pain.[75]	Opioids (Rx) Long-term use: ≥ 90 days, ≥ 10 prescriptions, and/or ≥ 120 days supply	Age 18+ years	NA	≈ 5% of treatment episodes were long-term episodes with a mean duration ≈ 900 days
Boudreau D	2009	Trends in long-term opioid therapy for chronic non-cancer pain.[76]	Rx Opioids Long-term use: ≥ 90 days, ≥ 10 prescriptions, and/or ≥ 120 days supply	Age 18+ years	≈ 4-5% (one-year period prevalence)	Incidence: ≈ 9-12/1,000/year
Hargreave M	2010	Factors associated with a continuous regular analgesic use - a population-based study of more than 45,000 Danish women and men 18-45 years of age.[77]	Paracetamol/Ibuprofen/ASA (OTC/Rx) ≥ 7 tablets per month during last year	Age 18-45 years (*n* = 45,279)	W: 27% M: 18%	Risk factors: Female sex, increasing age, poor self-rated health or fitness, smoking, lower education level (W), nulliparity (W), overweight (W), binge drinking (W), abstinence (W), underweight (M), marital status (M)

Table 2 Pharmacoepidemiological studies of persistent or regular analgesic use in the general population (cont.)

Author #1	Year	Title	Definition	Population	Prevalence	Selected findings
Svendsen K	2012	Differential patterns of opioid use: defining persistent opioid use in a prescription database.[14]	Opioids (Rx) > 180 DDD or > 4,500 mg OMEQ, and at least three quarters of a year	Total Norwegian population	1%	Cancer patients excluded ↑ Women
Fredheim OM	2013	A pharmacoepidemiological cohort study of subjects starting strong opioids for nonmalignant pain: a study from the Norwegian Prescription Database.[78]	Opioids (Rx) Long-term users: Dispensed a second prescription within 70 days and dispensed an opioid in each year of the study period	Total Norwegian population	NA	Cancer patients excluded Risk factors: Age > 60 years, past use of weak opioids The mean DDD increased in the study period
Fredheim OM	2014	Chronic pain and use of opioids: a population-based pharmacoepidemiological study from the Norwegian Prescription Database and the Nord-Trondelag Health Study.[79]	Opioids (Rx) > 180 DDD or > 4500 mg OMEQ, and at least three quarters of the year	Age 20+ years (*n* = 45,837)	1%	Cancer patients excluded Risk factors (of future persistent use): Occasional use, benzodiazepine use, physical inactivity, strong pain intensity, polypharmacy
Svendsen K	2014	Persistent opioid use and socio-economic factors: a population-based study in Norway.[80]	> 365 DDD or > 18,000 mg OMEQ, in all quarters of the year	Age 35+ years, Norwegian population	0.6%	Cancer patients excluded Risk factors: Disability pension, divorced/separated, lower education level, unemployment, low income
Zhou Y	2014	Trends in the use of aspirin and nonsteroidal anti-inflammatory drugs in the general U.S. population.[81]	ASA/NSAIDs (OTC/Rx) Regular use: ≥ 3 times per week for the last 3 months	Age 18+ years (*n* = 31,428 and *n* = 27,157)	ASA: 12% → 19% NSAIDs: 9% → 13%	↑ Women ↑ Age (reversed U shape) ↑ Severe headache/migraine

M: men, NA: not applicable/not available, W: Women

Table 3: Pharmacoepidemiological studies of high-risk analgesic use in the general population

Author #1	Year	Title	Definition	Population	Prevalence	Selected findings
Sihvo	2000	Frequency of daily over-the-counter drug use and potential clinically significant over-the-counter-prescription drug interactions in the Finnish adult population.[82]	OTC Continuous (daily or almost daily) or temporary use last two days	Age 16+ years (*n* = 10,477)	Analgesics: 4% NSAIDs: 4%	Interactions (with beta-blockers, diuretics, ACE inhibitors, % of users): Ketoprofen: 15% Ibuprofen: 10% ASA: 6%
Helin-Salmivaara A	2005	Frequent prescribing of drugs with potential gastrointestinal toxicity among continuous users of non-steroidal anti-inflammatory drugs.[83]	NSAIDs (Rx) Continuous use: ≥ 182 DDDs/year	Nested case-control study in a systematic sample of the Finnish population (*n* = 7,652 cases)	NA	14.5% concurrent use (increased bleeding risk) Odds ratio (OR) drugs increasing GI bleeding risk: 5.2 (ref. non-continuous use)
Porteous T	2005	How and why are non-prescription analgesics used in Scotland?[56]	OTC Use last two weeks General use	Age 18+ years (*n* = 1,501)	37%	Possible inappropriate use: 21% of users Contraindications (diseases): 9% Drug-drug interactions: 3% Risk factors: Decreasing age. female sex, higher education
Wilcox CM	2005	Patterns of use and public perception of over-the-counter pain relievers: focus on nonsteroidal anti-inflammatory drugs.[84]	NSAIDs (OTC/Rx) At least 2 x 5 days use last 12 months	Age 18+ years (*n* = 9,062)	17%	54% of NSAID users unaware of side effects 26 % of OTC only users exceeded the recommended dose 8 % of Rx users exceeded the prescribed dose
Silvani MC	2006	Gastro-intestinal problems and concomitant medication in NSAID users: additional findings from a questionnaire-based survey in Italy.[85]	NSAIDs (OTC/Rx) Use last week Chronic use: Daily or frequent use > 6 months	Age 18+ years (*n* = 2,738)	23%	NSAID use among those reporting dyspepsia/ulcer: 24% occasional, 6% chronic Use of more than one NSAID: 16% of users Glucocorticoids/SSRI: ≈18% NSAID use Anticoagulants: ≈6% NSAID use
Adams R	2011	Cause for concern in the use of non-steroidal anti-inflammatory medications in the community - a population-based study.[86]	NSAIDs (OTC/Rx) Current use	Age 18+ years (*n* = 3,175)	11% W: 13% M: 10%	NSAID use: Hypertension: 16% Chronic kidney disease: 16% CVD: 20% ACE-inhibitors: 12%
Stosic R	2011	Responsible self-medication: perceived risks and benefits of over-the-counter analgesic use.[87]	Paracetamol/NSAIDs (OTC) Once or more per month (regular use)	Age 18+ years (*n* = 1,901 and *n* = 2,209)	2001-09: 67% → 55% Once a year: 85%	2009: 96% used paracetamol appropriately 69% used NSAIDs appropriately 3% used more than max. ibuprofen OTC dose (1200 mg) ↓ Age

Table 3: Pharmacoepidemiological studies of high-risk analgesic use in the general population (cont.)

Author #1	Year	Title	Definition	Population	Prevalence	Selected findings
Boudreau DM	2013	A survey of adult awareness and use of medicine containing acetaminophen.[88]	Paracetamol (OTC/Rx) Use last two weeks	Age 21-79 (*n* = 360, general population)	36%	1.1% of the general population exceed 4 g/day The majority did not identify paracetamol-containing drugs correctly
Koffeman AR	2014	High-risk use of over-the-counter non-steroidal anti-inflammatory drugs: a population-based cross-sectional study.[89]	NSAIDs (OTC) Use last four weeks	Age 18+ years (*n* = 118, general population and *n* = 264, high-risk patients)	General: 30% High-risk: 13%	Dosage exceeding maximum: Among 9% of users in the general population and 3% among high-risk users At least 10% NSAID use in the high-risk groups examined

M: men, NA: not applicable/not available, W: Women

1.11 PERSISTENT ANALGESIC USE

Although much is known about the use of analgesics in general, less attention has been given to long-term or persistent analgesic use. Table 2 summaries studies on persistent, high-intensity or regular use of analgesics. Most of the studies have focused on opioid use,[14,73-76] while a few studies have focused on frequent use in general or frequent use of non-opioid analgesics.[8,72,77] The majority of studies is based on self-reported data,[8,72-74,77] while a few utilize prescription databases.[14,57,75,76] The definitions of regular/frequent or persistent analgesic use varies widely and makes comparison of prevalence measures difficult. In the USA, the prevalence of self-reported opioid use during the last month is around 2%,[73,74] while the one-year period prevalence of persistent opioid use is 4-5%.[75] A Norwegian study based on the total population reports a point prevalence of persistent opioid use of 1.1%, in the widest definition.[14] In Finland, the one-year period prevalence of heavy NSAID use (≥ 182 DDD/year) is reported to be 1.5%.[57] Finally, two studies report a prevalence of self-reported regular use of non-opioids ~20%[8,77], with the Danish study reporting a prevalence of 27% among women and 18% among men.[77] To our knowledge no study utilizes prescription databases to study persistent analgesic use in general, i.e., including all the major analgesic groups (NSAIDs, opioids and paracetamol).

1.12 HIGH-RISK USE OF ANALGESICS

Studies on high-risk use of analgesics, i.e., use in the presence of contraindications, potential drug interactions, or high risk of adverse effects in the general adult population are summarized in Table 3. The majority of the studies focus on NSAID use and OTC analgesics. Porteous et al. report possible inappropriate use among 21% of OTC analgesic users in Scotland.[56] In a study by Wilcox et al., more than half of NSAID users were unaware of adverse effects, while one quarter of users of OTC NSAIDs only used more than the recommended dose.[84] Silvani et al. report that almost one third of those reporting dyspepsia/heartburn or gastrointestinal (GI) ulcer report NSAID use, 16% of users use more than one NSAID, and that NSAIDs are frequently used concomitantly with potential interacting drugs.[85] Adams et al. report that 69% of NSAID users had one or more contraindications, e.g., CVD, chronic kidney disease (CKD), hypertension.[86] An Australian study found a decrease in appropriate use, i.e., use in the absence of contraindications or drug interactions, after OTC ibuprofen was released to general sales.[87]

1.13 RISK FACTORS FOR ANALGESIC USE

In this dissertation I define «risk factor» as a «characteristic associated with an increased probability of occurrence of an event or disease», without necessarily implying a causal relationship.[90] However, there is some ambiguity about this term in the literature. Porta defines a risk factor as being causally related to the outcome, a «risk marker» as a factor with a non-causal association, and "risk indicator" as a common term for both.[91] "Predictor" is often used in the same meaning as I use risk factor in this dissertation but I prefer to reserve predictor as a statistical term or for actual prediction studies. A whole range of risk factors for analgesic use has been reported in the literature. Here I only refer what seems to be the most important factors.

Pain is the obvious risk factor for analgesic use.[29,50,52,53,62,64,72,73,92] The measures of pain used in the studies on analgesic use vary largely and are mainly based on simple, self-reported, dichotomous measures. However, some studies have included measures of pain severity.[29,52,72,73,92] More intense pain, as recorded by the general practitioner (GP), increases the likelihood of being prescribed a stronger analgesic, although the GP's prescribing seems to be more influenced by the patient's previous use of analgesics than the pain intensity.[93] None of the aforementioned studies utilized experimental pain tests as a measure of pain.

Furthermore, as Antonov and Isacson point out, there may be factors other than pain explaining analgesic use.[49] Some of these factors are only important via pain, while others may exert an effect independent of pain.

Female sex is one of the most commonly reported risk factors for analgesic use, with studies based on both self-report and prescription databases showing a higher use among women.[11,14,49-53,55-57,61,62,64,74,77,92] In contrast, a few studies on regular/frequent analgesic use report no sex difference.[8,72,73]

Age is a risk factor for analgesic use, although large variations exist between different studies. The reported age trends seems to be mostly influenced by the prescription status, i.e., OTC, Rx or total use, frequency of use and analgesic type in question. Studies on analgesic use in general have shown conflicting age trends in the prevalence of use, with either a positive trend[49] or no or negative trend with increasing age.[50-52] Several studies report that OTC analgesic use decreases with age,[53,55,56,87] while an inverse trend is observed for Rx analgesics.[53,55] *Frequent* or *regular* use of OTC or Rx analgesics increases with age.[8,72,77] NSAID use in general is reported to both decrease[64] and increase with age,[86] Rx NSAID is

commonly used in all ages,[11] and increases with age in those without rheumatoid arthritis.[57] Opioid use increases with age.[61,62,74]

Other commonly risk factors for analgesic use include poor self-reported health,[29,49,53,56,62,73,77] and lower levels of education[62,72,74,77] Higher analgesic use among those with highest education has also been reported,[50,52] possibly explained by a relatively higher use of OTC analgesics among those with highest education.[56] Furthermore, analgesic use has been reported to be associated with poor mental health,[50,62,72] low levels of physical activity/fitness,[29,50,77] alcohol use and smoking,[50,62,77] and factors relating to work status, e.g., unemployment or disability pension.[29,72]

1.14 Pain sensitivity and analgesic use

In 2005, Edwards proposed the hypothesis that "individual differences in pain sensitivity and pain inhibition, which reflect natural variability in CNS pain processing, place individuals at reduced or elevated risk for the development of chronic pain (…)".[94] He suggested that the most pain sensitive individuals have a reduced endogenous pain inhibition and a greater risk of developing chronic pain, and that increased basal or inherent pain sensitivity may be a diathesis of chronic pain. Most chronic pain conditions are associated with dysfunctionality in the normal physiological pain processes.[3(p510)] The potential causal pathways between pain sensitivity and chronic pain are, however, not clear. On the one hand, increased pain sensitivity may be a consequence of chronic pain.[95] On the other hand, increased pain sensitivity may put people at risk of clinical pain.[19] Severe or untreated acute pain is a potential risk factor for development of chronic pain, possibly through sensitization of the CNS.[94] Highly pain sensitive subjects may experience more severe acute pain, with a consequently higher risk of chronic pain.[94] As an increased risk of pain would intuitively confer an increased risk of analgesic use, this suggests that highly pain sensitive subjects are more likely to use analgesics, i.e., increased pain sensitivity is a risk factor for analgesic use. However, it has been suggested that the efficacy of analgesics is reduced in highly pain sensitive subjects.[94] If this is true, increased pain sensitivity, as a marker of hampered endogenous pain inhibition, not only increases the risk of chronic pain but also reduces the efficacy of analgesics. As previously shown, the effectiveness or efficacy of classical analgesics in chronic pain seems limited. Analgesics exert their effect by "recruiting endogenous pain-inhibitory systems" (Figure 1),[94] the same systems that may be dysfunctional in highly pain sensitive subjects. Increased pain sensitivity may be a marker of

central sensitization and more centralized pain phenotypes.[96] This could suggest that the highly pain sensitive subjects represent a sub group with more centralized pain phenotypes, e.g., fibromyalgia, a sub group that responds poorly to classical analgesics.

To further add complexity to this matter, analgesic use may lead to a paradoxical increase in pain. Chronic opioid use may cause opioid-induced hyperalgesia (OIH), a state of increased pain sensitivity due to opioid use.[97-99] Common features of OIH include a generalized, ill-defined and diffuse pain, not necessarily located at the source of damage or disease,[97] an increase in pain intensity over time, widespread pain and increased pain sensitivity toward external stimuli.[99]

Several studies have been conducted on the association of preoperative pain sensitivity and postoperative pain, with some of the studies using analgesic use within the first days after surgery as a proxy measure of pain.[100] The results on analgesic use have been conflicting. Some studies found that suprathreshold heat pain was positively correlated with the amount of postoperative analgesic use, while other studies found a negative correlation between heat pain threshold or pressure pain tolerance and postoperative analgesic use. The low sample sizes, highly selected study populations and the focus on pain after surgery makes it hard to generalize these results into more general analgesic use in the general population.

In summary, there is a knowledge gap of the association between pain sensitivity, chronic pain and the use of analgesics. As far as we know, no studies on the association between pain sensitivity and analgesic use in the general population have been published.

2 PURPOSE AND AIMS

The purpose of this dissertation was to study the use of analgesics in a general population, including risk factors for use and characteristics of the users. This included the study of prevalence and frequency of use, change in use over time, use in the presence of contraindications and drug interactions, prevalence, incidence rate and risk factors for persistent use, and the importance of pain sensitivity for the use of analgesics.

The specific research questions were:

Paper I:

- What is the prevalence of self-reported analgesic use in the population and the change in use over time?
- What is the prevalence of regular analgesic use among subjects with contraindications or potential drug interactions?

Paper II:

- What is the prevalence and incidence rate of persistent analgesic use and what are the risk factors?
- What is the association between chronic pain, including different dimensions of chronic pain severity, and persistent analgesic use?

Paper III:

- Does pain sensitivity influence the use of analgesics?
- Adjusting for other factors, do more pain sensitive subjects use more analgesics than less pain sensitive subjects?
- Is increased pain sensitivity a risk factor for future persistent analgesic use?

