Epidemiology of anxiolytic and hypnotic drug use in the general population in Norway

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SUMMARY

Background
Drugs for mental disorders have been on the market for more than 50 years, but there is still a need for more knowledge about the use and impact of these drugs in real-life conditions. Appropriate use of anxiolytics or hypnotics may relieve or reduce severe problems, whereas inappropriate use may represent problems of personal or public health.

Aims
This thesis aims to study the epidemiology of anxiolytic and hypnotic drug use and, to a lesser extent, antidepressant drug use in the general population in Norway - in both cross-sectional and prospective cohort studies.

Material and methods
This thesis is based on data from 1) four health surveys done by the National Health Screening Service (now the Norwegian Institute of Public Health) in the counties of Østfold in 1985/1988 and Aust-Agder in 1986/1989, and in Oslo and Oppland/Hedmark in 2000-2001 and 2) the Norwegian Prescription Database (NorPD). Information on drug use was at first collected from health surveys, later from NorPD. Mental health status was measured by the screening tool “Hopkins symptom checklist” (HSCL-10) that was part of the health surveys. Information on deaths was obtained from the Norwegian Causes of Death Register.

Results
- Daily users of anxiolytics or hypnotics showed higher crude mortality than non-users. However, after adjustment the difference was markedly reduced.
- The majority of incident users of hypnotics received prescriptions for z-hypnotics (benzodiazepine related drugs) rather than benzodiazepines, the choice of benzodiazepines predicted most strongly by previous use of anxiolytics and male gender.
- The main factor associated with use of anxiolytics or hypnotics among people with mental distress was the use of analgesics.
The main factor associated with use of antidepressants among people with mental distress was not participating in the labour market. Mental distress was a predictor of later use of anxiolytic drugs. Women showed a higher proportion of use of psychotropic drugs than men, and there were also gender differences when studying mortality and incidence rates.

Conclusion

The health surveys offered selection bias and information bias that was eliminated when data were retrieved from NorPD. The health survey study populations were large enough to minimize random error, and from NorPD complete data were collected. The findings encourage general practitioners to be observant on mental distress as this is related to later anxiolytic drug use, that for selected populations is further associated with increased mortality. The gender differences observed for mortality, prevalence and incidence rates may lead us to question whether women suffer from more anxiety and depression than men, if they complain more, or if the truth is a combination of the two arguments.
ACKNOWLEDGEMENTS

The studies presented in this thesis were carried out at the Division of Epidemiology, Norwegian Institute of Public Health, during the years 2004-2010.

I would like to express my sincere gratitude to my first supervisor, Svetlana Skurtveit. Svetlana has, in fact, supervised me for 10 years as she also followed me through my Masters degree and a smaller research project before this PhD, both of which were carried out at the Division of Forensic Toxicology and Drug Abuse, Norwegian Institute of Public Health. Svetlana has a very humble way of explaining her aim when supervising someone: she would like them to become better researchers than she is herself.

My second supervisor, Kari Furu, aroused my interest for pharmacoepidemiology as early as during my second year of pharmacy studies, giving inspiring lectures on community pharmacy. Thanks to both Svetlana and Kari for their patience, for always being there for me and for encouraging me to continue when I was on the point of giving up my PhD. Because of their complementary professional skills they have given me supervision of very high quality, and I have never wished for better input.

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“Remember that research is the most important thing,” Jørgen G. Bramness once told me. I am afraid this has not been my mantra, as I have instead spent a lot of time and effort becoming a World Champion in orienteering. I give credit to Jørgen (previously EPLI, now Norwegian Centre for Addiction Research) for his enthusiasm, ability to communicate
research findings not only to “the church” and for instructive cooperation on papers. Further from EPLI, Anders Engeland offered valuable statistical help on one paper, Marte Handal and Randi Selmer were kind enough to give feedback on part of my thesis and Tove Granum helped me with the layout. Solveig Sakshaug and a number of other good colleagues at EPLI answered my questions on this and that.

Asbjørg Christophersen (Division of Forensic Toxicology and Drug Abuse, Norwegian Institute of Public Health) was my first supervisor during my Masters and applied for financial support for a smaller research project which I did prior to this thesis. I am grateful that she gave me basic knowledge and led me into the world of research.

I am very grateful that this project has been financially supported by the Norwegian ExtraFoundation for Health and Rehabilitation through EXTRA funds, after the Norwegian Council for Mental Health approved my application. Thanks to the Norwegian Community Pharmacy Foundation for financial support in the early phase. I am grateful for being granted access to data from health surveys carried out by the National Health Screening Service of Norway (now Norwegian Institute of Public Health) in cooperation with local health services, as well as from the Norwegian Prescription Database and Statistics Norway. Paper IV is a part of the project, “The epidemiology of prescription drug use. A record-linkage study in Norway” which is financially supported by The Norwegian Research Council.

I would like to thank my parents for encouraging me to spend time on school or studies as well as my interests in several other arenas throughout my younger years. You never put any pressure on me, but rather worried that my days were too busy.

Finally, a very special thank you to Anders. You became my boyfriend during my second year of PhD work and you are already my husband; marriage seems to be quicker to organise than a PhD! Anders was kind and clever enough to propose to me last autumn during my extra effort to finish my PhD, giving me something nice to plan and think of besides the hard work. Thank you for your care, humour, patience, “dinner is ready” and for not bothering me with questions about research matters. Without your support this would have been so much harder.

Anne Margrethe Hausken, May 2010
LIST OF PAPERS

The thesis is based on the following papers, which will be referred to by their Roman numerals.


<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC</td>
<td>Anatomical therapeutic chemical classification system</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BZD(s)</td>
<td>Benzodiazepine(s), ATC code: N05BA or N05CD</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CIDI</td>
<td>Composite international diagnostic interview</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>DDD</td>
<td>Defined daily dose</td>
</tr>
<tr>
<td>DSM-IV</td>
<td>Diagnostic and statistical manual of mental disorders, 4th version</td>
</tr>
<tr>
<td>GABA</td>
<td>Gamma-aminobutyric acid</td>
</tr>
<tr>
<td>GHQ</td>
<td>General health questionnaire</td>
</tr>
<tr>
<td>GP</td>
<td>General practitioner</td>
</tr>
<tr>
<td>GQL</td>
<td>Gothenburg quality of life instrument</td>
</tr>
<tr>
<td>HADS</td>
<td>Hospital anxiety and depression scale</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>HSCL</td>
<td>Hopkins symptom checklist</td>
</tr>
<tr>
<td>HUBRO</td>
<td>Health survey in the Norwegian county Oslo</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International statistical classification of diseases and related health problems, 10th version</td>
</tr>
<tr>
<td>MHI</td>
<td>Mental health index</td>
</tr>
<tr>
<td>NorPD</td>
<td>Norwegian Prescription Database</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>OPPHED</td>
<td>Health survey in the Norwegian counties Oppland and Hedmark</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>OTC</td>
<td>Over the counter (without prescription)</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SMR</td>
<td>Standardized mortality ratio</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>TCA</td>
<td>Tricyclic antidepressant</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>Z-hypnotic(s)</td>
<td>Benzodiazepine related hypnotic(s), ATC code: N05CF</td>
</tr>
</tbody>
</table>
1.0 BACKGROUND

In Norway, prescriptions of anxiolytic and hypnotic drugs were filled by 6% and 8% of the population, respectively, in 2009 (1, 2). Appropriate use of these psychotropic drugs may relieve or reduce severe problems, whereas inappropriate use may represent problems of personal or public health. This thesis deals with some aspects of the epidemiology of psychotropic drug use in the general Norwegian population.

1.1 General introduction

Drug therapy is one of the most frequently used treatments of the majority of diseases and complaints, including mental disorders, in Western countries (3). Prior to marketing, every drug is subject to a randomized controlled trial (RCT), usually involving carefully selected patients over limited periods of time. The results of these trials form the basis for approval by regulatory bodies. Drugs for mental disorders have been on the market for more than 50 years but there is still a need for more knowledge about the use and impact of these drugs in real-life conditions. Pharmacoepidemiological studies are post-marketing observational studies that can be performed independently of the drug marketing company and preferably as population-based studies. This thesis relies on population-based observational data from different parts of Norway.

Pharmacoepidemiology can be defined as the application of epidemiological reasoning, methods and knowledge in the study of the uses and effects (beneficial and adverse) of drugs in human populations (4). The aim of pharmacoepidemiology is to describe, explain, control and predict the uses and effects of pharmacological treatments in a defined time, space and population. Pharmacoepidemiological research can be divided into two main fields; the first includes studies of variation in drug use in populations, drug use patterns, identification of predictors of use, and generation of hypotheses exploring variations of drug use. The other field includes case-control and cohort studies of for example side effects or adverse drug effects and studies investigating long-term effects of specific drugs in a population setting.
1.2 Mental disorders

There are numerous ways to classify and define different mental disorders, most likely because the field of mental health is far from straight-forward. The following definitions of mental disorders refer to tools commonly used by Norwegian general practitioners (GPs) and psychiatrists.

1.2.1 Definitions of the mental disorders relevant to this thesis

Anxiety

Fear, worry and anxiety are normal reactions to external and internal events that are perceived as threatening or dangerous (5). The mental anxiety experience is followed by physical symptoms such as palpitations, sweating or freezing (5). Anxiety disorders are characterized by excessive worry and trouble controlling worry, more than the somatic manifestations (6).

Insomnia

Insomnia can be defined as difficulty initiating or maintaining sleep for at least 1 month, which results in clinically significant distress or impairment in normal daytime functions (7). Insomnia may also be characterised by poor-quality or non-restorative sleep (7).

Depressive disorders

Depressive disorders are characterized by persistent low mood, loss of interest and enjoyment, neurovegetative disturbance and reduced energy, causing varying levels of social and occupational dysfunction (7). Depressive symptoms include depressed mood, anhedonia, weight changes, libido changes, sleep disturbance, psychomotor problems, low energy, excessive guilt, poor concentration and suicidal ideation (7).

1.2.2 Measuring mental disorders or mental distress

There are two main ways of measuring mental disorders or mental distress: by clinical diagnoses, or by self-reporting. A clinical diagnosis according to the International statistical classification of diseases and related health problems, 10th version (ICD-10) (8) or the Diagnostic and statistical manual of mental disorders, 4th version (DSM-IV) (6) can be given by GPs or psychiatrists, or estimated from the “Composite international diagnostic interview” (CIDI) (9) performed by trained interviewers. The less time-consuming method of self-reporting on a questionnaire is usually preferred in population-based surveys. The participants then answer questions related to mental health; forming an instrument like “Hopkins symptom
checklist” (HSCL-25, HSCL-10 among others) (10), “Mental health index” (MHI) (11), “General health questionnaire” (GHQ) (12), the Gothenburg quality of life instrument (GQL) (13) or “Hospital anxiety and depression scale” (HADS) (14). A Norwegian study comparing HSCL-25 to CIDI concluded that HSCL-25 was acceptable as a screener for diagnosis of depression, but not of anxiety disorder (15).

HSCL-10 and MHI-5 seem equally good as short instruments to measure mental distress and to predict mental disorders; however they both predict depression better than other diagnoses (16). HADS was found in a review to hold good case-finding properties for anxiety and depression; however no items regarding sleeping difficulties are included (17).

1.2.3 Mental health in Norway and abroad
In a Norwegian study using CIDI, the 12-month prevalence of all mental disorders was 33% and the life-time prevalence was 52% (18). In a survey carried out in the Norwegian county Nord-Trøndelag, 20.4% of the adult population had anxiety and/or depressive symptoms according to the HADS (19). From the same survey, the prevalence of sleep problems among patients in general practice was estimated to be 11.2%, of which almost two-thirds were believed to be caused by a medical condition and one-fourth by a mental condition (20).

A World Health Organization (WHO) study of patients in general practice conducted in 14 different countries, found that 24% had a current mental disorder; reaching ICD-10 criteria, whereas another 9% had a sub-threshold disorder (21). Being troubled by severe mental symptoms certainly can be considered a sign of poor perceived mental health but this is not the same as having a psychiatric diagnosis, although it may indicate an increased risk of developing one (22). Poor mental health is probably a strong predictor of psychotropic drug use, however not all individuals with mental distress will take psychotropic drugs (23, 24).
1.3 Psychotropic drugs

1.3.1 Classification
In this thesis I deal with a selection of drugs acting on the central nervous system (CNS): anxiolytics or hypnotics/sedatives, as well as antidepressants (Table 1). In the rest of this thesis I will use the term psychotropic drugs for these three drug groups. All drugs are classified according to the Anatomical therapeutic chemical classification system (ATC), and I will refer to this classification (25).

Anxiolytic drugs (ATC code N05B) are agents that alleviate anxiety, tension, and anxiety disorders, promote sedation and have a calming effect without affecting clarity of consciousness (26). Anxiolytics prescribed in Norway are mainly benzodiazepines (BZDs) (2). Hypnotics and sedatives (ATC code N05C) are used to induce drowsiness or sleep or to reduce psychological excitement or anxiety (26). BZDs and BZD related hypnotics (z-hypnotics) are the two main drug groups used for insomnia in Norway (2). Antidepressants (ATC code N06A) are mood-stimulating drugs used in the treatment of depressive disorders (26). Two-thirds of antidepressant drugs prescribed in Norway are selective serotonin reuptake inhibitors (SSRIs) (2).

1.3.2 History
The benzodiazepine era started globally with the release of chlordiazepoxide (Librium®) and diazepam (Valium®) in the early 1960s (27). The new drugs were soon preferred to the barbiturates, which had been used since the latter part of the 19th century. In 1978, Lader explained that this had happened because BZDs were more effective, safer in overdose, less liable to induce independence and had less effect on liver oxidizing enzymes (28). Five years later, Hollister stated “this is the benzodiazepine era”, although he simultaneously suggested that BZDs are not so remarkably different from the barbiturates (27). By the time of data collection for our first study (1985-1989), BZDs were practically the only anxiolytic and hypnotic drugs in Norway (29). Alternative hypnotic drugs were marketed in the 1990s, with the BZD related drugs z-hypnotics. In Norway, z-hypnotics are zopiclone and zolpidem and these drugs now dominate the market of hypnotic drugs (2, 29). Like BZDs, drugs for depression were first marketed in the 1960s (30). The non-selective monoamine reuptake inhibitors known as tricyclic antidepressants (TCAs) such as amitriptyline were, in the 1980s, supplemented by the sedative antidepressant mianserin; whereas the 1990s saw the massive introduction of SSRIs, but also other antidepressant drugs (Table 1) (31).
Table 1: A list of substances included in the thesis; with ATC codes and year of marketing authorisation and year of withdrawal, available in Norway in 1985-2007.
Source: Norwegian Drug Wholesales statistics, Norwegian Institute of Public Health.

<table>
<thead>
<tr>
<th>ATC code</th>
<th>Substance</th>
<th>Marketing</th>
<th>Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>N05B</td>
<td><strong>ANXIOLYTICS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N05BA01</td>
<td>Diazepam</td>
<td>1963</td>
<td></td>
</tr>
<tr>
<td>N05BA04</td>
<td>Oxazepam</td>
<td>1987</td>
<td></td>
</tr>
<tr>
<td>N05BA12</td>
<td>Alprazolam</td>
<td>1994</td>
<td></td>
</tr>
<tr>
<td>N05BB</td>
<td><strong>Diphenylmethane derivatives</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N05BB01</td>
<td>Hydroxyzine</td>
<td>1964</td>
<td></td>
</tr>
<tr>
<td>N05BE</td>
<td><strong>Azaspirodecanedione derivatives</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N05BE01</td>
<td>Buspironone</td>
<td>1992</td>
<td></td>
</tr>
<tr>
<td>N05C</td>
<td><strong>HYPNOTICS AND SEDATIVES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N05CD02</td>
<td>Nitrazepam</td>
<td>1965</td>
<td></td>
</tr>
<tr>
<td>N05CD03</td>
<td>Flunitrazepam</td>
<td>1984</td>
<td></td>
</tr>
<tr>
<td>N05CD05</td>
<td>Triazolam</td>
<td>1983</td>
<td>1991</td>
</tr>
<tr>
<td>N05CF</td>
<td><strong>Benzodiazepine related drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N05CF01</td>
<td>Zopiclone</td>
<td>1994</td>
<td></td>
</tr>
<tr>
<td>N05CF02</td>
<td>Zolpidem</td>
<td>2000</td>
<td></td>
</tr>
<tr>
<td>N06A</td>
<td><strong>ANTIDEPRESSANTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N06AA02</td>
<td>Imipramine</td>
<td>1982</td>
<td>1999</td>
</tr>
<tr>
<td>N06AA04</td>
<td>Clomipramine</td>
<td>1970</td>
<td></td>
</tr>
<tr>
<td>N06AA06</td>
<td>Trimipramine</td>
<td>1981</td>
<td></td>
</tr>
<tr>
<td>N06AA09</td>
<td>Amitriptyline</td>
<td>1961</td>
<td></td>
</tr>
<tr>
<td>N06AA10</td>
<td>Nortriptyline</td>
<td>1965</td>
<td></td>
</tr>
<tr>
<td>N06AA12</td>
<td>Doxepin</td>
<td>1970</td>
<td></td>
</tr>
<tr>
<td>N06AB</td>
<td><strong>Selective serotonin reuptake inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N06AB03</td>
<td>Fluoxetine</td>
<td>1996</td>
<td></td>
</tr>
<tr>
<td>N06AB04</td>
<td>Citalopram</td>
<td>1995</td>
<td></td>
</tr>
<tr>
<td>N06BA05</td>
<td>Paroxetine</td>
<td>1993</td>
<td></td>
</tr>
<tr>
<td>N06BA06</td>
<td>Sertraline</td>
<td>1996</td>
<td></td>
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<tr>
<td>N06BA08</td>
<td>Fluvoxamine</td>
<td>1990</td>
<td></td>
</tr>
<tr>
<td>N06BA10</td>
<td>Escitalopram</td>
<td>2002</td>
<td></td>
</tr>
<tr>
<td>N06AG</td>
<td><strong>Monoamine oxidase A inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N06AG02</td>
<td>Moclobemide</td>
<td>1990</td>
<td></td>
</tr>
<tr>
<td>N06AX</td>
<td><strong>Other antidepressants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N06AX03</td>
<td>Mianserin</td>
<td>1982</td>
<td></td>
</tr>
<tr>
<td>N06AX06</td>
<td>Nefazodone</td>
<td>1996</td>
<td>2003</td>
</tr>
<tr>
<td>N06AX11</td>
<td>Mirtazapine</td>
<td>2000</td>
<td></td>
</tr>
<tr>
<td>N06AX12</td>
<td>Bupropion</td>
<td>2000</td>
<td></td>
</tr>
<tr>
<td>N06AX16</td>
<td>Venlafaxine</td>
<td>1999</td>
<td></td>
</tr>
<tr>
<td>N06AX18</td>
<td>Reboxetine</td>
<td>1999</td>
<td></td>
</tr>
<tr>
<td>N06AX21</td>
<td>Duloxetine</td>
<td>2004</td>
<td></td>
</tr>
</tbody>
</table>

Drugs available as injections only are not included.
1.3.3 Pharmacology and clinical implications

Benzodiazepines

The major molecular targets of the BZDs are inhibitory neurotransmitter receptors directly activated by the amino acid gamma-aminobutyric acid (GABA) (30). The major type of GABA receptor in the brain, termed the GABA_A receptor, is an integral membrane chloride channel that mediates most of the rapid, inhibitory neurotransmission in the CNS. BZDs bind to this receptor/ion channel complex and allosterically modulate its activity (30). The conformational change in the GABA_A receptor increases the affinity of GABA binding, thus enhancing the actions of GABA on the Cl^- conductance of the neuronal membrane (32). Increasing the membrane potential of the neurone inhibits neuronal firing, and this reduces arousal of the cortical and limbic systems in the CNS (33). BZDs can cause cognitive (34) and psychomotor (35) impairment and have residual effects on the day following intake (36). BZDs carry the risk of drug abuse, dependence (37, 38) and the development of tolerance (39).

