Faculty of Health Sciences, Institute of Community Medicine

Aspects of Active Smoking and Breast Cancer

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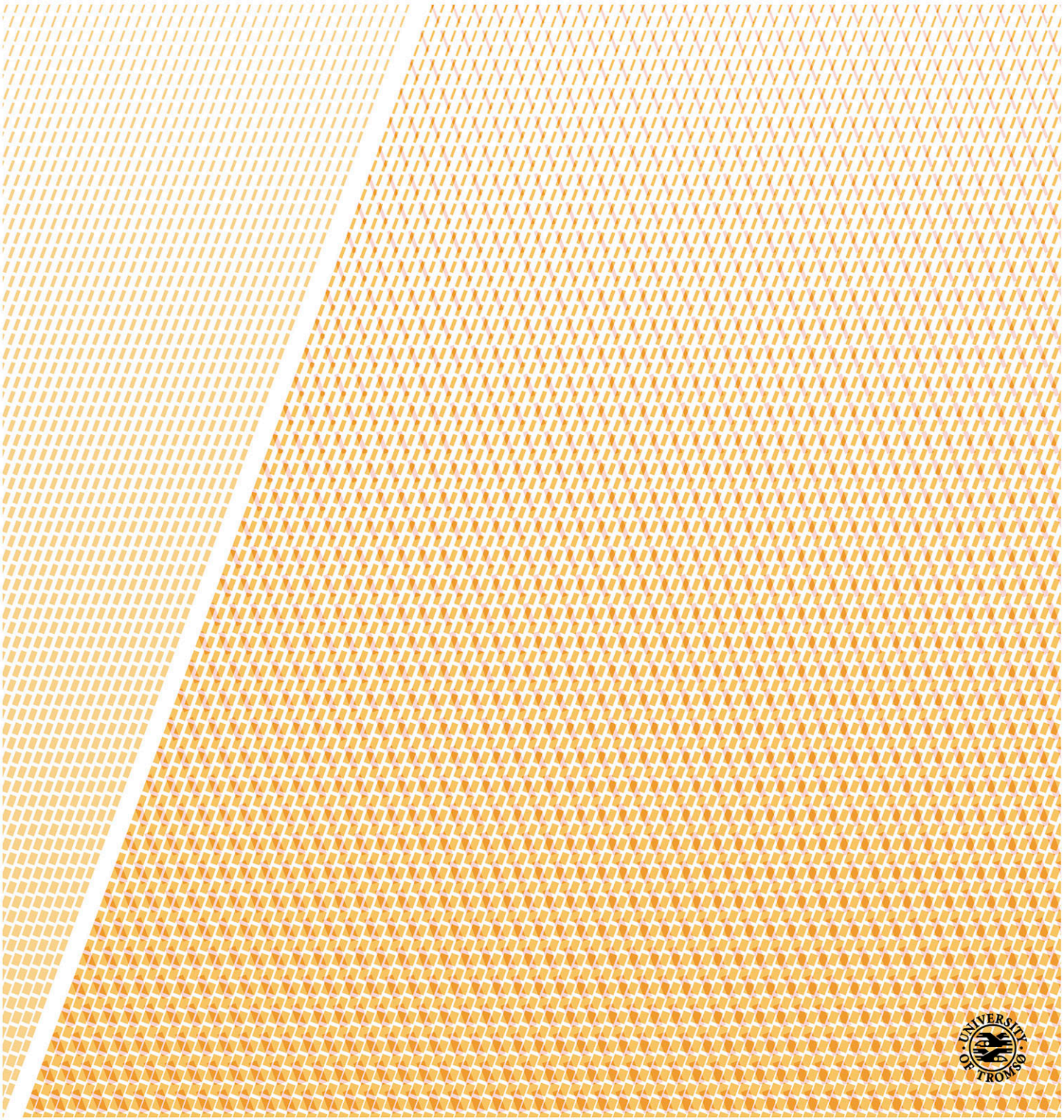
A dissertation for the degree of Philosophiae Doctor



THESIS

Acknowledgements

I wish to express my gratitude to

My main supervisor, Professor Inger Torhild Gram, for her vast knowledge of science and her dedicated supervision during every detail of this research project.

My co-supervisor, Professor Elisabete Weiderpass for bringing her structure and experience to our team.

My dear friend and colleague, Ranjan Parajuli, PhD, for the long hours working side by side in our office, for always being positive and encouraging, an invaluable discussion partner, and the person with whom I could share frustrations and difficulties.

Data manager Knut Hansen for his contribution during the strenuous first 18 months of the project, merging all the data files into a complete new cohort.

Trudy Perdrix-Thoma for invaluable help during preparations of the manuscripts.

To the Department of Community Medicine, the Epinor school, and my friends there: Kristin, Karina, Bent-Martin, Ammar, Torhild, Mona, Gerd, and all the others.

To my beloved, patient, and beautiful wife Rita, and my children Hedda, Sofie, Edvard, and Alma.

Tromsø, August 2014

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1 Summary

According to the World Health Organization, breast cancer is by far the most frequently diagnosed cancer, and the most frequent cause of cancer death among women in the world. Tobacco smoking is the single largest cause of cancer worldwide and has been linked to cancer in most organ systems. The association between breast cancer and smoking has been debated for decades, and more than 150 epidemiological studies have been conducted in this field, with various conclusions. The aim of this thesis was to illuminate the association between smoking and breast cancer incidence, mortality, and to study the socioeconomic consequences of smoking-associated breast cancer in a large Norwegian cohort with a high number of female smokers. The cohort included 302,865 women recruited from three large Norwegian health surveys, and is one of the largest cohorts that exists today. During 14 years of follow-up we identified 7490 cases of breast cancer, and 1106 breast cancer deaths. The main analyses compared ever smokers to never smokers. In Paper I we investigated the association between active smoking and breast cancer incidence. We found an increased risk of 15% for ever smokers overall, as well as an increased breast cancer risk with increasing number of cigarettes smoked per day, smoking duration, number of pack-years smoked, and lower age at smoking initiation. We found an increasing risk with longer smoking duration before first childbirth, and no increased risk among those who started to smoke after first childbirth. In Paper II we investigated the association between smoking and breast cancer mortality, which revealed a 15% increased risk of breast cancer mortality for ever smokers. Most of the results for the different smoking exposures considered were not statistically significant. In particular, no statistically significantly increased breast cancer mortality was found for women who initiated smoking before first childbirth. In Paper III, we used level of education as a validated measure of socioeconomic status, and investigated whether level of education had an impact on the risk of smoking-associated breast cancer. We did not find an increased risk of smoking-associated breast cancer in women with high level of education, but we were able to confirm that smoking before first childbirth remains a risk factor for breast cancer, regardless of educational achievement. Smoking-associated breast cancer does not seem to have an important impact on social inequalities in health. This thesis confirms the weak, but significant association between smoking and breast cancer observed in recent cohort studies. Furthermore, weak but significantly increased breast cancer mortality was observed among current smokers. High level of education is not associated with smoking-

associated breast cancer. Active smoking, in particular active smoking before first childbirth, emerges as a risk factor for breast cancer incidence.

2 List of papers

Paper I

Bjerkaas E, Parajuli R, Weiderpass E, Engeland A, Maskarinec G, Selmer R, Gram IT. **Smoking duration before first childbirth: an emerging risk factor for breast cancer? Results from 302,865 Norwegian women.** Cancer Causes Control 2013;24:1347-56.

Paper II

Bjerkaas E, Parajuli R, Engeland A, Maskarinec G, Weiderpass E, Gram IT. **The association between lifetime smoking exposure and breast cancer mortality – results from a Norwegian cohort.** Cancer Medicine 2014 Jul 30. Pubmed PMID: 25073713 (online).

Paper III

Bjerkaas E, Parajuli R, Engeland A, Maskarinec G, Weiderpass E, Gram IT. **Social inequalities and smoking-associated breast cancer – results from a prospective cohort study.** Preventive Medicine 2014 (Submitted).

3 Abbreviations

BMI – body mass index

CI – confidence interval

CONOR – Cohort of Norway study

EPIC - European Prospective Investigation into Nutrition and Cancer

HR – hazard ratio

IARC – International Agency for Research on Cancer

REK – Medical Research Ethics Norway

RR – relative risk

SES – socioeconomic status

WHEL – Woman's Healthy Eating and Living study

4 Introduction

In 1999, the World Health Organization arranged the first international conference on women and tobacco use.[1] The growing knowledge on smoking-associated diseases such as cancer, chronic obstructive pulmonary disease and cardiovascular disease, together with the rising epidemic of tobacco use among women and youths, drew attention to the need for gender-specific tobacco control strategies for the 21st century.

The available knowledge on the relationship between tobacco smoking (hereafter referred to simply as smoking) and a variety of human cancers is based primarily on epidemiological evidence.[2] In 1950, the landmark study by Richard Doll investigated the incidence of lung cancer among medical doctors who were smokers. This study led to the definition of tobacco as a carcinogenic substance.[3] Indeed, Doll's study found an increasing risk of lung cancer with increasing number of cigarettes smoked; an observation that was controversial at the time, but that was later confirmed in numerous studies.

The scientific conclusions of a causal association between smoking and cancer, as well as between smoking and other diseases, are the result of an ever-increasing body of scientific evidence and have been the object of constant conflict between the scientific community and the tobacco industry. Smoking is the leading preventable cause of death globally,[4] and the World Health Organization expects one billion smoking related deaths to occur in the 21st century.[5]

In this thesis we wanted to study the associations between active smoking and breast cancer incidence and mortality, and to examine if smoking-associated breast cancer may have an impact on socioeconomic differences in health.

4.1 The four-stage model of the smoking epidemic

In 1994, Lopez and colleagues described a four-stage model of the smoking epidemic in developed countries.[6] This model illustrates the substantial time lag between smoking initiation and smoking-associated death, and shows that the health consequences of smoking appear many decades after smoking cessation (Figure 1).

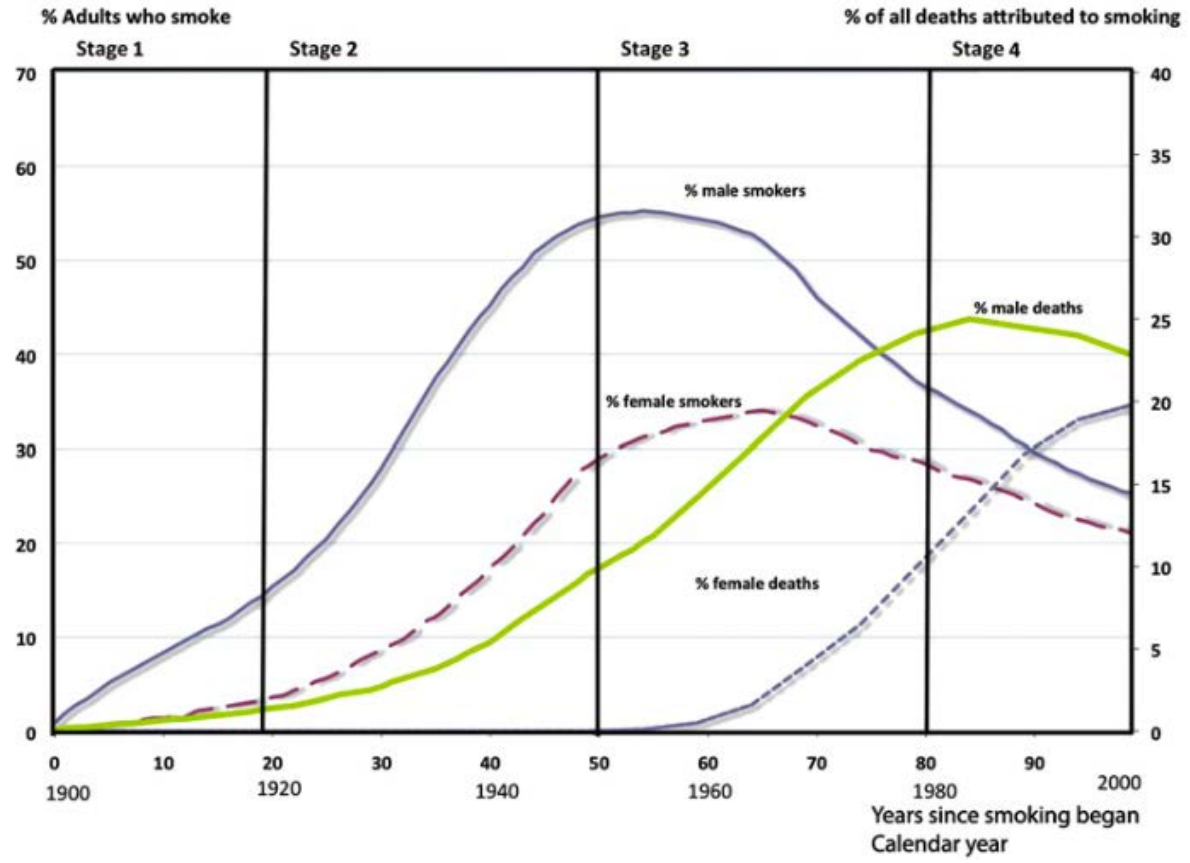

Figure 1: The four-stage model of the smoking epidemic. From Lopez et al. (1994).[6] Reprinted with permission.

In Figure 1, stage 1 illustrates the beginning of the smoking epidemic in 1900, when the smoking prevalence was less than 20%, smokers were mostly men, and smoking had caused few deaths. Stage 2 illustrates a rapid increase in male smoking prevalence towards a peak of 40% to 80% in 1950, the start of the main increase in female smoking prevalence and the start of the main increase in smoking-associated mortality. Stage 3 illustrates a flattening and convergence in smoking prevalence among male and female smoking prevalence, while smoking-associated mortality rose from 10% to about 30% of all deaths, mostly in men. Stage 4 illustrates a continued increase in smoking-associated mortality, peaking at about 1/3 of all deaths among men, with a smaller proportion among women. This figure illustrates that the health consequences of smoking depend on smoking prevalence in the population and that these consequences will occur later in women, as they joined the smoking epidemic later than men. This fact is important when studying the consequences of smoking for women, and when trying to compare health disparities between genders.

An updated report suggested that in the future the four-stage model should be applied to each gender separately, especially in less developed countries (Figure 2).[7] However, the main message stands: the time lag between smoking initiation and smoking-associated mortality is universal and not gender-, nor society-specific.