3 MATERIALS AND METHODS

3.1 DATA SOURCES

3.1.1 The Tromsø Study

The Tromsø Study is an epidemiological, population-based study covering a broad range of health problems and diseases. So far, six waves, referred to as Tromsø 1-6, have been carried out between 1974 and 2008. The participants consist of inhabitants from the municipality of Tromsø, Norway.[101,102] The Tromsø Study has been extensively described in cohort profiles[101,102] and on the Tromsø Study home page, www.tromsostudy.com. This dissertation includes participants from Tromsø 5 (2001-02) and Tromsø 6 (2007-08). English translations of the full questionnaires are available from the home page, and relevant pages are included in the Appendix.

In Tromsø 5, carried out in 2001-02, participants from the second visit in Tromsø 4 (1994-95) were re-invited. Very briefly, those invited to the second visit of Tromsø 4 consisted of all men aged 55-74 years and women aged 50-74 years plus smaller random samples of the other age groups < 85 years.[102] Additionally, the eligible population in Tromsø 5 was extended with 1,916 subjects aged 30, 40, 45, 60 or 75 years. The attendance rate was higher in the group who had participated in Tromsø 4 (89 percent) compared to the rest (57 percent).[102] In total, 8,130 men and women aged 30-89 years attended Tromsø 5, with an attendance rate of 79% percent. Due to withdrawn consents, the available sample size was n = 8,039.

Tromsø 6 was conducted in 2007-08. Invited subjects included all inhabitants aged 40-42 years and 60-87 years (n = 12,578), a 10 % random sample aged 30-39 years (n = 1,056), a 40% random sample aged 43-59 years (n = 5787). Once more, participants of the second visit to Tromsø 4 were invited, if they were not already included in the groups mentioned above (n = 341).[101] In, total 12,984 men and women aged 30-87 years attended (66% attendance rate). Due to withdrawn consents, the available sample size was n = 12,981.

The participants of Tromsø 5 and 6 received a questionnaire (Q1) with the invitation around two weeks before they attended. At attendance, they were delivered a second questionnaire (Q2) which included follow-up questions to entry questions in Q1.[101]

The participants of Tromsø 6 underwent a health screening, including physical examinations, blood samples and measurement of pain sensitivity.[101] Furthermore, a subgroup were invited to a more extensive second examination, including morning urine samples. Those invited included first-visit participants aged 50-62 years or 75-84 years, a 20% random sample of those aged 63-74 years, and participants of the second visit in Tromsø 4 (< 75 years), if not already included.[102] The second visit occurred about four weeks after the first visit,[101] and this sub group (n = 7,307) was older than the total Tromsø 6 sample.

3.1.2 The Norwegian Prescription Database

The NorPD, established January 1, 2004, is a national registry of all prescriptions dispensed to individual patients from Norwegian pharmacies.[103] NorPD does not capture drugs dispensed in hospitals, nursing homes, or directly from the physician, or OTC drugs. Recorded information of relevance to the current project include the encrypted person-identifier (used for record linkage), number of packages dispensed, package size, administration form (tablets, capsules etc.), ATC code, number of dispensed DDDs, category of prescription, reimbursement codes and date of dispensing.[103]

3.2 CENTRAL VARIABLES

In the following section is a description of the analgesic use measures, i.e., outcome of interest, and a description of other variables used. This is, however, limited to central variables and/or where a more thorough explanation is called for. Other variables not presented here are defined and described in the respective papers.

3.2.1 Outcome variables: Analgesic use

Self-reported use of non-prescription and prescription analgesics (Paper I-III)

Self-reported use of OTC or Rx analgesics were measured by the questions: "How often have you during the last four weeks used the following medicines? Painkillers on prescription. Painkillers non-prescription", with the options not used/less than every week/every week, but not daily/daily. These questions were identical in Tromsø 5 and Tromsø 6. The variables were recoded to dichotomous measures of use (no/yes) last four weeks. Furthermore, we created mutually exclusive variables divided into those reporting no use, OTC analgesics only, Rx analgesics only and both OTC and Rx analgesics. Individuals with missing on either questions were excluded. These variables were used for the estimation of prevalence in the different

prescription categories, and in total (Paper I). In Paper II, we used a measure of daily/weekly OTC use, employing the original frequency variable.

Self-reported regular use of analgesics (Paper I & II)

In addition to the frequency question, participants in Tromsø 6 were asked to list all drugs, both OTC and Rx, used regularly the last four weeks. The drugs listed were coded according to the ATC-DDD 2007 version. Analgesics were defined as either NSAIDs, opioids or other analgesics and antipyretics (see section 1.3). Unfortunately, we were not able to compare this variable with the Tromsø 5 data due to differences in the questions used. In the context of high-risk use (Paper I), "paracetamol" includes the ATC codes N02BE01 and N02AA59 (paracetamol + codeine), the latter is otherwise classified as an opioid.

Self-reported analgesic use last 24 hours (Paper III)

At attendance, participants were interviewed about their use of analgesics the last 24 hours. Analgesic use last 24 hours was defined as a positive response to this question, regardless of the type of analgesic.

Persistent analgesic use (Paper II & III)

No universal definition of persistent analgesic use exists but we based our definition on an adaptation of previously published methods.[75,104,105]. Using the prescription registry data, we defined treatment episodes of analgesic use (Figure 3).[75] Consecutive analgesic prescriptions were said to belong to the same treatment episode if the time gap between the prescriptions was ≤ 180 days. Consequently, a treatment episode started if there were no analgesic prescriptions within the preceding 180 days and an analgesic prescription within the following 180 days. The prescription with no subsequent prescriptions in the following 180 days was defined as the last prescription of the treatment episode. If several prescriptions were dispensed on the same date they were collapsed into one, i.e., the DDDs were summed. The average daily dose was calculated as the cumulative number of DDDs dispensed from the first prescription to the second to last prescription, divided by the number of days between the first and last prescription.[104] The duration of the last prescription within a treatment episode was estimated as the number of DDDs dispensed divided by the average daily dose. The duration of the last prescription was limited to maximum 180 days. The duration of a treatment episode was the number of days between the first and last prescription plus the estimated duration of the last prescription. Individuals could have several treatment episodes within the study

period. To decide if a treatment episode with analgesics was a persistent treatment episode, we used proportion-of-days-covered (PDC) and the duration of the treatment episode. The PDC is a measure of the proportion of days within a time interval with an available supply of drugs,[106] or more specific to this context: the proportion of days within a treatment episode with one DDD of analgesics available. PDC was calculated as the cumulative number of DDDs within a treatment episode divided by the treatment duration of the episode.[105] We defined persistent treatment episodes as those with a duration ≥ 90 days and PDC ≥ 40%. We chose 90 days as a reflection of the Norwegian reimbursement system for drugs, in addition to the definition of chronic pain, i.e., pain with duration of three months or more. A bit simplified, reimbursement is given when the need for treatment amounts to at least three months per calendar year. Finally, we conducted a range of sensitivity analyses of the different dimensions used in the definition, i.e., gap between prescriptions, treatment duration and the PDC (see Supplement of Paper II).

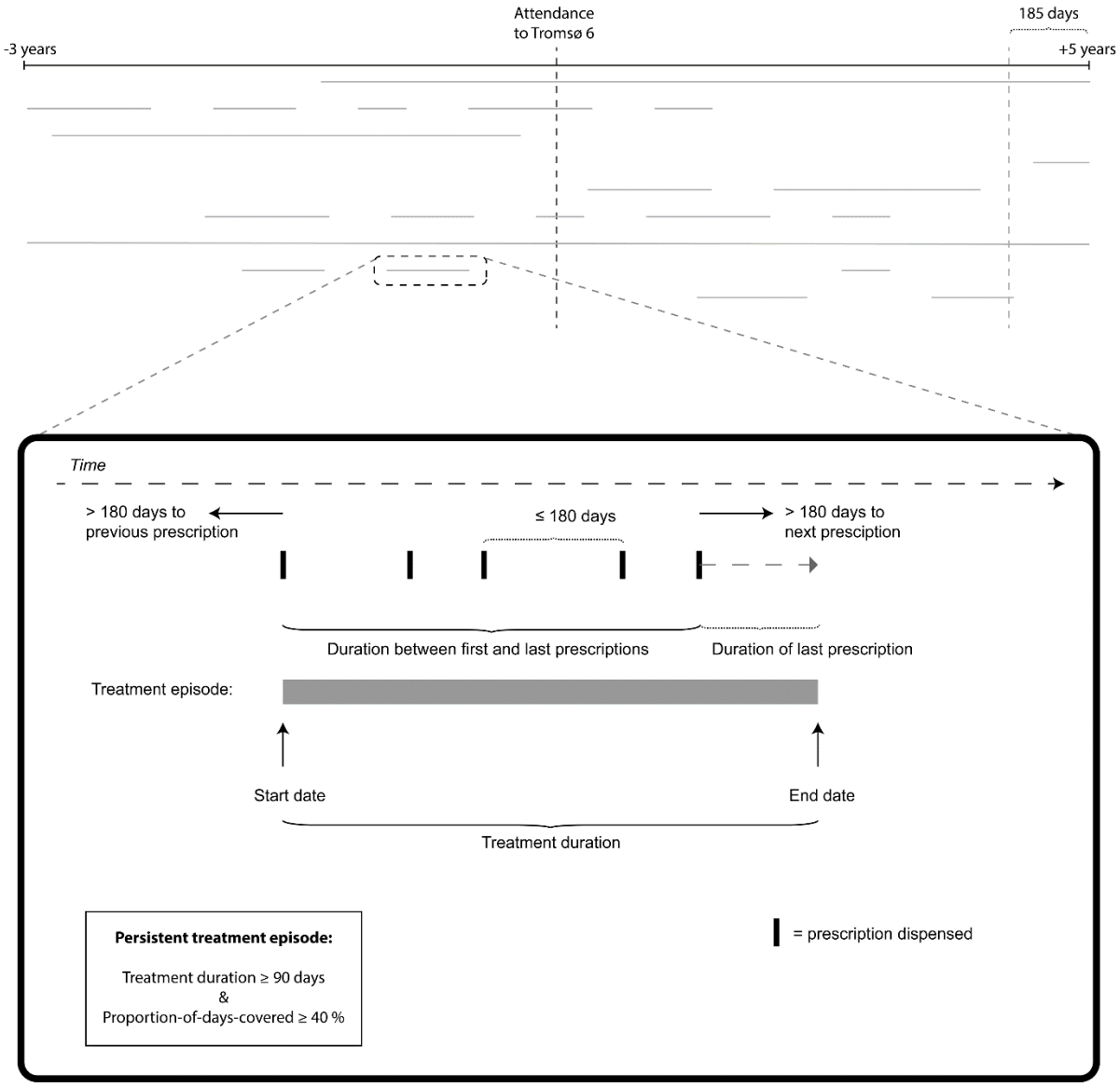

Figure 3 Definition of treatment episodes with analgesics and persistent analgesic use. The top part shows the treatment episodes in the study period, i.e., three years before to five years after attendance, illustrated as grey horizontal lines. An individual could have several treatment episodes. The zoomed in part shows the definition of treatment episodes: Vertical bars represent the date when prescriptions are dispensed. The treatment episode is illustrated by the grey area. Proportion-of-days-covered is calculated as the sum of defined daily doses (DDD) dispensed within a treatment episode divided by the duration of that treatment episode. Prevalent users: a persistent treatment episode includes the attendance date. Incident users: no persistent use in the three years before and including the attendance date, and the first persistent episode within the 4.5 year of follow-up (this analysis stops 185 days before the end of the study period).

3.2.2 Exposure variables/independent variables

Cardiovascular disease (Paper I)

Cardiovascular disease wad defined as a positive response on either of the questions on myocardial infarction, stroke or angina pectoris ("Do you have or have you had …"). Persons with missing on either of the questions were excluded. This group was defined as the secondary CVD risk group.

In an attempt to estimate the cardiovascular risk among those with no history of CVD, i.e., primary CVD risk, we used the NORRISK risk score, i.e., the Norwegian adaptation of the Systematic Coronary Risk Evaluation (SCORE) risk score.[107] The NORRISK score estimates the ten-year risk of fatal CVD, using sex, age, systolic blood pressure, total cholesterol and smoking, among persons aged 40-69 years. The calculated NORRISK score produced results that were similar to a previous report.[108] We restricted this analysis to those with no history of CVD (total n = 9,000), as defined above, i.e., this variable represents a sub group of subjects with no history of CVD, which was further stratified into subjects with or without high CVD risk. We used age stratified cut-offs for the NORRISK score to define high risk, as defined in a national guideline: 40–49 years: > 1%, 50–59 years: ≥ 5%, and 60–69 years: ≥ 10%.[109] We also considered using Framingham heart risk score[86] or SCORE.[107] However, we deemed the NORRISK score to be the most valid measure for our study population. NORRISK is also included in a national guideline distributed to physicians and is also available as an online risk calculator.[109]

Chronic kidney disease (Paper I)

Estimated glomerular filtration rate (eGFR) was estimated by the Chronic Kidney Disease Epidemiology collaboration (CKD-EPI) formula using serum creatinine, sex, age and ethnicity (assuming 100% "white or other").[110] Serum creatinine was available for n = 12,827 subjects. However, to produce a more valid measure of CKD, we also included data on albuminuria. Morning urine samples, including measurements of albuminuria, were collected in three consecutive days (n = 7,218) among those who attended the second visit.[101] Persistent microalbuminuria and albuminuria were defined as previously described.[111] CKD was defined as eGFR < 60 ml/min per 1.73 m^2 or ≥ 60 ml/min per 1.73 m^2 and either macroalbuminuria or persistent microalbuminuria. Due to missing in the variables, the final sample was n = 6,834. The results on CKD were generally consistent with a previous report from a similar Norwegian health survey.[111]

Gastrointestinal ulcer (Paper I)

Gastrointestinal ulcer was defined as a positive response to either of the questions on stomach ulcer, duodenal ulcer or ulcer surgery ("have you ever had …", missing excluded). As an additional measure, we included use of histamine H_2 antagonists (A02BA), misoprostol (A02BB) or proton pump inhibitors (A02BC) as a contraindication. The secondary measure was therefore a history of GI ulcer *and/or* the use of these drugs. This choice was motivated by a previous study, where use of "anti-reflux medications" were considered a relative contraindication toward NSAID use.[86]

Chronic pain (Paper I-III)

Chronic pain was assessed by the question in Q1 "Do you have persistent or constantly recurring pain that has lasted for three months or more?" Those who answered "yes" were invited to answer a section of follow-up questions in Q2. This included chronic pain duration (years, months), chronic pain frequency (daily/weekly/monthly/less than monthly), number of chronic pain body locations, and an 11-point numerical rating scale (NRS) for usual and maximal pain intensity.

In paper I, the chronic pain question was used as it was reported in Q1 (prevalence: 32.8%). However, several participants answered Q2 despite replying "no" to the entry question in Q1. To account for this discrepancy and to correct likely false negative and positive replies to the entry question, we used information from Q2 to recode the chronic pain variable in Paper II and III (as described in the Supplement of Paper II); those who reported no chronic pain in Q1 but a pain duration ≥ three months *and* maximal pain intensity > zero *and* pain frequency > less than once a month *and* at least one pain location were recoded to having chronic pain (n = 349). Conversely, those who reported chronic pain in Q1 but pain duration < three months *or* maximal pain intensity = zero *or* a frequency = less than once a month were recoded to having no chronic pain (n = 53). The recoding increased the prevalence of chronic pain to 35.0%. This choice was assessed by also using the original chronic pain variable in key analysis but this did not have a large impact on the results.

The different dimensions of chronic pain was coded as follows: Duration: no chronic pain, ≥ three months and < three years, ≥ 3 and < 10 years, ≥10 and < 20 years, and ≥ 20 years. Frequency: no chronic pain, less than daily, and daily. Usual and maximal pain intensity: no chronic pain, mild pain (NRS = 1-3), moderate pain (NRS = 4-6), and severe pain (NRS = 7-

10). Number of body locations: no chronic pain, one location, two to three locations, four to six locations, and seven or more locations.

Psychological distress (Paper I-III)

Hopkins Symptoms Checklist 10-item version (HSCL-10) is an instrument to measure psychological distress.[112] The instrument consists of ten items assessing symptoms of both anxiety and depression during the last week. Each item gets a score ranging from one (no complaint) to four (very much), while the average score of the ten times provides a measure of psychological distress. Missing values were replaced by the mean score of the item. However, if three or more items were missing, the whole score was set to missing. Psychological distress was defined as a HSCL-10 score above 1.85.[112]

Physical activity (Paper II-III)

Physical activity was assessed by several different questions in Tromsø 6. As a measure of physical activity, we used the frequency of exercise assessed by the question: "How often do you exercise (with exercise we mean for example walking, skiing, swimming or training/sports)?" This was categorized into never or less than weekly, once a week, two to three times a week, and approximately every day. The questions on leisure time physical activity, including the frequency of exercise, has previously been shown to be a reasonably valid measure of vigorous physical activity in a comparable health survey.[113]

Cold pressor test (Paper III)

In the CPT, participants submerged their dominant hand and wrist in circulating cold water and held it there as long as possible, up to a maximum of 106 s.[101,114] Before the test participants were screened, and those who were unwilling to participate, did not understand instructions, or had medical contraindications or risk of adverse effects were excluded.[115] Participants rated their pain intensity on NRS after four seconds and subsequently every nine seconds. Endurance time was recorded on hand-withdrawal. We used the CPT endurance time as measure of pain tolerance and a proxy measure of pain sensitivity.