It is worth mentioning the indistinct boundary between anxiolytics and hypnotics. Anxiolytics may be used to aid sleep and thus be used as a hypnotic drug. People may change from one of these drug groups to the other without changing diagnosis. Their mechanism of action is similar. However, there are differences in their pharmacokinetics. The BZDs used in Norway, both anxiolytics and hypnotics, have long elimination half-lives. Abroad there are also BZD hypnotics with shorter half-lives which are preferred to avoid daytime sedation. Because of lack of relevance to this thesis, I have chosen not to describe the pharmacokinetics of BZDs in more detail here but refer to the literature (30).

Z-hypnotics

Like BZDs, the z-hypnotics bind at GABA_A receptors. However, z-hypnotics have a shorter onset and duration of action which is favourable unless sleep maintenance is the main problem (40). Noticeably, the drugs have different affinity for the GABA_A receptor subtypes. The GABA_A receptor selectivity is low for BZDs, medium for zopiclone and high for zolpidem (40, 41). The more selective receptor profile of zolpidem is expected to cause fewer adverse effects on sleep architecture (42), myorelaxation and respiratory depression (43), but current research still concludes that the different z-hypnotics are quite similar in clinical use (40). Reviews have stated that zopiclone and zolpidem can be abused (44), however the abuse liability is lower than that observed with BZD hypnotics (45).
Antidepressants
Most of the drugs used in the treatment of depression, like SSRI, TCA and others, in different ways inhibit the reuptake of serotonin and/or noradrenaline; resulting in increased release of the neurotransmitter(s) (32). These drug effects suggest that depression might be associated with decreased neurotransmitter activity; however some compounds like mianserin are antidepressant although they don’t affect reuptake, while cocaine blocks reuptake without being an antidepressant (32). Antidepressants are also used for other indications, such as anxiety and obsessive-compulsive disorder.

1.3.4 Guidelines, therapeutic recommendations and common practice
In Norway in 1990, the Directorate of Health issued, “Guide to the prescription of addictive drugs” (46). Revised and updated guidelines were published in 2001 by the Norwegian Board of Health Supervision with the modified title, “Addictive drugs. Prescribing and Justification” (47). After the reorganization of the Norwegian health administration from 2002 it was decided that the newly created Directorate of Health and Social Affairs (later renamed the Directorate of Health) would be responsible for issuing technical directives and guidelines. No new guidelines on the use of addictive drugs have been issued.

Norwegian therapeutic recommendations suggest that BZDs should be used as anxiolytics for shorter periods of time only, and, as hypnotics, intermittent use with the lowest possible dose is preferred (48, 49). Non-pharmacological treatment is the first choice in light to moderate anxiety and in chronic primary insomnia (≥3 weeks), and as a supplement to z-hypnotic drugs in acute situational insomnia (49). This is mainly in concordance with guidelines in the UK and the USA (50-52).

There are studies discussing guidelines and/or common prescription practice both in Norway (53) and abroad (40, 44, 45, 50, 54-56). Some review authors have (clearly or vaguely) recommended the use of z-hypnotics in preference to BZD hypnotics (42, 45, 55), while British guidelines recommend the use of BZD hypnotics with a short terminal elimination half-life (not marketed in Norway) in preference to z-hypnotics because of equal effects and lower prices (52).

In Norway, more than 80% of BZDs are prescribed by GPs (57). Several studies have covered GPs’ or psychiatrists’ attitudes to and prescribing of BZD anxiolytics, BZD hypnotics and/or
z-hypnotics (20, 58-62). At the time of initiating BZD prescription, some GPs seem to feel overwhelmed by the psychosocial problems of patients, and find BZDs to be “the lesser evil” (58). Regarding duration of treatment, both GPs and psychiatrists may agree with guidelines, however they find them hard to follow (61, 63). GPs’ knowledge about z-hypnotics has been questioned, both in Norway and abroad (59, 61-63). In a recent national survey of all GPs practising in Norway, sleep hygiene advices were the most commonly used treatment strategy, whereas hypnotics were believed to have the best short-term efficacy (20). Antidepressants were considered by the GPs to be the best option for long-term management of sleep problems. The authors mention as one possible explanation of this finding that depression very often coexists with insomnia: alleviating depressive symptoms are likely to also reduce sleep problems (20).

The use and misuse of BZDs is disputed. However, the concept of inappropriate use must be approached with caution. Strictly speaking it is defined as use that does not meet clinical needs, in doses that do not match individual requirements, for an inadequate period of time, or at a cost that is not acceptable for the patient or the community (64).

At population level, however, inappropriate use may be suspected if there are important unexplained differences, for example, in the use of BZDs between different population groups. One way to explore this is to examine the use of BZDs in relation to specific mental health conditions (24).
1.4 Population-based sources of data on psychotropic drug use at an individual level in Norway

The possibility of doing high quality research on drug exposure in Norway has steadily improved, as information on drug use has been collected, step by step, in more detail, and closer to the actual user. There has been a development from annual reports of drug sales as reported from wholesalers, via health surveys, to the current nationwide prescription database.

1.4.1 Population-based health surveys

Since the early 1970s, a series of population-based health surveys have been conducted by the National Health Screening Services, now part of the Norwegian Institute of Public Health, in different Norwegian counties. These health surveys have collected information about drug use at an individual level (65). The questions about drug use in general have developed from simple questions with only a dichotomous outcome, to answer alternatives specifying the frequency of drug use (66). The drug categories included have also developed, from questions about the use of antihypertensive drugs only to a battery of drug categories (67).

Most of the health surveys included a physical examination with, for example, blood pressure measurement and blood samples. At the physical examination, a supplementary questionnaire was usually handed out. Questions about anxiolytic and hypnotic drug use were at first included in the supplementary questionnaire, leading to a lower response rate than if they had been part of the main questionnaire (68). However, from the year 2000, questions on anxiolytic and hypnotic drug use were included in the main questionnaires (67).

1.4.2 The Norwegian Prescription Database

The Norwegian Prescription Database (NorPD) covers the entire nation (4.8 million inhabitants) (69). From January 1st 2004, all pharmacies in Norway have been legally obliged to provide data on all dispensed prescriptions to the Norwegian Institute of Public Health. NorPD contains information on all individuals not living in institutions who have received prescription drugs dispensed at pharmacies (70). All prescriptions from ambulatory care are stored in the database. Antidepressants are covered by the national reimbursement system in Norway, whereas anxiolytics and hypnotics are not. However, in contrast to prescription databases in Denmark and Finland, NorPD includes full information about non-reimbursed drugs in addition to the reimbursed (71).
All drugs in Norway are classified according to their main substance in ATC, which is useful in order to retrieve and analyse data about psychotropic drugs on a substance level. Even if identical substances are marketed as different, competing drug trademarks; in different packages and with different sales codes, ATC gathers all identical substances under one code. Another useful research tool is the defined daily dose (DDD): The assumed average maintenance dose per day for a drug, used for its main indication in adults (25). NorPD offers the number of DDD for each prescribed drug substance to each person; making it possible to calculate the amount of the drug prescribed and the duration of treatment for each individual.

NorPD does not include medications for individuals in hospitals and nursing homes. Estimates of the use of psychotropic drugs among people over 70 years will be low because a significant proportion will be in nursing homes, from where data is only available on an institutional level.

1.5 The history of psychotropic drug use in Norway

1.5.1 Anxiolytics and hypnotics

Aggregated level

BZDs dominated the sales of anxiolytics and hypnotics from the 1960s until the mid 1990s (29). Sales of benzodiazepines increased sharply in Norway in the 1960s and 1970s. In the 1980s, there was an increasing focus on the use of benzodiazepines and problems associated with negative effects (29). The sale of anxiolytics (N05BA) was reduced from 29 DDD/1000 inhabitants/day in the early 1970s to 17 DDD/1000 inhabitants/day in 1997 (72). This was followed by a small increase. However, since 2006, sales have once more decreased and been below 20 DDD/1000 inhabitants/day (2).

Wholesaler statistics for anxiolytics and hypnotics from 1985 to 2009 are shown in Figure 1. For BZDs used as hypnotics, there was a peak in the use in the period 1984–1990. The peak of 43 DDD/1000 inhabitants/day (1989) and the following decline to 25 DDD/1000 inhabitants/day (1994) were due to the introduction and withdrawal of the hypnotic drug triazolam (Halcion®) in 1983 and 1991, respectively (29). In 1994, z-hypnotics were introduced. After this, the sale of BZD hypnotics was further reduced. However, z-hypnotics contributed to the total sale of hypnotics again rising to above 40 DDD/1000 inhabitants/day.
since 2005 (2, 29). Total sales of anxiolytics and hypnotics levelled out somewhat in 2008 and 2009 after several years of increase (29).

**Figure 1** Sales of BZD anxiolytics (ATC code N05BA), BZD hypnotics (N05CD) and z-hypnotics (N05CF) in Norway 1985-2009. Source: Norwegian Drug Wholesales statistics, Norwegian Institute of Public Health. ATC/DDD version 2010.

Individual level
A study from a rural part of Norway (Værøy and Røst in Lofoten) in 1971, showed that anxiolytics and hypnotics were prescribed to 17% of the women and 11% of the men (73). In 1980, the corresponding total number for both genders was 25% in Østfold (74), a county still known to have an extensive consumption of these drugs (2). The studies from 1971 and 1980 showed that two thirds of BZD users were women and that the prevalence of use increased with age (73, 74).

The establishment of the nationwide prescription database in 2004 made it possible to present individual data on the use of anxiolytics and hypnotics for the whole country. Data from NorPD shows that during each of the years 2004-2009, 8% of the inhabitants filled prescriptions for hypnotics, and the percentage increased slowly (1). During the past six years, the number of inhabitants filling prescriptions for BZD hypnotics (N05CD) decreased, while the corresponding number for z-hypnotics (N05CF) increased a bit more, explaining the overall rise (1).
To describe use on an individual level, I will use “one year prevalence”, the number of users who filled at least one prescription during a certain year per 100 inhabitants in the population sample; in this case the whole of Norway. Figure 2a shows one year prevalence of use of BZD hypnotics in Norway in 2004-2009 for adult men in 10-year age groups. The prevalence increases with increasing age and decreases annually within the age groups. The same tendencies are shown for women in Figure 2b.

**Figure 2a** One year prevalence (%) of use of benzodiazepine hypnotics among adult men in Norway 2004-2009. Source: NorPD.

**Figure 2b** One year prevalence (%) of use of benzodiazepine hypnotics among adult women in Norway 2004-2009. Source: NorPD.
During 2004-2009, the prevalence of z-hypnotics in Norway increases or is practically stable within each age group for both men and women (Figure 3a and 3b). Comparing the age groups, the prevalence increases with increasing age.

**Figure 3a** One year prevalence (%) of use of z-hypnotics among adult men in Norway 2004-2009. Source: NorPD.

**Figure 3b** One year prevalence (%) of use of z-hypnotics among adult women in Norway 2004-2009. Source: NorPD.
1.5.2 Antidepressants

Aggregated level

The total sale of antidepressants (N06A) has increased every year except one (2005) since they were marketed (2, 72), however the development for each category of antidepressants deviates from this. The sale of TCA has decreased slowly and the sale of SSRI has increased rapidly since the introduction of SSRI in 1990. Wholesaler statistics for antidepressants from 1985 to 2009 are shown in Figure 4.

Figure 4 Total sales of antidepressants (ATC code N06A), dominated by SSRI (N06AB) and the tricyclic antidepressants (N06AA) in Norway 1985-2009. Source: Norwegian Drug Wholesales statistics, Norwegian Institute of Public Health. ATC/DDD version 2010.

A Norwegian study of the sale of SSRI and other antidepressants 1990-2004 showed large changes in the sale of each antidepressant drug during the period, most likely as a consequence of new drugs being marketed and side effects of existing drugs being reported (31).
1.5.3 Norway compared to other countries

Psychotropic drug sales data from the Nordic countries are compared by Nordic Medico Statistical Committee by the use of DDD/1000 inhabitants/day (75). Norway is most often placed in the middle of the consumption statistics. In 2007, Finland and Iceland had a higher consumption of BZD anxiolytics than Norway, whereas Denmark and Sweden had a lower consumption. The latter two countries were the only ones to show a reduction in BZD anxiolytics since 1995.

Regarding BZD hypnotics, Finland was the highest consumer in 2007; with approximately twice as many DDD/1000 inhabitants/day as Iceland, whereas Denmark, Norway and Sweden consumed even less. Noticeably, all the Nordic countries reduced the consumption of BZD hypnotic drugs by at least 60% between 1995-2007, except for Finland; showing a stable level.

For z-hypnotics, Iceland showed the highest consumption in 2007; and nearly twice that of Norway, Finland and Sweden. Denmark was at the bottom consuming only one-third as much as Iceland. All five countries have shown a marked increase in the consumption of z-hypnotics since they were introduced, however the increase has been moderate during the past few years.

For antidepressants in general, Iceland had the highest consumption in 2007, whereas Norway had the lowest; and this also counted for SSRI alone. All the Nordic countries showed a decreasing consumption of TCA and an increasing consumption of SSRI during 1995-2007.

Surveys in six European countries in 2001-2003 reported a prevalence of psychotropic drugs ranging from 6% to 19%, however there were no separate data for anxiolytics, hypnotics or antidepressants (76).
1.6 **Previous epidemiological findings**

1.6.1 Benzodiazepine use and mortality

The use of BZDs and later mortality has been studied in general populations (77-82) and in subgroups such as patients dependent on prescription drugs (83), drug misusers (84) or drugged drivers (85, 86). The sources of information on drug use were questionnaires, interviews, diagnosed dependency or results from blood tests taken from drivers. The definition of BZD use in general populations varied, as did the population sample size and the period of follow-up. Some authors have found increased all-cause mortality after BZD use (78-80, 83-86), whereas others have not (77, 81, 82).

1.6.2 Hypnotic drug use

The use of hypnotic drugs has been studied earlier both in Norway (87-90) and abroad (75, 76, 91-95), sometimes as part of studies on the use of BZDs or psychotropic drugs in general. The sources of information on drug use have been questionnaires, interviews of GPs or general population, journal data, prescription data or sales data.

In Norway, a study using data from NorPD showed that 7.9% of the population received at least one prescription of a hypnotic drug in 2005 (88), comparable to the 6.9% found from telephone interviews a few years earlier (89). In a survey in the Norwegian county Nord-Trøndelag, 3.5% of the participants answered on a questionnaire that they had used sleep medications and 3.1% had used sedatives, in both cases on a daily or almost daily basis during the past 12 months, but the authors explained that there was a possible overlap because the categories were not mutually exclusive (90). In Norway, wholesaler statistics show an increasing annual amount of hypnotics sold (96), however a change in the sales of different hypnotic drugs was observed after restrictions in the prescription status of flunitrazepam in 2003 (87).

Abroad, studies on long-term use of BZDs or z-hypnotics are easy to find (97-100), whereas studies on incident use; the early phase of every history of long-term use, are scarce. Some authors have studied the aggregated incidence of BZD hypnotics, z-hypnotics and BZD anxiolytics (91, 94).
Recent studies have found z-hypnotics to be prescribed more often than BZDs (92, 95). Concomitant use of any other psychotropic drug was associated with higher use of BZDs with medium acting time, but lower use of z-hypnotics (92). When studying zopiclone and zolpidem separately, the drugs showed divergent patterns: concomitant use of any other psychotropic drug was associated with lower use of zolpidem, whereas concomitant use of antidepressants was associated with higher use of zopiclone (92).

As far as I know, predictors of which hypnotic drug is chosen at the start of insomnia treatment have not been studied.

### 1.6.3 Factors associated with psychotropic drug use

In cross-sectional studies, the use of one or more categories of psychotropic drugs in the general population has been shown to be associated with certain health, lifestyle and socioeconomic factors: female gender (24, 93, 101), increasing age (24, 93, 101), poor self-reported somatic health (24, 93, 101-103), diagnosed concurrent chronic somatic morbidity (104), help seeking for mental/emotional problems (101, 105), mental distress indicators (106), psychological pathology (24, 93, 101), psychiatric co-morbidity (104), the use of analgesics (107), the prescription of other psychotropics (108), smoking (105, 109), heavy drinking (110), marital status (111), low educational level (93, 101, 112), low income (111) and non-participation in the labour market (110, 113).

The sources of information on drug use have been questionnaires, interviews, GPs’ medical records or journal data. As far as I know, there has not been any prospective cohort study investigating mental distress as a predictor of anxiolytic drug use.

The use of psychotropic drugs among people with mental distress or mental disorders has been studied both for institutionalized (114-116) and non-institutionalized populations (23, 24, 76, 90, 101, 104, 107, 108, 117).

The use of psychotropic drugs among people with mental distress in non-institutionalized populations has ranged from 15% (23) to 48% (101); however this variation may partly be explained by different measures of both mental distress and drug use. One study showed that men scoring over the GHQ-30 score threshold (>5) for psychiatric morbidity had a risk of receiving a psychotropic drug prescription 49 times higher than the general sample (117).
Studies on predictors of BZD use are less common, as most longitudinal studies focus on long-term and chronic use of BZDs (98, 99). Research on predictors of BZD use in non-institutionalized populations with mental distress symptoms rather than mental disorders is lacking.