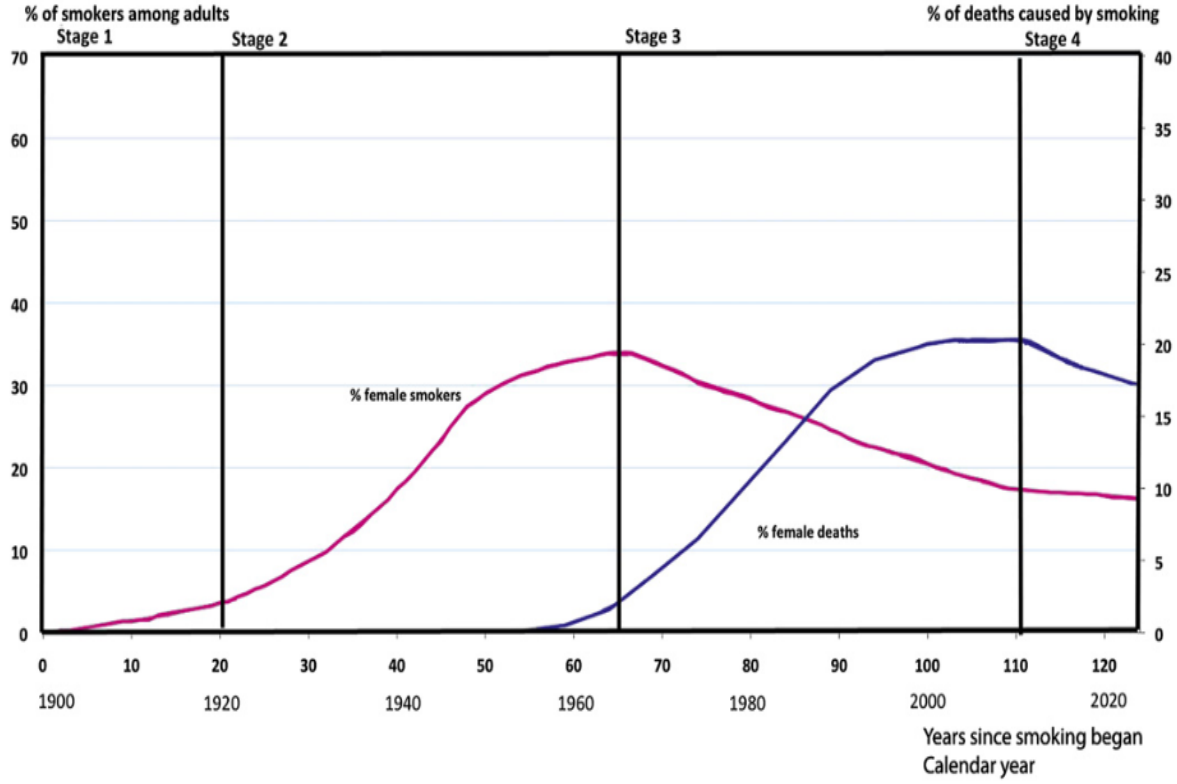

Figure 2: Stages of the worldwide smoking epidemic, modified for female smokers. From Thun et al (2012).[7] Reprinted with permission.

This time lag implies that the real health consequence of smoking among women can only be seen in studies with a long follow-up period, which could partly explain why previous studies on breast cancer and smoking did not reveal any significant association.

4.2 Smoking in Norway

In 1973, 43% of young women (16-24 years of age) and 32% of all women (16-74 years of age) in Norway were current smokers (Figure 3).

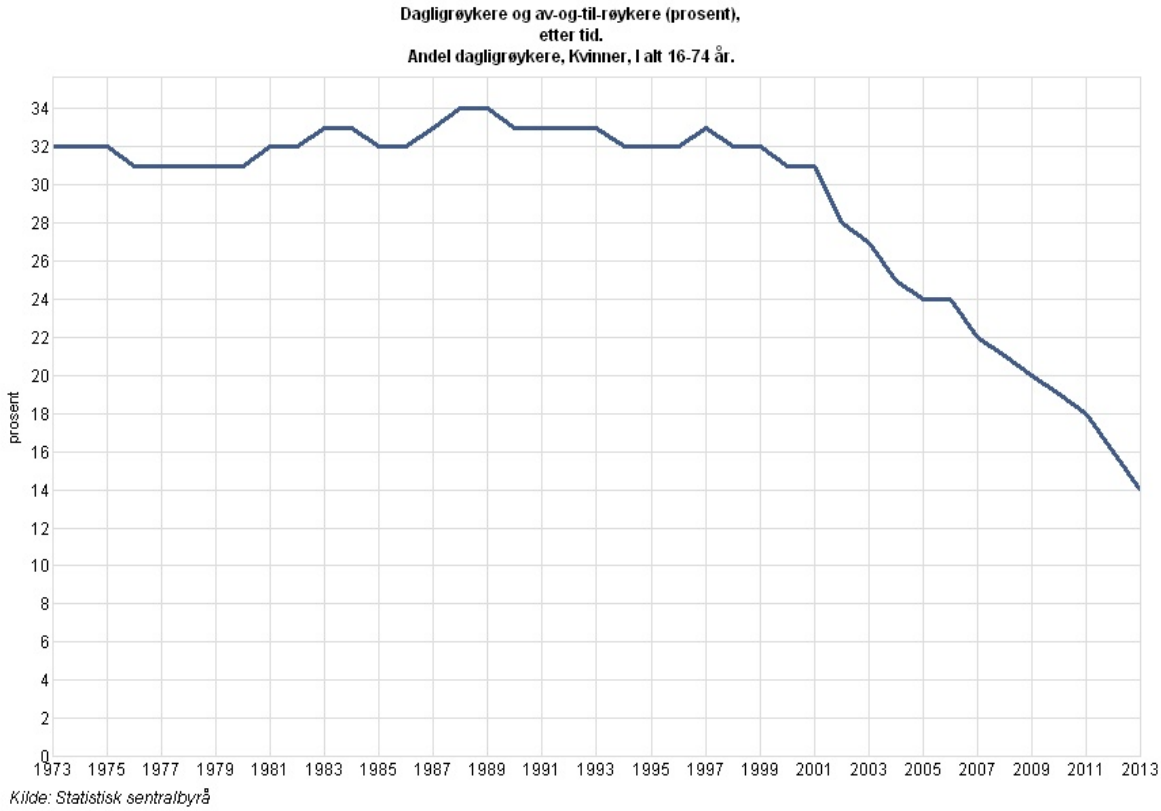

Figure 3: Prevalence (%) of female current smokers aged 16-74 years in Norway, 1973-2013. From Statistics Norway.[8] Reprinted with permission.

The smoking prevalence among Norwegian women has changed substantially during the past decades.[9] Figure 4 shows that in the birth cohorts 1920-1944, smoking prevalences of 35% and 50% were observed in 1940 and 1970, respectively. The prevalence peaked in the late 1960s, when female current smokers represented more than 50% of the 1940-1944 birth cohort. Between 1970 and 2000 the prevalence stabilized at around 32%. A large decrease in current smokers occurred after 2000, and today only 12% of women aged 16-24, and 16% of all women are current smokers.[10] Age at smoking initiation has also declined gradually in the past century (Figure 5).

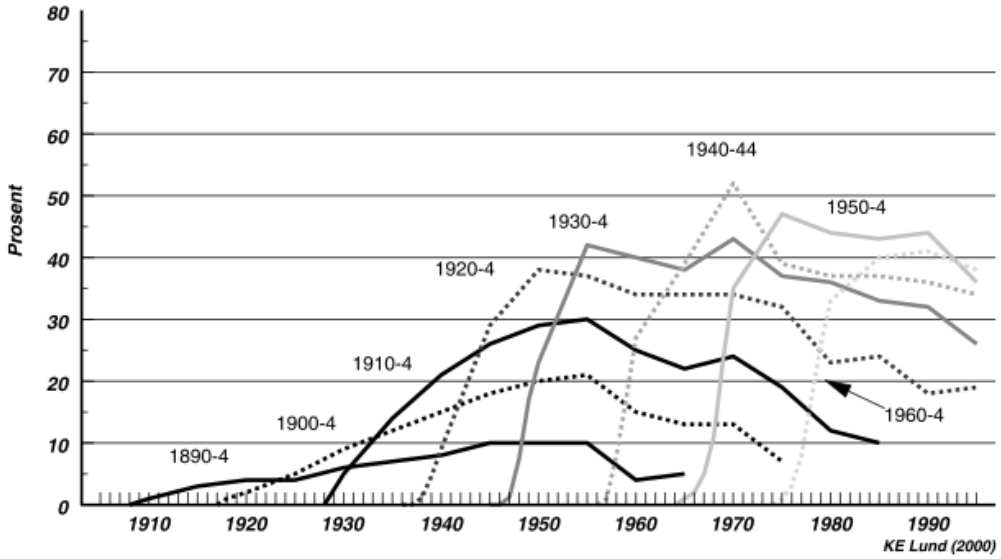

Figure 4: Prevalence of female smokers in 5-years birth cohorts (1890-1964) in the period 1910-1995. Norway's Public Reports, 2000:16. Y-axis: smoking prevalence (percent). X-axis: birth year.[9] Reprinted with permission.

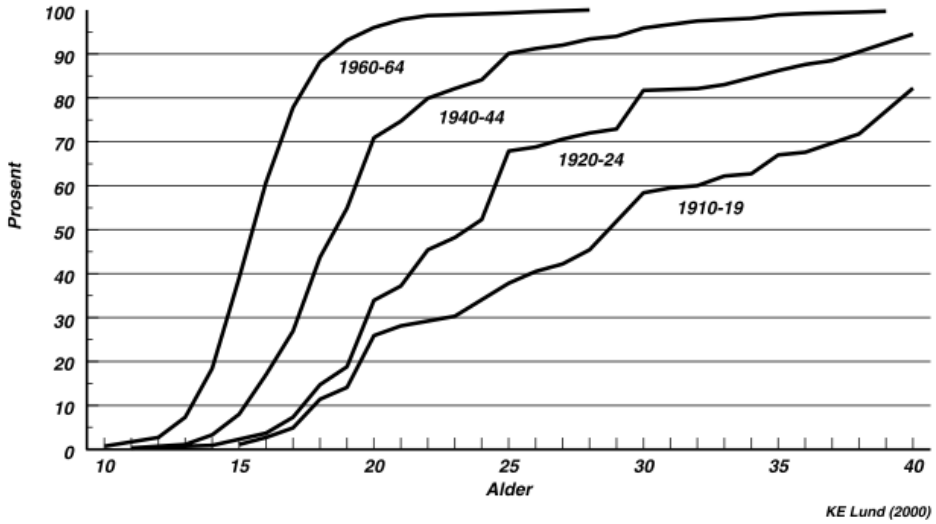

Figure 5: Age at smoking initiation in different birth cohorts in Norway (cumulative percent). Norway`s Public Reports, 2000:16. Y-axis: smoking prevalence (percent). X-axis: age at smoking initiation.[9] Reprinted with permission.

Smoking patterns also reveal socioeconomic differences, as there is a higher proportion of current smokers among women with a lower level of education. These women also have an earlier age at smoking initiation, use more harmful smoking products, and have a lower frequency of smoking cessation than women with a higher level of education. Women with a higher level of education are more likely to report occasional smoking.[10]

5 The epidemiology of breast cancer

5.1 Introduction

Breast cancer is the most common cancer among women worldwide in terms of both incidence and mortality. Indeed, breast cancer accounts for 25% of all female cancers, with 1.7 million new cases and 0.5 million deaths globally.[5] About 55% of all new breast cancer cases are diagnosed in the developing world, and this incidence is rapidly increasing. The etiology of breast cancer is multifactorial, involving endocrine and reproductive factors.[5] In general, the high breast cancer rates in developed countries are the consequence of a higher prevalence of known risk factors, many of which – early age at menarche, low parity, late age at first childbirth, exposure to exogenous hormones, and late age at menarche – relate to estrogen exposure in breast tissue.[11] At least three major mechanisms have been suggested to explain how estrogens might cause breast cancer,[10] but the understanding of this process remains incomplete.

In Norway, breast cancer represents 22% of all new cancer cases in women, with 2956 new cases reported to the Cancer Registry of Norway in 2012.[12] Breast cancer incidence in Norway has increased gradually since the introduction of mammography screening in the 1990s. A decline in breast cancer incidence was seen for the first time between 2005 and 2009, but in 2010 the incidence again increased, before a new decline after 2011 (Figure 6).

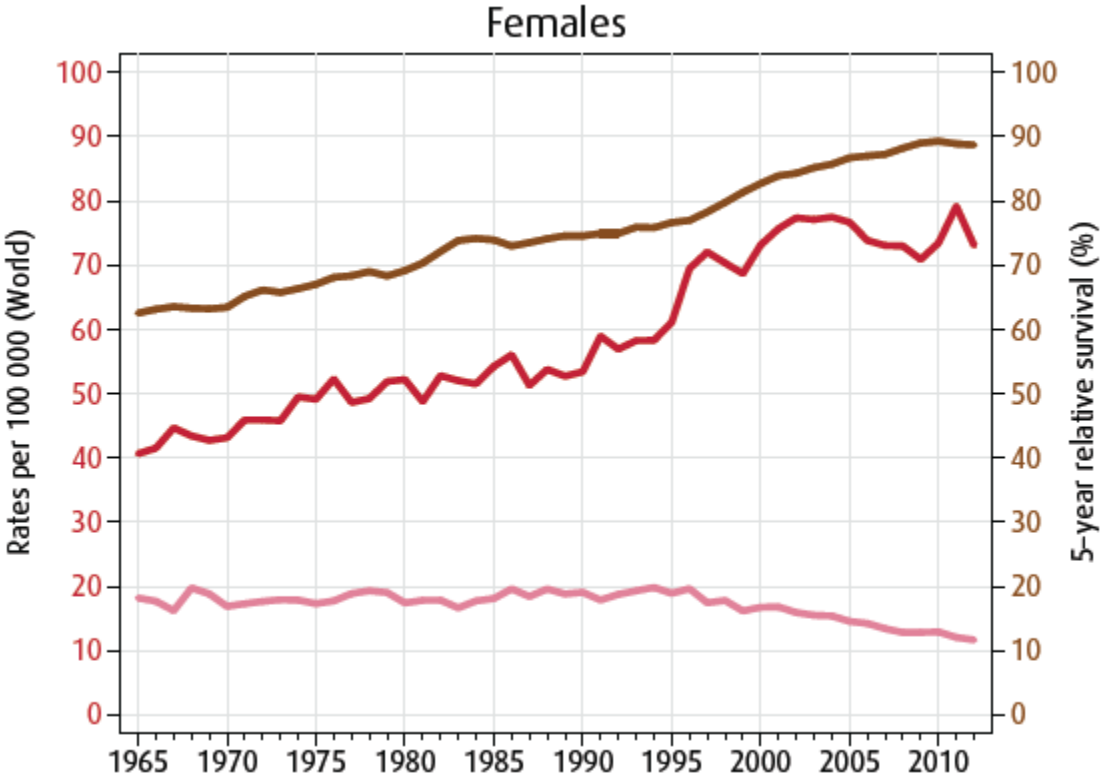

Figure 6: Trends in breast cancer incidence and mortality in Norway and 5-year relative survival. Cancer Registry of Norway, 2014.[12] Breast cancer incidence: red line. Breast cancer mortality: pink line. Reprinted with permission.