The CPT equipment consisted of a Julabo FP40-HE water bath (Julabo Labortechnik GmbH, Germany) from which water was pumped to an external 13-L container, with a constant temperature of 3.0 °C and circulation speed of 22 L/min. The intentional sample included all participants attending the first visit in Tromsø 6 (n = 12,984). However, due to limitations on capacity some participants were not tested.[115] As a result, subjects < 60 years were prioritized,

due to the lower sampling rate for these age cohorts. Additionally, some subjects were excluded due to medical or technical reasons as described in Figure 6, creating an available sample for analysis of n = 10,486.

3.3 STUDY DESIGN

3.3.1 Paper I

We used the Tromsø 5 and Tromsø 6 study to analyze the change in self-reported analgesic use over time, while the analysis of prevalence of analgesic use in high-risk groups was conducted in the Tromsø 6 population (Figure 4). We considered several contraindications or drug interactions not reported in the paper, including: asthma, heart failure, reduced liver function, reduced lung function/chronic obstructive pulmonary disease, age ≥ 65 (implicitly done), medication overuse headache, pregnancy, addiction/misuse, and alcohol use. In regards to the drug interactions, we decided to focus on pharmacodynamic drug interactions and group effects.

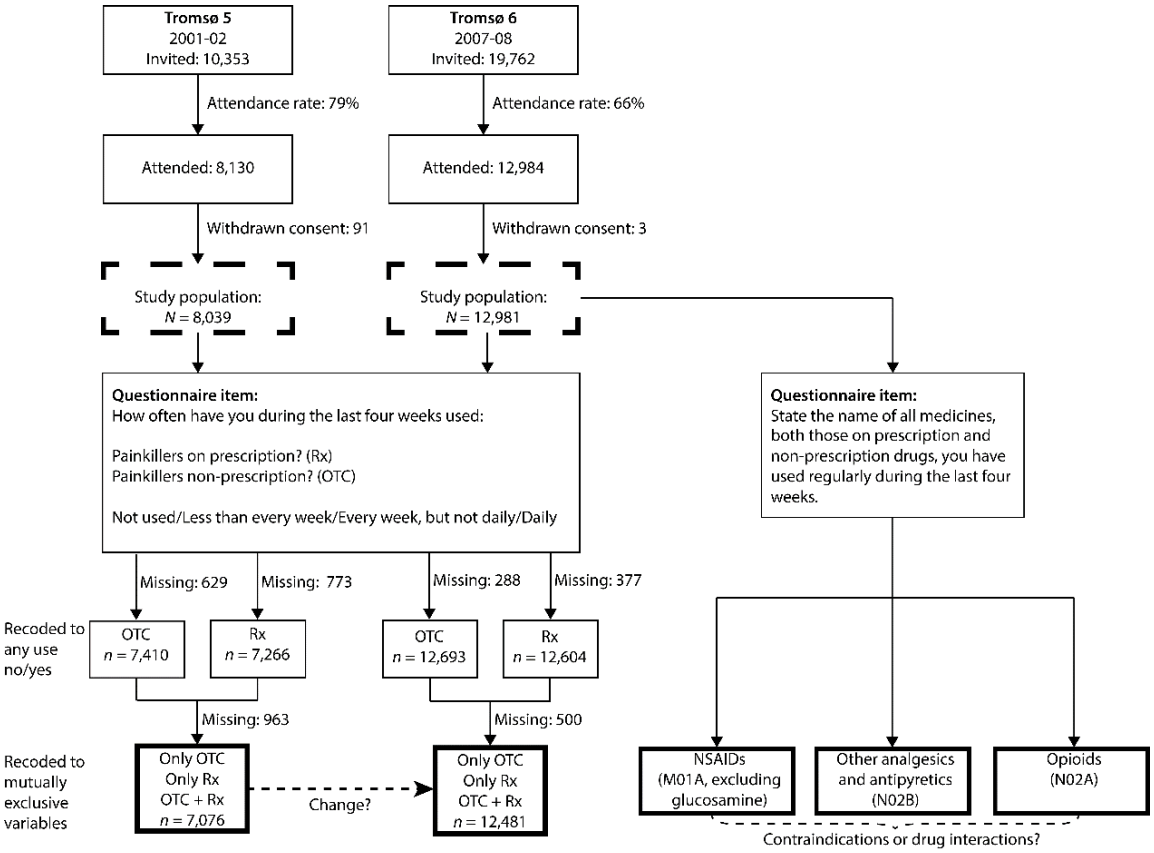

Figure 4 Flow chart of Paper I. From Samuelsen et al. (2015). Licensed under CC BY.

3.3.2 Paper II-III

For Paper II and III we linked the Tromsø 6 study with NorPD. Paper II and III generally had the same study design. We examined persistent analgesic use based on the aforementioned definition among all participants of the Tromsø 6 study (*n* = 12,981) within the range three years before to five years after attendance using NorPD (Figure 3 and Figure 5). We constructed a new cohort by excluding all those who had a persistent treatment episode of analgesics within the three years before (and including) the attendance date (*n* = 1,076). This cohort (*n* = 11,905) was followed for 4.5 years.

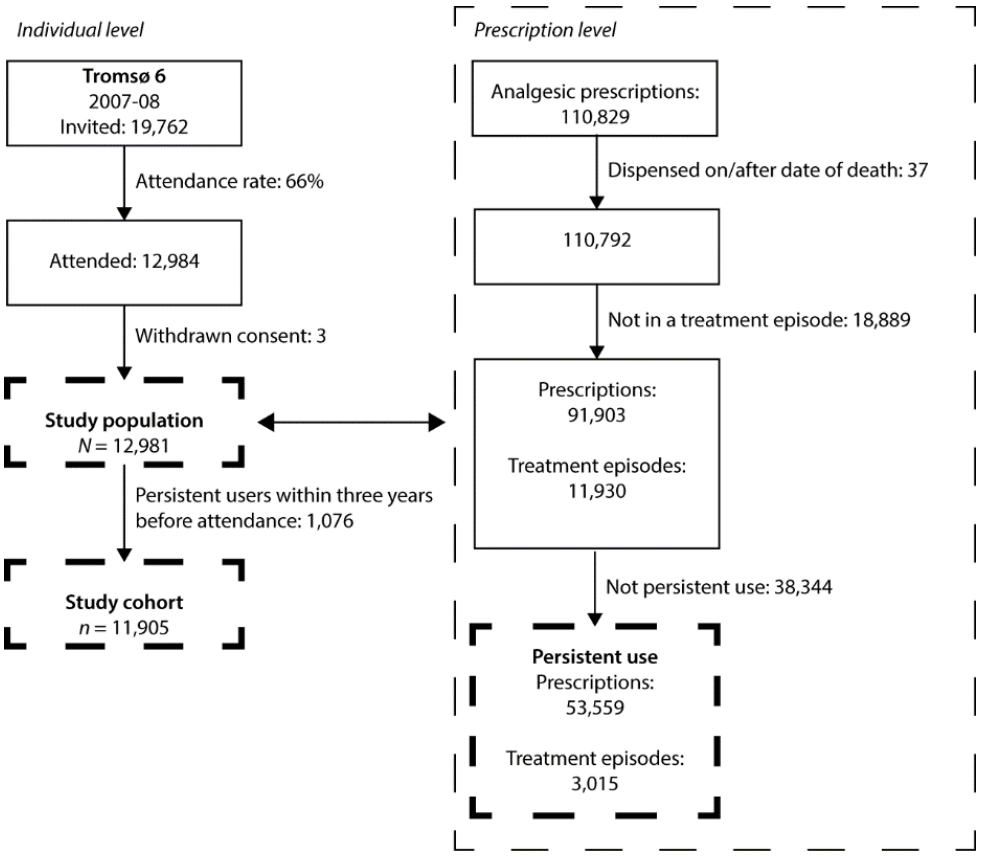

Figure 5 Flow chart of Paper II.

In paper III, we limited the study population to those who had complete CPT tolerance data (*n* = 10,486, Figure 6). The prospective study cohort consisted of 9,657 persons who were followed for 4.5 years. We analyzed the association between baseline pain sensitivity and future persistent analgesic use. In addition, we analyzed cross-sectional associations between pain sensitivity and different measures of analgesic use, including persistent analgesic use, at attendance.

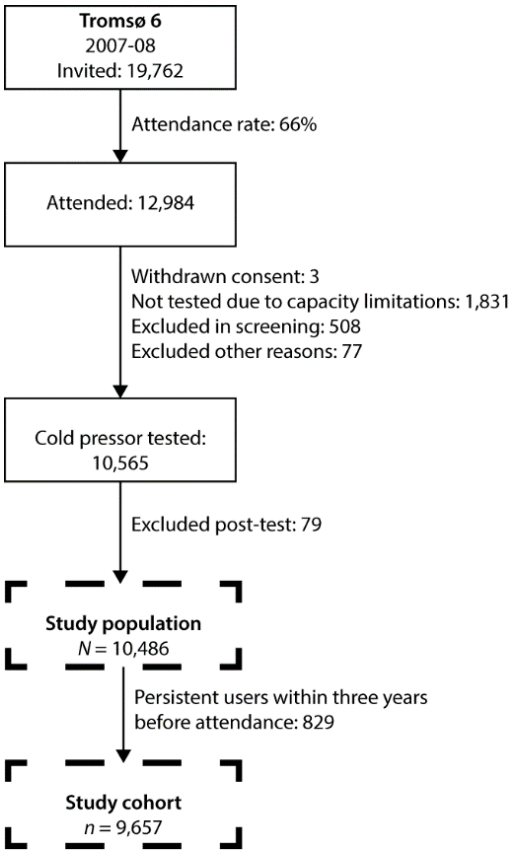

Figure 6 Flow chart of Paper III. Excluded other reasons: Technical error, medical reasons, lack of comprehension, etc. Excluded post-test: Technical error, lack of comprehension, etc.

3.4 DIRECTED ACYCLIC GRAPHS

We employed, directed acyclic graphs (DAGs) for variable specification and model selection in paper II and paper III.[116(pp175-9)] The variables were selected based on the literature and plausibility. An example from paper II is shown in Figure 7.

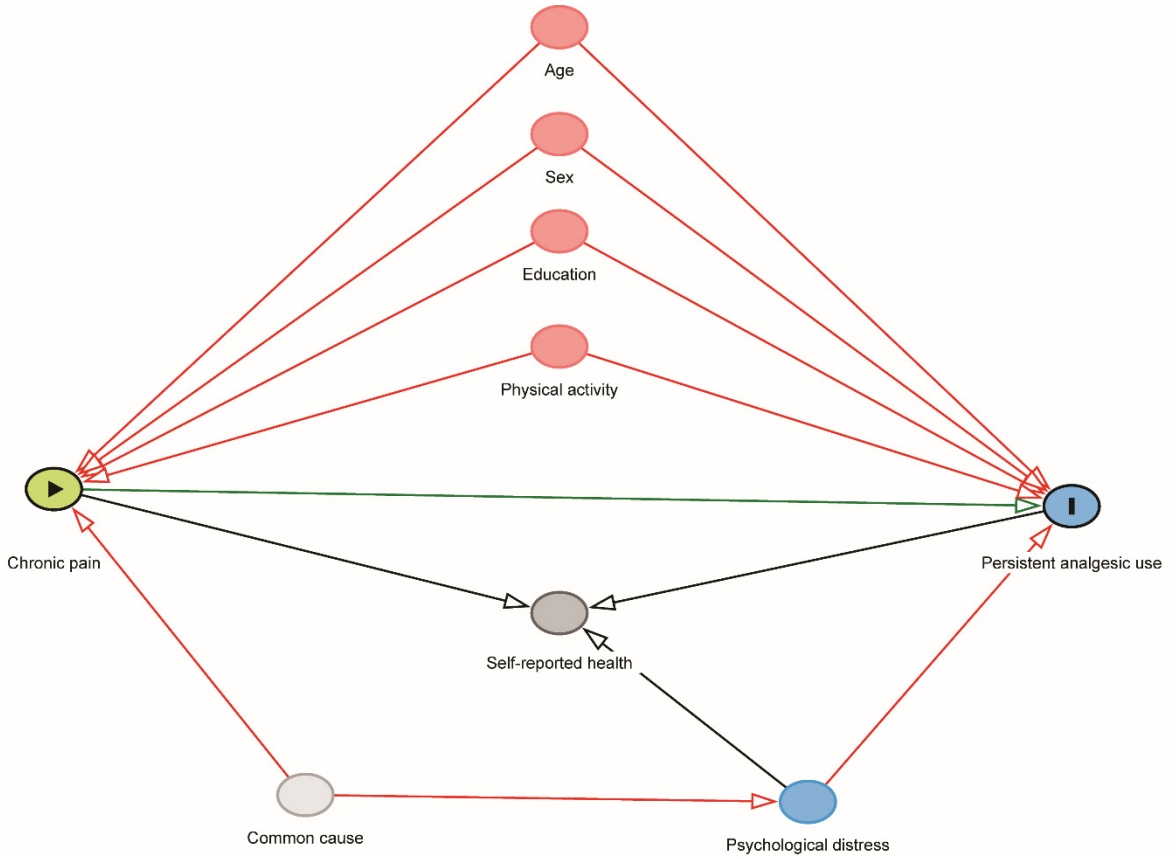

Figure 7 Directed acyclic graph (DAG) of the association of chronic pain with persistent analgesic use and the multiple regression model used in the analysis. Age, sex, education, psychological distress and physical activity are considered confounders. The association between chronic pain and psychological distress is likely bidirectional, and depicted in the DAG with an unknown common cause. Self-reported health is not included due to the qualitative collinearity with chronic pain, or the role as a potential mediator, or, as shown in the DAG, a collider.

3.5 STATISTICAL ANALYSIS

3.5.1 Paper I

Change in analgesic use between Tromsø 5 and Tromsø 6 was analyzed with generalized estimating equations with a logit link function; the analysis of the total analgesic use was a test of change in prevalence. However, the test in the specific prescription subgroups was not a test of change in "prevalence" *per se* but rather a test comparing "no use" in Tromsø 5 to use of the specific prescription category in Tromsø 6 (resembling a multinomial logistic regression where each level is compared separately to the base/reference level, i.e., "no use"). Analysis of differences in analgesic use between contraindications/drug interactions groups was performed by logistic regression, adjusting for age and sex, and the likelihood ratio test.

3.5.2 Paper II

Cox proportional hazard regression was used to assess the association between baseline risk factors at attendance and future persistent analgesic use. The start date of the *first* persistent treatment episode was defined as the event date, while date of death or end of follow-up was the censoring dates.

3.5.3 Paper III

The prospective analysis was the same as in Paper II; we analyzed the risk of future persistent analgesic use with Cox proportional hazard regression. CPT endurance time was dichotomized into those who endured the entire test (106 s) and those who withdrew the hand before, and entered as an independent variable.

Cox proportional hazard regression was also used to assess the cross-sectional associations between different measures of analgesic use and pain sensitivity. However, in this model CPT endurance time was entered as the survival time, hand withdrawal as the event and completing the entire test as censoring. The analgesic use measures were (separately) entered as independent variables, in addition to potential confounders.

3.5.4 Software

Stata (College Station, Texas, USA), versions 13.0-14.1, was used for all analyses. DAGs were created and analyzed in DAGitty (www.dagitty.net).[117]

3.6 ETHICS

This project has been approved by the Regional Committee for Medical and Health Research Ethics, North Norway (2012/1636). The record linkage between the Tromsø Study and NorPD was approved by the Norwegian Data Protection Authority (Datatilsynet, reference: 31488/4/lt). This research has been conducted in accordance with the 1964 Helsinki declaration and its later amendments. Written informed consent was obtained from all included participants. We pursued to adhere to the Strengthening the reporting of observational studies in epidemiology (STROBE) statement in the conduction and the reporting of the studies.[118]

4 RESULTS

4.1 PAPER I

- The age-adjusted prevalence of analgesic use last four weeks increased from 53.7% to 59.6% in women and from 29.1% to 36.7% in men between Tromsø 5 (2001-02) and Tromsø 6 (2007-08). Corresponding crude prevalences were 51.1% to 57.2% and 26.1% to 33.9%.
- The majority of use consisted of non-prescription analgesics alone, with age-adjusted prevalence increasing from 36.7% in Tromsø 5 to 42.9% in Tromsø 6 in women and from 21.3% to 27.1% in men.
- The increase was due to an increase in use of OTC analgesics, and it seemed to be explained by an increase in sporadic use, i.e., a frequency of monthly or less.
- Prevalences of regular use last four weeks of NSAIDs, other analgesics and antipyretics (i.e., predominantly paracetamol) or opioids were 12.7%, 12.5% and 3.7%, respectively.
- The prevalence of regular NSAID use in important contraindication groups were: chronic kidney disease: 8.6%, gastric ulcers: 12.0%, high primary CVD risk: 11.1%, and CVD: 6.7%. According to age- and sex adjusted logistic regression, the prevalence of NSAID use was only statistically significantly lower among those reporting a history of CVD, i.e., secondary risk, compared to those not reporting this contraindication.
- The prevalence of regular NSAID use in important drug interactions groups were: warfarin: 2.8%, ASA, low dose: 5.8%, SSRIs: 22.0%, oral glucocorticoids: 12.6%, and ACE inhibitors: 6.5%. According to age- and sex adjusted logistic regression, the prevalence of NSAID use was statistically significantly lower among users of warfarin, ASA, and ACE inhibitors compared to non-users, while it was higher among SSRI users.
- The prevalence of regular opioid use was much higher among those reporting regular use of other CNS depressants (18.1%), i.e., benzodiazepines, z hypnotics or barbiturates, compared to non-users of CNS depressants (2.9%).