### 1.7 Why study anxiolytics and hypnotics?

Appropriate use of BZDs can be defined as use by indication – mainly as treatment for anxiety or sleeping problems. However, the use of BZDs can cause cognitive (34) and psychomotor (35) impairment and carry the risk of drug abuse and dependence (37, 38). Therefore, the comprehensive use of BZDs has been controversial (118, 119) and the drugs are constantly being discussed and studied. BZDs are known to be habit forming and they may cause dependency (37, 38, 120) and adverse drug reactions (39, 120, 121). BZD use increases the risk of falls among the elderly (122). Both BZDs and z-hypnotics are known to be traffic-hazardous drugs (35), and impaired drivers increase the risk of road traffic accidents (123). Taking into account that more drivers are apprehended with BZDs than with heroin or amphetamine, one can ask whether BZDs are a greater threat to traffic safety (124).

Apprehension on suspicion of driving under the influence of drugs, combined with detection of BZDs or z-hypnotics in the blood, seems to indicate an elevated risk of premature death (85).

For z-hypnotics, there are fewer and milder described adverse effects compared to BZDs. Zopiclone may cause a bitter taste, whereas zolpidem can cause CNS-associated adverse effects such as headache and daytime somnolence (41). Antidepressants may cause adverse effects that can be difficult to separate from the depressive diagnosis: dry mouth, fatigue, dizziness, headache and reduced libido (125). A Norwegian study showed a slightly increased risk of being involved in a road traffic accident after receiving a prescription for any antidepressant drug (126).

Inappropriate use of psychotropic drugs represents a personal and public health problem. The economic aspect is worth mentioning, as drugs which affect the CNS (ATC code N) currently have the second highest per cent share per ATC group of the total sales in Norway; 17 % (measured in NOK) (2).
Problematic aspects of the use of anxiolytics and hypnotics are well documented, and the epidemiology of use in general has been studied thoroughly. On the other hand, most existing studies tend to focus on long-term use, abuse, use among the elderly, use in the general population or in institutions. We lack knowledge about subgroups of the general population, such as, non-institutionalised middle-aged people who have symptoms of mental distress although not necessarily enough to be diagnosed as having a mental disorder.
2.0 AIMS OF THE STUDY

The main objective of this thesis was to study the epidemiology of anxiolytic and hypnotic drug use and, to a lesser extent, antidepressant drug use in the general population in Norway – in both cross-sectional and prospective cohort studies.

The specific research questions were:

- Does anxiolytic and hypnotic drug use in the 1980s predict higher mortality in a general middle-aged population? (Paper I)
- Does co-medication with other drugs predict the type of hypnotic drug chosen in incident users? (Paper II)
- What health, lifestyle and sociodemographic factors are associated with anxiolytic, hypnotic and/or antidepressant drug use among people with mental distress? (Paper III)
- Do mental distress symptoms predict later anxiolytic drug use? (Paper IV)
- Are there gender differences in the epidemiology of anxiolytic, hypnotic and antidepressant drug use? (Papers I-IV)
3.0 MATERIAL AND METHODS

3.1 Sources of data and study population

This thesis is based on data from four health surveys and the Norwegian Prescription Database: surveys done by the National Health Screening Service (now the Norwegian Institute of Public Health) in the counties of Østfold in 1985/1988 and Aust-Agder in 1986/1989 (paper I) (68), and in Oslo and the counties of Oppland/Hedmark in 2000-2001 (papers III and IV) (127, 128) and the Norwegian Prescription Database (papers II and IV) (1). Both genders were included in all the study populations. The materials used in the different papers are presented in Table 2.

Table 2 The study populations in papers I-IV

<table>
<thead>
<tr>
<th>Area of study</th>
<th>Study period</th>
<th>Information on drug use</th>
<th>Age at baseline</th>
<th>Respondents (Response rate %)</th>
<th>Female (% of respondents)</th>
<th>Paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Østfold and Aust-Agder</td>
<td>1985/1988, 1986/1989</td>
<td>Health survey; supplemental questionnaire</td>
<td>40-42</td>
<td>23 154 (76.3)</td>
<td>11 910 (51.4)</td>
<td>I</td>
</tr>
<tr>
<td>Oslo and Oppland/Hedmark</td>
<td>2000-2001</td>
<td>Health survey; main questionnaire</td>
<td>30, 40, 45, 59/60, 75/76</td>
<td>31 274 (49.5)</td>
<td>17 186 (55.0)</td>
<td>III, IV</td>
</tr>
<tr>
<td>Norway</td>
<td>2004-2007</td>
<td>Prescription database</td>
<td>All ages</td>
<td>All individuals who filled prescriptions</td>
<td></td>
<td>II, IV</td>
</tr>
</tbody>
</table>

3.1.1 Health surveys


These population-based health surveys were carried out in the counties of Østfold in 1985 and 1988 and in Aust-Agder in 1986 and 1989. Østfold and Aust-Agder are counties characterised by a high-population use of anxiolytic and hypnotic drugs. In total, 30 354 subjects aged 40-42 years were invited to participate (68). The health surveys were part of a project that started with health surveys in other counties in the 70s, and was directed towards cardiovascular disease (129, 130). Two examinations, targeting two different generations of people 40-42 years at the time of the survey, were carried out with a 3 year interval. One self-administered questionnaire was part of the letter of invitation. The questions on drug use were included in the supplementary questionnaire, which was handed out at the medical examination, and returned in pre-stamped envelopes. The questionnaires provided information on various health, lifestyle and socioeconomic factors, and are found in Appendix I.
In total, 23,154 individuals attended the medical examination, giving a total response rate of 76.3%. Of these, 19,032 individuals responded the supplementary questionnaire (9,111 men and 9,921 women).

Among these 19,032 individuals, the question on anxiolytic or hypnotic drug use was answered by 85% of the men and 83% of the women. We wanted to study a healthy population, and excluded individuals suffering from or with symptoms indicating heart infarction, angina pectoris, diabetes and stroke before hazard ratios were estimated. This was done because such individuals already had a possible elevated risk of death.

Health Surveys in Oslo (2000-2001) and Oppland/Hedmark (2000-2001)
These population-based health surveys were carried out in the counties of Oslo, Oppland and Hedmark in 2000-2001. The Oslo Health Study (HUBRO) (128) and the Oppland and Hedmark Health Study (OPPHED) (127) were performed in a very similar way, but whereas HUBRO covers an urban population (Oslo is the capital of Norway), OPPHED covers a rural population, as Oppland and Hedmark do not host any of the 20 biggest towns in Norway. An invitation to attend a health screening was sent to all individuals born in 1924 (HUBRO only), 1925, 1940, 1941 (HUBRO only), 1955, 1960 and 1970 (127, 128). A total of 63,160 citizens were invited. Of these, 31,274 individuals attended a physical examination and/or filled in at least one questionnaire, giving a total response rate of 49.5%.

For our study (papers III and IV), only individuals born 1940, 1941, 1955 and 1960 were selected, that is, those who were about 40, 45 and 60 years old. The drug use questions were included in the main questionnaire (131-133), which was part of the invitation letter. The main questionnaires in HUBRO and OPPHED were identical and can be found in Appendix II. Several of the questions have been evaluated or validated and deemed acceptable (65). The National Population Register was used to identify eligible subjects.

3.1.2 Health or population registries
The Norwegian Prescription Database (NorPD)
Data on anxiolytic drug use for paper IV were taken from the NorPD which covers the entire nation. NorPD contains information on all prescriptions to individuals not living in institutions, who have received prescription drugs dispensed at pharmacies (70). All prescriptions from ambulatory care, whether publicly reimbursed or not, are stored in the
database. Anxiolytics and hypnotics are prescription drugs in Norway, and thus the drug use data for this thesis cover the whole Norwegian non-institutionalised population.

The data collected for our study were patient unique identifying number (encrypted), sex, age, the date of dispensing and drug information (ATC code and DDD). Information on drugs studied is given in the Variables section. The study period was 2004-2006 (paper II) and 2004-2007 (paper IV). In paper II, all individuals of age 18-69 years were selected, whereas in paper IV, age cohorts that were 40-41, 45-46 and 59-61 years old at baseline were selected.

The National Population Register
Information about marital status (papers I and IV) was retrieved from the National Population Register (134).

The Norwegian Causes of Death Register
Number of deaths for different groups and both sexes were obtained from the Norwegian Causes of Death Register (135). In paper I, this was used to calculate mortality. In paper IV, this was used to exclude individuals who died or emigrated between baseline (2000-2001) and the release of NorPD (January 1st 2004). During further follow-up (2004-2007) information on deaths was available from NorPD.

3.2 Design
Table 3 shows the study design used in each of the papers.

Table 3 Design in papers I-IV

<table>
<thead>
<tr>
<th>Design</th>
<th>Paper number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Cohort study</td>
<td>x</td>
</tr>
<tr>
<td>Cross-sectional study</td>
<td></td>
</tr>
</tbody>
</table>
3.3 Variables

3.3.1 Dependent variables

The dependent variables used in the different papers are shown in Table 4.

Table 4 Dependent variables used in papers I-IV

<table>
<thead>
<tr>
<th>Domain</th>
<th>Examined</th>
<th>ATC code</th>
<th>Paper number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Mortality</td>
<td>Hazard ratio</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Drug use</td>
<td>Incident users; z-hypnotics versus BZD hypnotics</td>
<td>N05CF/N05CD</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Use of anxiolytic drugs</td>
<td>N05B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Use of hypnotic drugs</td>
<td>N05C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Use of antidepressants</td>
<td>N06A</td>
<td></td>
</tr>
</tbody>
</table>

Mortality

For the dependent variable “hazard ratio” (HR) in paper I, information about deaths was retrieved from the Norwegian Causes of Death Register that is kept by Statistics Norway (69). The number of observation years was calculated for each person from the time of medical examination to either the time of death, the time of emigration or the end of follow-up period (27.01.2006).

Drug use

This thesis deals mainly with anxiolytics (papers I, III and IV) and hypnotics (papers I, II and III). In paper III, antidepressants are also included. An overview of the substances on the Norwegian market is given in Table 1. Information on drug use as dependent variables was collected from health surveys (paper III) or NorPD (papers II and IV).

Incident users in 2006 of BZD hypnotics or z-hypnotics were identified from NorPD for paper II. We identified incident users as individuals filling a prescription in 2006, without any recorded prescription of any hypnotic substance during the 730 days (2 years) prior to that prescription. BZD hypnotics were nitrazepam or flunitrazepam; ATC code N05CD, whereas z-hypnotics were zopiclone and zolpidem; ATC code N05CF.

The use of anxiolytics in 2004-2007 was identified from NorPD for paper IV; ATC code N05B. The anxiolytics used in Norway are three BZDs – diazepam, oxazepam and alprazolam – and two non-BZDs – hydroxyzine and buspirone. Users were defined as having filled one or more anxiolytic drug prescriptions during 2004-2007.
The use of different types of drugs was, for paper III, recorded from health surveys, with the following questions and answering alternatives: “How often during the last four weeks have you taken (a) anxiolytics (b) hypnotics and/or (c) antidepressants? (1) Daily; (2) Every week, but not daily; (3) Less often than every week; (4) Not taken during the last four weeks. Individuals who answered 1, 2 or 3 were defined as users. People who had used anxiolytics and/or hypnotics were treated together, but if some of these also had used antidepressants, they were categorised as antidepressant users instead. People who had used neither of these drug categories were defined as non-users.

3.3.2 Independent and/or confounding variables
The independent variables used in the different papers are shown in Table 5.

Drug use
Information on drug use as independent variables for papers I, III and IV was collected from health surveys. In HUBRO and OPPHED (papers III and IV), the question on use of anxiolytics, hypnotics or antidepressants and answering alternatives read “How often during the last four weeks have you taken (a) anxiolytics (b) hypnotics and/or (c) antidepressants? (1) Daily; (2) Every week, but not daily; (3) Less often than every week; (4) Not taken during the last four weeks. Individuals who answered 1, 2 or 3 were defined as users. The questions on use of analgesics or other prescription drugs were similar. In Østfold and Aust-Agder (paper I), the use of anxiolytics, hypnotics or analgesics during the past month was asked for, with the same answering alternatives as in HUBRO and OPPHED; however there were no questions on antidepressants or the category “other prescription drugs”.

Users of analgesics were, in papers I and III, defined as people who answered that they had used analgesics daily or every week during the previous month. People who used analgesics less than every week were defined as non-users according to probable common monthly use of analgesics among women because of menstrual pain. The use of analgesics was defined in the same way for men. There were separate questions regarding the use of analgesics on prescription or over the counter (OTC) in HUBRO and OPPHED (papers III and IV), both contributing to the “use of analgesics” variable. In paper IV, individuals who had used OTC analgesics less frequently than every week were defined as non-users. In Østfold and Aust-Agder, there was only one question on analgesic drug use, which did not distinguish between prescribed and OTC drugs.
Information on drug use as independent variables for paper II was retrieved from NorPD. Filled prescriptions two years prior to the participants’ first prescription for hypnotics were registered for the following drugs: BZD anxiolytics, antidepressants, antipsychotics and lithium, opioid analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and anti-diabetic drugs (oral insulin for injection).

Table 5 Independent and/or confounding variables used in papers I-IV

<table>
<thead>
<tr>
<th>Domain</th>
<th>Examined</th>
<th>Paper number</th>
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<tr>
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<td>I</td>
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<tr>
<td>Drug use (ATC code)</td>
<td>Use of anxiolytic drugs (N05B)</td>
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<td></td>
<td>Use of hypnotic drugs (N05C)</td>
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<td></td>
<td>Use of antidepressants (N06A)</td>
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<td></td>
<td>Use of antipsychotics (N05A)</td>
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<td></td>
<td>Use of analgesics(^a)</td>
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<td></td>
<td>Use of other prescribed drugs</td>
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<tr>
<td>Health status</td>
<td>HSCL-10 score(^b)</td>
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<td></td>
<td>Mental distress for which one sought help</td>
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<td></td>
<td>Self-reported health</td>
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<td></td>
<td>CVD or diabetes symptoms or drugs</td>
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<td></td>
<td>Musculo skeletal pain</td>
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<td></td>
<td>Body mass index</td>
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<td></td>
<td>Blood pressure</td>
<td>x</td>
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<tr>
<td></td>
<td>Blood test variables</td>
<td>x</td>
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<td></td>
<td>Use of health services other than GP</td>
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<tr>
<td>Lifestyle</td>
<td>Smoking</td>
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<td></td>
<td>Alcohol consumption</td>
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<td></td>
<td>Coffee consumption</td>
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<td></td>
<td>Physical activity</td>
<td>x</td>
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<tr>
<td>Demographics</td>
<td>Gender</td>
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<tr>
<td></td>
<td>Age</td>
<td>x</td>
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<td></td>
<td>Marital status</td>
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<td></td>
<td>Prescriber's speciality</td>
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<td>Socioeconomic factors</td>
<td>Educational level</td>
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<td></td>
<td>Domestic work as main occupation</td>
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<tr>
<td></td>
<td>Receiving sick leave, unemployment benefits, rehabilitation benefits or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>disability pension(^c)</td>
<td>x</td>
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</table>

\(^a\) Paper I, III and IV: analgesics in general; prescribed or over the counter  
\(^b\) Paper II: opioid analgesics (N02A) or NSAIDs (M01A); prescribed only  
\(^c\) Paper I: not unemployment benefits  
\(^c\) Paper II: only disability pension
Health status
Information on health status was collected from health surveys for papers I, III and IV.

**HSCL-10 score**
Mental distress symptoms measured by HSCL-10 score were used both during selection (paper III) and as an independent variable (paper IV) (Table 5). The questionnaires in HUBRO and OPPHED included Hopkins symptom checklist-10 (HSCL-10); a screening instrument measuring mental distress symptoms in the general population, which is derived from the widely used HSCL-25 (108). HSCL measures certain aspects of mental distress by symptom questions and has shown good psychometric properties (10).

The 10-item version (HSCL-10) captures symptoms of depression and nervousness during the previous week and consists of the following ten items: suddenly scared for no reason; feeling fearful; faintness, dizziness, or weakness; feeling tense or keyed up; blaming yourself for things; difficulties falling asleep or staying asleep; feeling blue; feeling of worthlessness; feeling everything is an effort; feeling hopeless about the future. Each item was rated on a scale of 1 (not troubled) to 4 (troubled a lot), and the mean score was used as a measure of mental health. Individuals answering fewer than six of the ten questions were given no mean score.

In paper III, HSCL-10 score was rather a selection criterion than an independent variable. There were two age groups for both sexes, and only the 15% with the highest mean HSCL-10 score in each group were selected for the study. The cut-off values were for adult women: ≥ 1.80; elderly women: ≥ 1.90; adult men: ≥ 1.60; elderly men: ≥ 1.60.

In paper IV, participants in each of the two age groups for both sexes were divided into quartiles (Q1-Q4) according to their HSCL-10 score at baseline. Baseline characteristics were shown for each quartile in each of the two age groups for both sexes. In the multivariate analysis, HSCL-10 score quartile was an independent variable, with the lowest quartile as referent.

*Mental distress for which one sought help*
The question on mental distress read: “Have you experienced mental distress for which you have sought help?” with answering alternatives “yes” and “no” (paper IV).
Self-reported health

Self-reported health was measured by the question: “How would you describe your present state of health?” in papers III and IV. The response categories were poor, not very good, good and very good; in the analyses they were dichotomised into “good or very good” and “poor or not very good”. Similar questions are used and validated elsewhere (136).

CVD or diabetes symptoms or drugs

Participants ticked “yes” or “no” for questions on present or previous myocardial infarction, angina pectoris, stroke and diabetes, and were asked to report if they were now using medicines because of high blood pressure or cholesterol. From this, two groups were defined in paper IV: Those 1) with and 2) without a history of cardiovascular disease (CVD) and diabetes or CVD and diabetes drug use. The questions on CVD and diabetes have been validated, suggesting that questionnaire information on myocardial infarction is reliable and more reliable than similar information on stroke (underreporting) and diabetes (reporting error difficult to quantify) (137).

Musculo skeletal pain

Six potential areas for musculo skeletal pain were listed in the questionnaire. The participants reported if they had suffered from pain and/or stiffness in muscles and joints in these areas in the course of the last four weeks, by ticking off “very troubled”, “somewhat troubled” or “not troubled” in each of the six areas. In the analyses we did not distinguish between “very troubled” and “somewhat troubled”, and the number of painful areas was divided into “no”, “1-2” or “3-6 painful areas” (paper IV).

Body mass index

Weight and height were measured at the medical examination, and the Body mass index (BMI) was calculated in papers I and IV. The values were dichotomised into BMI < 30 and BMI ≥ 30 kg/m², which is classified by WHO as obese (138).

Blood pressure

The medical examination comprised measurements of systolic and diastolic blood pressure. Mean values of both systolic and diastolic blood pressures were among the baseline characteristics in paper I. In paper IV, the limit between normal and high blood pressure was set at > 140/90 mm Hg (48).
Blood test variables

At the medical examination, venous non-fasting blood samples were drawn for measurements of serum total cholesterol, glucose and triglycerides to be determined at the Central Laboratory of Ullevål Hospital, Oslo (68). Total cholesterol, triglycerides and high-density lipoprotein (HDL) were among the baseline characteristics in paper I.