Breast cancer is the third most common cause of cancer mortality in Norway, after lung and colon cancer, with 645 deaths among woman in 2012. In Norway, as in many other developed countries, breast cancer mortality has declined since the early 1990s, most likely due to increased breast cancer awareness, improvement in treatment, and increasing screening coverage[5, 12-15] (Figure 6). Establishing multi-disciplinary management teams has provided optimization of breast cancer care in many developed countries. However, large inequalities exist in worldwide breast cancer survival, with 84% survival in the United States compared to 30% in Bhopal, India.[16] There are also lingering differences according to cancer stage at diagnosis.[16]

5.2 Key points

When performing prospective studies on the consequences of smoking-associated health problems, there are some issues to be aware of:

- Due to the long latency period between smoking initiation and development of disease, a long follow-up period is important.

- Smoking prevention programs have led to a reduction in smoking prevalence in many developed countries in recent years. However, the consequences of smoking will still be seen for decades due to the aforementioned time lag.
- Smoking prevalence is decreasing in most developed countries, but increasing in many less developed countries
- Because smoking is very common and breast cancer is a common disease, even the smallest increase in risk conferred by smoking may have a great impact on breast cancer incidence from a population perspective.

5.3 Active smoking and breast cancer incidence

Altogether more than 150 epidemiological studies, both case-control and cohort studies, have been performed on the association between active smoking (hereafter referred to as smoking) and breast cancer.[2] Since 2004, most cohort studies have reported a weak, but significantly increased risk of breast cancer among current (between 9% and 32%) and former smokers (between 5% and 18%).[17-27] Cohort studies are usually given more weight than case-control studies, as the cohort study design avoids the possibility of recall bias.

Eight national and international consensus reviews have been published on active smoking and breast cancer risk.[2, 28-34] The evidence of an association between breast cancer and active smoking has been inconsistent, leading to past conclusions that smoking was not a risk factor for breast cancer.[35-37] The monograph *Tobacco smoke and involuntary smoking* was published by the International Agency for Research on Cancer (IARC) in 2004. It concluded that there was a causal relationship between smoking and cancers of the lung, oral cavity, nasal cavity and paranasal sinuses, nasopharynx, oropharynx, hypopharynx, larynx, esophagus, stomach, pancreas, liver, kidney, ureter, urinary bladder, cervix, and myeloid leukemia. Moreover, they concluded that there was a lack of carcinogenicity for cancers of the breast and endometrium.[30] The same year, the report of the United States Surgeon General concluded there was “no causal relationship between active smoking and breast cancer”.[33]

In 2005, the California Environmental Protection Agency concluded that the weight of the evidence (including toxicology of environmental constituents, epidemiological studies and breast biology) was consistent with a causal association between environmental tobacco exposure and premenopausal, but not postmenopausal, breast cancer.[31] The report published

in 2009 by the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk[32] was the first to thoroughly analyze the current scientific data for both active and passive smoking and breast cancer according to many of the known measures of smoking exposure, such as smoking duration, pack-years, age at smoking initiation, and smoking in relation to first childbirth. This report concluded that the relationship between active smoking and breast cancer is consistent with causality. The IARC Monograph Volume 100E, published in 2012, reviewed more than 150 epidemiological studies on this association. They found that all large cohort studies since 2002 consistently showed a small positive association, with relative risks (RRs) between 1.1 and 1.3, and concluded that there is limited evidence that smoking causes breast cancer.[2] In the 2014 report, the United States Surgeon General was still reluctant to conclude that a causal association exists between smoking (active or passive) and breast cancer.[34]

Several recent meta-analyses and reports have evaluated the association between smoking before first childbirth and the increased risk of breast cancer.[26, 32, 34, 38] The Canadian Report concluded that the available data suggest an association between active smoking before first childbirth and an increased risk of breast cancer.[32] A meta-analysis published in 2011 included 23 papers with the aim to investigate the association between smoking before first childbirth and breast cancer, and concluded that a causal association between smoking and breast cancer was unlikely.[38] The authors revealed a 10% (95% CI 1.07-1.14) increase in the risk of breast cancer among women who initiated smoking before first childbirth compared with never smokers, but considered that the overall risk increase was too small to be categorized as a positive association. Another meta-analysis published in 2013 by Gaudet and colleagues included 15 cohort studies and found an increased risk of 21% (95% CI 1.14-1.28) for the same association. They concluded that their study supported the suggestion that smoking before first childbirth increases breast cancer risk.[26] A meta-analysis presented in the 2014 United States Surgeon General report found a 16% significantly increased risk for breast cancer and smoking before first childbirth (HR=1.16, 95% CI 1.12-1.20) when nine recent cohort studies were included.[34]

The results of these recent meta-analyses showed a significant increased risk of breast cancer when comparing women who smoked before their first childbirth with never smokers, but their conclusions were different. However, these studies did not consider their results according to the magnitude of smoking before first childbirth, as per known measures of

smoking exposure, which is essential. In the large cohort studies from 2013, the highest risks were found among women who smoked the most before their first childbirth.[25, 26, 39] Smoking in the period before first childbirth emerges as a risk factor for breast cancer.

An overview of most of the cohort studies on smoking and breast cancer incidence published since 2004 is included in the appendix.

5.4 Smoking and breast cancer mortality

Several studies have been performed on smoking with death from breast cancer, as outcome. However, most papers studying the association between smoking and breast cancer mortality assessed smoking status (current/former) *during*, or *after* breast cancer diagnosis instead of *before* diagnosis.[40-47]

Assessments of smoking exposure before or after breast cancer diagnosis are fundamentally different, as a survival study looks at the period from diagnosis to death (often considering the effect of treatment), whereas a mortality study may look at the number of overall deaths during a certain time period.[48] A mortality study may consider the period before diagnosis (during cancer development) together with the period after diagnosis. Some papers do not clearly point out these differences, which may sometimes confuse the reader.

One of the first studies on smoking and breast cancer mortality was the report from the Cancer Prevention Study II (1994) carried out in the United States. They found a 26% statistically significantly increased breast cancer mortality among current smokers and a non-significantly reduced mortality among former smokers, as compared to never smokers.[51] Later, the report by Pirie and colleagues from the Million Women Study found a 13% significantly increased risk of breast cancer mortality associated with current smoking.[52] A 2013 short report from the Woman's Healthy Eating and Living (WHEL) study in the United States, which included 2953 women and 249 breast cancer deaths during 7.3 years of follow-up, found breast cancer mortality to be non-significantly increased when smoking exposure (current/former) was assessed at breast cancer diagnosis. The authors did a similar analysis among women with high number of pack-years before breast cancer diagnosis, as a proxy for lifetime smoking exposure, and found a significantly increased mortality of 54% in the same cohort for women who smoked more than 20 pack-years.[53] Furthermore, a pooled

study including three cohorts from the United States (1059 breast cancer deaths during 11 years of follow-up) found a 54% significantly increased breast cancer mortality among former smokers with a lifetime smoking exposure of more than 35 pack-years, and a non-significantly increased mortality for those with a lifetime smoking exposure of less than 35 pack-years.[54] Current smokers in this study had a mean exposure of 39 pack-years, and revealed a 61% significantly increased risk for breast cancer mortality.
These recent papers on smoking and breast cancer-associated mortality found an increased risk when assessing lifetime smoking exposure, but not when analyzing by smoking status (never, former, current, ever).

An overview of some of the cohort studies on smoking and breast cancer mortality is included in the appendix.

5.5 Female smoking, level of education and breast cancer

Inequalities in health among groups with different socioeconomic status (as measured by level of education, occupation and income), constitute one of the main challenges for public health authorities. The direction of the socioeconomic gradient varies between cancer sites. Among women, it tends to be negative for lung, stomach, esophagus and cervical cancer, while a positive association has been observed for malignant melanoma, colon, ovary and breast cancer.[55, 56] At the same time, differences in smoking habits remain one of the main explanations for socioeconomic inequalities in health.

In recent decades, the magnitude of smoking exposure in Norway has changed substantially between different socioeconomic groups. During the early stages of the smoking epidemic, smoking was more common among groups with a high level of education.[9] This situation changed in the 1960s, when smoking prevalence increased among those with a lower level of education. A similar pattern was observed in many Northern European countries, and in the United Kingdom.[57]

Smoking among women worldwide is increasing and the age at smoking initiation among women seems to be equal to that among men.[4, 58-60] Today, smoking is more common among those with a lower level of education, and as a consequence, smoking has become an indicator of socioeconomic status, and generates social inequalities in health.[57, 61] An increasing burden

of smoking-associated health problems in women, and in those with lower socioeconomic status can be expected in the future.[59] Today, breast cancer is more common among women with a high level of education, and smoking is more common among women with a lower level of education. As smoking emerges as a possible risk factor for breast cancer, a more detailed approach of the socioeconomic implications becomes necessary.

6 Concepts of causality for smoking and breast cancer

How can we determine if there is a causal association between smoking and breast cancer? In 1965, Hill attempted to distinguish causal from non-causal associations. His considerations of causality are still widely used as guideline when judging evidence in epidemiological studies,[62, 63] though other guidelines have also been suggested.[64]

6.1 Biological plausibility

Smoking has been established as carcinogenic to humans, leading to increased risk of cancer incidence and mortality from many cancer types.[5, 30, 52] The IARC has found more than 70 carcinogenic chemicals in tobacco smoke,[30] a number of which are also found in human breast tissue.[65] Thus an association between smoking and breast cancer is biologically plausible. A relatively weak association between smoking and breast cancer, as compared to other cancers such as lung cancer, may be due to the fact that a relatively low dose of the carcinogens found in tobacco smoke can be found in human breast tissue.[65]

Difficulties in finding associations between smoking and breast cancer were commonly explained by the anti-estrogenic effect of smoking,[35, 66] in which the low level of blood estrogens in smokers was thought to oppose the carcinogenic effects of tobacco smoke. Previous epidemiological studies observed an earlier age at menopause,[67] a higher risk of osteoporosis,[68] a lower risk of endometrial cancer,[69, 70] and possibly a lower postmenopausal mammographic density among smokers.[71] Recent studies have found a positive association between level of blood estrogens, progesterone and androgens, and both pre- and postmenopausal breast cancer.[72, 73] One of these studies on postmenopausal breast cancer revealed a higher level of blood estrogens in heavy smokers,[72] which was in contrast with previous assumptions.[74] Hence the increased level of blood estrogens in smokers may be an important observation when explaining the increased risk of breast cancer that has been reported in most cohort studies carried out since 2004.

6.2 Consistency

Since 2004, at least 12 studies[17-20, 22-27, 38, 39, 75, 76] have consistently reported an increased risk of breast cancer among current, active smokers, as compared with never smokers. Moreover,

the majority of these studies reported a significant association. Several large reports and meta-analyses have also been done, with conclusions on the association ranging from "no causal relationship"[33, 38] to "the association between smoking and breast cancer is consistent with causality"[32] to "…support the hypothesis that active smoking increases breast cancer risk".[26] The last citation comes from the latest report from the United States Surgeon General (page 283), which claims insufficient convincing evidence for a causal association, stating "the evidence is suggestive but not sufficient to infer a causal relationship between active smoking and breast cancer".[34] The scientific evidence is still not consistent enough to generate a consensus on the causal association between smoking and breast cancer.

6.3 Specificity

The criterion for specificity for active smoking and breast cancer is a major challenge when assessing smoking-associated diseases such as breast cancer. Indeed, breast cancer is a very heterogeneous disease and does not have only one cause. Smoking affects the risk of a number of diseases, accurately portraying the lack of specificity of this exposure.

6.4 Dose-response relationship

The RRs for the associations between active smoking and breast cancer are not as high as for many other smoking-associated diseases, which makes the conclusion of a causal association even more difficult. However, this lack of evidence of causality must take into consideration that cancer development often takes decades.[2] Long latency periods between initial exposure and disease makes long a follow-up period necessary if valid conclusions are to be drawn.

Previous studies often assessed smoking as a simple binomial variable, i.e., smoking/non-smoking, without considering different measures of smoking exposure. Recent studies have found higher lifetime smoking exposures, i.e., longer smoking duration, higher number of cigarettes smoked per day, and/or higher number of pack-years, to be important for this association, indicating that breast cancer risk increases with increasing dose-response, and thus the amount of exposure should be evaluated when trying to determine the causality of this association.

6.5 Strength of the association

Breast cancer incidence is high in many populations that have a high smoking prevalence, but there is no scientific evidence linking smoking to high breast cancer incidence in any population. The associations found for smoking and breast cancer are weak, and as mentioned, any causal association is still under debate.

In general, large studies allow for better precision, but are not necessarily better due to problems of validity (e.g., chance of selection bias and confounding). Large studies yield low p values and more narrow CIs.[77] Importantly, p values and CIs relate to precision, not validity, which in most cases will be the most relevant factor when determining the quality of a study. Power directly depends on the number of observed events, and there is an indirect relationship between power and sample size, which arises because more subjects usually means more events.[78]

Some epidemiologists are cautious when interpreting the results of cohort studies that show weak associations between an outcome and an exposure (hazard ratio [HR] between 2 and 0.5) due to the high risk of bias that comes with weak associations.[79] Nevertheless, public health researchers must consider weak associations as they may have important impacts in a large population or in populations where the exposure is common. A high RR risk increases the chance of causality; however, a low RR should not be immediately interpreted as a lack of causality. For this reason, identifying associations with low RRs may have important consequences from a public health perspective.