4.2 PAPER II

- The prevalence of persistent analgesic use was 4.3% in general and 10.2% among those reporting chronic pain.
- The prevalence increased with chronic pain severity and was 16.6% among those reporting usual chronic pain severity as severe (NRS 7-10) and 15.3% among those reporting chronic pain in seven or more places on the body.
- If self-reported daily use of OTC analgesics last four weeks was included, the prevalence of persistent analgesic use was 5.2% in general.
- The incidence rate of persistent analgesic use within the 4.5 years of follow-up was 21.2 per 1,000 person-years.
- The median persistent analgesic user used analgesics for 382 days in total (of the eight-year study period; a user could have more than one episode during the study period), while 15.6% of persistent analgesic users had a total treatment duration above five years.
- Risk factors for persistent analgesic use were chronic pain, increasing age (non-linearly), female sex and lower education level. Although the results were less clear, being less physical active also seemed to be a risk factor. Furthermore, the risk increased in a dose dependent manner with increasing chronic pain severity, as measured by several chronic pain dimensions, i.e., duration, frequency, intensity, and number of body locations.

4.3 PAPER III

- Analgesic use was associated with increased pain sensitivity, i.e., reduced pain tolerance as measured by the CPT, at the cross-sectional level. This was consistently seen for all measures of analgesic use, including persistent analgesic use, self-reported OTC or Rx analgesic use, regular use of analgesics or analgesic use in the 24 hours before the CPT.
- Regular users of opioids alone were statistically significantly more pain sensitive than regular users of non-opioids. Only opioid users were statistically significantly more pain sensitive than non-users of analgesics after adjustment for confounders.
- Increased pain sensitivity was a risk factor for future persistent analgesic use in crude analysis. However, this association was non-significant after adjustment for potential confounders, i.e., age, sex, education level and chronic pain.

5 DISCUSSION

5.1 DISCUSSION OF MAIN FINDINGS

5.1.1 Prevalence and trends in analgesic use

We found a prevalence of analgesic use last four weeks of 57.2% among women and 33.9% among men in Tromsø 6 (2007-08). This is higher than the previously reported prevalence measures in Nordic studies from the 80s and 90s,[49-54] suggesting an increase in the use. However, all of these studies used a dichotomous measure with a two-week recall period, as opposed to our frequency question with a four-week recall period. A longer recall period may to a larger degree capture sporadic users.[54] A recent Norwegian study with data from 2006-08 reports a prevalence of OTC use of 47%.[68] Although their estimate is somewhat higher than ours (≈ 41%), maybe due to differences in age- and sex distribution and the definition of use, this largely confirms our findings. Taken together, the use of OTC analgesics in the Norwegian adult population is extensive.

We found an increase in the total prevalence of analgesic use between 2001-02 and 2007-08. Looking into this numbers, the prevalence of OTC analgesic use increased, while Rx analgesic use showed no statistically significant difference (crude prevalence of the Rx variable: Tromsø 5: 15.9% vs. Tromsø 6: 15.0%). However, the sales of both OTC analgesics and Rx analgesics in Norway increased between 2001 and 2008, with the largest relative increase for the OTC analgesics (personal communication, Christian Berg, Norwegian Institute of Public Health). An increase in sales may be due to an increase in the proportion of users, more intense treatment among users or a combination of both (or more being sold but never used, i.e., discarded). There is a possibility that there is a difference in the association between sales and prevalence between OTC and Rx analgesics. An increase in OTC sales could mainly reflect an increase in prevalence, while an increase in Rx sales could mainly reflect more intensive treatment prescribed by the physician. However, according to NorPD, the prevalence of use of Rx analgesics increased between 2004 and 2008.[59(search:8Mar'16)] The prevalence before the inception of NorPD in 2004 is unknown but the prevalence of prescription analgesics in Denmark increased between 2002 and 2004.[42]. Potential methodological issues with our findings, like possible misclassification of OTC and Rx use, are discussed in their respective sections below.

Three recent studies with repeated cross-sectional design are particular relevant to our study.[70,71,81] Ruscitto et al. report an increasing prevalence of any prescription analgesic use in Scotland from 16% to 18% between 1995 and 2010.[70] Paracetamol, gabapentinoids and opioid use increased, while the use of ASA and non-selective NSAIDs decreased. Interestingly, the proportion reporting use of multiple analgesic drug classes was higher in 2010. Sarganas et al., with data from 1998 to 2008-2011, report findings in Germany that are strikingly similar to our results.[71] The prevalence of analgesic use (here: ASA, diclofenac, ibuprofen, naproxen, paracetamol) increased from 19% to 21%. Although the prevalence estimates cannot be directly compared, the increase was, as in our study, explained by an increase in the use of OTC analgesics only. Finally, Zhou et al. report an increasing trend of regular ASA and NSAID use in the USA, with prevalences increasing from 12% to 19% and 9% to 13%, respectively, between 2005 and 2010.[81]

The sales of NSAIDs has been relatively stable in Norway in the years after the steep drop in sales after the Vioxx case (2004).[45] In Denmark, the prevalence of prescription NSAID use increased until 2004, while it has been decreasing thereafter.[12] In recent years several studies have shown an increasing use of opioids,[66,67,69,70] sometimes referred to as the "opioid epidemic".

In summary, analgesic use has increased over the last three-four decades. The reasons for this increase could be several, including better treatment of pain, increasing prevalence of pain, increasing longevity, increased availability, introduction of new analgesics or new indications, and marketing.

Increasing analgesic use may be explained by an increasing prevalence of painful conditions, e.g., musculoskeletal chronic diseases, as suggested by others.[70,71] The prevalence of chronic pain may be increasing.[119] The first study to evaluate the chronic pain prevalence in Norway reports a prevalence of 24% in 2000,[119] compared to our finding of 33-35% in 2007-08. A direct comparison of the prevalence estimates, however, is limited due to methodological reasons.[120] Nevertheless, increased attention to pain from prescribers and better pain management, in addition to increased awareness and higher expectations and demands from patients, may be more likely driving forces than the underlying prevalence of pain.[70,76]

Marketing of analgesics, particularly when new analgesics are introduced, could explain some of the increase in use. Hamunen et al. suggest marketing as an important contributor to the

increased sales of opioids observed in the Nordic countries in 2002-06.[48] The sales of NSAIDs increased pronounced after the introduction of the COX-2 inhibitors around 2000.[45]

We and others have suggested increased availability as a factor in the increased use.[71] In Norway, there was a vast increase in the number of pharmacies after the deregulation of the pharmacy sector and the abolishment of the pharmacy monopoly in 2001.[121] Furthermore, ibuprofen and paracetamol was released to general sales outside pharmacies in 2003.[121] In Australia, the prevalence of use of OTC NSAIDs (i.e., ibuprofen) increased between 2001 and 2009 after ibuprofen was switched to general sales status in 2004.[87] However, in the same period there was an increase in OTC analgesic use also in Germany, where the OTC analgesics are only available in the pharmacies or internet pharmacies.[71]

5.1.2 Persistent analgesic use

We found a point prevalence of persistent analgesic use of 4.3% and an incidence rate of 21.2 per 1,000 person-years. Assuming a relatively stable incidence rate, the period prevalence can be derived from the formula:[122]

$$Period\ prevalence = Point\ prevalence + Incidence\ rate \times Width\ of\ time\ period$$

Substituting the estimates from our cohort, i.e., closed population, into this formula produces a one-year period prevalence of slightly above six percent in the year after attendance. However, this must be viewed as a crude approximation based on a simplification, as the formula assumes a steady-state, while there is no simple relation between prevalence and incidence.[123(p136)]

As this is, to my knowledge, the first study of persistent analgesic use that includes all of the major analgesic groups, there is not much to directly compare with in the literature. Nevertheless, the point prevalence of persistent opioid use in Norway is around 1% (>180 DDD or >4500 mg oral morphine equivalents per year and prescriptions in three out of four quarters of a one year period, palliative treatment excluded) [14,79] and the one-year period prevalence of heavy NSAID use (≥ 182 DDDs/year) in Finland is 1.5%.[57] These definitions, while not identical to ours, try to capture the same "type" of persistent users. Fredheim et al. furthermore report a prevalence of persistent opioid use of 8% among those with severe/very severe chronic pain (chronic pain defined as at pain lasting at least six months and at least moderate intensity during the last week).[79] In comparison, we found a prevalence of general persistent analgesic use of 17% among those reporting usual chronic pain intensity as severe. However, differences in definition of both outcome and chronic pain makes it difficult to

compare these figures directly. Boudreau et al., using a method and definition that we partly based our definition on, report a one-year period prevalence of persistent opioid use in the USA of 4-5% and an incidence rate of persistent opioid use around 9-12/1,000/year.[76] In our data, the incidence rate of *any* analgesic use was around 10 times higher than the incidence of persistent analgesic use (data not shown). Boudreau et al. report an increase in both period prevalence and incidence of persistent opioid use in 1997-2005.[76] The point prevalence of persistent opioid use increased slightly during 2005-07 in Norway.[14] We also observed an increasing prevalence of persistent analgesic use within the study period.

Patients most often use NSAIDs as a single course of treatment (i.e., dispensed once) of short duration,[11,13] which is probably generalizable to the use of other analgesics. The vast majority of analgesic users therefore seem to consist of one-time or recurrent users with short treatment duration, while the prevalence of persistent analgesic use is relatively low. However, the relatively few persistent analgesic users seem to contribute to a considerable amount of the prescription volume of analgesics.

The duration of treatment can, under the aforementioned assumptions, be calculated as: [122]

$$Duration = \frac{Point\ prevalence}{(1 - Point\ prevalence)\ x\ Incidence\ rate}$$

Based on our estimates, the derived average duration of persistent analgesic use is therefore around 2 years. The average total duration of the persistent treatment episodes in the study period (i.e., the sum of all persistent treatment episodes for an individual) were also around 2 years. Although relatively few seems to use analgesics persistently, some use them for years on end.

Among those who reported chronic pain, 10% were defined as persistent users of prescription analgesics. In a Norwegian study, 42% of those with chronic pain treated their pain with analgesics, 32% physiotherapy and 31% no treatment,[119] while a Swedish study reports that 62% of those with chronic pain used analgesic last two weeks.[92] As we have shown, the use of OTC analgesics is extensive. If we, for example, included self-reported daily or weekly use of OTC analgesics in addition to persistent Rx analgesic use, almost one third of those with chronic pain used analgesics. Set aside the uncertainties of these estimates, our study suggest that a minority treat their chronic pain with analgesics persistently. This is consistent with the undocumented and low level of effectiveness of analgesics in chronic pain. Based on the principle of respondent analysis, as proposed by Moore et al. and others, the proportion of

responders may be small but when treatment response is achieved, it tends to last.[30] Adding to that, are the many and potential serious adverse effects leading to a high discontinuation rate. The group of persistent analgesic users may therefore consist of a dually selected group of responders to long-term treatment who at the same time do not experience troublesome adverse effects. However, we cannot based on our study say that the prevalence of persistent analgesic use represent a "correct" level. Chronic pain may be undertreated and there may be individuals who may benefit from persistent treatment that have not been reached. A final possibility is that some may use analgesics inappropriately, e.g., addiction, pharmacological irrational use, and where the need for persistent treatment should be reassessed and probably discontinued.

5.1.3 High-risk use

Several studies report a higher prevalence of NSAID use among those with a history of CVD[8,81,86] compared to those who do not have CVD. This is in contrast to our findings, where the prevalence was lower in the group with a history of CVD. This may reflect differences in awareness of contraindications against NSAID use. However, these findings may be confounded by age. NSAID use increased by age in the aforementioned studies.[8,81,86], while we found a decreasing prevalence with age, in line with an Italian study.[64] A decreasing age trend has also been reported for OTC NSAID use,[68] suggesting that the trend we observed was mainly driven by OTC use. As those with a history of CVD are older than those without, this could partly explain the difference between the studies. After adjusting for age and sex in our study, the prevalence of NSAID use was still statistically significantly lower among those with a history of CVD compared to those without. In a study of the Danish population, previous myocardial infarction or ischemic heart disease were associated with reduced odds of being prescribed NSAIDs.[11]

A previous study found no difference in NSAID use between those who were aware of their CKD or not.[124] However, the prevalence of current use was slightly higher among those with CKD compared to those without. In our study, the crude prevalence was lower among the CKD group, while there was no statistically significant difference after adjustment for age and sex differences. In a recent study, reporting of eGFR reduced the prescribing of NSAIDs, while the eGFR improved considerably after discontinuation, particularly among those with the most severe CKD.[125] These results underline the importance of monitoring the renal function in patients receiving NSAIDs.

A few studies report a higher NSAID use among those with a history of gastrointestinal ulcers,[8,81] compared to those who do not have gastrointestinal ulcers. Zhou et al. further analyzed this by multivariable regression and found that ASA or NSAID use was not affected by the presence of peptic ulcer disease,[81] in support of our findings.

In terms of GI bleeding risk and potential drug interactions, we found a pronounced lower prevalence of regular NSAID use among those reporting use of anticoagulants, and warfarin in particular, compared to non-users of these drugs. The prevalence of NSAID use was similar among those with or without concomitant use of oral glucocorticoids, while the prevalence of NSAID use was much higher among SSRI users compared to non-users. In a Finnish study, the odds of being prescribed concurrent prescriptions of drugs increasing the GI bleeding risk was five times higher among continuous NSAID users compared to non-continuous users. The odds ratios, however, were lowest for warfarin (1.8), followed by SSRIs (3.6) and glucocorticoids (8.0).[83] This suggests greater awareness of the interaction between NSAIDs and anticoagulants, than between NSAIDs and SSRIs or glucocorticoids, respectively. The strikingly high NSAID prevalence among SSRI users in our study is possibly explained by comorbidity between depression and pain.

Paracetamol use has received considerable attention lately, both in terms of possible adverse cardiovascular effects[40] and the potential of liver damage.[126] US studies report that about one percent of the population use paracetamol in doses exceeding the maximum dose,[88] and that hepatotoxic adverse effects of paracetamol continue to be a public health burden.[126] Increased availability of paracetamol may be associated with paracetamol overdoses and self-poisoning.[37(pp210-1)] Because of this, the regulatory authorities in Sweden have recently (2015) withdrawn OTC paracetamol tablets from general sales (supermarkets, petrol stations, etc.).[127] However this has so far not been deemed as necessary by the Norwegian authorities.[128] The sales of Rx paracetamol has increased considerably in Norway the last 10 years, while the sales of OTC paracetamol remains more or less at the same level.[128] Unfortunately, our study was unable to provide insight into this question, as we lacked frequency and dose of paracetamol use. However, we found that 12% of regular users of paracetamol-containing drugs reported use of more than one paracetamol-containing drug (brand), which could increase the risk of hepatotoxicity. The knowledge of which drugs contain paracetamol seems limited in the general population.[88] Nevertheless, the main finding of our study was that there is considerable high-risk use of NSAIDs. Restriction of NSAIDs to "pharmacy only" status has been suggested, as pharmacists can provide information and possibly detect high-risk

use.[89] In terms of availability, a restriction on OTC paracetamol sales would have little effect if the possible increase in cases of paracetamol-induced liver failure is linked to Rx use.[129] Such restriction may lead to higher NSAID use.[37(p210),129] Reduced paracetamol availability in two recall periods in Australia led to an increase in calls to poison centers regarding self-poisoning and accidental pediatric ingestions of ibuprofen.[130] Based on our findings and the safety profiles of NSAIDs, increased use of NSAIDs would thus represent an unwanted development.