Use of other health services than GP

This implied the use of a company doctor, psychologist, psychiatrist or other specialist, admission to hospital or home nursing service during the last 12 months (paper IV).

Lifestyle

Information on lifestyle was collected from health surveys for papers I, III and IV.

Smoking

The questions on smoking habits in the health surveys in Østfold and Aust-Agder (paper I) read: “Do you smoke daily at present?” with answering alternatives “yes” and “no”; “How many cigarettes do you or did you previously smoke daily? State the number of cigarettes.” A different question on smoking in HUBRO and OPPHED (papers III and IV) made it possible to separate previous smokers from other current non-smokers. The question read: “Have you smoked/do you smoke daily?” with answering alternatives “yes, now”, “yes, earlier” and “no”.

Alcohol consumption

The question on alcohol in Østfold and Aust-Agder (paper I) concerned alcohol consumption in the past 14 days, with five possible answering categories, and from this the dichotomous variable “teetotaller” versus “others” was made. In HUBRO and OPPHED (papers III and IV) alcohol consumption in the past year was asked for by giving eight possible answering categories, that was divided into three; “teetotaller”, “up to three times a week” and “4-7 times a week”.

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Coffee consumption
Participants were asked to tick off one category of number of cups of coffee usually drunk per day, and from this the dichotomous variable “up to four cups” and “five or more cups of coffee/day” was made in paper I.

Physical activity
Participants in Østfold and Aust-Agder (paper I) were asked to tick off one mean level out of four described levels of physical activity in their spare time. Ticking off the less active level meant “seldom/never physical active”. In HUBRO and OPPHED (papers III and IV), participants were asked to estimate the number of hours per week of a) light exercise and b) hard physical activity. Light and/or hard activity less than one hour per week was set as “low physical activity”.

Demographics
Information on demographics was collected from health surveys as well as health and population registries for papers I-IV.

Age
In paper I, the participants were all of the same age (40-42 years). In paper II, the participants were categorised into 10 year age groups; the youngest one (18-29 years) being the referent. In paper III and IV, adults and elderly were treated separately: 30/40/45 years and 60 years (paper III); 40/45 years and 60 years (paper IV). In paper III, within the adults, the 40/45 year old participants were compared to the reference group of those 30 years old.

Marital status
Information about marital status was retrieved from the National Population Register. In paper I, the variable was dichotomised into “married” and “unmarried or formerly married”. In paper IV, the variable was dichotomised into “married or in partnership” and “not married, widower, divorced or separated”.

Prescriber’s speciality
Prescriber’s speciality was retrieved from NorPD, and categorised into: “psychiatry”; “general practice”; and “other or no speciality” (paper II).
Socioeconomic factors
Information on socioeconomic factors was collected from health surveys for papers I, III and IV.

Educational level
Numbers of years of education was stated in HUBRO and OPPHED (papers III and IV). The variable was dichotomised into “< 13 years” and “≥ 13 years”, as Norway offers 13 years of compulsory education.

Domestic work as main occupation
The question on domestic work read: “Is domestic work your main occupation?” with answering alternatives “yes” and “no” (paper I).

Receiving social benefits
Participants were asked if they were receiving each of the four social benefits: sick leave, unemployment benefits, rehabilitation benefits or disability pension. In paper I, receiving sick leave, rehabilitation benefits or disability pension was united into one variable. In paper III, all four benefits were aggregated. In paper IV, information on disability pension only was used.
3.4 Ethics

3.4.1 Approval of the study
Data from Østfold and Aust-Agder: The Norwegian Data Inspectorate approved the surveys. Written informed consent was introduced in health surveys from 1992; later than the Østfold and Aust-Agder health surveys. Participants were informed that the data would be used for research purposes, but they were not asked to approve the later record-linkage to the National Population Register. This linkage was approved by the Regional Committee for Research Ethics, claiming the participants must be allowed to withdraw from the linkage. Participants were not contacted individually, but information on planned record-linkage and how to withdraw from this was published in the media.

Data from HUBRO and OPPHED: The Norwegian Data Inspectorate approved and the Regional Committee for Research Ethics evaluated each study (139). The studies have been conducted in full accordance with the World Medical Association Declaration of Helsinki (140).

Data from NorPD: The Norwegian Data Inspectorate approved both NorPD and the record-linkage to health survey data (HUBRO and OPPHED).

3.4.2 Funding and conflict of interest
This thesis was funded by a research grant from the Norwegian Foundation for Health and Rehabilitation and the Norwegian Council for Mental Health. Paper I was also supported by the Norwegian Community Pharmacy Foundation. I have received no other funding for this work from any commercial sources. Paper IV is a part of the project, “The epidemiology of prescription drug use. A record-linkage study in Norway” which is financially supported by the Norwegian Research Council.
3.5 Statistical methods

Table 6 summarises statistical packages and methods used.

Table 6  Statistics in papers I-IV

<table>
<thead>
<tr>
<th>Statistical package</th>
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<td></td>
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<tr>
<td>SPSS 12.0</td>
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<td>SPSS 14.0</td>
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<tr>
<td>Stata 9</td>
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<td>Chi-square test</td>
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<td>Student’s t-test</td>
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<tr>
<td>Multivariate logistic regression</td>
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<td>Cox regression</td>
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<tr>
<td>Likelihood ratio test</td>
<td>x</td>
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</table>

The statistical analyses were performed using the Statistical Package for the Social Sciences Programme (SPSS) version 12.0 (paper III) and version 14.0 (papers I, II and IV), and the Stata Release 9 (paper I). Descriptive statistics, univariate, and multivariate analyses were performed. All main analyses used dichotomous dependent variables.

Chi-square or chi-square for trend was used to test differences between proportions for categorical variables, whereas Student’s t-test was used for continuous variables. F-test was used to assess equality of mean values.

Those variables that reached a significance of p<0.05 in univariate analysis were entered into a Cox regression to determine their influence on mortality (paper I) or a multivariate logistic regression to determine their influence on drug use (papers II and III). In paper IV, variables with a p value <0.25 in univariate analysis were selected for the multivariate logistic regressions if considered scientifically relevant. This was done in accordance with Hosmer and Lemeshow, explaining that the more traditional level of significance (p<0.05) often fails to identify variables known to be important (141).

In paper I, hazard ratios (HRs) were estimated by using the Cox proportional hazard regression model. HRs were estimated in several steps: 1) crude HR for men and women daily using anxiolytics/hypnotics, 2) adjustment for the use of analgesics and smoking,
3) adjustment for some other possible confounders (marital status, coffee drinking, physical activity, sick leave and receiving rehabilitation benefit or disability pension) and 4) further adjustment including other variables that reached a significance of p<0.05 in the univariate analysis. Data from 4) was not shown as this did not substantially change the hazard ratios. The proportional hazard assumption was checked by a test based on Schoenfeld residuals, using the stptest procedure in Stata Release 9 (paper I).

Testing for interaction was done by likelihood ratio test in a model with and without the interaction term (papers I, II and IV).

Analyses were stratified by gender. However, in papers II and IV only aggregated results were presented; with gender as an independent variable.

Testing for interaction was done by likelihood ratio test in a model with and without the interaction term:

- between frequency of drug use and receiving disability pension (paper I)
- between age and gender (paper II)
- between HSCL-10 score and gender (paper IV)
4.0 SYNOPSIS OF PAPERS

4.1 Paper I


Objectives:
The aim of the study was to evaluate the effect of the consumption of anxiolytic or hypnotic drugs on total mortality in a general population.

Material and methods:
We followed a cohort of 7225 men and 7726 women aged 40-42 years who participated in health surveys between 1985-1989 in two Norwegian counties, with respect to deaths. The total response rate was 72.0% for men and 80.9% for women. Mean follow-up period was 18 years. The subjects were categorised according to frequency of anxiolytic or hypnotic drug use during the previous month: daily, every week, less than every week, not used during previous month.

Results:
- The proportion of anxiolytic or hypnotic drug users was 6.6% among men and 16.2% among women at baseline, when they were 40-42 years old.
- Altogether 402 men and 290 women died during follow-up.
- There was an increasing risk of death with increasing frequency of drug use.
- Crude hazard ratios (HRs) for daily users of anxiolytics or hypnotics were 3.1 (CI 2.0, 4.8) for men and 2.7 (CI 1.9, 4.0) for women, as compared with non-users last month.
- After adjustment for use of analgesics and smoking, the HRs were reduced to 2.4 (CI 1.5-4.0) for men and 2.1 (CI 1.4 -3.2) for women.
- After additional adjustment for marital status, coffee drinking, physical activity, sick leave and receiving rehabilitation benefit or disability pension; the HRs were further attenuated to 1.5 (CI 0.9-2.7) for men and 1.7 (CI 1.1-2.6) for women.

Conclusions:
Daily users of anxiolytic or hypnotic drugs in our study showed higher crude mortality than non-users. However, after adjustment for lifestyle and socioeconomic variables the difference was no longer significant for men and markedly reduced for women, suggesting that the remaining excess mortality is due to residual confounding.
4.2 Paper II


**Objectives:**
Drugs prescribed for treatment of insomnia are usually benzodiazepine hypnotics or the newer z-hypnotics, zopiclone and zolpidem. This paper explores possible explanations for the choice made and gives prevalence and incidence of use.

**Material and methods:**
Data from the Norwegian Prescription Database (2004-2006) covering the entire population was studied for incident users of hypnotics in 2006. Incident users were defined as individuals filling a prescription in 2006, without any recorded prescription of hypnotics during the 730 days (2 years) prior to that prescription. Age span studied was 18-69 years. Possible predictors for the first hypnotic drug prescribed being a benzodiazepine rather than a z-hypnotic were age, gender, previous psychotropic or analgesic drug use and prescriber speciality.

**Results:**

- In 2006, the prevalence of use of z-hypnotics was 4.8% (male) and 9.0% (female), whereas the prevalence of use of benzodiazepine hypnotics was 0.8% (male) and 1.0% (female).
- Of the 73 163 incident users of hypnotics in 2006, 3876 (5.3%) were prescribed benzodiazepine hypnotics. This means the majority of 69 287 (94.7%) were prescribed z-hypnotics.
- Incidence rates (number of new users per 1000 inhabitants) increased with age from the 18-29 year olds through every 10-year age group to the 60-69 year olds; for z-hypnotics from 10.4 to 31.0 (male) and from 14.9 to 50.8 (female); for benzodiazepines from 0.8 to 2.0 (male) and from 0.5 to 2.4 (female).
- For z-hypnotics, the incidence rates were markedly higher for females than for males. For benzodiazepines, there were only minor gender differences.
- The strongest predictors for being prescribed benzodiazepine hypnotics rather than z-hypnotics were previous use of anxiolytics (OR 1.8; CI 1.7-2.0) and male gender (OR 1.5; CI 1.4-1.6).
Other significant predictors for being prescribed benzodiazepine hypnotics rather than z-hypnotics were the use of antipsychotic or opioid drugs, and the prescriber being a psychiatrist.

**Conclusions:**
Z-hypnotics were commonly prescribed, and Norwegian drug therapy recommendations also suggest a preference for z-hypnotics. The clear predominance of the shorter acting z-hypnotics may be due to the fact that only longer acting benzodiazepines are available in Norway. Reasons for prescribing benzodiazepines rather than z-hypnotics may be co-existing psychiatric illness, such as anxiety, or a belief that benzodiazepine hypnotics are more effective than z-hypnotics.
4.3 Paper III


Objectives:
To explore psychotropic drug use in the general population and in particular among non-institutionalised individuals with mental distress symptoms.

Material and methods:
A total of 14,139 women and 11,665 men participating in the Oslo Health Study or the Oppland/Hedmark Study 2000-2001 submitted a self-administered questionnaire on health status and drug use, lifestyle and socioeconomic factors. The total response rate was 48.5%. Respondents answering they had used anxiolytics, hypnotics and/or antidepressants during the last four weeks were defined as users. A high Hopkins symptom checklist-10 (HSCL-10) score indicated mental distress. The 15% with the highest score in each gender and age group (adults: 30/40/45 years; elderly: 60 years) were studied in detail.

Results:
- The prevalence of anxiolytic/hypnotic drug use in the general population was, for women: adults 5%; elderly 20%; and for men: adults 4%; elderly 9%.
- The prevalence of anxiolytic/hypnotic drug use among those with mental distress was, for women: adults 14%; elderly 37%; and for men: adults 13%; elderly 25%. Except for elderly women, these figures were approximately three times higher than in the general population.
- The prevalence of antidepressant use among those with mental distress was, for women: adults 21%; elderly 30%; and for men: adults 15%; elderly 15%. These figures were nearly four times higher than in the general population.
- Use of analgesics was the main factor associated with use of anxiolytics/hypnotics among people with mental distress: Adult women (OR 2.4; CI 1.7-3.4); elderly women (OR 2.3; CI 1.4-3.8); adult men (OR 2.1; CI 1.3-3.3) and elderly men (OR 3.4; CI 1.9-6.0). Not participating in the labour market was the main factor associated with use of antidepressants.

Conclusions:
Among individuals with mental distress, regular use of analgesics was the main factor associated with use of anxiolytics/hypnotics in both genders regardless of age.
4.4 Paper IV


Objectives:
To study the relationship between mental distress and later use of anxiolytic drugs, taking into account potential confounders such as lifestyle and socioeconomic factors.

Material and methods:
In a prospective cohort study, data from population-based health surveys from three Norwegian counties (2000-2001) were linked to data from the Norwegian Prescription Database (2004-2007). In the surveys, 9 386 men (43.1% of invited) and 11 244 women (52.4%) participated. The two age cohorts were 40 and 45 years old (cohort 1) and 60 years old (cohort 2). Participants in each age group were divided into quartiles (Q1-Q4) separately for men and women according to the degree of mental distress, measured by increasing Hopkins symptom checklist-10 (HSCL-10) score at baseline. Multivariate logistic regression was performed to assess predictors of anxiolytic drug use.

Results:
- At baseline, increasing HSCL-10 score was associated with increasing use of specified drugs independently (hypnotics, antidepressants, analgesics with or without prescription, others), poor health, ever having sought help because of mental distress, musculo skeletal pain, being married or in partnership, low educational level, receiving disability pension, and current smoking (except for women 60 years old).
- There was a graded positive relationship between HSCL-10 score at baseline (2000-2001) and the chance of filling a prescription on anxiolytic drugs during follow-up (2004-2007) for the 40 and 45 year olds, but not for the 60 year olds. Genders were studied together.
- Predictors of use of anxiolytics, regardless of age, were: female gender, reported use of hypnotics, having previously sought help because of mental distress, and current smoking.

Conclusions:
HSCL-10 score was related to later use of anxiolytic drugs in a dose response manner for the 40 and 45 year olds.
5.0 DISCUSSION

5.1 Discussion of the major findings

The data analyses in this thesis have resulted in six major findings, listed below.

- Daily users of anxiolytics or hypnotics show higher crude mortality than non-users; however after adjustment the difference was markedly reduced.
- The majority of incident users of hypnotics receive prescriptions for z-hypnotics rather than benzodiazepines, the choice of benzodiazepines predicted most strongly by previous use of anxiolytics and male gender.
- The main factor associated with use of anxiolytics or hypnotics among people with mental distress is the use of analgesics.
- The main factor associated with use of antidepressants among people with mental distress is not participating in the labour market.
- Mental distress is a predictor of later use of anxiolytic drugs.
- Women show a higher proportion of use of psychotropic drugs than men, and there are also gender differences when studying mortality and incidence rates.

To obtain information on and read discussion of further findings, the discussion section of each paper is recommended.
5.1.1 Daily users of anxiolytics or hypnotics show higher crude mortality than non-users

Crude hazard ratios for daily users of anxiolytics and/or hypnotics in a middle-aged population (40-42 years) were 3.1 for men and 2.7 for women, as compared with non-users last month. Two adjustment models both attenuated the hazard ratios; the first one including use of analgesics and smoking, whereas the further adjustment included marital status, coffee drinking, physical activity, sick leave and receiving rehabilitation benefit or disability pension. The model including all variables gave hazard ratios of 1.5 (ns) (men) and 1.7 (women).

Earlier findings in this field vary; some authors have found increased all-cause mortality after use of benzodiazepines (BZDs) (78-80, 83-86), whereas other have not (77, 81, 82). In the study by Hublin et al, increased mortality was found for frequent users of tranquillizers and/or hypnotics in a population with an age range of 24-101 years (78). There, the effect attenuated with age, something also observed in a study of sleeping pill use and mortality (79). The three studies that did not find increased mortality covered the populations of the highest age (77, 81, 82), and age may be part of the explanation of the various findings.

We have identified ten prospective cohort studies examining the association of BZD use and mortality. All studies were from high-income countries within Europe and North America. The findings varied, and there are some possible reasons for this, other than age variations. Firstly, the definition of use of BZDs in the general population varied as follows: “daily use in past month” (as used in paper I); “use sometimes or more often”; “use often or very often”; “use at least 60 days per year” “use more than half of the 3 month assessment period”; “current use”. In addition, one study covered drug misusers in treatment centres with a definition of BZD use as “weekly or more frequent use” (84); one study covered BZD dependent users with no further definition of use, and two studies were of drugged drivers (85, 86). Secondly, the number of BZDs included in the studies varied and some studies were not restricted to BZDs, as either the sleeping pills included were not specified (79) or tranquillisers in general were studied, meaning that antipsychotics were included (78). The study populations covered different ages as mentioned above; they had varying sizes (n_{min} = 599; n_{max} = 1 099 830; paper I: 14 951), and were followed up for different lengths of time (5-22 years; paper I: 18 years). Our study like most other studies relied on information about BZD use given from participants, and this probably captured prescribed BZDs. On the other
hand one study focused on non-prescribed BZDs, according to information from drug misusers recruited to treatment programmes (84), and this may also have been the case for the studies of BZD dependents or drugged drivers (83, 85, 86).

Regarding data analysis, stratification was either done, like in our study, by frequency of use, or by number and/or type of BZDs. Most studies calculated all-cause mortality and presented adjusted hazard ratio (HR) (like paper I), relative risk (RR) or odds ratio (OR), whereas one study calculated standardized mortality ratio (SMR) (79) and another study compared all-cause mortality of users versus non-users in percent (77). Our study was one of four which controlled for several confounding factors (78, 80, 82), whereas others adjusted for age and/or sex only.