6.6 Temporality

Temporality refers to the necessity that the cause precedes the effect. This criterion is inarguable.[80] For this reason, studies on breast cancer incidence consider the smoking exposure that occurred before breast cancer diagnosis.

6.7 Experimental confirmation

Based on *in vitro* studies, Russo and colleagues hypothesized that smoking is more likely to induce neoplastic changes in the human breast in the period between menarche and first childbirth, when the breast cells have an increased susceptibility to carcinogens.[81-83] Their

studies revealed that the human breast undergoes a series of changes from birth, through puberty, childbirth and lactation. During puberty breast tissue changes from a predominantly ductal structure to a lobular structure with different histological lobular subtypes thanks to the introduction of numerous endogenous and exogenous hormones. Russo named the different lobular subtypes according to their degree of differentiation: Lobules 1, Lobules 2, Lobules 3, and the fully differentiated Lobules 4. The most common type of breast cancer, ductal carcinoma, originates in Lobules 1 in rodents. After childbirth, a period of active cell proliferation takes place and the lobular composition progresses to Lobules 2, Lobules 3, and Lobules 4 subtypes. After the lactation period, Lobules 3 remains the dominant structure until the fourth decade of life. When compared with parous women, the number of Lobules 1 in nulliparous women remains higher until after menopause. Experimental and biological studies suggest that Lobules 1 is biologically different than the other subtypes, and might exhibit different susceptibility to carcinogenesis. This may constitute a biological explanation as to why exposure to carcinogens before first childbirth may cause breast cancer later in life, and why childbirth protects against breast cancer. Timing of smoking has now emerged as one of the most important risk factors in the development of breast cancer, with breast tissues being the most vulnerable to smoking in the period between menarche and first childbirth. This has been confirmed in several recent epidemiological studies.[17-20, 24-26, 39, 75]

7 Aims of the thesis

I. To study the association between active smoking and breast cancer incidence

II. To study the association between active smoking and breast cancer mortality

III. To examine if smoking-associated breast cancer is associated with social inequalities in health

8 Materials and methods

8.1 Study population

The study population in all papers comprised 302,865 Norwegian women born between 1899 and 1975, participating in three large prospective cohort studies conducted by the National Health Screening Service (now the Norwegian Institute of Public Health): the Norwegian Counties Study (1974-1988), the 40 Years Cohort (1985-1999) and the Cohort of Norway (CONOR, 1994-2003) hereafter referred to as the surveys. The study population was followed for 14 years on average. We identified 7490 breast cancer cases and 1106 breast cancer-associated deaths during the follow-up period. The earliest surveys were initiated due to the high prevalence of cardiovascular disease in Norway; the methods for these surveys were adapted and further developed and improved based on experience gleaned from the Oslo I study (1972-1973).

Individuals were selected by age group and/or by county of residence, in order to obtain a representative sample of the Norwegian population. They then received an invitation and baseline questionnaire by mail, which were to be completed before attending the first health examination at the screening facility. The baseline questionnaire included detailed assessments of smoking habits, physical activity, and other lifestyle factors. The health examination included a physical examination, during which anthropometrics such as height and weight were obtained in a standardized manner by a trained nurse to avoid bias. In some surveys individuals received a second questionnaire at the first health examination, which could be completed either immediately or later at the individual's home. The average response rates varied between 56% and 88% in the included surveys.[84]

8.1.1 The Norwegian Counties Study

This survey was carried out in three Norwegian counties (Finnmark, Sogn og Fjordane, Oppland), and consisted of three rounds of health examinations carried out during the periods 1974-1978, 1977-1983, and 1985-1988. The first round included all residents aged 35-49 years in addition to a random sample of 10% of the general population aged 20-34 years. The second and third rounds included a combination of previous participants and new cohorts with

similar protocols and questionnaires. The attendance rates were 88%, 88%, and 84% at the three rounds of health examinations, respectively.[84-86]

8.1.2 The 40 Years Cohort

This survey was carried out between 1985 and 1999 and included about 420,000 Norwegian men and women from all 19 counties of Norway. Mostly men and women aged 40-42 years were invited, though individuals aged 65-67 years were invited in some of the counties in the first of four phases of this study. The participation rate overall was 69%.[87, 88] The 40 Years Cohort constitutes the largest cohort in the present analysis.

8.1.3 Cohort of Norway – CONOR

In this survey, regional data from 10 epidemiological surveys conducted between 1994 and 2003 were merged into a national database. Standardized protocols, procedures and questionnaires were used. The questions used in the CONOR study have been validated previously. The average response rate for the 10 epidemiological surveys included in the CONOR study was 56%.[84, 89, 90] A further description of these 10 surveys is included in the appendix.

8.2 Exposure information

After receiving specified exposure variables from the primary data of each survey, we created a standardized database for the pooled analysis. The smoking questions were similar, but not identical, across all surveys, and asked about current and former active daily smoking habits, smoking duration, and average number of cigarettes smoked per day. In some surveys, former smokers were asked about time since smoking cessation. Only the CONOR study asked about age at smoking initiation. In the other surveys we calculated this variable for both current (age at enrollment minus duration of smoking in years) and former (age at enrollment minus years since quitting and duration of smoking) smokers. We further categorized ever smokers according to the following factors: age at smoking initiation, numbers of cigarettes smoked per day, smoking duration in years, and number of pack-years (i.e., number of cigarettes smoked per day, divided by 20, multiplied by the number of years smoked). For parous women, the variable “smoking duration before first childbirth” was calculated in years as age at smoking initiation or duration of smoking in years, subtracted from age at first childbirth.

Participants that were neither current nor former smokers were classified as never smokers, and current and former smokers were classified as ever smokers. A very limited number of women who reported they were pipe smokers were included as cigarette smokers.

The CONOR files were used as a reference when merging the information from all the surveys into one dataset. We found common formats for variables such as age at menopause, age at menarche, oral contraceptive use, hormone replacement therapy use, and alcohol consumption, which were available only in phases III and IV of the 40 Years Survey, and in the CONOR study. Due to a large number of missing values for these variables in the final cohort, they could not be used to adjust the models in the main analysis. The proportion of missing values reached more than 50% either due to the fact that information was not collected, or that there was no answer from the participants in the questionnaires.

Information about physical activity was obtained using a self-reported measure. The subjects were categorized into three groups based on the level of physical activity reported at the time of enrollment: sedentary (reading, watching television and sedentary activity), moderate (walking, bicycling and/or similar activities ≥4 hours per week) and heavy (light sports or heavy gardening ≥4 hours per week, heavy exercise or daily competitive sports).

Information on number of children and age at first childbirth was obtained through linkages to Statistics Norway.

Level of education is a proxy for socioeconomic status.[56, 91] The most recent information on education in Statistics Norway represents the number of completed years of education, and was used instead of the self-reported information in the questionnaires. We used the number of completed years of education recorded in 1990 or 1980, and if this information was missing, we used that from 1970. Women were assigned to one of three categories according to duration of education: low (<10 years), moderate (10-12 years), high (>12 years). In Norway, compulsory school attendance changed from 7 to 9 years in 1965, therefore, <10 years of education means primary school with at most 2 years of additional education. Similarly, women with 10-12 years of education have completed secondary school or at most 5 years of professional training. Education lasting >12 years corresponds to university level education or lower level with several years of professional training.

In Papers I and II, a subanalysis was performed to assess the importance of alcohol consumption. We compared the results from the full cohort (with and without information on alcohol consumption) with the results from the subcohort with information on alcohol consumption. We used the Wald chi-square test for heterogeneity to compare HRs.[92] The results of our sensitivity analysis should be interpreted with caution, as the subcohort with alcohol consumption information constitutes only 38% of women from the full cohort, and had only 24% of the follow-up time as compared with the full cohort. Our results suggested that the importance of alcohol consumption in these studies is limited. Information on alcohol consumption was not used for any analysis in Paper III.

Please refer to section **10.3** for further discussion on alcohol consumption.

8.3 Follow-up and endpoints

Participants were followed through linkages to the Cancer Registry of Norway and the Central Population Register, using the unique 11-digit personal identification number, to identify all breast cancer cases, breast cancer deaths, emigrations and other deaths. These national registries are both accurate and virtually complete.[93] Individuals with preexisting cancers at enrollment were excluded from the study sample. Furthermore, to limit the chance of including individuals with cancer at baseline (reverse causation), we set the date of inclusion to January 1 the year after the baseline questionnaire was completed. By doing so, any individuals with existing cancers that had not yet been diagnosed at baseline (preexisting condition), but were registered in the Cancer Registry of Norway later that year, would have been excluded from study. All prevalent cancer cases (n=7138), women without information on smoking status (n=2808), level of education (n=6913), body mass index (BMI) (n=2478) and level of physical activity (n=4207) were excluded, leaving 302,865 women included in the final analytical cohort.

Person-years were calculated from the start of follow-up to the date of breast cancer diagnosis (Paper I and III), death from breast cancer (Paper II), the date of any other incident cancer diagnosis (except basal cell carcinoma), emigration, death from all other causes, or end of follow-up (31 December 2007), whichever occurred first. Breast cancer cases were classified according to the International Classification of Diseases, Revision 7 (code 170) and breast

cancer as the underlying cause of death according to the International Classification of Diseases, Revision 9 or 10. In Norway, to correct for errors and mistaken conclusions drawn by the physician, rules from the World Health Organization are used to ensure that the correct classification of cause of death is recorded on the death certificate.[94, 95]

8.4 Statistical analysis

All analysis were done in STATA version 12.0 (StataCorp, College Station, TX, USA) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Differences between groups were analyzed with the Student's t-test. The Wald chi-square test for heterogeneity was used to assume the statistical differences between HRs, whereas a p value of less than 0.05 indicated a significant difference between the tested HRs.[92, 96] Descriptive characteristics of the study population in each paper were presented as means with standard deviations or frequencies (%), or medians with interquartile ranges when a normal distribution was not expected. The Cox proportional hazards model, with age as the underlying time scale, was used to investigate the relationship between survival time (time from start of study to censoring or breast cancer diagnosis or mortality), and the independent variables included in the multivariate models to estimate HRs with 95% CIs for the associations between different measures of smoking exposure and outcome. The proportionality assumption was tested by the link test and assumed acceptable for all the analyses presented. Tests for linear trends were carried out by creating an ordinal exposure variable with equally spaced scores and including it in the models. All regression models require complete datasets, and women with missing information for one or more variables were excluded from the Cox model. Hence, all women in the analytical cohort had complete information on the covariates included in the multivariate analysis.

The confounders included in the multivariate models, decided *a priori*,[97] were age at enrollment, number of children, age at first childbirth, BMI, level of physical activity (sedentary, moderate, heavy) (Paper III), and years of education (<10, 10-12, ≥13) (Papers I and II). We analyzed the age and multivariate-adjusted HRs with 95% CIs according to the selected covariates included in the multivariate analyses.

We were not able to adjust for other putative confounding variables due to missing data in all, or in a large proportion of the cohort. Information on menopausal status was only present in

36% of the study sample, and thus was not included in the main multivariate analysis. To study the possible impact of menopausal status and breast cancer, we conducted a subanalysis among pre- and postmenopausal women separately (Paper I), with age 50 years used as a proxy for menopause in women without this information.[98] Therefore, we stratified the analysis on smoking exposure according to attained age less than 50 years and 50 years and older.[99] For this analysis, classification of women was based on age at breast cancer diagnosis, considering women premenopausal until age 50, and postmenopausal after age 50. Women who were premenopausal at baseline contributed to the premenopausal group for the period between enrollment and age 50, and to the postmenopausal group from age 51 until the end of follow-up. As described under "statistical analysis" in Paper I, this analysis did not reveal any substantial differences in the multivariate results.

In Paper III, we stratified by age at breast cancer diagnosis (≤50>) to assess differences in pre- and postmenopausal breast cancer (results not displayed).

The impact of menopausal status has been shown to be limited in most,[18, 19, 26, 75] but not all,[39] previous studies for this association.

8.5 Ethical aspects

All participants recruited as from 1994 gave written informed consent to participate in the surveys; before 1994 returning the completed questionnaire was considered sufficient as acceptance to participate. Our study was approved by the National Data Inspection Board, the Regional Committee for Medical Research Ethics (REK), and the Norwegian Directorate of Health. The data were handled in accordance with the permissions given by the above-listed government bodies. The data were used and published in a way that none of the participants can be recognized.

9 Results – summary of papers

9.1 Paper I - Smoking duration before first childbirth: an emerging risk factor for breast cancer? Results from 302,865 Norwegian women

In this paper we studied the association between smoking and breast cancer incidence. The main analysis was done with ever smokers as the exposure group and never smokers as the reference group. The different covariates for breast cancer risk were investigated and the dose-response results revealed a positive association between the risk of breast cancer and

level of education and alcohol consumption, and an inverse association between breast cancer and number of children, early age at first childbirth, BMI, and level of physical activity. The multivariate-adjusted results showed an increased risk of breast cancer of 15% for ever smokers (HR=1.15, 95% CI 1.10-1.21), 17% for former smokers (HR=1.17, 95% CI 1.10-1.24) and 14% for current smokers (HR=1.14, 95% CI 1.08-1.20). Increased risk was also found for the following measures of smoking exposure: smoking duration, number of cigarettes smoked per day, pack-years, and age at smoking initiation (all p values <0.001). For smoking initiation before first childbirth, we found consistent results in favor of an increased risk of breast cancer with increasing smoking duration before first childbirth (p<0.001). Those initiating smoking after first childbirth had a reduced risk (HR=0.93, 95% CI 0.86-1.02), and those who smoked more than 11 years before their first childbirth had a 60% increased risk (HR=1.60, 95% CI 1.42-1.80) when compared with never smokers.

9.2 Paper II - The association between lifetime smoking exposure and breast cancer mortality – results from a Norwegian Cohort

This paper studied the association between smoking before breast cancer diagnosis and breast cancer mortality. Our aim was to assess if the positive associations found for smoking and breast cancer incidence in Paper I, also could be found for smoking and breast cancer mortality in the same cohort.