We could not separate OTC use from Rx use in our measure of regular analgesic use, although the declining age trend and a comparison with the frequency questions suggested that the majority of regular NSAID use was due to OTC use. On the one hand, this is reassuring since the approved OTC dose is lower than the Rx dose, while the risk of adverse effects is higher in the elderly. On the other hand, this adds to the previous findings of a lack of awareness of the risks associated with OTC analgesics.[89] Potential high-risk use of OTC analgesics has been reported in a range of studies.[56,82,84,87,89] Furthermore, the use of doses above the recommended dose has been reported among OTC NSAID users.[84,89] Inappropriate use of OTC analgesics coupled with easy access to these drugs may put people at risk, underlining the importance of monitoring the utilization patterns on a population-level.

A question remains if our findings from 2007-08 are still valid today. The sales of NSAIDs remain close to the same level in 2014 as in 2008 (a slight increase). However, there has been more pronounced internal changes within the group, with diclofenac showing a decrease and naproxen an increase (mostly due to introduction of naproxen + esomeprazol).[44,45] In Denmark, the prevalence of Rx diclofenac was halved between 2008 and 2012.[12] This is favorable in terms of cardiovascular risk. However, in the last couple of years, the sales of COX-2 inhibitors is once again increasing in Norway after a regulatory change in reimbursement.[45] Likewise, increasing use of naproxen, as one of the NSAIDs producing the highest risk of GI ulcers, would require even more effort in identifying high-risk groups and the use of prophylactic drugs against ulcers.

5.1.4 Risk factors for analgesic use

The identified risk factors for persistent analgesic use were chronic pain, increasing age, female sex and lower education level. This was generally consistent with previously reported risk factors for analgesic use in general. The associations with low levels of physical activity and increased pain sensitivity were less clear. The reported physical activity variable was

statistically significant in crude analysis only. However, the point estimates did not change substantially in the multiple regression suggesting power as an explanation of this null finding. The notion that physical inactivity indeed is a risk factor was corroborated by using other variables on physical activity (data not shown).

The risk of persistent analgesic use increased with increasing chronic pain severity (Paper II). In Paper I, we found a gradient of worsening health and more pain over the different prescription categories, with concomitant users of OTC and Rx users generally scoring worse than users of Rx analgesics alone, which again was worse than users of OTC analgesic alone.

5.1.5 Pain sensitivity and analgesic use

Analgesic use was associated with increased pain sensitivity on the cross-sectional level. Increased pain sensitivity was a statistically significant risk factor for future persistent analgesic use only in the crude analysis. The interpretation of these findings is challenging. Following the proposed hypothesis by Edwards,[94] highly pain sensitive individuals have a greater risk of developing chronic pain. We have shown that chronic pain is, as expected, a risk factor for using analgesics persistently, suggesting that increased pain sensitivity would not only be a risk factor for chronic pain but also subsequent analgesic use. The most pain sensitive subjects may be more likely to seek help, i.e. the prescribing physician, and to be diagnosed with chronic pain. In that sense, increased pain sensitivity may not be a direct part of the etiology of chronic pain, but rather increases the likelihood of being diagnosed with chronic pain.[19]

However, the pharmacological effect of analgesics may be reduced among subjects with increased pain sensitivity. In that sense, increased pain sensitivity may be a marker of a dysfunctional endogenous pain inhibitory system, which at the same time may be a risk factor of chronic pain and of reduced effectiveness of the classical analgesics. The most pain sensitive subjects may have more centralized pain phenotypes, e.g., fibromyalgia or neuropathic pain that are particular resistant toward treatment with analgesics.[131] This is further complicated by the possibility that analgesic use in itself may cause hyperalgesia and increased pain sensitivity, and in particular opioid-induced hyperalgesia. Additionally, another hypothesis suggests that long-term COX inhibition by NSAID use may lead to suppression of *anti*-inflammatory lipid mediators and paradoxically increased pain.[17,132]

In our study, opioid users seemed to be more pain sensitive than NSAID users, whom again were more pain sensitive than non-users of analgesics. Although this may suggest increased

pain sensitivity due to analgesic use, a more plausible explanation is the severity of the underlying pain, e.g., treatment with analgesics according to the WHO pain ladder.[133] For instance, those reporting concomitant use of OTC and Rx analgesics seemed more pain sensitive than users of OTC alone. Our measure of regular use did not separate between OTC or Rx use, but as opioids are only available on prescription in Norway, the "opioids only" group would represent use of Rx analgesics only, while the other groups would represent a mixture of OTC or Rx use (although, as previously mentioned, the majority seemed to be regular OTC users). Furthermore, it would be difficult to separate pre-existing hyperalgesia from OIH,[134] particularly on the cross-sectional level.

We can only conclude that increased pain sensitivity is a characteristic associated with an increased probability of analgesic use, and as such is a risk factor after the definition used in this dissertation (although at the cross-sectional level the opposite may also be true: analgesic use is a risk factor for increased pain sensitivity). The main explanation seems to be increased pain sensitivity associated with the severity of the underlying pain, i.e., the indication for use of the analgesics, perhaps suggesting that the most pain sensitive subjects are those who have the greatest likelihood of seeking professional help. However, when it comes to potential causal pathways and mechanisms, future studies are needed. In recent years, there has been a growing interest in quantitative sensory testing and experimental pain tests in relation to analgesic use. Particularly, if experimental pain tests can be used to predict treatment response to analgesics[135,136] and in mechanism-based treatment of pain.[137]

5.2 METHODOLOGICAL CONSIDERATIONS

5.2.1 Selection bias and external validity

Selection bias is a systematic error in estimated associations between exposure and outcome which is caused by the procedures used to select subjects into a study or an analysis.[91] Another definition emphasizes that selection bias, or "sample distortion bias", occurs when the included subjects in a study is not representative of the larger population one wish to extrapolate the results to, i.e., exposures or outcomes of interest in the study sample are over-represented or under-represented.[90] Others argue that systematic differences between the study population and other populations is not selection bias, but "sampling bias" and refers to the generalizability or external validity of the findings.[91] No matter the nomenclature, non-response or non-participation bias is of particular relevance to health surveys. It occurs when the participants of the survey differ in several key characteristics from non-participants. The

study population must be representative of the source population to produce valid prevalence and incidence estimates. Furthermore, if the likelihood of participation in a health survey is conditional on the exposures and/or the outcome under study, measures of associations can also be biased. [138]

The source population of the Tromsø Study is the inhabitants of the municipality of Tromsø, with a population size of around 65,000 at the time of Tromsø 6. Although the sampling procedure of the Tromsø Study is complex, involving a mix of participants from previous waves, whole birth cohorts and random samples, the purpose is to produce a sample that is representative of the source population. However, the attendance rate in Tromsø 6 was 66%, with higher attendance rate among women than men.[101] The participation rate in Tromsø 6 was somewhat higher than in comparable contemporary health surveys.[101] It is, however, not the participation rate itself that determine the degree of bias in a study but rather the differences between the participants and non-participants.[139] Non-participants of the Tromsø Study tend to be younger, single and have a higher male to female ratio.[102] In a similar Norwegian health survey, the Nord-Trøndelag Health Study (HUNT), the prevalence of several chronic diseases were higher among non-participants, while the prevalence of musculoskeletal pain and headache were, perhaps surprisingly, lower among non-participants.[138] Taken together, this would suggest lower analgesic use among nonparticipants. On the contrary, a previous study based on Tromsø 3 (1986-87) reports higher use of controlled analgesics (mainly combined codeine analgesics) among non-participants compared to participants.[62] The period prevalence of analgesic use reported in Paper II was reasonably comparable to those reported for Troms County. In the HUNT study, inclusion of non-participants generally led to only small changes in the overall prevalence estimates.[138] Galea et al. conclude that "most empiric work suggests that declines in participation rates are not likely to have substantial influence on exposure-disease associations or point estimates of measures of interest".[139] In summary, the somewhat conflicting evidence makes it hard to conclude if, and how, non-participation bias has affected our estimates of analgesic use. However, there is reason to believe that non-response bias is of minor concern. If non-response bias is present, this has most likely led to an underestimation of analgesic use, based on the general assumption that less healthy subjects are less likely to participate.[138]

In terms of generalizability to the total Norwegian population, the total sales of analgesics (M01, N02A, N02B) in Troms County was slightly lower (about -3%) than the country average in 2008,[44] and therefore reasonable nationally representative. Regarding external

validity to other populations, The Tromsø population is considered a typical Northern European, predominantly Caucasian, urban population,[101] and our findings may be generalizable to similar populations.

5.2.2 Information bias and recall

Information bias is a systematic difference in the collection of information or measurement of variables between comparison groups, resulting in biased estimates or a distorted association between exposure and outcome.[90,91] Recall bias is a type of measurement or information bias that relates to the study participants' ability to recall or remember past events or experiences, and systematic differences between comparison groups occurring as a result.[90,91] Recall bias is of particular concern in case-control studies but the term is also used more generally in the context of self-reported measures, e.g., questionnaires. Random differences in the recollection of events, i.e., no systematic differences between comparison groups, leads to a loss of precision but not bias.[90] The consequence of information bias, however, is misclassification of the exposure and/or outcome variables.[140(p121)]

Poor recall in the self-reported analgesic use measures could therefore introduce bias and/or lead to a loss of precision. Recall and accuracy of drug use is reported to be better for prescription drugs than OTC drugs.[141(p769)] Likewise, drugs used chronically, and especially frequently dispensed drugs, are more likely to be recalled than acute use.[141(p769)] Recall of infrequent use of OTC NSAIDs is worse than frequent/repeated use, and data on frequent use thus seems more reliable than infrequent use.[142] Furthermore, the recall declines with increasing length of the recall period or with time passed since the drug was used.[141(p769),142] On the contrary, too short recall periods increases the likelihood of missing occasional drug users.[143] In terms of issues relating to poor recall, prescription registries provide an advantage, since registration is independent of the subject's memory or ability to recall. In our studies, self-reported infrequent use of OTC analgesics is most likely to be affected by poor recall, which may have resulted in underreporting.

The choice of questions and the design of the questionnaire will affect the response. In a cohort study, the use of three different ways of asking about analgesic use produced large variation in the prevalence; a measure asking respondents to name/list their analgesic drugs produced the highest prevalence, followed by a symptom-oriented measure, while a frequency measure produced the lowest prevalence.[144] Drug-specific and indication-specific questions seem to capture more of the users, i.e., increase the completeness, compared to general, open-

ended questions on drug use.[141(p769),145] Combining different measures could increase the completeness.[144] Providing examples, like drug photos, or drug names, could also increase the response.[141(p769),145] Finally, the ordering of the questions or items may affect the response. For instance, drugs listed early in a questionnaire have a higher likelihood of being selected, known as the primacy effect.[141(p769),145]

Dichotomous measures of analgesic use, as used previously in a range of studies, [49-54] have the disadvantage of not separating chronic and infrequent users.[54] In a study based on other Norwegian surveys with similar frequency questions on analgesic use as in our study, the authors argue that most of "the attendees found the answering categories suitable for their pattern of use" and that they had a high willingness to participate based on the high response rate.[143]

In addition to misclassification due to recall, there may also be misclassification according to the prescription status. There were separate questions on OTC and Rx analgesic use, respectively, in Tromsø 5 and Tromsø 6. However, no examples or definitions of OTC or Rx analgesics were provided in the questionnaires. The two most sold OTC analgesics, ibuprofen and paracetamol, are also available as (larger) Rx only packages. These Rx only packages may be misclassified as OTC analgesics. On the other hand, it is less likely that an exclusive Rx analgesic, e.g., tramadol, is misclassified as an OTC analgesic.

5.2.3 Missing data

Missing data is a potential source of bias. The mechanism or pattern of missing are usually divided into missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR), depending of the difference between observed and missing values; in MCAR there are no systematic differences, in MAR the differences can be explained by the observed data, while in MNAR the differences cannot be accounted for by the observed data.[146(p432)] In the face of missing data one is left with the options of either excluding individuals with missing or replacing the missing data using imputation. The choice of method is based on the proportion of missing and the assumed missing data pattern. If the proportion of missing is very low (some have suggested < 5%, although a general rule does not exist), exclusion of missing is not likely to produce substantial bias.[146(p437)] If the proportion of missing is large and/or not believed to be MCAR, multiple imputation is a commonly used technique of imputing missing data while retaining random variation.[118]

Complete case analysis ("listwise deletion") refers to restricting the analyses to individuals with complete data, i.e., on *all* variables in question. The advantage is that the sample size remains the same across analyses, making estimates directly comparable. The disadvantages are that substantial number of individuals may be lost, i.e., reduced power, if the combined proportion of missing is high, while bias may be introduced if the missing individuals differ from those who are completely observed.[147(pp15-8)] Another common approach is the available case analysis ("pairwise deletion"). [148] In this method, the maximum number of individuals with non-missing variables are included in each particular analysis, i.e., sample sizes differ between analyses.[146(p437),148] The advantage is that the data is fully utilized. The major disadvantage is that the analyses are based on different subsets of the data leading to inconsistency in the inferences based on the estimates. Available case analysis is also inefficient and could introduce bias.[147(pp15-8)]

A relatively common practice when working with questionnaire data is to impute missing as a negative response, as previously done in studies on analgesic use using self-reported dichotomous measures.[50,51] This assumption is based on the observed pattern that some participants seem to only answer the questions that are relevant to them, and leave the rest blank. Although this approach produce a conservative prevalence estimate, this is in fact an *ad hoc* single imputation. Single imputation, in general, leads to an underestimation of the standard error, and do not take into consideration the uncertainty of the imputed missing values.[147(p19)]

In this dissertation, the analyses were based on available case analyses, i.e., differing *n* values between analyses. The prevalence measures reported were the proportions after exclusion of missing, i.e., missing was not assumed to be a negative response. In general, the proportion of missing in the included variables was low, and we did not deem multiple imputation as necessary. In the statistical analysis section of paper I, the analyses were imprecisely reported to be "complete case analyses". Although this is strictly speaking not wrong when referring to the statistical software, this is misleading when it comes to the study design, as the reported *n* values evidently vary.

In terms of the questions on self-reported OTC or Rx analgesic use, the missing groups tended to be older, have a higher proportion of women, poorer health, lower education, and more pain or discomfort, compared to responders. Furthermore, the prevalence of persistent analgesic use, which was derived externally from NorPD, was 1.5-2 times higher among the missing group compared to the observed group. This suggests that the assumption of missing

equaling no use does not hold for these particular questions. Furthermore, it is plausible that analgesic use, for some people, may be stigmatized especially when the analgesic use has become problematic, leaving the respondent to either leave the question blank or reply as a non-user. However, the fundamental challenge with missing data is that the true status of the missing individuals is unknown.

The total proportion of missing on the self-reported OTC/Rx questions, i.e., missing on either or both questions, was higher in Tromsø 5 compared to Tromsø 6. If the MCAR assumption does not hold, this may have introduced bias in the analysis of change over time. However, sensitivity analyses by imputing missing in these questions as non-user or user, respectively, were generally consistent with the main results, with the aforementioned limitation of *ad hoc* imputations in mind.

Finally, a more subtle missing problem relates to the use of NorPD data in Paper II and III. Some prescriptions recorded in NorPD lack the personal identification number (PIN). As our study design was based on a record-linkage dependent on the PIN (i.e., the pseudonymized key), analgesic prescriptions registered without the PIN are not captured.[103] For example, 1.6-2.4% of opioid prescriptions in Norway 2004-07 lacked the PIN.[58] Persistent users are more likely to have been registered with the PIN, due to more frequent visits to the physician/pharmacy, reimbursement and stricter control of controlled analgesics. The lack of PIN for a small proportion of prescriptions may nevertheless have led to a slight underestimation of the prevalence, particularly the period prevalence of any use. However, for the estimation of persistent analgesic use we consider this source of error to be practically negligible.

5.2.4 Definition of persistent analgesic use

One of the key challenges with dispensing data is to define periods of drug use. The only things that are absolutely certain are the dispensing dates, type of drug, amount etc. – the rest is based on assumptions about the subsequent use. There may be gaps between the dispensing date and the actual use of the drug, if it is used at all.[141(p760)] It is challenging to estimate the point prevalence of drug use based on prescription data, as many users show an irregular dispensing pattern, making it difficult to separate long-term users from infrequent or episodic users.[149] Furthermore, there may be seasonal variations in actual drug use throughout the year, as well as irregularities in dispensing pattern due to stockpiling, e.g., before holidays[150] or due

to reimbursement, e.g., dispensings at the end of the calendar year due to no co-payment (in Norway: “frikort”).