We found a dose-response relationship for frequency of use of BZDs and mortality, supported by previous findings (78, 79). Other studies did not categorise the users according to frequency of use, but in Norway, a group of drivers who tested positive for a single traffic-hazardous medicinal drug (BZDs, opioids, muscle relaxants) showed SMR 9.8 (men) and 19.6 (women), changing to 16.9 (men) and 18.4 (women) for the group who tested positive for two or more of the drugs (85).

The review by Charlson et al pointed at limitations in the design and data of six studies on BZD use and mortality, including our paper I (142). The authors raise two crucial questions about the cohort design. 1) Among those who died, how many continued to use sleeping pills in the follow-up period? 2) Among those who survived, how many initiated use of sleeping pills during the follow-up period? Perhaps the only proper solution to this problem is to measure drug use several times during follow-up. One suggested study design could be similar to a design used to measure long-term use of BZDs (98), with death as an endpoint.

Findings from two studies illustrate the importance of studying different BZDs separately in order to discover differing risks associated with individual drugs. Rumble and Morgan did not find an increased risk of mortality among hypnotic drug users (81). However, an initial association was found between increased mortality and the use of sleep medication, but once this category was broken down into hypnotic drugs (mainly BZDs) and other sleep medication, only the “other” category remained significantly associated with increased mortality. Similarly, Kripke et al showed an association between sleeping pill use and an
increased risk of death (79), however the sleeping pills included were not specified – and were thus not restricted to BZDs. Separate analyses of diazepam and chlordiazepoxide, respectively, did not reveal increased mortality associated with these particular drugs.

BZDs are psychoactive drugs and are more often used by people who suffer from co-morbidity; somatic or psychological (106). Perhaps BZDs are merely a proxy for other risk factors associated with increased mortality. If there is, in fact, an increased mortality risk, it is not known whether this risk is carried by certain “at risk” populations who may have coexisting risk factors. In Norway, Mykletun et al recently studied associations between individual and combined anxiety/depression symptom loads, using the Hospital Anxiety and Depression Scale (HADS), and mortality in the county Nord-Trøndelag (143). Depression as a risk factor for mortality was comparable in strength to smoking, whereas co-morbid anxiety reduced mortality compared with depression alone. The relationship between anxiety symptoms and mortality was more complex with a U-shape and the highest mortality in those with the lowest anxiety symptom loads.

Only randomized controlled trials (RCTs) can control for the complexity of confounding factors to provide evidence of cause and effect. In paper I, we excluded individuals suffering from, or with symptoms indicating, heart infarction, angina pectoris, diabetes and stroke; in order to start out with a fairly healthy population. This exclusion may have resulted in lower hazard ratios compared to studies without such exclusions. However, among the participants there were both disability pensioners (2.2% of the men and 4.4% of the women) and people on sick leave or receiving rehabilitation benefit (3.0% of the men and 5.5% of the women); indicating some health problems. Further, during a follow-up period of 18 years the health status of participants 40-42 years old at baseline probably goes through greater changes than before selection, and therefore our study is still affected by coexisting risk factors. Kripke in fact suggested RCT as a requirement for those who introduce or approve new hypnotics (144).

Even after doing a study on psychotropic drug use and mortality, I find the field complex because of the varying methods used and the sometimes conflicting findings published. From our findings, I find it hard to conclude that there is a clinically relevant association between daily use of anxiolytics and hypnotics and increased total mortality.
5.1.2 The majority of incident users of hypnotics receive z-hypnotics rather than benzodiazepines

Most incident users of hypnotics in Norway in 2006 were prescribed z-hypnotics (94.7%) and only 5.3% were prescribed BZD hypnotics. I know of no similar studies. However, all the Nordic countries have established nationwide prescription databases making it possible to perform studies like paper II (71).

In our study, incidence rates (number of new users per 1000 inhabitants) for BZD hypnotics and z-hypnotics separately increased with age for both genders. Incidence rates were higher for women than for men, except for the younger BZD users. Two recent studies have looked at the total incidence of BZD anxiolytics, BZD hypnotics and z-hypnotics in France (94) and Taiwan (91). These aggregated incidence rates are less relevant to compare with our findings. The gender difference we found was also observed in France, whereas results for women and men separately were not given in the study from Taiwan.

Predictors for being prescribed BZD hypnotics rather than z-hypnotics among incident users in our study were male gender, previous use of anxiolytics, antipsychotics or opioid analgesics and the prescribing doctor being a psychiatrist. A study on the use of BZDs and z-hypnotics was carried out by Johnell and Fastbom using the Swedish Prescribed Drug Register (92). In Sweden, all current users were included, and the use of BZDs with medium acting time was associated with higher age, female gender, and concomitant use of other psychotropics, whereas z-hypnotics showed the opposite patterns. Interestingly, zopiclone and zolpidem showed different patterns regarding age, sex and concomitant use of other drugs, and Johnell and Fastbom emphasize the importance of examining the use of individual drugs instead of clustering them into drug classes. Further, they found that the two long-acting BZDs, flunitrazepam and diazepam, showed divergent patterns of use. Among the BZDs, we studied the hypnotics nitrazepam and flunitrazepam only, whereas Johnell and Fastbom studied several BZDs and categorised them according to their acting time. Their group of “long-acting” included the drugs we studied, nitrazepam and flunitrazepam; but was completed by the inclusion of clonazepam and diazepam. The Swedish study was restricted to people ≥ 75 years (mean age 82 years), in contrast to the age range of 18-69 years in our study; meaning that prevalence of use among Norwegians in our study is irrelevant to compare with the Swedish findings. Our measured prevalence of hypnotic drugs in 2006 was comparable to other prevalence findings from Norway. The prevalence we found for BZD
hypnotics (male: 4.8%; female: 9.0%) and z-hypnotics (male: 0.8%; female: 1.0%), added up to 8% whereas Kjosavik et al reported 7.9% from NorPD in 2005 and Pallesen et al found 6.9% from telephone interviews a few years earlier (88, 89).

In a French cohort of 1272 subjects aged 59-71 years, incident BZD or z-hypnotic drug use was associated with anxious and/or depressive symptoms, high non-psychotropic drug consumption and female gender (94). As BZD anxiolytics, BZD hypnotics and z-hypnotics were studied together, comparisons with our study are difficult to make.

Bachmann et al (59) suggested a possible lack of knowledge on sleep and hypnotics in general in a study among Norwegian general practitioners (GPs), and was supported in a comment by Bjørner (63). Norwegian GPs with a high level knowledge of clinical use and a restrictive attitude to z-hypnotics showed a lower prescription rate for BZDs and z-hypnotics, and the arguments for choosing zopiclone instead of zolpidem or vice versa were often irrational (59). Regarding GPs’ knowledge, Siriwardena et al found that GPs in Lincolnshire, UK, believed that z-hypnotics were more effective and safer than BZDs (62). This may explain the increase in z-hypnotics drug prescribing relative to BZD prescribing in the UK, but was not in agreement with current evidence or national guidance.

Paper II showed that in Norway in 2006, 3876 incident users of hypnotics were prescribed BZD hypnotics (5.3%). This may or may not be too worrying, depending whether one believes z-hypnotics to be a clearly better option than BZD for every incident hypnotic drug user or whether it is just another contribution to the stories of promising new drugs marketed, with rapidly rising levels of sales; at least until all possible consequences of their use are fully discovered.
5.1.3 The main factor associated with use of anxiolytics or hypnotics among individuals with mental distress is use of analgesics

The main factor associated with use of anxiolytics or hypnotics among individuals with mental distress was use of analgesics (paper III), confirming the findings published by Villaverde Ruiz et al (107).

Further, we found in paper III a prevalence of anxiolytic or hypnotic drug use approximately three times higher for the 15% with the highest Hopkins symptom checklist-10 (HSCL-10) score on mental distress than for the general population; except for elderly women. In order to compare our findings with earlier studies, it is relevant to add the prevalence of antidepressants to these numbers. Among responders with mental distress, the prevalence of psychotropic drugs then added up to 31% (men) and 43% (women), not far from the higher level of previous findings (101). In paper IV, at baseline, increasing HSCL-10 score was associated with increasing use of hypnotics and antidepressants. This population was part of the population in the cross-sectional study in paper III, explaining similar findings at baseline. Follow-up (paper II) showed that mental distress was found to be related to later use of anxiolytic drugs in a dose response manner among middle-aged people. Among the older people, use of hypnotics was the most important predictor of anxiolytic drug use. The boundaries between anxiolytics and hypnotics can be unclear, and among the older people we may have observed change of drug prescribed for the same indication, rather than the use of one drug predicting the use of another.

It might be a paradox that people receiving medical treatment for mental health distress or perhaps diagnosed mental disorder may not have a normal score on mental distress even if the treatment is successful. From another point of view, they perhaps would have scored even higher without medical treatment. Further, an important issue is whether the medical treatment has recently started or lasted for years. Finally, a large proportion of people with mental distress in our study were actually not taking psychotropic drugs; 44-73%, varying with gender and age.

Cloos and Ferreira provide a review of articles on the current use and rationale of BZDs in anxiety disorders (145). BZDs are considered by many clinicians to remain good treatment options, in both the acute and the chronic phase of the treatment of anxiety disorder, partially because of their rapid onset of action and their efficacy with a favourable side effect profile. A
qualitative study by Anthierens et al on GPs’ perspectives showed that clinicians feel overwhelmed by the psychosocial problems of their patients and considered themselves to be empathic by giving them BZDs as a relief (58). Given the lack of adequate alternatives and because of limited time, it was felt that in certain situations there are no other solutions and BZDs were perceived as the “lesser evil”. The addictive nature of BZDs was not considered to be a problem with first-time users, and the GPs thought that under-usage of BZDs because of a fear of addiction may leave patients suffering. This study is an example of BZD prescribing practices not always reflecting guidelines - as these guidelines perhaps do not provide the practical strategies required in a complex clinical setting. Sim et al propose a model for rational prescribing of BZDs, by the use of a checklist (56). The critical question is why the person is using a BZD, i.e. what benefits (perceived or real) are there? How will the person who ceases them manage the loss of those benefits?

Smolders et al compared GPs’ pharmacological treatment patterns for anxiety in patients with and without co-morbidity (104). Compared with patients with a single diagnosis of anxiety, anxious patients who also had chronic somatic morbidity or social problems were prescribed more BZDs, but no more antidepressants. When they simultaneously had other psychiatric conditions, they received twice as many BZDs and antidepressants during the year after anxiety was diagnosed.

Co-morbidity and co-medication are complex fields, and in the future pharmacists may play a more important role to patients filling prescriptions for one or more psychotropic drugs as well as analgesics. Pharmacists in Norwegian community pharmacies have so far not been paid specifically for drug use review one-to-one conversations with a patient. In Australia, New Zealand and the UK this is the case (146). If such services are to be paid by the health authorities, it is most likely that reimbursed drugs will be given priority, presuming an economic motivation. However, from a patient’s view it is not an obvious choice to exclude psychotropic drug users from receiving extended pharmaceutical assistance.

Patients may have symptoms of more than one mental disorder, as anxiousness, depression and insomnia can partly overlap; and the choice of drug is probably not always easy to make. Kripke analysed RCTs on insomnia patients, and found a greater incidence of depression among subjects receiving hypnotics versus those receiving placebo – suggesting hypnotics may be more likely to cause depression than to prevent it (147).
5.1.4 The main factor associated with antidepressant use among individuals with mental distress is to be out of the labour market

We found in paper III that among individuals with mental distress, not participating in the labour market was the main factor associated with use of antidepressants. In paper IV, the working status variable was restricted to receiving disability pension (yes/no), and predicted the use of anxiolytics for those aged 40/45 years only (OR 1.4). Further, in paper III, not participating in the labour market was the main factor associated with use of anxiolytics or hypnotics for adult men, and one of the factors associated with use for both adult and elderly women.

In paper III, the separate statements of main factors associated with anxiolytics/hypnotics or antidepressants, respectively, can be criticized because of the way psychotropic drug users were classified. People who had used antidepressants were defined as antidepressant users, regardless of their possible use of anxiolytics or hypnotics. Remaining in the group of anxiolytic or hypnotic drug users were those not using antidepressants. Even if we focus on anxiolytic and hypnotic drug users in this thesis, we treated antidepressant users as more unique in paper III, simply because receiving a prescription of 10 or 30 tablets of antidepressants is not as common as is the case with anxiolytics and hypnotics. Further, analyses of people using antidepressants exclusively (n=240) showed that they did not differ from the previously defined group of antidepressant users (n=648).

In a Norwegian study, Hartz et al found that receiving disability pension was associated with the use of BZDs 20 years later (148). Another study by Hartz et al stated that the chance of being prescribed a BZD as well as becoming a long-term user was higher among disability pensioners (149). Smolders et al found that anxious patients who also had social problems; defined as bad working conditions, unemployment, relation problems or grief, were prescribed more BZDs (104). A different finding was done by Verger et al who studied co-prescriptions of antidepressants and anxiolytics, and found that 60% of patients receiving antidepressants were also prescribed an anxiolytic (108). GPs co-prescribed anxiolytics more often for patients with stable jobs than for those with unstable or no jobs or those who were retired. The authors hypothesize that patients with regular jobs might demand more symptomatic relief than patients in other situations and GPs might consider anxiety and sleep problems as target symptoms in these patients, compared with unemployed patients. The potential for abuse might be another reason why GPs were less likely to prescribe anxiolytics...
to unemployed patients, suggesting the possibility of a stigma of unemployment. Noticeably, Verger et al studied patients with major depressive disease only, while in paper III we studied those with the 15% highest HSCL-10 score in the general population; and used no diagnostic cut-off.
5.1.5 Mental distress is a predictor of later use of anxiolytic drugs

Mental distress measured by HSCL-10 score was found to be related to later use of anxiolytic drugs in a dose response manner among middle-aged people. Perhaps more surprising was the fact that among those 60 years old, the dose response relationship disappeared. Others have done cross-sectional population-based studies and measured mental distress in other ways, and have found the presence of a mood or anxiety disorder to be strongly associated with the use of BZDs or z-hypnotics (93, 102).

We found in paper IV that previous help seeking for mental distress predicted anxiolytic drug use. Similarly, the European study of the epidemiology of mental disorders (ESEMeD) found help seeking for emotional problems in the previous year to be the most important predictor for the use of a BZD or an antidepressant (101). Tómasson et al found that among those consulting a doctor in Iceland during the previous 12 months (57%), the most important factor associated with use of any psychotropic drugs was having consulted a doctor for mental health problems (105). In the multivariate analyses, we included reported help seeking for mental distress as a confounder. This can be questioned as the search for help was not restricted to any time period.

Mental health status was in our study measured by HSCL-10, derived from the HSCL-25 (16). HSCL measures certain aspects of mental distress and has shown good psychometric properties (10). A validation study has demonstrated a high correlation between the HSCL-25 and the HSCL-10 (16). However, this instrument is a screening tool, and not a diagnostic instrument. Further, our measure of health status using HSCL-10 did not include a diagnosis-related cut-off. In paper III, we chose to study people with the 15% highest HSCL-10 score. This decision was not related to the HSCL-10 score cut-off value of $\geq 1.85$ known to indicate mental distress, and when we included as many as 15% of the participants, people with scores far below 1.85 had to be included. Initially, we considered using the cut-off value of $\geq 1.85$. However, women score higher than men without our knowing whether they in fact have more mental distress than men or if they “complain” more. Sandanger et al studied to what extent the symptom screening HSCL-25 predicted depressive disorders found by the diagnostic instrument Composite international diagnostic interview (CIDI), and suggested lower HSCL-25 score cut-off for men than for women (15). I presume it is possible that women “complain” more than men also during CIDI, and CIDI should perhaps not be regarded as a true measure of mental health status either. Sandanger et al in a later study were actually surprised by the
different properties HSCL-25 and CIDI showed when identifying cases (150). Choosing a certain highest percentage of each gender was our method of selecting similar groups. In paper IV, participants were divided into HSCL-10 score quartiles. The quartiles were gender specific for the same reason as we left the cut-off value.

Noticeably, the time frames assessing HSCL-10 score (last week), drug use (last month), and use of health services (up to 12 months) were different. This may complicate the interpretation of the associations, as the variables may change over time. In paper IV, among the dead who were excluded, there was a higher proportion that would have belonged to the quartile with the highest HSCL-10 score. This may have led to an underestimation of the effect of a high HSCL-10 score.

Among people with mental distress in the non-institutionalized population, we found that 31% of the men and 43% of the women used any psychotropic drug. Rundberg et al found that a lower proportion of 15% of women aged 50-59 with severe mental symptoms used psychotropic drugs (23). Noticeably, we studied the 15% with the highest HSCL-10 score, whereas Rundberg et al studied 22% of the participating women; those with severe mental distress as defined by the Gothenburg quality of life instrument (GQL) (13, 23). None of the studies used a diagnosis-related cut-off. However, we studied a slightly more homogenous group. The larger proportion of a general population included, the more people with lower levels of mental distress will presumably be represented. Further, our study included as users all those who had used psychotropic drugs during the previous month, whereas Rundberg et al included regular users only (23). The higher percentage of psychotropic drug use found in our study was thus not unexpected.

Mental distress can be measured not only by instruments like HSCL-10 score, as receiving a prescription of antidepressant drugs can be a proxy of depression. A Swedish study of previous and later use of BZDs among new antidepressant users can illustrate the indistinct boundary between the psychotropic drugs studied in this thesis and possible co-morbidity of depression and anxiety. Bingefors et al suggest there may be widespread treatment of depressive symptoms with BZDs, as new antidepressant users had an increasing and high use of BZDs compared to non-users in the year prior to their first antidepressant prescription (151). The BZD use remained high throughout the study period of five years.
5.1.6 Women show a higher proportion of use of psychotropic drugs than men

We observed gender differences in mortality, prevalence and incidence rates. Women showed a higher proportion of use than men, and this counted for all drug groups: anxiolytics, BZD hypnotics, z-hypnotics and antidepressants (papers I, II, III and IV). This is in concordance with other studies (24, 93, 101). Among users of anxiolytics or hypnotics, only women showed higher mortality after adjustment for lifestyle and socioeconomic variables (paper I). From this, one may conclude that women using these drugs have poorer health than men using the same drugs, and that the health is poorer in a way that increases mortality. Further, men (non-users and users together) showed a higher mortality than women (non-users and users together), and thus the minor increase from taking drugs was perhaps not enough to significantly increase mortality for men. Hypnotic drug incidence rates were higher for women than men for z-hypnotics, whereas for BZD hypnotics there were only minor gender differences (paper II). Male gender was one of the strongest predictors for being prescribed BZD hypnotics rather than z-hypnotics (paper II). BZD is more attractive to drug misusers than z-hypnotics, and as more men than women are misusers this may contribute to the gender difference.