The main analysis in this paper was done with ever smokers as the exposure group and never smokers as the reference group. The results showed a significantly increased risk of breast cancer mortality for ever (HR=1.15, 95% CI 1.02-1.30), and current (HR=1.15, 95% CI 1.02-1.32) smokers. For former smokers a non-significant 14% increase was observed (HR=1.14, 95% CI 0.97-1.34). A significantly increased risk was found among women who initiated smoking at 25 years of age of younger (HR=1.31, 95% CI 1.08-1.59), among those smoking for 11-20 years (HR=1.20, 95% CI 1.03-1.40), and among those smoking 11 or more cigarettes per day (HR=1.25, 95% CI 1.06-1.46). Parous women who initiated smoking 7 years or more before their first childbirth had a 24% (HR=1.24, 95% CI 0.98-1.58) non-significantly increased risk of breast cancer mortality compared to never smokers. The overall results revealed no dose-response relationships for any of the different measures of smoking exposure (age at smoking initiation, smoking duration, number of cigarettes smoked per day,

number of pack-years, and smoking duration before first childbirth, all p for trends ≥0.05) and breast cancer mortality.

9.3 Paper III - Social inequalities and smoking-associated breast cancer – results from a prospective cohort study

The aim of this paper was to investigate how smoking-associated breast cancer varies by socioeconomic status (SES). We used level of education as a well-established measure of SES. The participants were stratified into three levels of education (low, moderate, high), and further stratified by birth cohorts (year born ≤1950>). When using low level of education as reference, we found that breast cancer risk increases with increasing years of education, overall and stratified by birth cohort (all p for trends <0.01). For women born ≤1950, those with a higher education had a 62% increased breast cancer risk (HR=1.62, 95% CI 1.48-1.76) as compared with those with a low level of education. For women born >1950, the increased risk was 18% (HR=1.18, 95% CI 1.04-1.34).

Furthermore, we used never smokers as reference, and detected a 40% (HR=1.40, 95% CI 1.25-1.57) higher breast cancer risk for ever as compared to never smokers, a 14% (HR=1.14, 95% CI 1.05-1.24) higher risk for those with moderate education and a non-significant 10% higher risk for those with high education (HR=1.10, 95% CI 0.96-1.25) among women born ≤1950. No increase in smoking-associated risk was found among women born after 1950 for any level of education. Women with a high level of education did not have a significantly increased risk in any of the two birth cohorts when ever smokers were compared with never smokers.

For women with low level of education, a significant test for trend was revealed for all five (age at smoking initiation, smoking duration , number of cigarettes smoked per day, number of pack years and duration of smoking in relationship to first childbirth) measures of smoking exposure displayed in the table (all p values < 0.03).Compared with parous never smokers, women who had smoked 7 or more years before their first childbirth had a significantly increased risk of breast cancer for all three [low (HR=1.70, 95% CI 1.40-2.08); moderate (HR=1.38, 95% CI 1.24-1.55) and high (HR=1.37, 95% CI 1.17-1.60)] level of education. Longer duration of smoking before first childbirth were associated with increasing risk of breast cancer risk in all three categories of education (all p for trends <0.01).

10 Discussion of methods

10.1 Validity (external and internal)

Validity is an expression of the degree to which a test is capable of measuring what it is intended to measure[100] and is often separated into two components: internal validity and external validity. External validity, or generalizability, is the extent to which the result of a study is applicable to different populations in other places and at different time periods.[80, 100] Our study sample is large and the included surveys all have well validated individual datasets. In general, it may be difficult to generalize study results to wider populations, but we assume that our study conclusions can be generalized to the Caucasian and Western population.

Internal validity is the degree to which the results of an observation are correct for the particular group of people studied. Various types of bias, or systematic errors, can detract from internal validity. Bias is defined as results that differ in a systematic manner from the true values.[100] Bias concerns systematic errors, not random variation (lack of precision).

10.1.1 Selection bias

Selection bias occurs when there is a systematic difference between the characteristics of the people selected for a study and the characteristics of those who are not selected.[100] Selection bias is generally less probable in prospective cohort studies than in other epidemiological study designs, as the outcome is not known at the time of enrollment.[101] In the present pooled cohort, all the participants were randomly selected based on age and/or county, and represent a selection of the Norwegian population, both rural and urban. The participation rate was higher in the earliest surveys, ranging from 88% in the Norwegian Counties Study to 56% in the CONOR study. There is no available information on non-responders in our surveys, but we do not assume that they represent a skewed selection from the main cohort. Indeed, a low participation rate does not always indicate selection bias.[102] Previous reports showed that individuals who choose to participate in research studies have either a high or very low level of education,[103] but recent studies have found an increasing over-representation of highly educated women as the age of the study sample increases.[104] Breast cancer is more common

in women with a high level of education; therefore a low attendance rate may have influenced the risk estimates in our study, representing selection bias.
Loss to follow-up, or to exclusion prior to study enrollment, may have biased our results if the lost women differ from the study sample in respect to both the exposure and the outcome variables.

10.1.2 Recall bias

In prospective cohort studies, recall bias is of limited importance as information is collected at study enrollment. Most previous studies performed on the association between smoking and breast cancer had a case-control design, which may be subject to recall bias, a particular concern in studies of smoking exposure.[105]

10.1.3 Information bias and misclassification (measurement bias)

Measurement bias occurs when the individual measurements or classifications of disease or exposure are systematically inaccurate, i.e., they do not measure correctly what they are supposed to measure.[100] Information bias can be classified as differential (dependent on the outcome variable) or non-differential (not dependent on the outcome variable). Information bias in cohort studies tends to be non-differential (not affecting any groups more than others), which might dilute or underestimate the effect estimates. Standard protocols were used in the included surveys to minimize such errors.

10.1.4 Validity of outcome assessment: breast cancer incidence and mortality

The surveys included in this pooled cohort have been previously validated.[84, 85, 87, 89, 90] The outcomes of interest were breast cancer incidence (Papers I and III) and breast cancer mortality (Paper II). In a cohort study, information about endpoints should be obtained in the same manner, regardless of the exposure.[106]

Reporting to the Cancer Registry of Norway is mandatory for all primary cancers diagnosed by a physician based on clinical evidence, or by a pathologist based on the histological report. The Cancer Registry of Norway is regarded as one of the most complete in the world; in evaluations it has shown a high degree of comparability, accuracy and timeliness, with specific precision for breast cancer.[93]

Information about cause of death in Norway is reported by the physician completing the Cause of Death certificate, based on his/her clinical evaluation, previous knowledge of the deceased, previous radiologic examinations, and other relevant information. Lack of experience, lack of time, and lack of knowledge about the patient may lead to erroneous conclusions.[107] As previously mentioned, to correct for errors and mistaken conclusions drawn by the physician, rules from the World Health Organization are used in Norway to ensure that the correct classification of cause of death is recorded on the death certificate.[94, 95] If an autopsy is not performed to evaluate the cause of death, the physician's evaluation is reported to the official registry. Autopsy was, and perhaps is, the gold standard of diagnostics, but radiological, and other similar evaluations not previously available now provide novel diagnostic tools that can be used while the patient is still alive.[107] Hence autopsy may not be as necessary as it once was to determine cause of death.

A Norwegian report from 2012 compared the underlying cause of death in death certificates with the results from all medical autopsies (n=1773) in 2005.[94] The report revealed a change in the underlying cause of death in 61% of the cases, and a change in the International Classification of Diseases code assigned (major change) in 32% of the reports, illustrating a considerable uncertainty when cause of death is taken from death certificates only. Overall, the validity of the mortality data from the Norwegian Death Registry should be regarded with some reservation.

10.1.5 Validity of measures of smoking exposure

Smoking exposure in these the papers was defined as active current (i.e., daily), or former smoking at study enrollment. Smoking duration among current smokers refers to duration between initiation and study enrollment. Passive and occasional smoking was not assessed as no data was available; therefore passive and occasional smokers were included in the reference group (among never smokers). Norwegian occasional smokers often define themselves as non-smokers.[108]

The study by Dossus and colleagues demonstrated that excluding passive smokers from the reference group can increase the risk estimates between smoking and the outcome under investigation.[25] Exclusion of passive smokers from the reference group was also done by Gram and colleagues, which probably increased their risk estimates.[19]

In our cohorts, smoking information was self-reported in the baseline questionnaires, which avoids some bias in the ascertainment of exposure. Indeed, smoking exposure has been considered to be reported accurately by participants of similar studies.[104, 109] Furthermore, selection bias could be caused by a "healthy volunteers effect", as volunteers are often characterized as healthier than the general population.[110] Smokers may adopt health behaviors when participating in health studies, making it more difficult to detect associations. Our pooled cohort has a high number of ever smokers, reducing the concern that a large number of smokers did not attend the surveys.

To increase the accuracy of measures of smoking exposure in our study, differences in smoking behavior should have been measured throughout follow-up, instead of only at baseline. A report from the Million Women Study showed that among 20% of current smokers at baseline, 23% had quit smoking after 3 years, and 44% had quit smoking after 8 years of follow-up.[52] Also, being diagnosed with breast cancer may lead to a change in smoking habits; the report from the Nurses' Health Study showed that 38% of current smokers quit smoking and only 2% of former smokers started smoking again after breast cancer diagnosis.[24] To account for the missing follow-up data on smoking behavior, measures of smoking exposure were used in the present thesis, and ever smokers and never smokers were compared, using never smokers as the reference group in the main exposure analysis. Women who reported being a current or former smoker were classified as ever smokers. As most women in Norway initiate smoking before age 25,[12] we consider it unlikely that a significant number of women who reported they were never smokers at study enrollment (mean age at study enrollment 41 years) started smoking during follow-up; those classified as never smokers would likely have remained never smokers. Classification (measurement) bias was therefore reduced significantly by using ever and never smokers as the main exposure categories in our study, as we lack follow-up data.

The use of ever smokers in the analysis, instead of current and former smokers, makes it impossible to distinguish current smoking, which is often used as a surrogate for heavy smoking exposure,[111] and former smoking, often with a disparate smoking exposure history. Theoretically, using ever instead of current smokers in these analyses may have reduced the association between smoking and breast cancer.

In Paper II, our results using high number of pack-years as a proxy for lifetime smoking exposure are discussed. In our pooled cohort we found a mean exposure of 13 pack-years for current smokers, which was far less than in the study by Pierce and colleagues, which found a mean exposure among current smokers of 39 pack-years. Pierce and colleagues did the smoking assessment 2 years after breast cancer diagnosis, whereas our study did it at study enrollment before breast cancer diagnosis. Hence, selection bias in favor of long-term smokers and recall bias with respect to remembering smoking history may explain the very high mean exposure in the Pierce study. Also, mean age at enrollment in the Pierce study was 60, as compared with 44 years in our pooled cohort, which could explain why our current smokers had a shorter smoking duration than those reported other studies.[25, 26] As discussed in Papers I-III, we consider the high smoking exposure among the women in our surveys as a strength.

10.2 Confounding

In a study of the association between an exposure and the occurrence of a disease, confounding can occur when another exposure exists in the study population that is associated both with the disease and the exposure being examined. A high number of included individuals in a cohort study increase the chance of obtaining significant p values. At the same time, control of confounders may be extensively difficult in large studies, thus threatening study validity, which is not displayed through the p value.[100] In contrast to bias, it is possible to control for confounders by stratification and adjustment in multivariate models. Comparison between unadjusted and adjusted associations is the best evidence to support the presence of confounding if the estimates differ.[63] In the multivariate models of the papers in this thesis, parity, age at first childbirth, smoking duration, and BMI (and a subanalysis on alcohol consumption in Papers I and II) were included in an attempt to exclude the possibility that these factors confounded our results for smoking and breast cancer.

In Paper I, our Table 4 displays both age-adjusted and multivariate-adjusted risk estimates. In Papers II and III, we chose not to display both results as they were materially similar, indicating that the confounders included in the multivariate analysis were of minor importance in these papers. Age-analyses were also done for all the analyses in paper III, but were not displayed as all the results were materially similar to the results from the multivariate model.

10.2.1 Residual confounding

Bias that remains after adjustment is an example of residual confounding.[80] The findings of the papers included in this thesis may be the result of residual confounding in the following ways:

- We found an increased risk among women who start to smoke early in life. This may be confounded by **smoking duration** as women who start to smoke early also tend to smoke for a longer duration.
- Women who start smoking before their first childbirth may also have their **first childbirth later in life**, which also increases breast cancer risk. In addition, late first childbirth increases the risk of smoking initiation before first childbirth.
- Any difference in breast cancer risk before or after menopause may be **confounded by BMI** as there is an increased risk of breast cancer among premenopausal women with high BMI, and smokers generally have a lower BMI (opposing effect). Conversely, an increased risk of breast cancer among thin women before menopause may due to the face that leaner women tend to smoke more.
- Passive smokers were included in the reference group as never smokers, which may have diluted our results for the association between smoking and breast cancer. Cohort studies have been shown to underestimate the effect of smoking if passive smokers are included in the reference group, but some studies that were able to exclude passive smokers from the reference group did not show an increased risk.[18, 112] Moreover, the exclusion of passive smokers from the reference group[19, 39] (never active, never passive) could make the outcome difficult to compare with studies that do include passive smokers in the reference group.

(A biologic rationale for a genetic difference in breast cancer risk between active and passive smokers was presented in 2000 by Morabia and colleagues, and will not be discussed further in this thesis.[113])

10.3 Alcohol consumption

The confounding effect between alcohol consumption and breast cancer risk has been widely discussed.[19, 25, 114] The rationale for this is that heavy smokers report more alcohol consumption than never smokers, and when studying the effects of smoking, there is concern as to whether the carcinogenic effect comes from alcohol instead of smoking. The validity of self-reported alcohol consumption has been questioned, and is expected to be underreported in most cases, which may cause residual confounding.[105, 115] Alcohol consumption may be a greater problem among current than former smokers, as current smokers drink more than former smokers.[2, 18]

A large meta-analysis published in 2002 by Hamajiima and colleagues[114] included 53 epidemiological studies and reported that alcohol consumption could fully explain the increased breast cancer risk among smokers, and hence that alcohol, not smoking, was responsible for the increased risk of breast cancer reported in that study. This study is widely cited as it is large and well performed, but had a rather short follow-up period, used ever/never as the measure of smoking, and did not exclude passive smokers from the reference group.[116] However, it stands as one of the most important reports of this association. There is convincing evidence of a positive association between alcohol consumption and breast cancer,[117-120] and there seems to be a linear dose-response association, as each 10 grams of alcohol consumed per day increases the risk by between 7.1%[114] and 10%.[119] Given this association, and the results from Hamajiima and colleagues, it is difficult to disregard the potential influence of alcohol consumption on the association between active smoking and breast cancer.