No universal definition of long-term or persistent drug use exist. A definition of persistent use obviously needs to capture some aspects of use *over time*. However, a definition based exclusively on time between dispensing dates of prescriptions will not differentiate between low or high intensity use. Likewise, a definition based on intensity of use, e.g., a certain amount of DDDs per calendar year, will not fully differentiate high-intensity use over a shorter period from low-intensity use over a longer period. It has therefore been suggested that a persistence definition should be two-dimensional, quantifying both duration and intensity of drug use, more specifically through an hybrid of the *refill-sequence method* and the *PDC* method.[106] In the refill-sequence method, the time between a first prescription and an unacceptable gap between refills is calculated, allowing for some given gap between refills, i.e., “grace period”. The PDC method calculates the number of days with available supply of drugs within a fixed interval, with a given cut-off for the proportion, e.g., 80%, defining persistence. Other methods for determining persistence are the *anniversary* method, i.e., the use of the drug within an interval surrounding the “anniversary” from the first prescription and the *minimum-refills* method that defines a minimum number of prescriptions per year.[106] When the calculated duration of two prescriptions overlap, one can choose to add the number of overlapping days, or disregard the overlap. In the case when a drug is switched it is reasonable to disregard the overlap.[151] The validity of the chosen definition should be assessed with sensitivity analyses, i.e., varying key assumptions of the definition.[152]

Defining persistent drug use is challenging for drugs used regularly, e.g., statins, and even more challenging for drugs with a predominantly irregular pattern or which are taken sporadically.[152] Chronic analgesic use has previously been defined as the dispensing of at least 90 DDDs, under the assumption that this is “equivalent to 90 days of drug use at standard doses”.[153] Other studies have used ≈ 180 DDD per year, representing use of at least 0.5 DDD per day/half of the days in a year.[14,57] The assumption of 1 DDD/day has also been used for other drug groups, e.g., single dispensings of antiepileptic drugs.[154] However, the assumption of one DDD per day is less likely to hold for drugs us on as-needed basis and for symptomatic treatment, e.g., analgesics. Preliminary analyses of the mean number of DDD/day (data not shown) suggested that the individual analgesics have a mean dose below one DDD/day, which would imply that the assumption of one DDD/day would underestimate the treatment duration. The combined, total use of analgesics, however, was slightly above

one DDD/day. The estimation of treatment episodes with analgesics should therefore be based on individually calculated average doses, and not rely on assumption of fixed doses.[150] Finally, the actual consumed dose may be different than the dispensed dose or the DDD, e.g., different patient groups or low adherence.[150]

Repeated opioid use has been defined as four or more prescriptions per year, i.e., the minimum-refills model.[155] Persistent opioid use has been defined as dispensing of an opioid in consecutive years and > 365 DDDs in the last year of the study.[156] More complex methods, e.g., dynamic calculation of daily dosage, definition of typical dosages, daily dosage based on number of tablets, etc., have been used in the estimation of NSAID use.[11,157]

Svendsen et al., in their definitions of persistent opioid use, employed three dimensions of opioid use: intensity of use, i.e., amount dispensed, distribution, i.e., number of quarters of a year, and, in their strictest definition, frequency, i.e., number of prescriptions per year.[14] Likewise, Von Korff et al. defined persistent opioid use by treatment duration, number of prescriptions and a measure of amount, i.e., days supply.[75]

Our definition was based on the works by Poluzzi et al.[104,105] and Von Korf et al.[75] and included three criteria: gap length between prescription fills, duration of the treatment episode and PDC, i.e., intensity of use. As no universal definition of persistent analgesic use exists, the choice of cut-offs are arbitrary. However, we based our choices on tacit knowledge from the pharmacy, the literature and sensitivity analysis, as described below.

First, we chose a treatment duration ≥ 90 days, i.e., three months. This was partly based on the Norwegian reimbursement system where one is allowed to collect a maximum of three months' supply of drugs each time for reimbursed prescriptions. Likewise, we wanted the definition to be analogous to the chronic pain question in Tromsø 6, i.e., "persistent or constantly recurring pain lasting three months or more". Finally, 90 days has been used in the study by Von Korff et al.[75]

The second criteria was the gap length. For prescriptions to be included in the same treatment episode the gap between the prescriptions had to be ≤ 180 days, i.e., six months, also used by Von Korff et al.[75] A gap length twice of the "three-month-rule" used in the pharmacies seemed reasonable. This was supported by published work based on the waiting time distribution that shows that each NSAID or opioid analgesic prescription has an average duration about 117-210 days.[122,149,158]

The third and final criteria was PDC. We chose a cut-off of ≥ 40%, which was based on a range of sensitivity analyses (see the Supplement of paper II) and what we felt would be a clinical relevant cut-off (Table 4). The PDC cut-off was chosen to represent a minimum cut-off of persistent analgesic use; a higher cut-off would lead to a lower prevalence (as shown in the sensitivity analysis in the Supplement of Paper II) and an even more selected group of high-intensity persistent users. There is not much support in the literature but cut-offs in the range 50-80% have been used for drugs used more chronically, i.e., antihypertensive drugs, statins or antidepressants,[106] including when the unit of measure is the DDD.[105] A previous study used a medication possession ratio (equivalent to the PDC) of ≥ 50% for regular analgesic use and ≥ 25% for occasional analgesic use.[159]

Table 4 Clinical scenarios of the definition of persistent analgesic use. The table shows the minimum number of tablets per year or per week for selected analgesics, common tablet sizes and possible combination use of analgesics. The assumption is a treatment duration of 365 days and a proportion-of-days-covered ≥ 40%, i.e., ≥ 146 DDD dispensed in these 365 days.

Analgesic	**Defined daily dose (mg)**	**Common tablet strength (mg)**	**Tablets per year**	**Tablets per week**
Paracetamol	3000	1000	438	8
Ibuprofen	1200	600	292	6
Paracetamol/codeine	4 tablets	400/30	584	11
Paracetamol + ibuprofen (50% + 50%)	See above	See above	219 + 146	4 + 3
Paracetamol/codeine + paracetamol (25% + 75%)	See above	See above	146 + 329	3 + 6
Oxycodone	75	10	1095	21

We did not use the number of prescriptions within a treatment episode as a criterion. A persistent episode could therefore consist of only two prescriptions dispensed within 180 days, as long as the duration was ≥ 90 days and PDC ≥ 40%. The proportion of persistent treatment episodes consisting of only two prescriptions was around 10%; the proportion decreased by increasing PDC cut-off. This means that our definition may have included use of a more episodic nature. The prevalence of persistent analgesic use was one percent among those not reporting chronic pain, suggesting inclusion of analgesic users for pain of shorter duration. This may have been avoided by introducing a criterion of minimum number of

prescriptions within a treatment episode and/or setting a higher PDC cut-off. The number of prescriptions within a persistent treatment episode is thus a useful additional criterion to explore in future studies.

We chose to combine the use of either NSAIDs, paracetamol (i.e., other analgesics and antipyretics) or opioids into a joint measure. This meant that we treated all prescriptions within these groups as an "analgesic" prescription, and prescriptions dispensed on the same date were collapsed into one, i.e., the DDDs were summed. The rationale behind this decision were: 1) we wanted an overall measure of analgesic use, 2) we wanted to capture those who combined different analgesic groups, and 3) capture those who switched analgesic groups during treatment. Based on clinical guidelines and practice, and one-year period prevalences (see Supplement of Paper II), the use of more than one analgesic group is to be expected in the treatment of chronic pain. As an example, a person may use both paracetamol and tramadol but not in a sufficient amount that any of the drugs reach the persistence threshold alone. However, the combined use of these analgesics reaches the threshold.

The main limitations of this approach are that it relies on the DDD and the assumption that the DDDs are equianalgesic, and it combines different analgesic drugs into a single measure, regardless of differences in for example DDD/day for different substances. For the opioids it has previously been shown that the assumption of equianalgesia for one DDD between different opioids is less than optimal, and that the use of morphine equivalents could be used as a replacement or an addition to the DDD.[160] However, as our study did not focus exclusively on opioids and since there exist no conversion factors of analgesic equivalency between the main analgesic groups, morphine equivalents was not an option, leaving us with the DDD as the best approach.

5.2.5 Validity and agreement of the analgesic use measures

In this context, validity (or accuracy) refers to a comparison with a gold standard, while agreement refers to a comparison between different methods for data collection were neither source is superior.[141(pp758,760)] Prescription databases and pharmacy dispensing data are commonly considered to have a high accuracy and to be the gold standard for data on drug use.[152]

The agreement between self-reported analgesic use and dispensing records is generally moderate ($\kappa \sim 0.5$), with higher agreement when the fixed-time method is used.[161,162] Furthermore, a study comparing self-reported ibuprofen or paracetamol use and objective

measurements of metabolites in urine finds a rate of underreporting of 15-17%.[163] In all, this suggests that self-reported analgesic use is subject to underreporting, while overreporting is less common.[161] We conducted no formal validation study of the analgesic measures used. However, in preliminary analyses the agreement between self-reported Rx use and prescription registry data (e.g., dispensings last six months, our persistence definition etc.) was similar to the cited previous reports, i.e., around moderate agreement. Potential reasons for limited agreement between self-reported drug data and dispensing data include poor adherence, inaccurate reporting (e.g., recall bias, unwillingness to participate, and stigma) and the previously discussed methodological issues, like questionnaire design, conduction of the interviews, and definition of drug use.[161,162]

We used several different measures of analgesic use. The point prevalence of persistent Rx analgesic use was four percent, daily or weekly self-reported Rx analgesic use last four weeks were four and five per cent, respectively, while self-reported regular use of either NSAIDs, opioids or paracetamol use last four weeks were 21%. The latter measure included both OTC or Rx use but the prevalence of opioid use, which are Rx only in Norway, was four percent. Overall, the different measures seemed to be relatively consistent with each other. However, due to the previously discussed limitations of these measures, e.g., prescription database data is a proxy of use, recall bias in self-reported measures, persistence definition highly dependent on the cut-offs chosen, and differences in exposure windows, a direct comparison is challenging.

5.2.6 Validity of the chronic pain definition

The most accurate and complete self-reported diagnosis data is recorded for concrete, chronic and well-known diseases, e.g., diabetes mellitus, asthma and cancers, while assessment and measurement of symptom-based conditions, like pain conditions is, more challenging.[141(p771)] A similar definition of chronic pain as in our study has previously been used (persistent or constantly recurring pain, although *more* than three months duration).[92] A Norwegian validation study, comparing different measures of chronic pain, reports the highest prevalence for a measure that only included duration, i.e., "do you have pain lasting more than six months?''.[120] The authors argue that this measure captures subjects with mild pain or less and that a measure including at least moderate pain would exclude this group but retain those with persistent pain. Thus, the screening question used in our study may have captured subjects with pain that are "more a nuisance than a chronic disability".[28] However, the role of more

severe chronic pain for persistent analgesic use was explored by analysis of several dimensions of chronic pain severity, including chronic pain intensity.

5.2.7 Validity of the cold pressor test

A valid test is an unbiased test, and for experimental pain tests the question on validity is whether the test actually measures pain. However, pain is a subjective experience and cannot be measured or quantified in the same sense as for example blood pressure.[17] Experimental pain models, although providing a way of quantifying the pain, thus provide a proxy of pain. As previously mentioned, pain is not exclusively bound to a stimulus, as pain may occur by other mechanisms.[15] In experimental pain models, like the CPT, a nociceptive stimulus is applied in a controlled setting and the psychophysical response toward this stimulus is measured.[17] This experimentally induced pain may therefore be different from clinical pain. Therefore it has been recommended that both the sensory and the affective dimensions should be measured, as certain analgesic interventions may affect one dimension selectively.[164] However, the CPT produces a deep, tonic, dull, aching pain of "clinical quality and intensity".[20] This is opposed to pain threshold tests where the clinical relevance is more questionable.[19] The reliability, i.e., reproducibility, of the CPT is satisfactory.[20] A follow-up of the CPT conducted in Tromsø 6 showed that the CPT has a good stability over time, i.e., a test-retest correlation of $\alpha = 0.82$.[165] It has been stated that experimental models that induce tonic, deep pain are needed in studies on responses to analgesic treatment,[135] and that the CPT is ideal in the study of the effects of analgesics.[20] However, there may be variability in the efficacy against CPT-induced pain between the different analgesic groups.[20]

5.2.8 Confounding

Confounding occurs when other factors associated with the exposure influence the outcome, resulting in a distortion of the association between exposure and outcome.[91] An apparent but confounded association is thus explained partly or fully by the confounders. In DAG terminology, confounding refers to an open, non-causal path ("backdoor path") between exposure and outcome, i.e., the confounder is a common cause (or on the path leading to or from the common cause) of the exposure and outcome.[116(p177)] If one controls for the confounder, either by restriction, stratification or regression, the path is closed. In the DAG presented in the methods section (Figure 7), open, non-causal paths between the main exposure, chronic pain, and the outcome, persistent analgesic use, are marked with red. Based on this example, the unconfounded, direct effect of chronic pain on persistent analgesic use can be estimated when adjusting for the confounders age, sex, education, physical activity and

psychological distress. Adjusting for the collider, self-reported health, introduces bias, i.e., a non-causal path is opened.

5.2.9 Effect modification

Effect modification, or interaction, is present when the association between exposure and outcome differs in different strata or levels of another variable, or when the observed joint effect of the exposure and the effect modifier is greater or smaller than the expected, i.e., synergism or antagonism, respectively.[140(pp185-6)] Interactions may be present on both a multiplicative scale and an additive scale, with the latter particularly relevant if the aim is intervention on a public health level. Interactions should be specified *a priori* based on (biological) plausibility. According to the principle of hierarchical backward elimination, interaction terms ought to be assessed before confounding. The rationale is that assessment of confounding involving effect modifiers becomes irrelevant in the presence of strong interaction.[116(p170)]

I will illustrate effect modification with an example from paper II. The possible interaction between sex and chronic pain for the risk of persistent analgesic use was specified *a priori*. As shown in Table 5, a statistically significant interaction on the multiplicative scale between chronic pain and sex was found (p = .0044). The risk of persistent analgesic use was higher among women with chronic pain, compared to men with chronic pain. The interactions was also apparent on the additive scale. The interaction suggests that women with chronic pain are more likely than men with chronic pain to become persistent analgesic users. However, as the effects did not differ substantially we decided to report the overall estimate without the interaction term, i.e., the "average effect" of chronic pain over the sexes.[140(p213)]

Table 5 Example of additive and multiplicative interaction from Paper II. Adapted from Szklo.[140(p206)]

Sex	Chronic pain	Incidence/1,000 person-years	Attributable risk	Hazard ratio (relative risk)
Women	No	15.6 (13.8-17.6)	Ref.	1.00
	Yes	38.1 (34.4-42.2)	22.5	2.40 (2.03-2.85)
Men	No	15.6 (13.9-17.6)	Ref.	1.00
	Yes	26.7 (22.9-31.1)	11.1	1.65 (1.35-2.01)

5.3 ETHICAL CONSIDERATIONS

Autonomy, integrity and informed consent are keystones and creates the ethical foundation on which medical research is built. These three terms are closely connected: if we renounce one

of them, we renounce all.[166(p41)] Participation in a research project should therefore be voluntary, and the potential participant must be given necessary and adequate information about the study in question and its harms and benefits. The decision to participate should be made by a competent individual who are not subject to undue influence.[167] Even after the decision to participate is made, the participant should be given the possibility to withdraw from the study at any time. Informed consent can be given orally, by voluntary actions, or as a signed, written consent form. Although all these options are valid from an ethical point of view, the written informed consent is preferable due to proof that the consent is given.[167]

NorPD is a *pseudonymized* registry. Pseudonymization means that all personal identifiers, including name and PIN, is de-identified and substituted with a pseudonym, i.e., an identifier/key.[168] Pseudonymization makes it possible to follow an individual over time or to link with other data sources but without knowing the individual's identity. According to Norwegian legislation, informed consent is not required for registration in pseudonymized registers.[169] Nevertheless, one may argue that mandatory registration in national health registries is compromising an individual's autonomy. However, the individual will benefit from being registered, both directly through improved health care and indirectly through the benefits from research; a right to withdraw "would harm both medical care and the quality of medical research",[170] and could create inequalities in the population in regards to who gets registered or not. The latter could violate the central general ethical principle that burdens and benefits should be uniformly distributed across groups or individuals in a society.[167] Finally, the informed consent may be waived in "studies using health-related registries that are authorized under national regulations".[167]

In the Tromsø study the participants provide written informed consent that specifically mentions potential linkage to NorPD and other national health registries. In long-term studies (e.g., 10 years) with passive follow-up it would be most appropriate to inform the participants and/or to seek a renewal of the informed consent. However, when the follow-up is active, like in repeated waves of the Tromsø Study, the participant can decide to participate or not. Participation can thus be deemed to be a renewed consent by voluntary action.[167]

6 CONCLUDING REMARKS AND IMPLICATIONS

The use of analgesics has increased in Norway over the last decades, a trend that is also observed in several other countries. In the bigger perspective this trend may reflect better treatment of pain and the acknowledgement of chronic pain as a disease in its own right. However, the increasing trend may also be influenced by marketing, introduction of new analgesics, availability, increasing longevity, attitudes toward analgesic use and changes in the prevalence of pain. The increase observed in our study seemed to be primarily in sporadic users of non-prescription analgesics, while the recent years' sales statistics may suggest that the use of analgesics in the population is leveling out. Nevertheless, as close to sixty per cent of women and one third of men reported use of analgesics in a four-week period, the use of analgesics is extensive. Particularly worrisome was the sign of high-risk use among persons with contraindications or concomitant use of interacting drugs; most notably a history of gastrointestinal ulcers, cardiovascular disease, chronic kidney disease, and interactions increasing the bleeding risk or affecting renal function/blood pressure. A relatively low share of all users seemed to be persistent analgesic users; based on the definition and methodology we developed, the prevalence of persistent prescription analgesic use was four percent in general. Estimation of persistent drug use based on prescription registry data is methodologically challenging, and our method was highly dependent on the different cut-offs used, adding uncertainty to the model. Yet, we conclude that the majority of those reporting chronic pain do not use analgesics persistently. This is consistent both with an unfavorable adverse effects profile of persistent analgesic use, particularly for the non-steroidal anti-inflammatory drugs and the opioids, but also with the growing body of evidence suggesting limited effectiveness of classical analgesic in chronic pain states. This underlies the difficulty and the challenge in the treatment of chronic pain, and the need for new analgesics with different mechanisms of action and higher efficacy.