Among people with mental distress, the prevalence of anxiolytic or hypnotic drug use was similar for men (13%) and women (14%) (paper III). In contrast to this, Marino found that when men scored above the threshold of psychiatric morbidity in the General health questionnaire (GHQ-30) they had a risk of receiving a psychotropic drug 49 times higher than the general sample, whereas women had no significant increase of risk (117). Marino suggest that a greater weight is given by the GPs to distress symptoms exhibited by men compared to women and that in the presence of these manifestations a more serious clinical problem is assumed, leading to the prescription of a psychotropic drug.

Further, among people with mental distress, the ORs of later filling prescriptions of anxiolytics were comparable for the two sexes within age groups (paper IV). Women scored higher than men on HSCL-10. We are not sure whether women in fact had more mental distress or if they were using the scale differently from men, when rating themselves from 1 to 4 on each of the 10 symptom questions. This has previously been discussed in the section “Mental distress is a predictor of later use of anxiolytic drugs” of this thesis.
Moving from a relative level to an absolute level can give further information on gender differences, as similar HRs or ORs can have different practical implications. In paper I, the mortality among daily users was 912 for men and 505 for women per 100 000 person years (paper I; table 2). Despite this difference, hazard ratios for men and women were similar. In paper IV, the level of use of anxiolytics among women is almost twice that for men in each HSCL-10 score quartile (Paper IV; tables 3a and 3b). In that study, odds ratios for men and women were quite similar for the two genders and only results from men and women combined are presented. The adjusted OR for gender were above one for both age groups and, as men were used as the reference, this means being a woman was a predictor of anxiolytic drug use. The actual size of OR for both age groups was 1.7 and this illustrates the different level of the absolute numbers of users among men and women (paper IV; table 4).

The Australian researchers Hollingworth and Siskind point out that women have a higher prevalence of anxiety and sleeping disorders, but that it is unclear whether this accounts for all of the additional psychotropic drug use they found among women compared to men (152). In a Swedish questionnaire-based study of analgesic drug use, women reported pain more often than men (153). However, this did not explain the whole gender difference, and the author presumes biological as well as environmental and psychological causes are involved (153).
5.2 Methodological strengths and limitations

NorPD is a nationwide prescription database, with detailed information on patient, dispensed drug, prescriber and pharmacy (1). Compared to studying, for example, selected hospital, GP or pharmacy records, NorPD data are, for many purposes, superior. Health surveys in Norwegian counties are also comprehensive, giving information on health, lifestyle and socioeconomic variables. Despite the collection of huge amounts of data from large populations, there are methodological challenges that require consideration.

The validity of a study is usually separated into two components: the validity of the inferences drawn as they pertain to the members of the source population (internal validity) and the validity of the inferences as they pertain to the people outside that population (external validity or generalizability) (154)

There are two kinds of error in research: systematic error and random error. Systematic error alter estimation in a given direction. Random error is the error that remains after systematic error is eliminated. Most violations of internal validity can be classified into three general categories of systematic error: selection bias, information bias or confounding (154, 155), described in the following sections.

5.2.1 Selection bias

Selection bias is systematic error that results from the way subjects are selected into the study or because there are selective losses of subjects before data analysis (156). It is difficult to determine the magnitude of selection bias, but the direction of the bias may be indicated. In the health surveys used in this thesis, there were no other selection criteria besides age. Thus, the main source of selection bias in the papers using data from health surveys (I, III and IV) is non-response, either non-attendance to the screening, or non-response to the questionnaires or to single items in the questionnaire. Statements about bias due to non-response are therefore statements about defined variables.

Our studies from Oslo, Oppland and Hedmark (papers III and IV) had a lower response rate than the study from Østfold and Aust-Agder (paper I). Research has shown that in the Oslo Health Study (HUBRO), there was overrepresentation of less educated people and receivers of disability pension among the non-attendees (157). Further, disability pension may be used as an indicator of poor or reduced health: either physical or mental. This implies that the
participants were healthier than the general population. The differences regarding education, disability pension and health will not necessarily affect the associations studied. In paper IV, the lower attendance of disability pensioners is a possible sign of more mental distress among non-attendees. However, if there is an identical attendance percentage of drug users and non-users among people with and without mental distress, OR will not be biased (158). Further, the prospective study design in paper IV probably makes selection bias less likely to influence the estimates of the effects of HSCL-10 score on subsequent anxiolytic use (158).

The attendance in HUBRO increased from 30% to 46% through reminders, and the effect of this was studied (159). Small changes were observed among the 75-76 years old for the estimated prevalence figures of diabetes, poor self-reported health, HSCL-10 score and daily smoking. Among individuals of ages included in our study, almost no changes were observed. We do not have any information about the non-participants in the studies from Oppland and Hedmark (OPPHED), that together with Oslo form papers III and IV, or from Østfold and Aust-Agder (paper I).

After publishing paper IV, I compared the prevalence of use of anxiolytics in 2005 for participants in the health surveys HUBRO and OPPHED to the corresponding prevalence for all inhabitants in the counties of Oslo and Oppland/Hedmark as they were all invited. Table 7 shows that the prevalence for the health survey participants is from 1.5 to 2.8 percentage points lower than for the whole county/counties. This means that among the participants available to our study – before the exclusion of e.g. users of anxiolytics at baseline – a smaller proportion used anxiolytics during one randomly selected year of the follow-up period, compared to the general population. This may reduce the external validity, while the associations studied are less likely to be altered.

Increasing the response rate will not necessarily make a population more representative (160). In the study of Bootsma-van der Wiel et al, the response rate increased from 74 to 87% by an additional recruitment, and the population added had poorer health. However, those who refused to participate during the additional recruitment were healthier than the population first sampled. In the end, the first sample did not differ from the source population with respect to health, sociodemographic factors and mortality. The authors concluded that given a moderately high direct response, an additional effort to prevent selection bias is not necessary.
Table 7 Prevalence of use of anxiolytics (ATC code N05B) for participants in health surveys in the counties of Oslo (HUBRO), Oppland and Hedmark (OPPHED) and for all inhabitants in the counties; they were all invited.

Source: NorPD 2005

<table>
<thead>
<tr>
<th>County/counties</th>
<th>Oslo</th>
<th>Oppland/Hedmark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age* 40/45 60</td>
<td>40/45 60</td>
<td></td>
</tr>
<tr>
<td><strong>Men - prevalence of use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health survey participants (%)</td>
<td>4.9 6.5</td>
<td>3.8 7.0</td>
</tr>
<tr>
<td>The whole county/counties (%)</td>
<td>6.8 8.7</td>
<td>6.0 8.5</td>
</tr>
<tr>
<td><strong>Women - prevalence of use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health survey participants (%)</td>
<td>7.3 13.5</td>
<td>7.6 13.5</td>
</tr>
<tr>
<td>The whole county/counties (%)</td>
<td>10.1 16.1</td>
<td>9.5 15.7</td>
</tr>
</tbody>
</table>


The response rates in our studied counties are different (min = Oslo, 46%, max = Østfold, 77%), meaning the consequences of increased response would perhaps differ. Further, in paper I, non-response would probably affect the prevalence estimates of BZD use at baseline. However it is less likely that the association between the frequency of drug use and total mortality is affected.

In cross-sectional studies, the primary source of selection bias is “selective survival”, as only survivors can be included in cross-sectional studies (156). Prevalent users are “survivors” of the early period of pharmacotherapy, which can introduce bias if risk varies with time, similarly to studies of operative procedures that follow patients after they have survived surgery (161). In paper III, people with mental distress who were prevalent users of anxiolytics or hypnotics were “survivors”, in contrast to those having stopped using the drugs before baseline for reasons like decreased mental distress or experienced side effects. The consequence of this can be seen by pulling the baseline one step backwards. Including people who will later stop using the drugs will firstly result in a higher prevalence of use, and secondly associations may be altered if the quitters are different from other non-users.

When data were retrieved from NorPD (paper II and part of data for paper IV), selection bias was eliminated. However, data on the use of medicines in the hospital and nursing homes are not registered on an individual level in the database. For the substances we studied in paper II, these omissions account for 8% of total sales in Norway. In paper IV the highest age group included in the study is 60 years. This would suggest a rather smaller loss of drug use data caused by hospital and nursing home stays compared to an older study population.
A cross-sectional study of medication data from 23 nursing homes in Bergen, Norway, showed that psychotropic drugs were taken on a daily basis by as many as 59% of all residents, most commonly as long-term treatment (162).

We are not sure whether drugs dispensed are actually used. However, our data is based on dispensed drugs rather than prescribed drugs and this rules out primary non-compliance, which is a problem with using prescribing data, for example, the United Kingdom General Practice Research Database (GPRD) (163, 164). Information on diagnosis or severity of the conditions treated is not available from NorPD. Categorising people according to drug treatment rather than medicinal diagnosis is not necessarily problematic or wrong, but knowing the diagnosis would be clarifying. There is an indistinct boundary between anxiolytics and hypnotics. Anxiolytics may be prescribed to aid sleep, meaning that in paper IV, people who used hypnotics at baseline may use anxiolytics instead during follow-up without changing diagnosis. Not all BZDs in Norway are anxiolytics and BZDs primarily used for indications other than anxiety were not included. Numerous non-hypnotic drugs are prescribed for insomnia in the USA (165), and there is as far as I know some prescribing of antidepressants and antihistamines for this indication in Norway (20). Further, there is an increasing prescribing of melatonin, the hormone regulating the body’s daily rhythm (96).
5.2.2 Information bias

Information bias results from incorrect determination of exposure or outcome, or both (166). In a cohort study, if information is gathered differentially for the exposed than for the non-exposed, then bias in one given direction results; whereas in contrast, non-differential misclassification; “noise in the system”, tends to obscure real differences (166).

When using data from NorPD (papers II and part of paper IV), information bias is eliminated. In papers using data from health surveys (I, III and part of IV), answers to questions about drug use depend on the memory of the responders. Van den Brandt showed that recall of drug use decreased with increasing age and with increasing number of prescribed drugs per subject, but no difference in recall was observed between men and women (167). The time frame for recollection of drug use is crucial. Increasing the length of the period increases the risk for underreporting. The recall problem was thus assumed to be small in our health survey studies with a recall period of four weeks and since the population was 30-60 years old. Further, fixed questions on drug categories, as used in the health surveys, can be a tool to enhance memory. Additionally, there were perhaps a limited number of multi-drug users, due to the exclusion of certain groups of chronically ill subjects. A disadvantage of using shorter time periods is the under-representation of occasional users of drugs. Overall, the drug use questions did probably contribute to a high quality of information obtained and thus to an improved internal validity.

The definition of drug use in studies mentioned in this thesis, varies from use during the last 24 hours (24) to use during the last year (78). Ray et al studied the association of BZD use with fall risk, and by changing the definition of BZD use from “use the past week” at baseline to “use on a given day” during follow-up, the fall incidence rate ratio increased from 1.02 to 1.44 (122). This was not related to memory, but was rather an example that, for drugs taken intermittently, asking for use before baseline reveals a risk of misclassification and further underestimation of associations.

Overall, our estimates of psychotropic drug use based on health survey data may be too low, as drugs for psychological/psychiatric problems are particularly prone to underreporting (167), perhaps because of the stigma of mental illness. Underreporting of the frequency of drug use will likely bias the estimates towards the null.
5.2.3 Confounding
Confounding is systematic error resulting from the fact that a secondary variable is linked both to the exposure and to the event of interest, which can wholly or partially explain their association (168). This can be taken into account or corrected for during the analysis. In this study, I addressed confounding by using multivariate and stratified analyses, either gender or age specific. In paper I, crude hazard ratios were markedly reduced, and for men the hazard ratio was no longer significant after the use of each of two adjustment models. This suggests that the remaining excess mortality is due to residual confounding, that is, if there were even more variables in the model, it is likely that the hazard ratios were even lower and not significant, also for women.

Random error is the error that remains after the systematic errors described above (selection bias, information bias and confounding) are eliminated. This is the portion of variation in a measurement that has no apparent connection to any other measurement or variable, generally regarded as due to chance (155). This deviation results in a loss of precision, but is not systematic in a given direction. A common way to reduce random or sampling error, or to increase precision, is to enlarge the size of the study. The study population in our health surveys was large, and for analyses of subgroups of drug users, small sample size was not a problem. From the nationwide database NorPD, complete data were collected.
6.0 CONCLUDING REMARKS AND FURTHER PERSPECTIVES

Anxiolytic or hypnotic drugs alone can probably never completely solve life crises, insomnia or anxiety. However they can be helpful for limited periods of time.

The use of benzodiazepine (BZD) anxiolytics and hypnotics in Norway is reduced (Figure 1). However; owing to the increased use of antidepressants and z-hypnotics, it is likely that some of the quitters change over to these drugs. When working towards a reduction in the total use of psychotropic drugs, the recent experience made in Denmark is worth noting: The Institute of Rational Pharmacotherapy registered lower use of both anxiolytics, hypnotics in general and z-hypnotics after mass distribution of three brochures to physicians, their co-workers and inhabitants (169). Approximately 75% of the quitters did not compensate with another psychotropic drug (169).

There has been and still is a lot of focus on BZD anxiolytics and hypnotics. As the total use decreases, the population using it becomes more selected. There could be reason to believe that the aspects of dependence and abuse are likely to contribute to maintained interest.

For z-hypnotics, we do not yet know all the aspects of use. The drugs were thought to be safer than BZDs, however, they can be abused as well (44). The question is perhaps not if the future will bring another new generation of anxiolytic and hypnotic drugs with less initial concern of use, but when this happens and what drugs will be a part of it. Melatonin or related drugs may play a more important role in the future. In Norway, the sale of melatonin (ATC code N05CH01) has increased almost 175% from 2004 to 2009 (2, 96).

Some possible implications of the findings:

- The increased mortality found among users of anxiolytic or hypnotic drugs in a general middle-aged population can perhaps serve as a warning to prescribers that there are possible unwanted long-term consequences from the use of these drugs.

- The choice of an optimal drug for each new patient with insomnia; a BZD or a z-hypnotic, has to be concluded from what aspect is more important for the individual patient, such as acting time, co-morbidity, drug interactions and abuse potential.
The association found between use of analgesics and anxiolytics/hypnotics among people with mental distress can make us ask whether pain for some people has led to mental distress and further treatment for this. Perhaps the methods used to relieve or cope with pain, both medical treatment and non-medical treatment, can be further optimized.

The association found between not participating in the labour market and the use of antidepressants among people with mental distress can lead to a “chicken and egg” dilemma: What happened first; receiving social support or becoming depressed? There is reason to believe people’s health, both mental and somatic, could benefit from going to work either full or part time, with adjusted tasks if needed. Such a practice can be a challenge in a society that requires increasing effectiveness; however in the end it may even be cost-effective.

Mental distress was found to be related to later use of anxiolytic drugs in a dose response manner among middle-aged people. Theoretically, GPs’ screening of middle-aged people using HSCL-10 would tell us where to put the effort in order to prevent later mental health problems which demand medical treatment. In practice, far from all middle-aged people visit a GP regularly. Inviting them to visit a GP in order to reveal mental distress would perhaps not give the optimal participation. A relevant question is whether GPs can be more effective at picking up mental health problems even if people visit them for other reasons.

Gender differences were observed for mortality, prevalence and incidence rates. Women showed a higher proportion of use than men for all the studied drug groups: anxiolytics, BZD hypnotics, z-hypnotics and antidepressants. Researchers have questioned whether women suffer from more pain than men, if they complain more, or if the truth is a combination of the two arguments. We found that among people with mental distress, the OR of later filling prescriptions on anxiolytics was quite similar for the two genders within age groups, whereas the level of use was higher in women.
Interestingly, when studying the Norwegian counties separately there are large differences in the number of filled prescriptions of anxiolytic and hypnotic drugs. In the county with the highest use of anxiolytics the one year prevalence of use, age-adjusted to the Norwegian population 2009 for men and women separately, was two times that of the lowest (29). For BZD hypnotics, the county with highest use had a one year prevalence three times that of the lowest for both sexes. For z-hypnotics the county with highest use showed a one year prevalence one and a half times that of the lowest. These differences are comparable to or larger than those existing between the Nordic countries.

Perhaps there are significant health differences between counties. Further, there may be geographically different therapy traditions, which are sustained although prescribers can move between counties and countries and in the end are replaced by new generations. The possible difference between rural and urban populations is another factor that makes me curious of even more aspects of the epidemiology of anxiolytic and hypnotic drug use in Norway.
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8.0 ERRATA

Synopsis of papers: Paper II
Results, 2nd bullet point:
Of the 73,163 (not 73,173) incident users...

Paper I
Page 914, Materials and methods:
The total response rate was high; 72.0% (not 72.1%) for men and 80.8% (not 80.1%) for women. All participants who were medically examined got this questionnaire and 82% of them responded (not 69%). The additional questionnaire included a question covering use of anxiolytics and hypnotics, which was answered by as many as 85% (men) and 83% (women) of the responders (not 98%).
APPENDICES

Appendix I: The Østfold Health Study 1985/1988
The Aust-Agder Health Study 1986/1989

- Main questionnaire 1985 and 1986
- Main questionnaire 1988 and 1989
- Supplementary questionnaire 1985 and 1986
- Supplementary questionnaire 1988 and 1989

Appendix II: The Oslo Health Study (HUBRO) 2000-2001
The Health Study in Oppland and Hedmark (OPPHED) 2000-2001

- Main questionnaire (Norwegian)
- Main questionnaire (English)
Appendix 1
### Spørreskjema i Østfold 1985 og Aust-Agder 1986

#### Familie
- Har en eller flere av foreldre eller søsknen hatt hjerteinfarkt (dør på hjertet) eller angins pectoris (hjertekrampe)?
- Angina pectoris (hjertekrampe)?
- Hjerneslag?
- Sukkesyke?
- Er de under behandling for:
- Høy blodtrykk?
- Bruker de nitroglycerin?

#### Egen Sykdom
- Har de, eller har de hatt:
  - Hjerteinfarkt?
  - Angina pectoris (hjertekrampe)?
  - Hjerneslag?
  - Sukkesyke?
- Er de under behandling for:
  - Høy blodtrykk?
  - Bruker de nitroglycerin?

#### Symptomer
- Får de smerte eller ubehag i brystet når de:
  - Går i bakker, trepper eller fort på flat mark?
  - Går i vanlig takt på flat mark?
- Dersom de får smerte eller vondt i brystet ved gange, pieler de da å:
  - Stoppa?
  - Sekte farten?
  - Fortsætte i samme takt?
- Dersom de stopper eller saktner farten, forsvinner smertene da?
  - Etter mindre enn 10 minutter?
  - Etter mer enn 10 minutter?
- Har de vanskelig:
  - Hoste om morgenen?
  - Oppsynt fra brystet om morgenen?