At least 11 prospective cohort studies on smoking before first childbirth and breast cancer, all of which adjusted for alcohol consumption, found an increased risk, mostly with a dose-response association.[18-20, 22-26, 39, 75] Some argue that this association should be measured only among never drinkers, to exclude the chance of bias from alcohol. In the paper by Dossus and colleagues, a positive association between smoking and breast cancer was found only among non-drinkers, but this study did not include information on the amount of alcohol consumed, and did not report whether any dose-response was present.[25] Rosenberg and colleagues found a positive association between smoking and breast cancer risk after controlling for smoking initiation and alcohol consumption, as well as a non-significant association among never drinkers.[39]

Information on alcohol consumption in our study was categorized according to weekly consumption (<weekly, weekly, >weekly), not total consumption (i.e., grams per week), as weekly consumption was available for more study participants. Grams per week may give a better estimation of total alcohol consumption, especially if the drinking pattern is dominated by high consumption on weekends ("binge drinking"). In our subanalysis on alcohol consumption we found materially the same results as in the full pooled cohort (Papers I and II). Smoking is particularly prevalent among heavy drinkers and much less common among abstainers.[116, 121] Consumption of alcohol seems to follow social gradients; a high level of education and income increases alcohol consumption.[116] The lack of alcohol information in Paper III may cause confounding, both with smoking exposure and level of education, which is a major limitation of this paper.

It is still debated whether alcohol is a confounder of the association between smoking and breast cancer. Alcohol consumption should most likely be considered in relation to duration of drinking and amount consumed, and maybe in relation to the period of life in which alcohol was consumed. No studies to-date have successfully adjusted for alcohol consumption before first childbirth when assessing smoking exposure before first childbirth and breast cancer. The recent study by Liu and colleagues found that alcohol consumption before first childbirth was dose-dependently associated with breast cancer, independent of drinking after first pregnancy.[122] More studies should be conducted on the importance of alcohol consumption, and probably other known carcinogens, in the time window between menarche and first childbirth, as alcohol consumption among adolescents in Norway is increasing: 10% of all 15-year-olds now drink alcohol at least once a week.[123]

Although it is questionable whether alcohol consumption is a confounder for the association between smoking and breast cancer, we consider the missing information on alcohol consumption a main limitation of the papers included in this thesis.

10.4 Mammography screening

Mammography screening for breast cancer was not common in Norway during the first 20 years of follow-up in our study. The Norwegian Breast Cancer Screening Program includes women aged 50 to 69 years. It started at the end of 1995 and became a nationwide program in 2005,[124] just 2 years before the end of our follow-up period. Therefore it seems unlikely that this biased our results to any great extent.

The 2014 report from the Behavioral Risk Factor Surveillance System in the United States indicated that participation in mammography screening is substantially lower among current smokers compared to non-smokers.[125] This was also found in previous studies.[126] A lower participation among smokers may have decreased the number of cases detected among current smokers, possibly leading to an underestimation of the association between smoking and breast cancer among current smokers. Also, lower mammography screening participation among current smokers may lead to an overestimation of the association between smoking and breast cancer mortality among current smokers, as compared with former and never smokers, due to the possibility that breast cancer is not detected in time.

10.5 Validity of variables for level of education

To classify each participant according to level of education, we used the most recent information regarding duration of education obtained from Statistics Norway to assign participants to one of three categories: low (<10 years), moderate (10-12 years), and high (>12 years). In1965, duration of compulsory school attendance in Norway changed from 7 to 9 years, therefore, <10 years of education means primary school with at most 2 years of additional education. Similarly, women with 10-12 years of education have completed secondary school, or at most 5 years of professional training. Education lasting >12 years corresponds to university level education, or a lower level of education with several years of professional training.

Information on education in Statistics Norway comes from four population censuses conducted in 1970, 1980, and 1990 (each census year is November 1st).[129, 130] In the 1970 census (as in the census of 1960) education was coded according to information from personal visits to each household. In the 1980 and 1990 censuses, register data for highest duration of education was used to determine level of education. From the 1970 census onwards, education was coded according to the Norwegian Standard Classification of Education, which is compatible with the International Standard Classification of Education.[131]

Higher education is associated with increased breast cancer risk. As demonstrated by Braaten and colleagues (2004), the increased risk conferred by education can be explained by known risk factors such as lower parity, higher age at first childbirth, BMI, use of oral contraceptives and hormone replacement therapy, and alcohol consumption. They suggested that if

reproductive factors and anthropometrics are used in the model, it is redundant to keep level of education as a covariate in the model.[56] As an established risk factor for breast cancer, level of education was discussed and included as an adjusting variable in the main model of seven[20, 23, 25-27, 39, 76] of the most recent cohort studies on the association between active smoking and breast cancer. Our pooled cohort also comprised information on income, but it was problematic to use this information in a longitudinal study, as it is difficult to compare income levels across groups recruited at different time periods.

10.6 Time variable in the model

We used the semiparametric Cox proportional Hazards model[132] to find our risk estimates. The time-independent model was used with age (at enrollment) as the time scale. In the Cox model, the assumption underlying the model was that the risk factor is associated with the fixed relative increase in the instantaneous risk of the outcome of interest, compared with the reference hazard[63] i.e. the hazard among those exposed is constant at any given point in time (Figure 8A).

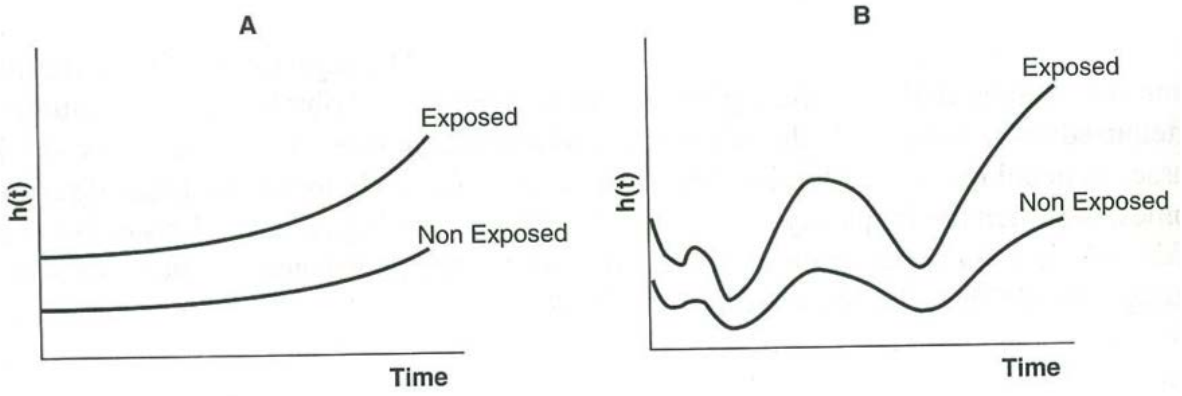

Figure 8: Hazard over time in two hypothetical situations. From Szklo/Nieto: p 266. Reprinted with permission.[63]

As our study had a long follow-up period, the hazard will fluctuate with time ("calendar effect") due to changes in treatment protocols, mammography screening programs, use of hormone replacement therapy at certain time periods, or similar, as illustrated in Figure 8B. To account for some of these changes, stratification by birth cohort is recommended[133] and was performed in all papers in this thesis. Using other "time-dependent" time scales such as follow-up time does not afford the same opportunity to stratify by birth cohort.[133]

One problem of using age as the time scale (underlying time variable) is that the three included surveys were conducted decades apart, and the model considers a woman who was 40 years of age at inclusion in 1975 in exactly the same manner as a women who was 40 years of age at inclusion in 1995, though they were included 20 years apart. A model using calendar year of birth would have accounted for this possible bias. However, when stratifying by birth cohort, our model with age should have accounted sufficiently for this problem.

The use of a time model consistent with the data is important, but it may not always make a large difference.[134] We conclude that, despite some downsides, the use of age (at enrollment) as the time variable for this longitudinal study is the most appropriate.

11 Discussion of main results

The main findings are discussed in the respective papers (Papers I-III). The discussion below is focused on the main messages of the three papers.

11.1 Paper I

In this paper we found that current, former, and ever smoking was associated with breast cancer incidence. By showing statistically significant dose-response associations with smoking exposures, and duration of smoking before first childbirth, this paper adds more epidemiological evidence to the notion that there is an association between smoking and breast cancer, with excellent power.

A dose-response relationship is regarded as strong evidence that a cause-effect relationship exists.[63] Our observation is reflected in other recent studies on smoking and breast cancer incidence. Gaudet and colleagues[26] found a similar risk increase of 45% for women who smoked 11 years or more before their first childbirth. The study from the United States Black Women's Cohort by Rosenberg and colleagues[39] found a doubling in risk for premenopausal breast cancer among those with a history of more than 20 pack-years, and smoking more than 5 years before their first childbirth. No association was found for postmenopausal breast cancer in this study. Also, the study by Dossus and colleagues[25] from the European Prospective Investigation into Nutrition and Cancer (EPIC) found a 73% risk increase (HR=1.73, 95% CI 1.29-2.32) for every increase of 20 pack-years. Nyante and colleagues[27]

found the highest risks among women without a family history of breast cancer, or late menarche.

More than 150 studies have been performed on the association between smoking and breast cancer. Regardless, this issue is still under debate. A majority of studies now conclude that there is a consistent, albeit weak, increase in risk for current smokes, and that the risk seems to increase with increasing smoking exposure. Ideal study designs, such as intervention studies or randomized controlled trials, are not possible, and the perfect epidemiological cohort study for this association is difficult to conduct. This study adds information on the association between smoking and breast cancer, and supports the notion that smoking before first childbirth is a risk factor for breast cancer.

11.2 Paper II

As smoking arises as a risk factor for breast cancer, the need for more studies in relation to this association emerges. Paper II showed that lifetime smoking exposure was significantly associated with the risk of breast cancer mortality among ever smokers compared with never smokers, but without clear dose-response associations. Since the association between smoking and breast cancer is not strong, high risk estimates for smoking and breast cancer mortality was not expected. Two recent studies that assessed smoking exposure before breast cancer diagnosis have been published; one by Saquib and colleagues,[135] and one by Pierce and colleagues.[111] In both of these papers, the assessment of current smoking at diagnosis did not reveal any risk increase for breast cancer. When reanalyzing the same data according to smoking intensity and duration before diagnosis, a different conclusion was reached, with a 54% increased risk of dying from breast cancer (HR=1.54, 95% CI 1.07-2.32) reported in the Saquib paper. Similarly, a 54% increased risk (HR=1.54, 95% CI 1.24-1.91) was found in the Pierce paper among former smokers who smoked more than 35 pack-years.

However, when comparing these results with the results from Paper II, there is a concern regarding selection bias in the studies by Saquib and colleagues and Pierce and colleagues. The cohort in the Saquib paper had less than 5% current smokers, and among those, one-third had a smoking exposure of more than 20 pack-years. Similarly, the current smokers in the Pierce paper had a mean smoking exposure of 39 pack-years. Analysis for this high exposure among current smokers was not possible in Paper II, as we had too few women who smoked

more than 20 pack-years. Our results for 11 pack-years or more rendered a non-significant 21% risk increase (HR=1.21, 95% CI 0.66-2.23) for breast cancer mortality.
Our use of ever smokers in the analysis instead of current and former smokers made it impossible to distinguish between current smoking, which is often used as a surrogate for heavy smoking exposure, and former smoking, often with a disparate history of smoking exposure. It is possible that the use of current instead of ever smokers could have revealed stronger risk estimates.

"Competing risk" occurs when another event takes place among participants that is different from the disease under observation. The possibility of dying from smoking-associated diseases other than breast cancer during follow-up, such as cardiovascular disease, lung cancer, or chronic obstructive pulmonary disease, is a concern in mortality studies. Removing competing risks by statistical maneuvers without altering the mortality estimates for breast cancer is difficult.[80, 136] Our dataset lacks information on causes of death other than breast cancer, ovarian cancer, and colorectal cancer, which makes any proper estimate of competing risks difficult. Competing risks therefore remains as a major limitation of Paper II.

Further prospective cohort studies should be performed, possibly in cohorts with very high smoking exposure, in order to draw solid conclusions on the association between of smoking exposure and breast cancer mortality. In paper II we found that using ever smoking as a measure of lifetime smoking exposure conferred a significantly increased risk of breast cancer mortality compared with never smokers, but our results were difficult with the recent papers due to the lack of participants with very high smoking exposure.

11.3 Paper III

Significant associations were found for ever, current and former smoking and breast cancer incidence in Paper I, making this cohort suitable for a more detailed approach of the socioeconomic implications of this association. The social gradient in many diseases are well known, but varies between cancer sites. For breast cancer, the association with higher SES is reported for income, occupation or socioeconomic group, and for level of education.[55, 56, 137, 138] In this paper, we used level of education, a well-established measure of SES.[91, 139]
We confirmed the elevated breast cancer risk with higher educational achievement, as compared to lower educational achievement, in accordance with the literature. [55, 56, 137, 138] The

observation of a non-significant risk increase for smoking-associated breast cancer in women with higher education in both birth cohorts shows that never and ever smokers with high level of education has a similar risk of breast cancer, indicating that smoking has a limited impact on women with higher education. Further, a significant difference is observed in the cohort born in and before 1950 between women with low and high level of education. This observation may indicate a socioeconomic gradient for smoking-associated breast cancer in this age group, which is difficult to explain based on our previous knowledge of a higher breast cancer risk among higher educated women. Smoking may have a stronger impact on breast cancer risk in this category of elderly women, possibly reducing the importance of other known breast cancer risk factors.

The analyses for the different smoking exposures: age at smoking initiation, smoking duration, number of cigarettes smoked per day, pack-years and smoking duration before first childbirth, mostly showed an increasing breast cancer risk with increasing smoking exposure. In particular, the results for women with low level of education revealed a significant trend for all measures of smoking exposure. As previously discussed in the thesis, recent literature shows the importance of analyzing the smoking and breast cancer association with increasing smoking exposures, not only by smoking status (ever, current, former, never), to promote the importance of dose-response. The results for smoking duration before first childbirth shows an increasing risk with increasing duration of smoking for all levels of education, and as previously discussed, it supports the notion that smoking in this time period is an important risk factor for breast cancer.

Except from the observation of an increased smoking-associated breast cancer risk among low and moderately educated women born in and before 1950, which is not observed among women with high education, our study finds limited evidence that smoking-associated breast cancer have an important impact on social inequalities in health.