Our study provides epidemiological data on the association between analgesic use and pain sensitivity, and we have suggested hypotheses for future research. Particularly the role of opioid-induced hyperalgesia should be explored, also in epidemiological studies, while the hypothesis of paradoxically increased pain due to NSAID use should be tested. In the future, the use of experimental pain tests may help guide the choice of analgesics, as an addition to the empirical treatment by trial and error. This would not only improve treatment but also

reduce the proportion of pain patients that are unnecessary exposed to potential adverse effects of analgesics.

Based on this dissertation, a few clinical implications can be suggested. Prescribers need to take into account the patient's comorbidity, risk of adverse effects and use of other drugs before prescribing an analgesic. Renal function should be measured, cardiovascular and gastrointestinal bleeding risk should be assessed, and drug interactions checked, particularly in patients on long-term NSAID treatment and in the elderly. As persistent users remain on treatment for a long time, the need for treatment and the risk of adverse effects should be continuously assessed. The pharmacist should provide information about the analgesics, both prescribed and OTC, in an attempt to detect potential high-risk use, e.g., drug interactions, concomitant use of several analgesics and/or non-prescription and prescription analgesics. At the population-level, the use of analgesics must be continuously monitored. Regulators need no assess whether the availability of the different analgesics is appropriate, based on current knowledge. Our results indicate high-risk use of analgesics on an overall level but future studies are needed to study separate analgesics, preferably stratified on non-prescription and prescription use. Particularly the safety of non-prescription analgesics must be further studied.

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Appendix I
Questionnaire 1
Tromsø 5

10. EXERCISE AND PHYSICAL ACTIVITY

10.1 How has your physical activity in leisure time been during this last year?
Think of a weekly average for the year.
Time spent going to work is count as leisure time. Answer both questions.

	Hours per week: None	Less than 1	1-2	3 or more
Light activity *(not sweating/out of breath)...*	☐	☐	☐	☐
Hard physical activity *(sweating/out of breath).....*	☐ 1	☐ 2	☐ 3	☐ 4

10.2 Describe exercise and physical exertion in your leisure time. If your activity varies much e.g. between summer and winter, then give an average. The question refers only to the last year.
(Tick the most appropriate box)

Reading, watching TV or other sedentary activity? ..... ☐ 1

Walking, cycling or other forms of exercise at least 4 hours a week? ..... ☐ 2
(Include walking or cycling to work, Sunday walk/stroll,etc.)

Participation in recreational sports, heavy gardening, etc.? ☐ 3
(Note: duration of activity at least 4 hours a week)

Participation in hard training or sports competitions, regularly several times a week? ..... ☐ 4

11. FAMILY AND FRIENDS

11.1 Do you live with:

	Yes	No
Spouse/partner?.....	☐	☐

11.2 How many good friends do you have? *Number of friends* ☐☐

Count the ones you can talk confidentially with and who can give you help when you need it. Do not count people you live with, but do include other relatives.

11.3 How much interest do people show for what you do?
(Tick only once)

Great interest	Some interest	Little interest	No interest	Uncertain
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11.4 How many associations, sport clubs,groups, religious communities or similar do you take part in? *Number* ☐☐
(Write 0 if none)

11.5 Do you feel that you can influence what happening in your local community where you live? *(Tick only once)*

Yes, a lot	Yes, some	Yes, a little	No	Never tried
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

12. ILLNESS IN THE FAMILY

12.1 Have one or more of your parents or siblings had a heart attack (heart wound) or angina pectoris (heart cramp)? .....

	Yes	No	Don't know
	☐	☐	☐

12.2 Tick for the relatives who have or have had any of the illnesses: *(Tick for each line)*

	Mother	Father	Brother	Sister	Child	None of these
Cerebral stroke or brain haemorrhage	☐	☐	☐	☐	☐	☐
Heart attack before age of 60 years	☐	☐	☐	☐	☐	☐
Asthma.....	☐	☐	☐	☐	☐	☐
Cancer	☐	☐	☐	☐	☐	☐
Diabetes	☐	☐	☐	☐	☐	☐

12.3 If any relatives have diabetes, at what age did they get diabetes (if for e.g. many siblings, consider the one who got it earliest in life):

Don't know, not applicable	Mother's age	Father's age	Brother's age	Sister's age	Child's age
☐	☐☐	☐☐	☐☐	☐☐	☐☐

13. USE OF MEDICINES

With medicines, we mean drugs purchased at pharmacies. Supplements and vitamins are not considered here.

13.1 Do you use:

	Now	Previously, but not now	Never used
Blood pressure lowering drugs	☐	☐	☐
Cholesterol-lowering drugs	☐	☐	☐

13.2 How often have you during the last 4 weeks used the following medicines?
(Tick once for each line)

	Not used in the last 4 weeks	Less than every week	Every week but not daily	Daily
Painkillers non-prescription	☐	☐	☐	☐
Painkillers on prescription	☐	☐	☐	☐
Sleeping pills	☐	☐	☐	☐
Tranquillizers	☐	☐	☐	☐
Antidepressants	☐	☐	☐	☐
Other prescription medicines ...	☐ 1	☐ 2	☐ 3	☐ 4

13.3 For those medicines you have checked in points 13.1 and 13.2, and that you've used during the last 4 weeks:

State the name and the reason that you are taking/have taken these (disease or symptom):
(Tick for each duration you have used the medicine)

Name of the medicine: *(one name per line)*	Reason for use of the medicine	How long have you used the medicine: Up to 1 year	1 year or more
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

If there is not enough space here, you may continue on a separate sheet that you attach

14. THE REST OF THE FORM IS TO BE ANSWERED BY WOMEN ONLY

14.1 How old were you when you started menstruating? *Age in years* ☐☐

14.2 If you no longer menstruating, how old were you when you stopped menstruating? *Age in years* ☐☐

14.3 Are you pregnant at the moment?

Yes	No	Uncertain	Above fertile age
☐ 1	☐ 2	☐ 3	☐ 4

14.4 How many children have you given birth to? *Number of children* ☐☐

14.5 Do you use, or have you ever used?
(Tick once for each line)

	Now	Before, but not now	Never
Oral contraceptive pills/mini pill/ contraceptive injection	☐	☐	☐
Hormonal intrauterine device (IUD) *(not ordinary IUD)*..	☐	☐	☐
Estrogen *(tablets or patches)*	☐	☐	☐
Estrogen *(cream or suppositories)*	☐	☐	☐

14.6 If you use/have used prescription estrogen:
How long have you used it? *Number of years* ☐☐

14.7 If you use contraceptive pills, mini pill, contraceptive injection, hormonal IUD or estrogen, what brand do you use?

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Appendix II
Questionnaire 1
Tromsø 6

The Tromsø Study

The form will be read electronically. Please use a blue or black pen
You can not use comas, use upper-case letters.

2007 – 2008 Confidential

HEALTH AND DISEASES

1 **How do you in general consider your own health to be?**

- ☐ Very good
- ☐ Good
- ☐ Neither good nor bad
- ☐ Bad
- ☐ Very bad

2 **How is your health compared to others in your age?**

- ☐ Much better
- ☐ A little better
- ☐ About the same
- ☐ A little worse
- ☐ Much worse

3 **Do you have, or have you had?**

	Yes	No	Age first time
A heart attack	☐	☐	
Angina pectoris *(heart cramp)*	☐	☐	
Cerebral stroke/brain hemorrhage	☐	☐	
Atrial fibrillation	☐	☐	
High blood pressure	☐	☐	
Osteoporosis	☐	☐	
Asthma	☐	☐	
Chronic bronchitis/Emphysema/COPD	☐	☐	
Diabetes	☐	☐	
Psychological problems *(for which you have sought help)*	☐	☐	
Hypothyroidism	☐	☐	
Kidney disease, *not including urinary tract infection (UTI)*	☐	☐	
Migraine	☐	☐	

4 **Do you have persistent or constantly recurring pain that has lasted for 3 months or more?**

☐ Yes ☐ No

5 **How often have you suffered from sleeplessness during the last 12 months?**

- ☐ Never, or just a few times
- ☐ 1-3 times a month
- ☐ Approximately once a week
- ☐ More that once a week

6 **Below you find a list of various problems. Have you experienced any of this during the last week (including today)?** (Tick once for each complaint)

	No complaint	Little complaint	Pretty much	Very much
Sudden fear without reason	☐	☐	☐	☐
Felt afraid or anxious	☐	☐	☐	☐
Faintness or dizziness	☐	☐	☐	☐
Felt tense or upset	☐	☐	☐	☐
Tend to blame yourself	☐	☐	☐	☐
Sleeping problems	☐	☐	☐	☐
Depressed, sad	☐	☐	☐	☐
Feeling of being useless, worthless	☐	☐	☐	☐
Feeling that everything is a struggle	☐	☐	☐	☐
Feeling of hopelessness with regard to the future	☐	☐	☐	☐

USE OF HEALTH SERVICES

7 **Have you during the last 12 months visited:**
If YES; how many times?

	Yes	No	No. of times
General practitioner (GP)	☐	☐	
Psychiatrist/psychologist	☐	☐	
Medical specialist outside hospital *(other than general practitioner/psychiatrist)*	☐	☐	
Physiotherapist	☐	☐	
Chiropractor	☐	☐	
Alternative practitioner *(homeopath, acupuncturist, foot zone therapist, herbal medicine practitioner, laying on hands practitioner, healer, clairvoyant, etc.)*	☐	☐	
Dentist/dental service	☐	☐	

8 **Have you during the last 12 months been to a hospital?**

	Yes	No	No. of times
Admitted to a hospital	☐	☐	
Had consultation in a hospital without admission;			
At psychiatric out-patient clinic	☐	☐	
At another out-patient clinic	☐	☐	

9 **Have you undergone any surgery during the last 3 years?**

☐ Yes ☐ No

USE OF MEDICINES

10 **Do you currently use, or have you used some of the following medicines?** (Tick once for each line)

	Never used	Now	Earlier	Age first time
Blood pressure lowering drugs	☐	☐	☐	
Cholesterol lowering drugs	☐	☐	☐	
Drugs for heart disease	☐	☐	☐	
Diuretics	☐	☐	☐	
Drugs for osteoporosis	☐	☐	☐	
Insulin	☐	☐	☐	
Tablets for diabetes	☐	☐	☐	
The drugs for hypothyroidism Thyroxine/levaxin	☐	☐	☐	

11 **How often have you during the last 4 weeks used the following medicines?** (Tick once for each line)

	Not used in the last 4 weeks	Less than every week	Every week, but not daily	Daily
Painkillers on prescription	☐	☐	☐	☐
Painkillers non-prescription	☐	☐	☐	☐
Sleeping pills	☐	☐	☐	☐
Tranquillizers	☐	☐	☐	☐
Antidepressants	☐	☐	☐	☐

12 **State the name of all medicines -both those on prescription and non-prescription drugs- you have used regularly during the last 4 weeks.** Do not include vitamins, minerals, herbs, natural remedies, other nutritional supplements, etc.

If there is not enough space for all medicines, continue on a separate sheet.

When attending you will be asked whether you have used antibiotics or painkillers the last 24 hours. If you have, you will be asked to provide the name of the drug, strength, dose and time of use.

FAMILY AND FRIENDS

13 **Who do you live with?** (Tick for each question and give the number)

	Yes	No	Number
Spouse/partner	☐	☐	
Other people older than 18 years	☐	☐	
People younger than 18 years	☐	☐	

14 **Tick for the relatives who have or have had**

	Parents	Children	Siblings
A heart attack	☐	☐	☐
A heart attack before age of 60	☐	☐	☐
Angina pectoris *(heart cramp)*	☐	☐	☐
Cerebral stroke/brain haemorrhage	☐	☐	☐
Osteoporosis	☐	☐	☐
Gastric/duodenal ulcers	☐	☐	☐
Asthma	☐	☐	☐
Diabetes	☐	☐	☐
Dementia	☐	☐	☐
Psychological problems	☐	☐	☐
Substance abuse	☐	☐	☐

15 **Do you have enough friends who can give you help when you need it?**

☐ Yes ☐ No

16 **Do you have enough friends whom you can talk confidentially with?**

☐ Yes ☐ No

17 **How often do you normally take part in organised gatherings, e.g. sport clubs, political meetings, religious or other associations?**

☐ Never, or just a few times a year
☐ 1-2 times a month
☐ Approximately once a week
☐ More than once a week

WORK, SOCIAL SECURITY AND INCOME

18 **What is the highest level of education you have completed?** (Tick once)

☐ Primary/secondary school, modern secondary school
☐ Technical school, vocational school, 1-2 years senior high school
☐ High school diploma
☐ College/university less than 4 years
☐ College/university 4 years or more

19 **What is your main activity?** (Tick once)

☐ Full time work ☐ Housekeeping
☐ Part time work ☐ Retired/benefit recipient
☐ Unemployed ☐ Student/military service

20 **Do you receive any of the following benefits?**

- ☐ Old-age, early retirement or survivor pension
- ☐ Sickness benefit (on sick leave)
- ☐ Rehabilitation benefit
- ☐ Full disability pension
- ☐ Partial disability pension
- ☐ Unemployment benefits
- ☐ Transition benefit for single parents
- ☐ Social welfare benefits

21 **What was the household's total taxable income last year?** Include income from work, pensions, benefits and similar

- ☐ Less than 125 000 NOK
- ☐ 125 000-200 000 NOK
- ☐ 201 000-300 000 NOK
- ☐ 301 000-400 000 NOK
- ☐ 401 000-550 000 NOK
- ☐ 551 000-700 000 NOK
- ☐ 701 000 -850 000 NOK
- ☐ More than 850 000 NOK

22 **Do you work outdoor at least 25% of the time, or in cold buildings (e.g. storehouse/industry buildings)?**

- ☐ Yes
- ☐ No

PHYSICAL ACTIVITY

23 **If you have paid or unpaid work, which statement describes your work best?**

- ☐ Mostly sedentary work *(e.g. office work, mounting)*
- ☐ Work that requires a lot of walking *(e.g. shop assistant, light industrial work, teaching)*
- ☐ Work that requires a lot of walking and lifting *(e.g. postman, nursing, construction)*
- ☐ Heavy manual labour

24 **Describe your exercise and physical exertion in leisure time. If your activity varies much, e.g. between summer and winter, then give an average. The question refers only to the last year.** (Tick the most appropriate box)

- ☐ Reading, watching TV, or other sedentary activity.
- ☐ Walking, cycling, or other forms of exercise at least 4 hours a week *(include walking or cycling to work, Sunday-walk/stroll, etc.)*
- ☐ Participation in recreational sports, heavy gardening, etc. *(note:duration of activity at least 4 hours a week)*
- ☐ Participation in hard training or sports competitions, regularly several times a week.