#### Mosjong
- Bevegelse og kroppssalg anstrengelse i deres fritid. Hvis aktiviteten varierer meget, leks, male- som sommer og vinter, så ta et gjennomsnitt.
- Spørsmålet gjelder bare de siste året.
- Satt kryss i den ruta hvor JA passer best
- Leser, ser på fjernsyn eller annen stillesattende beskjæftigelse?

#### Salt/Flett
- Hvor ofte bruker de salt kjett eller salt fisk til middag?
  - Satt kryss i den ruta hvor JA passer best
- Aldri eller sjeldnere enn en gang i måneden?
- Opp til en gang i uken?
- Opp til to ganger i uka?
- Mer enn to ganger i uka?
- Hvor ofte pieler de stra ekstra salt på middagsmaten?
  - Satt kryss i den ruta hvor JA passer best
- Selten eller aldri?
- Av og til ofte?
- Altid eller nesten alltid?

#### Kaffe
- Hvor mange kopper kaffe drørke de vanligvis daglig?
  - Satt kryss i den ruta hvor JA passer best
- Drikker bare kaffe, eller mindre enn en kopp?
  - 1 - 4 kopper
  - 5 - 8 kopper
  - 9 eller flere kopper

#### Arbeid
- Har de i løpet av de siste 12 månedene fått arbeidsledighetsstrygd?
  - Satt kryss i den ruta hvor JA passer best
- Er de for tidlig sykmeldt, eller får de atteføringssperre?
  - Satt kryss i den ruta hvor JA passer best
- Har de full eller delvis utrepsjon?
  - Satt kryss i den ruta hvor JA passer best
- Har de vanligvis skiftet oud eller nattarbeid?
  - Satt kryss i den ruta hvor JA passer best
- Har de i det siste året hatt:
  - Satt kryss i den ruta hvor JA passer best
  - For det meste stillsittende arbeid?
  - (t.d. skrivebordsarbeid, urmaskiner, montering)
  - Arbeid som krever at de går mye?

#### Etterundersøkelse
- Hvis denne helseundersøkelsen viser at de bør undersøkes nøyere, hvilken almenpraksisrende lege ønsker de å bli henvist til?
- Skriv navnet på lægen her

---

**Referanse:**

277. [Kilde](https://www.sporreskjema.no/)

Ikke skriv her
SPØRESKJEMA I ØSTFOLD 1988 OG AUST-AGDER 1989

A. FAMILIE
Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller anna bocêtoris (hjertekrampe)? ........................................... 12

B. EGEN SYKDOM
Har De, eller har De hatt: ........................................................ 13
- Hjerteinfarkt? ........................................................................ 13
- Angina pectoris/hjertekrampe? ........................................... 14
- Hiperesia? ............................................................................. 15
- Sukkerrøyse? ....................................................................... 16
- Hvis De har sukkeresyke, i hvilket år ble diagnosen stilt? ...... 17
- Er De under medicamentsbehandling for høyt blodtrykk? ... 19

C. SYMPTOMER
Får De smerte eller ubehag i brystet når De: .................................. 20
- Går i bakker, trepper eller fort på flat mark? ......................... 20
- Går i vanlig takt på flat mark? ............................................... 21
- Dersom De får smerte eller vondt i brystet ved gange, piker De da å: Stoppe? ................................................................. 22
- Sakte fart? ............................................................................ 22
- Fortsætte i samme takt? ....................................................... 23
- Dersom De stopper eller sletter farten, forsvinner smertene de: Etter mindre enn 10 minutter? ........................................ 23
- Etter mer enn 10 minutter? .................................................. 23
- Har De vanligvis: 
  Høste om morgenen? ............................................................. 24
  Oppsprett fra brystet om morgenen? ..................................... 25

D. MOSJON
Bevegelse og kroppssignal anstrengelse i Deres fritid. Hvis aktiviteten varierer meget f.eks. mellom sommer og vinter, så ta et gjennomsnitt. Spørsmålet gjelder bare det siste året.
- Satt kryss i den ruta hvor JA passer best:
  - Passer sommer og vinter, og sommerliggende pasjeevner ........................................... 26
- Passerer, sykler eller beveger Dam på annen måte mindre en 4 timer i uka? ........................................................ 27
  - (Her skal De også regne med gang og sykling til arbeidslivsn.helpers, sendeboliger m.m.)
- Driver mosjonssikret, tyngre hagearbeid m.m.? 
  (Merk at aktiviteten skýr være mindre enn 4 timer i uka) ....... 28
- Trener hardt eller driver konkurranseidrett regelmaessig og flere ganger i uka? ............................................... 30

E. SALT/FETT
Hvor ofte bruker De salt kjøtt eller salt fisk til middag?
- Satt kryss i den ruta hvor JA passer best:
  - Kjøtt eller salt-kjøtt en gang i månedet? ............................. 27
  - Opplost i gis i uka ................................................................ 27
  - Opplost to ganger i uka ..................................................... 28
  - Mer enn to ganger i uka .................................................... 29
- Hvor ofte pleier De stro ekstra salt på middagstrømmen?
- Satt kryss i den ruta hvor JA passer best:
  - Pleier det i alle månedene? ............................................... 26
  - Avgi og till i frisfôr ............................................................ 27
  - Atti og næsten altid ........................................................... 28
- Hva slags margarin eller smør bruker De til vanlig på bord?
- Satt kryss i den ruta hvor JA passer best:
  - Bruker ikke smør eller margarin på bord? ......................... 29
  - Smør .............................................................................. 30
  - Hard margarin ................................................................. 31
  - Myk (Soft) margarin ......................................................... 32
  - Smør/margarin blanding .................................................... 33
- Hva slags fôr blir til vanlig brukt til matlaging i Deres husholdning?
- Satt kryss i den ruta hvor JA passer best:
  - Smør eller hard margarin .................................................. 30
  - Myk (Soft) margarin eller oljekjøtt ................................... 31
  - Smør/margarin blanding .................................................... 32

F. RØYKING
Røyker De 
Sigaretter daglig? ................................................................. 31
(*håndfriet eller fabrikkfremstilt) 
Sigarrer eller snurter/sigarrillos daglig? .................................. 32
Pipe daglig? ........................................................................... 33
- Hvis De ikke røyker daglig nå, børst du da: 
  - De røykt daglig tidligere? ............................................... 34
  - Hvis De svarte JA, hvor lenge er det siden De slutte? ..... 35
  - Mindre enn 1 år? ................................................................ 35
  - Mer enn 1 år? .................................................................. 36
- Besøvares av dem som røyker nå eller som har røykt tidligere:
  - Hvor mange år blir sammen har De røykt daglig? ........... 37
  - Hvor mange sigaretter røyker eller røykte De daglig? ..... 38
  - Oppgi tallet på sigaretter daglig (håndfriet + fabrikkfremstilt) .................................................. 39

G. KAFFE
Hvor mange kopper kaffe drukker De vanligvis daglig?
- Satt kryss i den ruta hvor JA passer best:
  - Drikker ikke kaffe, eller mindre enn en kopp ........................ 40
  - 1-4 kopper ........................................................................ 41
  - 5-8 kopper ....................................................................... 42
  - 9 eller flere kopper ........................................................... 43
- Hva slags kaffe drukker De vanligvis daglig?
  - Kollekaffe ........................................................................ 44
  - Filterkaffe ....................................................................... 45
  - Pulverkaffe ...................................................................... 46
  - Kaffemix eller kaffe .......................................................... 46
  - Drikker ikke kaffe ............................................................. 47

H. ARBEID
Har De i det siste året hatt:
- Satt kryss i den ruta hvor JA passer best:
  - Før det meiste stillesett arbeid? ........................................ 48
    (f.eks. skrebbonstjøtt, trærøvere, stort handel, byggearbeid, jordbruk, landbruks, barbering, servicearbeid, korte arbeid og forstørre fest) .................................................. 48
  - Arbeid som krever at De går mye .................................... 49
    (f.eks. ambulansfører, fottmand, jordbruksarbeid, byggearbeid, tvert ganger) .................................................. 49
  - Tunge arbeid, som f.eks. skreppe, bent, tvert ganger og forstørre fest) .................................................. 50
    (hansløs eller nattarbeid) ................................................. 51
  - Er husarbeid i hjemmet hovedverket? Deres? .................... 52
    (f.eks. husarbeid, behandling, mektig mektig mektig mektig mektig mektig) .................................................. 53
  - Har De daglig uansett for sykdom eller funksjonshemmede i familien? ........................................................ 54
  - Har De i kapet av de siste 12 måneder fått arbeidslidenskedsrydd? ........................................................ 54
  - Er De for tiden sykmeldt, eller får De tilførselsrydd? ....... 55
  - Har De full eller delvis undervisningsjobb? ....................... 56

I. ETTERUNDETSØKELSE
Hvis denne helseundersøkelsen viser at De bor underutsøkt nærmere:
- Hvilken almenpraktiserende lege/kommunelege ønsker De da å bli henvert til? ............................................................. 57
- Ingen spesiell lege ............................................................. 58
<table>
<thead>
<tr>
<th>A</th>
<th>Bruker De mediciner mot høyt blodtrykk?</th>
<th>Ja Nei</th>
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<tr>
<td></td>
<td>Hvis Ja, i hvilket år begynte De å bruke</td>
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<td></td>
<td>høyrettmedisin ........................................</td>
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<td>Gir høyrettmedisinen Dem noe ubehag?..............</td>
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<td>Går De regelmessig til legemessi for høyrettmedisin?</td>
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<td>Har De øyrsyksom? ....................................</td>
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<td></td>
<td>Har en eller flere av foreldre eller saken høyrettmedisin?</td>
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<th>B</th>
<th>Har De eller har De hatt sår på magesekk eller tolvingertarm?</th>
<th>Ja Nei</th>
<th>19</th>
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<td>Hvis Ja, hva sår sår? ...........................................</td>
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<td>Mavesekk (Ventrikkel) ..........................................</td>
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<td>Tolvingertarm (Duodenum) .......................................</td>
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<td>Vet ikke ..................................................................</td>
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<td>Hvilket år ble diagnosen stiltet første gang?................</td>
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<td>Er De operert for sår? ..........................................</td>
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<td>Hvis Ja, i hvilket år ble De operert? ..........................</td>
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<td>Har De gått ned i vekt etter operasjonen? .....................</td>
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<td>Hvis Ja, om trenger du mange kilo? .............................</td>
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<td>Bruker De: Miljøentlekk? .......................................</td>
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<td>Vitamin B-12-sprayte .............................................</td>
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<th>Har De sukkersykdom? ...........................................</th>
<th>Ja Nei</th>
<th>31</th>
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<td>Hvis Ja, i hvilket år ble diagnosen stiltet første gang?</td>
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<td>Bruker De: Insulin? .............................................</td>
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<td>Sukkertabletter? ..................................................</td>
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<td>Bare diet? ..................................................................</td>
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<td>Er De påpasselig med å følge det behandlingsopplag som De har fått?</td>
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<tr>
<td></td>
<td>Har en eller flere av foreldre eller saken sukkersyke?</td>
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<thead>
<tr>
<th>D</th>
<th>Har De: Coeliak? ..................................................</th>
<th>Ja Nei</th>
<th>37</th>
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<tbody>
<tr>
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<td>Psoriasis? ..................................................................</td>
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<td>Har en eller flere av foreldre eller saken: Coeliak?</td>
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<td>Psoriasis? ..................................................................</td>
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<th>E</th>
<th>Er det, eller tror De at det er forurensing på arbeidsplassen som kan skade helsen?</th>
<th>Ja Nei</th>
<th>41</th>
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<tbody>
<tr>
<td></td>
<td>Hvis Ja, dreier det som om kryss en eller flere ..................................................</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gaser ..................................................................</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Støy ....................................................................</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Giftige stoffer ..................................................</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Giftige væsker ...................................................</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>F</th>
<th>Hvor ofte har De drukket øl, vin eller brenevin i løpet av de siste 14 dager?</th>
<th>Ja Nei</th>
<th>46</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drikker alkohol? .........................................................................................</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ikke drukket siste 14 dager, men er ikke totalavholdende .............................</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1-4 ganger .................................................................................................</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-10 ganger ...............................................................................................</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mer enn 10 ganger .......................................................................................</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>G</th>
<th>Hvor ofte har De drukket alkohol de siste 14 dager, har det ført til at De har følt Dame verus?</th>
<th>Ja Nei</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Har det vært perioder av Deres liv de De har drukket for mye alkohol? ......</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>H</th>
<th>Hvor ofte har De drukket smertestillinge medisin i løpet av siste måned?</th>
<th>Ja Nei</th>
<th>51</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daglig .................................................................................................</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hver uke, men ikke daglig ....................................................................</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sjeldnere enn hver uke ........................................................................</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ikke drukket siste måned ......................................................................</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>I</th>
<th>Hvor ofte har De drukket beroligende nerverbilde eller sovemedisin i løpet av siste måned?</th>
<th>Ja Nei</th>
<th>53</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daglig ...................................................................................................................</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hver uke men ikke daglig .....................................................................................</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sjeldnere enn hver uke .......................................................................................</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ikke drukket siste måned ....................................................................................</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 2
Helseundersøkelsen

Personlig innbydelse
# 1. EGEN HELSE

### 1.1 Hvordan er helsen din nå? (Sett bare ett kryss)

<table>
<thead>
<tr>
<th>Dårlig</th>
<th>Ikke helt god</th>
<th>God</th>
<th>Svært god</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### 1.2 Har du, eller har du hatt?:

- Astma: [ ] JA [ ] NEI
- Hoysnue: [ ] JA [ ] NEI
- Kronisk bronkit/amytem: [ ] JA [ ] NEI
- Diabetes (suksesyke): [ ] JA [ ] NEI
- Benskjeør (osteporose): [ ] JA [ ] NEI
- Fibromyalgi/kronisk smertesyndrom: [ ] JA [ ] NEI
- Psykiske plager som du har søkt hjelp for: [ ] JA [ ] NEI
- Hjertefuktart: [ ] JA [ ] NEI
- Angina pectoris (hjertekrampe): [ ] JA [ ] NEI
- Hjerneslag/hjerneskadning (<drypp>): [ ] JA [ ] NEI

### 1.3 Har du merket anfall med plutselig endring i pulsen eller hjertakerd siste året?: [ ] JA [ ] NEI

### 1.4 Får du smerte eller utbøt i bryset når du:

- Går i bakker, trapper eller fort på flat mark?: [ ] JA [ ] NEI
- Hvis du får slike smertek, plener du du å:
  - Stopp?: [ ] JA [ ] NEI
  - Sjølme fatter?: [ ] JA [ ] NEI
  - Forbata i samme takt?: [ ] JA [ ] NEI

### 1.6 Dersom du stopper, forsvinner smertene da etter mindre enn 10 minutter?: [ ] JA [ ] NEI

### 1.7 Kan slike smertek opptre selv om du er i ro?: [ ] JA [ ] NEI

# 2. MUSKEL OG SKJELETTPLAGER

### 2.1 Har du vært plaget med smerter og/eller stivhet i musker og ledd i løpet av de siste 4 ukene? (Variåhet angis bare hvis du har haft plaget)

<table>
<thead>
<tr>
<th>Variåhet</th>
<th>I slekt</th>
<th>2-åker</th>
<th>3-åker</th>
<th>Ikke plaget</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>T</td>
<td></td>
</tr>
</tbody>
</table>

- Nakke/skuldrer: [ ] JA [ ] NEI
- Armer, hender: [ ] JA [ ] NEI
- Øvre del av ryggen: [ ] JA [ ] NEI
- Korsryggen: [ ] JA [ ] NEI
- Høfner, ben, fotter: [ ] JA [ ] NEI
- Andre steder: [ ] JA [ ] NEI
- Ader stikk: [ ] JA [ ] NEI

### 2.2 Har du noen gang hatt:

- Brudd i hånde/underarm: [ ] JA [ ] NEI
- Lårhalsbrudd: [ ] JA [ ] NEI

# 3. ANDRE PLAGER

### 3.1 Under finner du en liste over ulike problemer. Har du opplevt noe av dette de siste 14 døgnet? (Sett ett kryss for hvert plages)

- Plutselig frykt uten grunn: [ ] JA [ ] NEI
- Flerer dag rekk eller engstelig: [ ] JA [ ] NEI
- Målhet eller svimmelhet: [ ] JA [ ] NEI
- Flerer dag ępset eller oppsaget: [ ] JA [ ] NEI
- Latt før å bliandre dag selv: [ ] JA [ ] NEI
- Søvnpåvirkning: [ ] JA [ ] NEI
- Nedtrykt, tungsindig: [ ] JA [ ] NEI
- Følelse av å være uennig, lite verdi: [ ] JA [ ] NEI
- Følelse av at alt er et sitt: [ ] JA [ ] NEI
- Følelse av høyabet utbatt, travl: [ ] JA [ ] NEI

### 4. BRUK AV HELSETJENESTER

### 4.1 Hvor mange ganger de siste 12 månedene har du selv brukt:

- Allmennpraktiserende lege: [ ] JA [ ] NEI
- Bedriftslege: [ ] JA [ ] NEI
- Psykolog eller psykologer: [ ] JA [ ] NEI
- (Privat eller på poliklinikk): [ ] JA [ ] NEI
- Annen spesialist (privat eller på poliklinikk): [ ] JA [ ] NEI
- Legevakth (privat eller offentlig): [ ] JA [ ] NEI
- Sykehusinlegging: [ ] JA [ ] NEI
- Hjemmesykepleie: [ ] JA [ ] NEI
- Fysioterapeut: [ ] JA [ ] NEI
- Kiropraktor: [ ] JA [ ] NEI
- Tannlege: [ ] JA [ ] NEI
- Alternativ behandling: [ ] JA [ ] NEI

# 5. OPPVEKST OG TILHØRIGHET

### 5.1 Hvor lenge har du samlet bodd i Norge?

- 10 år: [ ] JA [ ] NEI

### 5.2 Hvor lenge har du samlet bodd i kommunen?

- 0 år: [ ] JA [ ] NEI

### 5.3 Hvor bodde du det meste av tiden før du fylte 16 år?

- (Kryss av for å markere alternativ og spesifiseringen)

### 5.4 Har du flyttet i løpet av de siste fem årene?

- JA, en gang: [ ] JA [ ] NEI
- JA, flere ganger: [ ] JA [ ] NEI

# 6. VEKT

### 6.1 Anslå din vekt da du var 25 år gammel: [ ] holde kg
10. MOSJON OG FYSISK AKTIVITET

10.1 Hvordan har din fysiske aktivitet i triftiden vært det siste året?
Tanken er at et ukentlig gjennomsnitt for året. Arbeidsgiver regnes som trift. Besvar begge spørsmålene.