12 Conclusions

12.1 Paper I

- Active smoking increases breast cancer risk
- The risk increases with increasing smoking exposure, i.e., longer smoking duration, higher number of cigarettes smoked per day, and higher number of pack-years

- Smoking initiation before first childbirth increases the risk of breast cancer

12.2 Paper II

- Lifetime smoking exposure increases the risk of breast cancer mortality
- Smoking before first childbirth do not increase the risk of breast cancer mortality
- Dose-response associations were not revealed

12.3 Paper III

- Increasing level of education increases breast cancer risk
- Smoking for several years before first childbirth increases breast cancer risk, regardless of level of education
- Smoking-associated breast cancer has limited impact on social inequalities in health

13 List of references

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PAPER I

Eivind Bjerkaas, Ranjan Parajuli, Elisabete Weiderpass, Anders Engeland, Gertraud Maskarinec, Randi Selmer, Inger Torhild Gram

Smoking duration before first childbirth: an emerging risk factor for breast cancer? Results from 302,865 Norwegian women.

Cancer Causes Control (2013) 24:1347–1356
PubMed: PMID: 23633026

PAPER II

Eivind Bjerkaas, Ranjan Parajuli, Anders Engeland, Gertraud Maskarinec, Elisabete Weiderpass, Inger Torhild Gram

The association between lifetime smoking exposure and breast cancer mortality – results from a Norwegian cohort

Cancer Medicine (2014) Jul 30. doi: 10.1002
Pubmed PMID: 25073713

PAPER III

Eivind Bjerkaas, Ranjan Parajuli, Elisabete Weiderpass, Anders Engeland, Gertraud Maskarinec, Inger Torhild Gram

Social inequalities and smoking-associated breast cancer – results from a prospective cohort study

(Submitted to Preventive Medicine, 2014)

Appendices

1. Surveys questionnaires
2. Description of methodology
3. Summary of cohort studies examining the association between smoking and breast cancer incidence and mortality published after 2004
4. Variable descriptions
5. Other publications during the PhD period

Appendix 1

Surveys Questionnaires

QUESTIONNAIRE THREE COUNTIES
FINNMARK COUNTY
ROUND 1 AND 2 (NORWEGIAN)

A

	JA	NEI
Har De, eller har De hatt:		
Hjerteinfarkt? 33	☐	☐
Angina pectoris (hjertekrampe)? 34	☐	☐
Annen hjertesykdom? 35	☐	☐
Åreforkalkning i bena? 36	☐	☐
Hjerneslag? 37	☐	☐
Sukkersyke? 38	☐	☐
Er De under behandling for:		
Høyt blodtrykk? 39	☐	☐
Bruker De:		
Nitroglycerin? 40	☐	☐

B

	JA	NEI
Får De smerter eller ubehag i brystet når De:		
Går i bakker, trapper eller fort på flat mark? 41	☐	☐
Går i vanlig takt på flat mark? 42	☐	☐
Hvis De får smerter eller ubehag i brystet ved gange, pleier De da å:		
1 Stanse? 43	☐	
2 Saktne farten?	☐	
3 Fortsette i samme takt?	☐	
Hvis De stanser eller saktner farten, forsvinner smertene da:		
1 Etter mindre enn 10 minutter? 44	☐	
2 Etter mer enn 10 minutter?	☐	
Får De smerter i tykkleggen når De:		
Går? 45	☐	☐
Er i ro? 46	☐	☐
Hvis De får leggsmerter, besvar da:		
Forverres smertene ved raskere tempo eller i bakker? 47	☐	☐
Gir smertene seg når De stopper? 48	☐	☐
Har De vanligvis:		
Hoste om morgenen? 49	☐	☐
Oppspytt fra brystet om morgenen? 50	☐	☐

C

	JA
Bevegelse og kroppslig anstrengelse i Deres **fritid**. Hvis aktiviteten varierer meget f.eks. mellom sommer og vinter så ta et gjennomsnitt. Spørsmålet gjelder bare det siste året. **Sett kryss i den ruten hvor „JA" passer best.**	
1 Leser, ser på fjernsyn eller annen stillesittende beskjeftigelse? 51	☐
2 Spaserer, sykler eller beveger Dem på annen måte minst 4 timer i uken? (Heri medregnes også gang eller sykling til arbeidsstedet, søndagsturer m.m.)	☐
3 Driver mosjonsidrett, tyngre hagearbeid e.l.? (Merk at yirksomheten skal være minst 4 timer i uken.	☐
4 Trener hardt eller driver konkurranseidrett, regelmessig og flere ganger i uken?	☐

G

	JA	NEI
Har noen i Deres husstand (utenom Dem selv) vært innkalt til nærmere undersøkelse hos distriktslegen etter forrige hjerte-kar undersøkelse? 80	☐	☐

D

	JA	NEI
Røyker De daglig for tiden? 52	☐	☐
Hvis svaret var „JA" på forrige spørsmål, besvar da:		
Røyker De sigaretter daglig? (håndrullede eller fabrikkframstilte) 53	☐	
Hvis De ikke røyker sigaretter nå, besvar da:		
Har De røykt sigaretter daglig tidligere? 54	☐	☐
Hvis De svarte „JA", hvor lenge er det siden De sluttet?		
1 Mindre enn 3 måneder? 55	☐	
2 3 måneder - 1 år?	☐	
3 1 - 5 år?	☐	
4 Mer enn 5 år?	☐	
Besvares av dem som røyker nå eller har røykt tidligere:		
Hvor mange år tilsammen har De røykt daglig? 56-57 — Antall år:		
Hvor mange sigaretter røyker eller røykte De daglig? Oppgi antall pr. dag (håndrullede + fabrikkframstilte) 58-61 — Ant. sigaretter:		
Røyker De noe annet enn sigaretter daglig?		
Sigarer eller serutter/cigarillos? 62	☐	☐
Pipe? 63	☐	☐
Hvis De røyker pipe, hvor mange pakker tobakk (50 gram) bruker De i pipa pr. uke?		
Oppgi gjennomsnittlig antall pakker pr. uke. 64-66 — Ant. tobakkpk.		

E

	JA	NEI
Har De vanligvis skiftarbeid eller nattarbeid? 67	☐	☐
Kan De vanligvis komme hjem fra arbeidet:		
Hver dag? 68	☐	☐
Hver helg? 69	☐	☐
Har De i perioder lengre arbeidsdager enn vanlig? 70 (f.eks. under seosongfiske, onnearbeid)	☐	☐
Har De i løpet av siste året hatt:		
Sett kryss i den ruten hvor „JA" passer best.		
1 Overveiende stillesittende arbeid? 71 (f.eks. skrivebordsarb., urmakerarb., montering)	☐	
2 Arbeid som krever at De går mye? (f.eks. ekspeditørarb., lett industriarb., undervisn.)	☐	
3 Arbeid hvor De går og løfter mye? (f.eks. postbud, tyngre industriarb, bygningsarb)	☐	
4 Tungt kroppsarbeid? (f.eks. skogsarbeid, tungt jordbruksarb tungt bygningsarb)	☐	
Har De i løpet av de siste 12 mnd måttet flytte fra hjemstedet på grunn av forandring i arbeidssituasjonen? 72	☐	☐
Er husmorarbeid Deres hovedyrke? 73	☐	☐
Har De i løpet av de siste 12 mnd fått arbeidsledighetstrygd? 74	☐	☐
Er De for tiden sykmeldt, eller får De attføringspenger? 75	☐	☐
Har De full eller delvis uførepensjon? 76	☐	☐

F

	JA	NEI	VET IKKE
Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)? 77	☐	☐	
Er to eller flere av Deres besteforeldre av finsk ætt? 78	☐	☐	
Er to eller flere av Deres besteforeldre av samisk ætt? 79	☐	☐	

MELDING OM SKJERMBILDEFOTOGRAFERING OG HJERTE-KARUNDERSØKELSE

(Gjelder bare den person brevet er adressert til)

Skjermbildefotograferingen kommer nå til Deres distrikt.

Tid og sted for Deres frammøte vil De finne nedenfor.

Også denne gangen vil en del av befolkningen få tilbud om hjerte-karundersøkelse. De tilhører denne gruppe. En orientering om undersøkelsen er gitt i vedlagte brosjyre.

Vennligst fyll ut spørreskjemaet på baksiden og ta det med til undersøkelsen. Ta også med tuberkulinkort eller helsebok, om De har.

Fravær bes eventuelt meldt på vedlagte seddel.

Med hilsen

HELSERÅDET FYLKESLEGEN
STATENS SKJERMBILDEFOTOGRAFERING

Født dato Personnr. Kommune Kretsnr.

Møtested Kjønn Første bokstav etternavn Dag og dato Klokkeslett

SKRIV IKKE HER!

T. S. M.: (17) M: (18) (19) / (24) (25) / (30) (31) (32)

QUESTIONNAIRE THREE COUNTIES STUDY, SOGN OG FJORDANE AND OPPLAND COUNTIES, ROUND 1 AND 2

A

	JA	NEI
Har De, eller har De hatt:		
Hjerteinfarkt? 33		
Angina pectoris (hjertekrampe)? 34		
Annen hjertesykdom? 35		
Åreforkalkning i bena? 36		
Hjerneslag? 37		
Sukkersyke? 38		
Er De under behandling for:		
Høyt blodtrykk? 39		
Bruker De:		
Nitroglycerin? 40		

B

	JA	NEI
Får De smerter eller ubehag i brystet når De:		
Går i bakker, trapper eller fort på flat mark? 41		
Går i vanlig takt på flat mark? 42		
Hvis De får smerter eller ubehag i brystet ved gange, pleier De da å:		
1 Stanse? 43		
2 Saktne farten?		
3 Fortsette i samme takt?		
Hvis De stanser eller saktner farten, forsvinner smertene da:		
1 Etter mindre enn 10 minutter? 44		
2 Etter mer enn 10 minutter?		
Får De smerter i tykkleggen når De:		
Går? 45		
Er i ro? 46		
Hvis De får leggsmerter, besvar da:		
Forverres smertene ved raskere tempo eller i bakker? 47		
Gir smertene seg når De stopper? .. 48		
Har De vanligvis:		
Hoste om morgenen? 49		
Oppspytt fra brystet om morgenen? .. 50		

C

	JA
Bevegelse og kroppslig anstrengelse i Deres **fritid**. Hvis aktiviteten varierer meget f.eks. mellom sommer og vinter så ta et gjennomsnitt.	
Spørsmålet gjelder bare det siste året.	
Sett kryss i den ruten hvor „JA" passer best.	
1 Leser, ser på fjernsyn eller annen stillesittende beskjeftigelse? 51	
2 Spaserer, sykler eller beveger Dem på annen måte minst 4 timer i uken? .. (Heri medregnes også gang eller sykling til arbeidsstedet, søndagsturer m.m.)	
3 Driver mosjonsidrett, tyngre hagearbeid e.l.? ..... (Merk at yirksomheten skal vare minst 4 timer i uken.	
4 Trener hardt eller driver konkurranseidrett, regelmessig og flere ganger i uken?	

D

	JA	NEI
Røyker De daglig for tiden? 52		
Hvis svaret var „JA" på forrige spørsmål, besvar da:		
Røyker De sigaretter daglig? ..... 53 (håndrullede eller fabrikkframstilte)		
Hvis De ikke røyker sigaretter nå, besvar da:		
Har De røykt sigaretter daglig tidligere? . 54		
Hvis De svarte „JA", hvor lenge er det siden De sluttet?		
1 Mindre enn 3 måneder? 55		
2 3 måneder - 1 år?		
3 1 - 5 år?		
4 Mer enn 5 år?		
Besvares av dem som røyker nå eller har røykt tidligere:		
Hvor mange år tilsammen har De røykt daglig? 56-57	Antall år:	
Hvor mange sigaretter røyker eller røykte De daglig? Oppgi antall pr. dag 58-61 (håndrullede + fabrikkframstilte)	Ant. sigaretter:	
Røyker De noe annet enn sigaretter daglig?		
Sigarer eller serutter/cigarillos? ... 62		
Pipe? 63		
Hvis De røyker pipe, hvor mange pakker tobakk (50 gram) bruker De i pipa pr. uke?	Ant tobakkpk.	
Oppgi gjennomsnittlig antall pakker pr. uke. 64-66		

E

	JA	NEI
Har De vanligvis skiftarbeid eller nattarbeid? 67		
Kan De vanligvis komme hjem fra arbeidet:		
Hver dag? 68		
Hver helg? 69		
Har De i perioder lengre arbeidsdager enn vanlig? ..... 70 (f.eks. under sesongfiske, onnearbeid)		
Har De i løpet av siste året hatt:		
Sett kryss i den ruten hvor „JA" passer best.		
1 Overveiende stillesittende arbeid? .. 71 (f.eks. skrivebordsarb., urmakerarb., montering)		
2 Arbeid som krever at De går mye? .. (f.eks. ekspeditørarb., lett industriarb., undervisn.)		
3 Arbeid hvor De går og løfter mye? .. (f.eks. postbud, tyngre industriarb., bygningsarb.)		
4 Tungt kroppsarbeid? ..... (f.eks. skogsarbeid, tungt jordbruksarb tungt bygningsarb)		
Har De i løpet av de siste 12 mnd måttet flytte fra hjemstedet på grunn av forandring i arbeidssituasjonen? 72		
Er husmorarbeid Deres hovedyrke? 73		
Har De i løpet av de siste 12 mnd fått arbeidsledighetstrygd? 74		
Er De for tiden sykmeldt, eller får De attføringspenger? 75		
Har De full eller delvis uførepensjon? .. 76		

F

	JA	NEI	VET IKKE
Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)? . 77			

G

	JA	NEI
Har noen i Deres husstand (utenom Dem selv) vært innkalt til nærmere undersøkelse hos distriktslegen etter forrige hjerte-kar undersøkelse? 80		

MELDING OM SKJERMBILDEFOTOGRAFERING OG HJERTE-KARUNDERSØKELSE

(Gjelder bare den person brevet er adressert til)

Skjermbildefotograferingen kommer nå til Deres distrikt.

Tid og sted for Deres frammøte vil De finne nedenfor.

Denne gangen vil en del av befolkningen også få tilbud om hjerte-karundersøkelse. De tilhører denne gruppe. En orientering om undersøkelsen er gitt i vedlagte brosjyre.