25 **How often do you exercise?** (With exercise we mean for example walking, skiing, swimming or training/sports)

- ☐ Never
- ☐ Less than once a week
- ☐ Once a week
- ☐ 2-3 times a week
- ☐ Approximately every day

26 **How hard do you exercise on average?**

- ☐ Easy- do not become short-winded or sweaty
- ☐ You become short-winded and sweaty
- ☐ Hard- you become exhausted

27 **For how long time do you exercise every time on average?**

- ☐ Less than 15 minutes
- ☐ 15-29 minutes
- ☐ 30-60 minutes
- ☐ More than 1 hour

ALCOHOL AND TOBACCO

28 **How often do you drink alcohol?**

- ☐ Never
- ☐ Monthly or less frequently
- ☐ 2-4 times a month
- ☐ 2-3 times a week
- ☐ 4 or more times a week

29 **How many units of alcohol** (a beer, a glass of wine or a drink) **do you usually drink when you drink alcohol?**

- ☐ 1-2
- ☐ 3-4
- ☐ 5-6
- ☐ 7-9
- ☐ 10 or more

30 **How often do you drink 6 units of alcohol or more in one occasion?**

- ☐ Never
- ☐ Less frequently than monthly
- ☐ Monthly
- ☐ Weekly
- ☐ Daily or almost daily

31 **Do you smoke sometimes, but not daily?**

- ☐ Yes
- ☐ No

32 **Do you/did you smoke daily?**

- ☐ Yes, now
- ☐ Yes, previously
- ☐ Never

33 **If you previously smoked daily, how long is it since you quit?**

Number of years ☐☐

34 **If you currently smoke, or have smoked previously: How many cigarettes do you or did you usually smoke per day?**

Number of cigarettes ☐☐

35 **How old were you when you began daily smoking?**

Age in years ☐☐

36 **How many years in all have you smoked daily?**

Number of years ☐☐

37 **Do you use or have you used snuff or chewing tobacco?**

- ☐ No, never
- ☐ Yes, previously
- ☐ Yes, sometimes
- ☐ Yes, daily

DIET

38 **Do you usually eat breakfast every day?**

☐ Yes ☐ No

39 **How many units of fruit or vegetables do you eat on average per day?** (units means for example a fruit, a cup of juice, potatoes, vegetables)

Number of units ☐

40 **How many times a week do you eat warm dinner?**

Number ☐

41 **How often do you usually eat these foods?**
(Tick once for each line)

	0-1 times/ mth	2-3 times/ mth	1-3 times/ week	4-6 times/ week	1-2 times/ day
Potatoes	☐	☐	☐	☐	☐
Pasta/rice	☐	☐	☐	☐	☐
Meat *(not processed)*	☐	☐	☐	☐	☐
Processed meat *(sausages, hamburger, etc.)*	☐	☐	☐	☐	☐
Fruits, vegetables, berries	☐	☐	☐	☐	☐
Lean fish	☐	☐	☐	☐	☐
Fatty fish *(e.g. salmon, trout, mackerel, herring, halibut, redfish)*	☐	☐	☐	☐	☐

42 **How much do you usually drink the following?**
(Tick once for each line)

	Rarely/ never	1-6 glasses /week	1 glass /day	2-3 glasses /day	4 or more glasses /day
Milk, curdled milk, yoghurt	☐	☐	☐	☐	☐
Juice	☐	☐	☐	☐	☐
Soft drinks with sugar	☐	☐	☐	☐	☐

43 **How many cups of coffee and tea do you drink daily?** (Put 0 for the types you do not drink daily)

	Number of cups
Filtered coffee	☐
Boiled coffee (coarsely ground coffee for brewing)	☐
Other types of coffee	☐
Tea	☐

44 **How often do you usually eat cod liver and roe?**
(i.e. "mølje")

☐ Rarely/never ☐ 1-3 times/year ☐ 4-6 times/year
☐ 7-12 times/year ☐ More than 12 times/year

45 **Do you use the following nutritional supplements?**

	Daily	Sometimes	No
Cod liver oil or fish oil capsules	☐	☐	☐
Omega 3 capsules *(fish oil, seal oil)*	☐	☐	☐
Calcium tablets	☐	☐	☐

QUESTIONS FOR WOMEN

46 **Are you pregnant at the moment?**

☐ Yes ☐ No ☐ Uncertain

47 **How many children have you given birth to?**

Number ☐

48 **If you have given birth, fill in for each child: birth year, birth weight and months of breastfeeding** (Fill in the best you can)

Child	Birth year	Birth weight in grams	Months of breastfeeding
1	☐	☐	☐
2	☐	☐	☐
3	☐	☐	☐
4	☐	☐	☐
5	☐	☐	☐
6	☐	☐	☐

49 **Have you during pregnancy had high blood pressure?**

☐ Yes ☐ No

50 **If yes, during which pregnancy?**

☐ The first ☐ Second or later

51 **Have you during pregnancy had proteinuria?**

☐ Yes ☐ No

52 **If yes, during which pregnancy?**

☐ The first ☐ Second or later

53 **Were any of your children delivered prematurely (a month or more before the due date) because of preeclampsia?**

☐ Yes ☐ No

54 **If yes, which child?**

1st child	2nd child	3rd child	4th child	5th child	6th child
☐	☐	☐	☐	☐	☐

55 **How old were you when you started menstruating?**

Age ☐

56 **Do you currently use any prescribed drug influencing the menstruation?**

Oral contraceptives, hormonal intrautrine or similar ☐ Yes ☐ No

Hormone treatment for menopausal problems ☐ Yes ☐ No

When attending you will get supplementary questions about menstruation and any use of hormones. Write down on a sheet of paper the names of all the hormones you have used and bring it with you. You will also be asked whether your menstruation have ceased and possibly when and why.

Appendix III
Questionnaire 2
Tromsø 6

1. DESCRIPTION OF YOUR HEALTH STATUS

Mark the statement that best fits your state of health today by ticking once in one of the boxes under each of the five groups below:

1.01 **Mobility**

- ☐ I have no problems in walking about
- ☐ I have little problems in walking about
- ☐ I am confined to bed

1.02 **Self-care**

- ☐ I have no problems with self-care
- ☐ I have some problems washing or dressing myself
- ☐ I am unable to wash or dress myself

1.03 **Usual activities** (e.g. work, study, housework, family or leisure activities)

- ☐ I have no problems with performing my usual activities
- ☐ I have some problems with performing my usual activities
- ☐ I am unable to perform my usual activities

1.04 **Pain and discomfort**

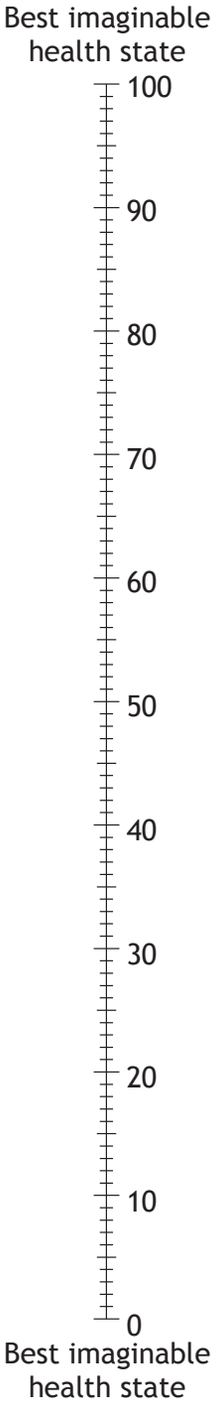
- ☐ I have no pain or discomfort
- ☐ I have moderate pain or discomfort
- ☐ I have extreme pain or discomfort

1.05 **Anxiety and depression**

- ☐ I am not anxious or depressed
- ☐ I am moderately anxious or depressed
- ☐ I am extremely anxious or depressed

1.6 To allow you to show us how good or bad your state of health is we have made a scale (almost like a thermometer) where the best state of health you can imagine is marked 100 and the worst 0. We ask you to show your state of health by drawing a line from the box below to the point on the scale that best fits your state of health.

Your own health state today



4. ILLNESS AND WORRIES

4.01 **Have you during the last month experienced any illness or injury?**

☐ Yes ☐ No

If YES: have you during the same period? (Tick once for each line)

	Yes	No
Been to a general practitioner	☐	☐
Been to a medical specialist	☐	☐
Been to emergency department	☐	☐
Been admitted to a hospital	☐	☐
Been to an alternative practitioner *(chiropractor, homeopath or similar)*	☐	☐

4.02 **Have you noticed sudden changes in your pulse or heart rythm in the last year?**

☐ Yes ☐ No

4.03 **Do you become breathless in the following situations?** (tick once for each question)

	Yes	No
When you walk rapidly on level ground or up a moderate slope	☐	☐
When you walk calmly on level ground	☐	☐
While you are washing or dressing	☐	☐
At rest	☐	☐

4.04 **Do you cough about daily for some periods of the year?**

☐ Yes ☐ No

If YES: Is the cough usually productive?

☐ Yes ☐ No

Have you had this kind of cough for as long as 3 months in each of the last two years?

☐ Yes ☐ No

4.05 **How often do you suffer from sleeplessness?** (tick once)

☐ Never, or just a few times a year
☐ 1-3 times a month
☐ Approximately once a week
☐ More than once a week

If you suffer from sleeplessness monthly or more often, what time of the year does it affect you most? (Put one or more ticks)

☐ No special time
☐ Polar night time
☐ Midnight sun time
☐ Spring and autumn

4.06 **Have you had difficulty sleeping during the past couple of weeks?**

☐ Not at all
☐ No more than usual
☐ Rather more than usual
☐ Much more than usual

4.07 **Have you during the last two weeks felt unhappy and depressed?**

☐ Not at all
☐ No more than usual
☐ Rather more than usual
☐ Much more than usual

4.08 **Have you during the last two weeks felt unable to cope with your difficulties?**

☐ Not at all
☐ No more than usual
☐ Rather more than usual
☐ Much more than usual

4.09 **Below, please answer a few questions about your memory:** (tick once for each question)

	Yes	No
Do you think that your memory has declined?	☐	☐
Do you often forget where you have placed your things?	☐	☐
Do you have difficulties finding common words in a conversation?	☐	☐
Have you problems performing daily tasks you used to master?	☐	☐
Have you been examined for memory problems?	☐	☐

If YES to at least one of the first four questions above: Is this a problem in your daily life?

☐ Yes ☐ No

4.10 **Have you during the last last year suffered from pain and/or stiffness in muscles or joints in your neck/shoulders lasting for at least 3 consecutive months?**
(tick once for each line)

	No	A little	A lot
Neck, shoulder	☐	☐	☐
Arms, hands	☐	☐	☐
Upper part of the back	☐	☐	☐
The lumbar region	☐	☐	☐
Hips, leg, feet	☐	☐	☐
Other places	☐	☐	☐

4.11 **Have you suffered from pain and/or stiffness in muscles or joints during the last 4 weeks**

	No	A little	A lot
Neck, shoulder	☐	☐	☐
Arms, hands	☐	☐	☐
Upper part of the back	☐	☐	☐
The lumbar region	☐	☐	☐
Hips, leg, feet	☐	☐	☐
Other places	☐	☐	☐

4.12 **Have you ever had:**

	Yes	No	Age last time
Fracture in the wrist/underarm?	☐	☐	
Hip fracture?	☐	☐	

4.13 **Have you been diagnosed with arthrosis by a doctor?**
☐ Yes ☐ No

4.14 **Do you have or have you ever had some of the following:**

	Never	Little	Much
Nickel allergy	☐	☐	☐
Pollen allergy	☐	☐	☐
Other allergies	☐	☐	☐

4.15 **Have you ever experienced infertility for more than 1 year?**
☐ Yes ☐ No

If Yes: was it due to:

	Yes	No	Do not know
A condition concerning you?	☐	☐	☐
A condition concerning your partner?	☐	☐	☐

4.16 **To which degree have you had the following complaints during the last 12 months?**

	Never	Little	Much
Nausea	☐	☐	☐
Heartburn/regurgitation	☐	☐	☐
Diarrhoea	☐	☐	☐
Constipation	☐	☐	☐
Alternating diarrhoea and constipation	☐	☐	☐
Bloated stomach	☐	☐	☐
Abdominal pain	☐	☐	☐

4.17 **If you have had abdominal pain or discomfort during the last year:**

	Yes	No
Was it located in your upper stomach?	☐	☐
Were you bothered as often as once a week or more during the last 3 months?	☐	☐
Became better after bowel movement?	☐	☐
Are the symptoms related to more frequent or rare bowel movements than normally?	☐	☐
Are the symptoms related to more loose or hard stool than normally?	☐	☐
Do the symptoms appear after a meal?	☐	☐

4.18 **Have you ever had:**

	Yes	No	Age last time
Stomach ulcer	☐	☐	
Duodenal ulcer	☐	☐	
Ulcer surgery	☐	☐	

4.19 **For women: Have you ever had a miscarriage?**
☐ Yes ☐ No ☐ Do not know
If Yes: number of times

4.20 **For men: Have your partner ever had a miscarriage?**
☐ Yes ☐ No ☐ Do not know
If Yes: number of times

4.21 **Is your diet gluten-free?**
☐ Yes ☐ No ☐ Do not know

4.22 **Have you been diagnosed with Dermatitis Herpetiformis (DH)?**
☐ Yes ☐ No ☐ Do not know

4.23 **Have you been diagnosed with coeliac disease, based on a biopsy from your intestine taken in an endoscopy examination?**

☐ Yes ☐ No ☐ Do not know

4.24 **Do you have your natural teeth?**

☐ Yes ☐ No

4.25 **How many amalgam tooth fillings do you have/have you had?**

☐ 0 ☐ 1-5 ☐ 6-10 ☐ 10+

4.26 **Have you been suffering from headache the last year?**

☐ Yes ☐ No

If No: go to section 5, food habits

4.27 **What kind of headache are you suffering from?**

☐ Migraine ☐ Other headache

4.28 **How many days per month do you suffer from headache?**

☐ Less than one day
☐ 1-6 days
☐ 7-14 days
☐ More than 14 days

4.29 **Is the headache usually:**
(tick one for each line)

	Yes	No
Pounding/pulsatory pain	☐	☐
Pressing/tightening pain	☐	☐
Unilateral pain *(right or left)*	☐	☐

4.30 **What is the intensity of your headache?**

☐ Mild *(do not hinder normal activity)*
☐ Moderate *(decrease normal activity)*
☐ Strong *(block normal activity)*

4.31 **What is the duration of the headache usually?**

☐ Less than 4 hours
☐ 4 hours – 1 day
☐ 1-3 days
☐ More than 3 days

4.32 **If you suffer from headache, when during the year does it affect you most?** (tick one or more)

☐ No special time
☐ Polar night time
☐ Midnight sun time
☐ Spring and/or Autumn

4.33 **Before or during the headache, do you have a transient:**

	Yes	No
Visual disturbances? *(flickering, blurred vision, flashes of light)*	☐	☐
Unilateral numbness in your face or hand?	☐	☐
Deterioration by moderate physical Activity?	☐	☐
Nausea and/or vomiting?	☐	☐

4.34 **Describe how many days you have been away from work or school during the last month due to headache?**

Number of days ☐☐

13. FOLLOW-UP QUESTIONS ON PAIN

You answered in the first questionnaire that you have protracted or constantly recurrent pain that has lasted for 3 months or more. Here, we ask you to describe the pain a little closer.

13.01 **How long have you had this pain?**

Number of years ☐☐ months ☐☐

13.02 **How often do you have this pain?**

- ☐ Every day
- ☐ Once a week or more
- ☐ Once a month or more
- ☐ Less than once a month

13.03 **Where does it hurt?** (Tick for all locations where you have protracted or constantly recurrent pain)

- ☐ Head/face
- ☐ Jaw/temporo-mandibular joint
- ☐ Neck
- ☐ Back
- ☐ Shoulder
- ☐ Arm/elbow
- ☐ Hand
- ☐ Hip
- ☐ Thigh/knee/leg
- ☐ Ankle/foot
- ☐ Chest/breast
- ☐ Stomach
- ☐ Genitalia /reproductive organs
- ☐ Skin
- ☐ Other locations

13.04 **What do you believe is the cause of the pain?** (Tick for all known causes)

- ☐ Accident /acute injury
- ☐ Long-term stress
- ☐ Surgical intervention/operation
- ☐ Herniated disk *(prolapse)* /lumbago
- ☐ Whiplash
- ☐ Migraine/headache
- ☐ Osteoarthritis
- ☐ Rheumatoid arthritis
- ☐ Bechterews syndrome
- ☐ Fibromyalgia
- ☐ Angina pectoris
- ☐ Poor blood circulation
- ☐ Cancer
- ☐ Nerve damage/neuropathy
- ☐ Infection
- ☐ Herpes zoster
- ☐ Another cause *(describe below)*
- ☐ Don't know

Describe the other cause:

.....

13.05 **Which kind of treatment have you received for the pain?** (Tick for all types of pain treatments you have received)

- ☐ No treatment
- ☐ Analgesic medications
- ☐ Physiotherapy/chiropractic treatment
- ☐ Treatment at a pain clinic
- ☐ Surgery
- ☐ Psycho-educative/relaxation training/ psychotherapy
- ☐ Acupuncture
- ☐ Complimentary medicine *(homeopathy, healing, aromatherapy, etc.*
- ☐ Another treatment

13.06 **On a scale of 0 to 10, where 0 corresponds to no pain and 10 corresponds to the worst possible pain you can imagine:**

How strong would you say that the pain usually is?	No pain	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐	Worst imaginable pain
How strong is the pain when it is in its strongest intense?	No pain	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐	Worst imaginable pain
To what degree does the pain interfere with your sleep?	No effect	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐	Impossible to sleep
To what degree does the pain interfere with performing common activities at home and at work?	No effect	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐	Can not do anything