<table>
<thead>
<tr>
<th>Timer pr. uke</th>
<th>Ingen</th>
<th>Under 1</th>
<th>1-2</th>
<th>3 og mer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Litt aktivitet (likvært/personverksplassen)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hard fysisk aktivitet</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

10.2 Angi bevegelse og kroppslig anstrengelse i din triftid. Hvis aktiviteten varierer meget f eks. mellom sommer og vinter, så ta et gjennomsnitt. Spørsmålet gjelder bare det siste året.

(Sev krys i den ruta som passer best)

- Leser, seri på fjernsyn eller annen
  stillestående bekaftigelse ...................................... 1
- Spaserer, sykler eller beveger deg på
  annen måte minst 4 timer i uka? ................................ 2
  (Her skal du også regne med gang eller
  sykling til arbeidsstedet, sondagsturer m.m.)
- Driver mosjonsidrett, tynge høgeverdi a l t? .................... 3
  (Mark at aktiviteten skal være minst 4 timer i uka)
- Trener hardt eller driver konkurransoseddrett
  regelmessig og flere ganger i uka ................................ 4

11. FAMILIE OG VENNER

11.1 Bor du sammen med noen?
JA: NEI

- Ektefelle/samboer ..............................................
- Andre personer, 18 år og eldre: ..................................
- Personer under 18 år: ...........................................

11.2 Hvor mange gode venner har du?
Antall venner

- Røgn med de du kan snakke fortrolig med og som kan gi deg hjelp dersom du trenger det.
- Tilfikk ikke de du bor sammen med, men ta med andre skikkelser.

11.3 Hvor stor interesse viser folk for å det du gjør?
(Sev bare ett kryss)

<table>
<thead>
<tr>
<th>Slør interesse</th>
<th>Nære interesse</th>
<th>Litt interesse</th>
<th>Ingen interesse</th>
<th>Usikker</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

11.4 Hvor mange foreninger, lag, grupper, kirkesamfunn e l t. deltar du i på triftiden?
(Sev skravde f eks. ingen)
Antall

11.5 Føler du at du kan påvirke det som skjer i lokalsamfunnet der du bor? (Sev bare ett kryss)
JA: NEI

- I en sa trulig ungdom av fem eller mer
- I en likvid ungdom av fem eller mer
- Har ikke forbått

| 1 | 2 | 3 | 4 | 5 |

12. SYKDOM I FAMILIEN

12.1 Har en eller flere av dine foreldre eller sosen hatt hjertefar (sår på hjertet) eller angina pectoris (hjertekrampe)?
JA: NEI

13. BRUK AV MEDISINER

Med medisiner mener vi her medisiner kjøpt på apotek. Kosthold og vitaminer regnes ikke med her.

13.1 Bruker du?

- Medisin mot høy blodtrykk
- Kolesterolstignende medisin
- Smertestillende uten respekt
- Smertestillende på respekt
- Sovemedisin
- Børnelignende medisin
- Medisin mot depressjon
- Annen medisin på respekt

13.2 Hvor ofte har du i løpet av de siste 4 ukene brukt følgende medisiner?
(Sev et kryss pr. linje)

<table>
<thead>
<tr>
<th>Daglig</th>
<th>Hver anden dag</th>
<th>Egentlig hver uke</th>
<th>Ikke brukt de siste 4 uker</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

13.3 For de medisintene som du har krysset av for i pkt. 13.1 og 13.2, og som du har brukt i løpet av de siste 4 ukene:
Angi navnet og hvilken grunn det er til du tar/er tatt disse (sykdom eller symptom):
(Krys av for hvor lenge du har brukt medisinen)

<table>
<thead>
<tr>
<th>Navn på medisinen:</th>
<th>(ett navn pr. linje)</th>
<th>Grunn til bruk av medisinen:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Inntil 1 år</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

14. RESTEN AV SKJEMAET SKAL BARE BESVARES AV KVINNER

14.1 Hvor gammel var du da du fikk menstruasjon allere første gang?
Aldr i år

14.2 Hvis du ikke lenger får menstruasjon, hvor gammel var du da den sluttede?
Aldr i år

14.3 Er du gravid nå?

<table>
<thead>
<tr>
<th>Ja</th>
<th>Nei</th>
<th>Usikker</th>
<th>Over bruktbar</th>
<th>Antall</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

14.4 Hvor mange barn har du født?
Antall barn

14.5 Bruker du, eller har du brukt?
(Sev et kryss for hver linje)

- P-piller/minipiller/p-prøyste
- Hormonspiral
- Østrogen (tablett eller plaseter)
- Østrogen (kram eller stikkpiller)

14.6 Hvis du bruker/har brukt ressoppliktig østrogen: Hvordan lenge har du brukt dette?
Antall år

14.7 Hvis du bruker p-pille, minipille, p-prøyste, hormonspiral eller østrogen; hvilket merke bruker du?
## 1. YOUR OWN HEALTH

### 1.1 How would you describe your present state of health? *(Mark only one answer with a cross)*

<table>
<thead>
<tr>
<th>Poor</th>
<th>Not very good</th>
<th>Good</th>
<th>Very good</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 1.2 Do you have any of these illnesses, or have you suffered from them in the past? 

#### Yes No  
<table>
<thead>
<tr>
<th>Disease</th>
<th>Age on last occasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>yrs</td>
</tr>
<tr>
<td>Hay fever</td>
<td>yrs</td>
</tr>
<tr>
<td>Chronic bronchitis/emphysema</td>
<td>yrs</td>
</tr>
<tr>
<td>Diabetes</td>
<td>yrs</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>yrs</td>
</tr>
<tr>
<td>Fibromyalgia / chronic pain syndrome</td>
<td>yrs</td>
</tr>
<tr>
<td>Mental disorders for which you sought help</td>
<td>yrs</td>
</tr>
<tr>
<td>Cardial infarction</td>
<td>yrs</td>
</tr>
<tr>
<td>Angina pectoris (cardiac spasm)</td>
<td>yrs</td>
</tr>
<tr>
<td>Stroke/cerebral haemorrhage (“drip”)</td>
<td>yrs</td>
</tr>
</tbody>
</table>

### 1.3 Have you ever noticed any sudden change of your pulse or heart beat during the past year?  

#### Yes No

### 1.4 Do you feel pain or discomfort when you:  

#### Yes No

- Walk up hills, climb stairs or walk fast on level ground?

### 1.5 If you do feel such pain, do you usually:  

#### Stop? Slow down? Continue at the same pace?

<table>
<thead>
<tr>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop?</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

### 1.6 If you stop, does the pain then disappear after less than 10 minutes?  

#### Yes No

### 1.7 Is such pain just as likely to occur when you are standing still or sitting / lying down?  

#### Yes No
### 2. MUSCULOSKELETAL DISORDERS

2.1 Have you suffered from pain and/or stiffness in muscles and joints in the course of the last 4 weeks?
*(Duration to be stated only if you have been troubled in this way)*

<table>
<thead>
<tr>
<th>Not troubled</th>
<th>Somewhat troubled</th>
<th>Very troubled</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Up to 2 weeks</td>
</tr>
<tr>
<td>Neck/shoulders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arms, hands</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper back</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower back</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hips, legs, feet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elsewhere</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.2 Have you ever:

<table>
<thead>
<tr>
<th>Broken (fractured) your wrist/lower arm?</th>
<th>Yes</th>
<th>No</th>
<th>Age on last occasion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>yrs</td>
</tr>
</tbody>
</table>

### 3. OTHER DISORDERS

3.1 Below is a list of various problems. Have you suffered from any of the following during the last week *(including today)*?
*(Put a cross for every problem)*

<table>
<thead>
<tr>
<th>Not troubled</th>
<th>Slightly troubled</th>
<th>Quite a lot troubled</th>
<th>Much troubled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suddenly feel panic for no reason</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suddenly feel frightened or anxious</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feel faint or dizzy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feel tense or harassed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Easily find fault with yourself</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleeplessness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feel depressed, dejected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feel useless, of little worth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feel that everything is a burden</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling of hopelessness for the future</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

### 4. USE OF THE HEALTH SERVICES

4.1 How many times during the last 12 months have you personally used:
*(One cross on each line)*

<table>
<thead>
<tr>
<th>None</th>
<th>1-3 times</th>
<th>4 times or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>General practitioner</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Company doctor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychologist or psychiatrist</td>
<td><em>(private or at an outpatient clinic)</em></td>
<td></td>
</tr>
<tr>
<td>Other consultant (specialist) <em>(private or at an outpatient clinic)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency service *(&quot;doctor-on-call&quot;) <em>(private or public)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission to hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home nursing service</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physiotherapist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chiropractor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dentist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alternative therapist</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5. WHERE YOU GREW UP / WHERE YOU BELONG

5.1 How long have you lived in Oslo altogether? ......................... yrs
(Write 0 if less than 6 months)

5.2 How long have you lived altogether in the district / sub-municipality of Oslo where you are living now? yrs
(Write 0 if less than 6 months)

5.3 Where did you live for most of the time before you reached the age of 16 years?
(Cross off one alternative and specify)

Same sub-municipality/district of Oslo .................. 

Another sub-municipality/district of Oslo ..................

Another county in Norway ....................... Which

Outside Norway ...........................

5.4 Have you moved in the course of the last five years?

No Yes, once Yes, several times

6. WEIGHT

6.1 Assess your weight when you were 25 years old: whole kg

7. FOOD AND DRINK

7.1 How often do you usually eat the following kinds of foods?
(Mark the appropriate answer with a cross on each line)

<table>
<thead>
<tr>
<th>Fruit/berries</th>
<th>Seldom/ Never</th>
<th>1-3 times. pr. mth</th>
<th>1-3 times. pr. week</th>
<th>4-6 times. pr. week</th>
<th>1-2 times. pr. day</th>
<th>3 times or more pr. day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheese (all kinds)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potatoes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooked vegetables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raw vegetables/salad</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat fish (e.g. salmon)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trout, mackerel, herring</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7.2 What kind of fat do you use most often? (One cross only on each line)

<table>
<thead>
<tr>
<th>Dairy-butter</th>
<th>Hard margarine</th>
<th>Soft/light margarine</th>
<th>Oil</th>
<th>Do not use</th>
</tr>
</thead>
<tbody>
<tr>
<td>On bread</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For cooking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7.3 Do you take the following food supplements?

Yes, daily Sometimes No

Cod liver oil, cod liver oil capsules, fish oil capsules? ................

Vitamin- and/or mineral supplement? ..................................
7.4 How much do you usually drink of the following?
(One cross per line).

<table>
<thead>
<tr>
<th>Drink</th>
<th>Seldom/Never</th>
<th>1-6 glasses pr.wk</th>
<th>1 glass pr.day</th>
<th>2-3 glasses pr. day</th>
<th>4 glasses or more pr. day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full cream milk, kefir, yoghurt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semi-skimmed milk, “cultura”, light yoghurt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skimmed milk (sour/sweet)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruit juice</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbonated bottled water</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CocaCola, Pepsi Cola or suchlike</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other “fizzy”/drinks/thirst quenchers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 2 3 4 5

7.5 Do you usually drink thirst quenchers / Cola:
With sugar □ 1 Without sugar □ 2

7.6 How many cups of coffee or tea do you drink daily?
(Write 0 if you do not drink coffee or tea daily)

<table>
<thead>
<tr>
<th>Number cups coffee</th>
<th>Number cups tea:</th>
</tr>
</thead>
</table>

7.7 What kind of coffee do you usually drink?
Filter/- instant coffee..............
“Boiled” (coarse ground)/ Cafeteria-made coffee
Other coffee (espresso etc.) ..... Do not drink coffee..................

7.8 How often have you consumed alcohol in the course of the past year?
(Low alcohol beer and non-alcoholic beer are not included)

<table>
<thead>
<tr>
<th>4-7 times pr. wk</th>
<th>2-3 times pr. wk</th>
<th>ca. once pr. wk</th>
<th>2-3 times pr. mth</th>
<th>About once pr. mth.</th>
<th>A few times in the past year</th>
<th>Have not drunk alcohol this past year</th>
<th>Have never drunk alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

To those who have consumed alcohol during the past year:

7.9 When you consumed alcohol, how many glasses or drinks did you usually consume?
Number □ □

7.10 How often in the course of the past year did you drink as many as at least 5 glasses or drinks in the course of one day?
Number of times □ □

7.11 When you drink, do you usually drink: (Put more than one cross if applicable)

<table>
<thead>
<tr>
<th>Beer</th>
<th>Wine</th>
<th>Spirits</th>
</tr>
</thead>
</table>

8. SMOKING

8.1 How much time do you usually spend each day in a smoke-filled room?..............Number whole hours: □ □

8.2 Did any of the adults in your home smoke when you were growing up?......................... Yes No

8.3 Are you living, or have you lived in the same house as a daily smoker after reaching the age of 20 yrs? Yes No
8.4 Have you smoked/do you smoke daily?... Yes, now □ Yes, earlier □ No □
If NEVER: Go straight to the questions on EDUCATION AND EMPLOYMENT

8.5 If you smoke daily at present, do you smoke: Yes □ No □
Cigarettes? .......................................................... □ □
Cigars/cigarillos? .................................................. □ □
A pipe? ................................................................. □ □

8.6 If you have smoked daily before, how long is it since you stopped smoking? ......... Number of years □ □

8.7 If you smoke daily now, or have smoked before:
How many cigarettes do you or did you usually smoke daily? ...................... Number cigarettes □ □
How old were you when you started to smoke daily? ................................. Age in yrs □ □
How many years altogether have you smoked daily? .................................. Number yrs. □ □

9. EDUCATION AND EMPLOYMENT

9.1 How many years of schooling/education have you completed altogether? ............. Number yrs. □ □

9.2 Are you currently employed?
Yes, full time □ 1 Yes, part time □ 2 No □ 3

9.3 Describe the activity going on at the place of work (department) where you carried out paid work for the longest period of time during the last 12 months. (E.g. Firm of Accountants, lower secondary school, pediatric department at a hospital, carpentry workshop, car repair workshop, bank, commodity trade, etc.)

Activity:  
If retired, state your activity and occupation before retirement.  
Applies also to 9.4.

9.4 What is/ was your occupation / title at this place of work?
(E.g. secretary, teacher, industrial worker, child nurse, cabinet maker, head of department, salesman, driver, etc.)
Occupation: ____________________________

9.5 In your main occupation, are you self-employed, do you work as an employee or as a family member without an agreed fixed wage?
Self-employed □ Employee □ Family member □

9.6 Do you think you are in danger of losing your present work or income in the course of the next 2 years………………………………………………………………………….. □ □

9.7 Are you receiving any of the following benefits? Yes □ No □
Sick pay (Certified as being ill)…………………………………….. □ □
Old-age pension, early retirement pension or widow(er)’s pension………………………….. □ □
Rehabilitation/training allowance………………………………. □ □
Disability pension (full or part)…………………………………… □ □
Daily allowance during unemployment……………………… □ □
Social assistance / benefit……………………………………… □ □
Interim allowance for single parents/supporters.. □ □
10. EXERCISE AND PHYSICAL ACTIVITY

10.1 What kind of physical activity have you undertaken in you spare time in the course of the past year?
Estimate a weekly average for the year.
From home to work is regarded as spare time. Answer both questions:

<table>
<thead>
<tr>
<th>Hours p.r. week</th>
<th>None</th>
<th>Less than 1</th>
<th>1-2</th>
<th>3 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(You do not sweat or feel out of breath)</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Hard physical activity</td>
<td>(You sweat and feel out of breath)</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

10.2 Describe the extent of movement and bodily exertion in your spare time. If the activity varies considerably, e.g. between summer and winter, then give an average. The question applies to the past year only.
(Mark the appropriate answer)

Read, watch TV or other sedentary activity? 

Walk, cycle or move about in some other way at least 4 times per week? 

Take part in physical exercise/sport, do heavy gardening work?
(Note that the activity must take place at least 4 times a week) 

Exercise hard or take part in competitive sport regularly and several times a week.

11. FAMILY AND FRIENDS

11.1 Do you live together with another person? Yes No 
If YES: Yes No 
Spouse/partner .......... 
Other persons, 18 yrs or older No Number 
Persons under 18 yrs .......... No Number 

11.2 How many good friends do you have? Number of friends 
Count those whom you can talk to in confidence and who can help you when you need help. Do not count those who you live together with, but include other relatives.

11.3 How much interest do people show in the things you do? (Only one cross)

Great interest Some interest Slight interest No interest Uncertain

11.4 How many societies, clubs, groups, congregations etc. do you take part in in your free time? Number
(Put 0 if none)

11.5 Do you feel that you can influence what happens in the local community where you live?
Yes, to a large degree Yes, to some degree Yes, to a slight degree No

12. SICKNESS IN THE FAMILY

12.1 Has either of your parents or any of your brothers/sisters had cardiac infarction, or angina pectoris (cardiospasm)? 
Yes No Do not know

[ ] [ ] [ ] [ ] [ ] [ ]
### 13. USE OF MEDICINES

Medicines, in this context, means medicines bought at a pharmacy. Food supplements and vitamins are not included here.

#### 13.1 Do you take?

<table>
<thead>
<tr>
<th>Medicine for high blood pressure</th>
<th>Now</th>
<th>Earlier, but not now</th>
<th>Never used</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cholesterol-reducing medicine</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>

#### 13.2 How often in the course of the last 4 weeks have you taken the following medicines?

(One cross per line)

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Daily</th>
<th>Every week but not daily</th>
<th>Less often than every week</th>
<th>Not taken during the last 4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painkillers, off prescription</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Painkillers, on prescription</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedatives</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tranquilisers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-depressives</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other medicine on prescription</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

#### 13.3 For those medicines you have crossed off in items 13.1 and 13.2, and you have taken during the last 4 weeks:

State the name of the medicines and your reason for taking/having taken them (disease, symptom):

(Cross off for how long you have taken the medicine)

<table>
<thead>
<tr>
<th>Name of medicine: (one name per line):</th>
<th>Reason for taking the medicine</th>
<th>How long have you taken the medicine?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Up to 1 yr</td>
</tr>
<tr>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

If there is not enough space here, continue on a separate page and enclose it with the form.
14. THE REST OF THE QUESTIONNAIRE IS TO BE ANSWERED BY WOMEN ONLY

14.1 How old were you when you had your first menstruation? .......... Age in yrs.

14.2 If you no longer have menstruation, how old were you when you stopped? Age in yrs

14.3 Are you pregnant at present?

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Not sure</th>
<th>Past fertile age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

14.4 How many children have you given birth to?.......... Number children

14.5 Do you use or have you used?
(One cross on each line)

- P-pill / minipill /p-injection ........
- Hormone loop ...........................
- Oestrogen (tablets or plaster)       
- Oestrogen (cream or suppositories)

No | Before, but not now  | Never

14.6. If you take / have taken oestrogen that is on prescription:

How long have you taken this? ................. Number yrs.

14.7 If you use the p-pill, mini-pill, p-injection, hormone loop or oestrogen; which preparation do you use?