Vennligst fyll ut spørreskjemaet på baksiden og ta det med til undersøkelsen. Ta også med skjermbildebevis, tuberkulinkort eller helsebok om De har.

Fravær bes eventuelt meldt på vedlagte seddel.

Med hilsen

HELSERÅDET FYLKESLEGEN
STATENS SKJERMBILDEFOTOGRAFERING

Født dato | Personnr. | Kommune | Kretsnr.

Møtested | Kjønn | Første bokstav etternavn | Dag og dato | Klokkeslett

SKRIV IKKE HERI

T. S. M.: (17) M: (18) (19) / (24) (25) / (30) (31) (32)

QUESTIONNAIRE THREE COUNTIES STUDY,
ALL COUNTIES COUNTY,
ROUND 3
NORWEGIAN

A FAMILIE

	JA	NEI	VET IKKE
Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)? 12			

B EGEN SYKDOM

	JA	NEI
Har De, eller har De hatt:		
Hjerteinfarkt? 13		
Angina pectoris (hjertekrampe)? 14		
Hjerneslag? 15		
Sukkersyke? 16		
Er De under behandling for:		
Høyt blodtrykk? 17		
Bruker De:		
Nitroglycerin? 18		

C SYMPTOMER

	JA	NEI	
Får De smerter eller ubehag i brystet når De:			
Går i bakker, trapper eller fort på flat mark? 19			
Går i vanlig takt på flat mark? 20			
Dersom De får smerter eller vondt i brystet ved gange, pleier De da å:			
Stoppe? 21			1
Saktne farten?			2
Fortsette i samme takt?			3
Dersom De stopper eller saktner farten, forsvinner smertene da:			
Etter mindre enn 10 minutter? 22			1
Etter mer enn 10 minutter?			2
Har De vanligvis:	JA	NEI	
Hoste om morgenen? 23			
Oppspytt fra brystet om morgenen? 24			

D MOSJON

Bevegelse og kroppslig anstrengelse i Deres fritid. Hvis aktiviteten varierer meget f.eks. mellom sommer og vinter, så ta et gjennomsnitt. Spørsmålet gjelder bare det siste året.

Sett kryss i den ruta hvor «JA» passer best

Leser, ser på fjernsyn eller annen stillesittende beskjeftigelse? 25	1
Spaserer, sykler eller beveger Dem på annen måte minst 4 timer i uka? ..... (Her skal De også regne med gang eller sykling til arbeidsstedet, søndagsturer m.m.)	2
Driver mosjonsidrett, tyngre hagearbeid e.l.? .. (Merk at aktiviteten skal vare minst 4 timer i uka).	3
Trener hardt eller driver konkurranseidrett regelmessig og flere ganger i uka?	4

E SALT/FETT

Hvor ofte bruker De salt kjøtt eller salt fisk til middag?

Sett kryss i den ruta hvor «JA» passer best

Aldri eller sjeldnere enn en gang i måneden 26	1
Opptil en gang i uka	2
Opptil to ganger i uka	3
Mer enn to ganger i uka	4

Hvor ofte pleier De strø ekstra salt på middagsmaten?

Sett kryss i den ruta hvor «JA» passer best

Sjelden eller aldri 27	1
Av og til eller ofte	2
Alltid eller nesten alltid	3

Hva slags margarin eller smør bruker De til vanlig på brød?

Sett kryss i den ruta hvor «JA» passer best

Bruker ikke smør eller margarin på brød 28	1
Smør	2
Hard margarin	3
Myk (Soft) margarin	4
Smør/margarin blanding	5

Hva slags fett blir til vanlig brukt til matlaging i Deres husholdning?

Sett kryss i den ruta hvor «JA» passer best

Smør eller hard margarin 29	1
Myk (Soft) margarin eller olje	2
Smør/margarin blanding	3

F RØYKING

	JA	NEI	
Røyker De daglig for tiden? 30			
Hvis svaret er «JA», svar da på dette:			
Røyker De sigaretter daglig? ..... 31 (håndrullet eller fabrikkframstilte)			
Hvis De ikke røyker sigaretter nå, besvar da:			
Har De røykt sigaretter daglig tidligere? 32			
Hvis De svarte «JA», hvor lenge er det siden De sluttet?			
Mindre enn 3 måneder? 33			1
3 måneder – 1 år?			2
1–5 år?			3
Mer enn 5 år?			4
Besvares av dem som røyker nå eller som har røykt tidligere:			
Hvor mange år tilsammen har De røykt daglig? 34			Antall år
Hvor mange sigaretter røyker eller røykte De daglig? Oppgi tallet på sigaretter daglig ..... 36 (håndrullet + fabrikkframstilte)			Antall sigaretter
Røyker De noe annet enn sigaretter daglig?	JA	NEI	
Sigarer eller serutter/sigarillos? 40			
Pipe? 41			
Hvis De røyker pipe, hvor mange pakker tobakk (50 gram) bruker De i pipa pr. uke?			
Oppgi gjennomsnittlig antall pakker pr. uke 42			Ant. tobakk pk.

G KAFFE

Hvor mange kopper kaffe drikker De vanligvis daglig?

Sett kryss i den ruta hvor «JA» passer best

Drikker ikke kaffe, eller mindre enn en kopp 45	1
1 – 4 kopper	2
5 – 8 kopper	3
9 eller flere kopper	4

Hva slags kaffe drikker De vanligvis daglig?

Kokekaffe 46	
Filterkaffe 47	
Pulverkaffe 48	
Koffeinfri kaffe 49	
Drikker ikke kaffe 50	

H ARBEID

	JA	NEI
Har De i løpet av de siste 12 måneder fått arbeidsledighetstrygd? 51		
Er De for tiden sykmeldt, eller får De attføringspenger? 52		
Har De full eller delvis uførepensjon? 53		
Har De vanligvis skiftarbeid eller nattarbeid 54		
Har De i det siste året hatt:		
Sett kryss i den ruta hvor «JA» passer best		
For det meste stillesittende arbeid? ..... 55 (f.eks. skrivebordsarb., urmakerarb., montering)		1
Arbeid som krever at De går mye? ..... (f.eks. ekspeditørarb., lett industriarb., undervisn.)		2
Arbeid hvor De går og løfter mye? ..... (f.eks. postbud, tyngre industriarb., bygningsarb.)		3
Tungt kroppsarbeid? ..... (f.eks. skogsarb., tungt jordbruksarb., tungt bygn.arb.)		4
Er husmorarbeid hovedyrket Deres? 56	JA	NEI

I ETTERUNDERSØKELSE

Hvis denne helseundersøkelsen viser at De bør undersøkes nærmere: Hvilken almenpraktiserende lege ønsker De da å bli henvist til?

Skriv navnet på legen her

..... 57

Ingen spesiell lege 60

Ikke skriv her

Ikke skriv her

QUESTIONNAIRE 40 YEARS STUDY, ROUND 1

A FAMILIE

Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)? 12

JA | NEI | VET IKKE

B EGEN SYKDOM

Har De, eller har De hatt:

JA | NEI

Hjerteinfarkt? 13
Angina pectoris (hjertekrampe)? 14
Hjerneslag? 15
Sukkersyke? 16

Er De under behandling for:

Høyt blodtrykk? 17

Bruker De:

Nitroglycerin? 18

C SYMPTOMER

Får De smerter eller ubehag i brystet når De:

JA | NEI

Går i bakker, trapper eller fort på flat mark? 19
Går i vanlig takt på flat mark? 20

Dersom De får smerter eller vondt i brystet ved gange, pleier De da å:

Stoppe? 21
Saktne farten? .....
Fortsette i samme takt? .....

1 2 3

Dersom De stopper eller saktner farten, forsvinner smertene da:

Etter mindre enn 10 minutter? 22
Etter mer enn 10 minutter? .....

1 2

Har De vanligvis:

JA | NEI

Hoste om morgenen? 23
Oppspytt fra brystet om morgenen? 24

D MOSJON

Bevegelse og kroppslig anstrengelse i Deres fritid. Hvis aktiviteten varierer meget f.eks. mellom sommer og vinter, så ta et gjennomsnitt. Spørsmålet gjelder bare det siste året.

Sett kryss i den ruta hvor «JA» passer best

Leser, ser på fjernsyn eller annen stillesittende beskjeftigelse? ..... 25 — 1

Spaserer, sykler eller beveger Dem på annen måte minst 4 timer i uka? ..... — 2
(Her skal De også regne med gang eller sykling til arbeidsstedet, søndagsturer m.m.)

Driver mosjonsidrett, tyngre hagearbeid e.l.? .. — 3
(Merk at aktiviteten skal vare minst 4 timer i uka).

Trener hardt eller driver konkurranseidrett regelmessig og flere ganger i uka? ..... — 4

E SALT/FETT

Hvor ofte bruker De salt kjøtt eller salt fisk til middag?

Sett kryss i den ruta hvor «JA» passer best

Aldri eller sjeldnere enn en gang i måneden ..... 26 — 1
Opptil en gang i uka ..... — 2
Opptil to ganger i uka ..... — 3
Mer enn to ganger i uka ..... — 4

Hvor ofte pleier De strø ekstra salt på middagsmaten?

Sett kryss i den ruta hvor «JA» passer best

Sjelden eller aldri ..... 27 — 1
Av og til eller ofte ..... — 2
Alltid eller nesten alltid ..... — 3

Hva slags margarin eller smør bruker De til vanlig på brød?

Sett kryss i den ruta hvor «JA» passer best

Bruker ikke smør eller margarin på brød ..... 28 — 1
Smør ..... — 2
Hard margarin ..... — 3
Myk (Soft) margarin ..... — 4
Smør/margarin blanding ..... — 5

Hva slags fett blir til vanlig brukt til matlaging i Deres husholdning?

Sett kryss i den ruta hvor «JA» passer best

Smør eller hard margarin ..... 29 — 1
Myk (Soft) margarin eller olje ..... — 2
Smør/margarin blanding ..... — 3

F RØYKING

JA | NEI

Røyker De daglig for tiden? 30

Hvis svaret er «JA», svar da på dette:

Røyker De sigaretter daglig? 31
(håndrullet eller fabrikkframstilte)

Hvis De ikke røyker sigaretter nå, besvar da:

Har De røykt sigaretter daglig tidligere? 32

Hvis De svarte «JA», hvor lenge er det siden De sluttet?

Mindre enn 3 måneder? ..... 33 — 1
3 måneder – 1 år? ..... — 2
1–5 år? ..... — 3
Mer enn 5 år? ..... — 4

Besvares av dem som røyker nå eller som har røykt tidligere:

Hvor mange år tilsammen har De røykt daglig? ..... 34 — Antall år

Hvor mange sigaretter røyker eller røykte De daglig?
Oppgi tallet på sigaretter daglig ..... 36 — Antall sigaretter
(håndrullet + fabrikkframstilte)

Røyker De noe annet enn sigaretter daglig?

JA | NEI

Sigarer eller serutter/sigarillos? 40
Pipe? 41

Hvis De røyker pipe, hvor mange pakker tobakk (50 gram) bruker De i pipa pr. uke?

Oppgi gjennomsnittlig antall pakker pr. uke ..... 42 — Ant. tobakk pk.

G KAFFE

Hvor mange kopper kaffe drikker De vanligvis daglig?

Sett kryss i den ruta hvor «JA» passer best

Drikker ikke kaffe, eller mindre enn en kopp ..... 45 — 1
1 – 4 kopper ..... — 2
5 – 8 kopper ..... — 3
9 eller flere kopper ..... — 4

Hva slags kaffe drikker De vanligvis daglig?

Kokekaffe 46
Filterkaffe 47
Pulverkaffe 48
Koffeinfri kaffe 49
Drikker ikke kaffe 50

H ARBEID

JA | NEI

Har De i løpet av de siste 12 måneder fått arbeidsledighetstrygd? 51

Er De for tiden sykmeldt, eller får De attføringspenger? 52

Har De full eller delvis uførepensjon? 53

Har De vanligvis skiftarbeid eller nattarbeid 54

Har De i det siste året hatt:

Sett kryss i den ruta hvor «JA» passer best

For det meste stillesittende arbeid? ..... 55 — 1
(f.eks. skrivebordsarb., urmakerarb., montering)
Arbeid som krever at De går mye? ..... — 2
(f.eks. ekspeditørarb., lett industriarb., undervisn.)
Arbeid hvor De går og løfter mye? ..... — 3
(f.eks. postbud, tyngre industriarb., bygningsarb.)
Tungt kroppsarbeid? ..... — 4
(f.eks. skogsarb., tungt jordbruksarb., tungt bygn.arb.)

JA | NEI

Er husmorarbeid hovedyrket Deres? 56

I ETTERUNDERSØKELSE

Hvis denne helseundersøkelsen viser at De bør undersøkes nærmere: Hvilken almenpraktiserende lege ønsker De da å bli henvist til?

Skriv navnet på legen her

..... 57

Ingen spesiell lege 60

Ikke skriv her

Ikke skriv her

QUESTIONNAIRE 40 YEARS STUDY, ROUND 2

A FAMILIE

Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)? 12

JA	NEI	VET IKKE

B EGEN SYKDOM

Har De, eller har De hatt:

	JA	NEI
Hjerteinfarkt? 13		
Angina pectoris(hjertekrampe)? 14		
Hjerneslag? 15		
Sukkersyke? 16		

Hvis De har sukkersyke, i hvilket år ble diagnosen stillet? ..... 17 — 19____

Er De under medikamentell behandling for høyt blodtrykk? 19

JA	NEI

C SYMPTOMER

Får De smerter eller ubehag i brystet når De:

	JA	NEI
Går i bakker, trapper eller fort på flat mark? 20		
Går i vanlig takt på flat mark? 21		

Dersom De får smerter eller vondt i brystet ved gange, pleier De da å:

Stoppe? 22	1
Saktne farten?	2
Fortsette i samme takt?	3

Dersom De stopper eller saktner farten, forsvinner smertene da:

Etter mindre enn 10 minutter? 23	1
Etter mer enn 10 minutter?	2

Har De vanligvis:

	JA	NEI
Hoste om morgenen? 24		
Oppspytt fra brystet om morgenen? 25		

D MOSJON

Bevegelse og kroppslig anstrengelse i Deres fritid. Hvis aktiviteten varierer meget f.eks. mellom sommer og vinter, så ta et gjennomsnitt. Spørsmålet gjelder bare det siste året.
Sett kryss i den ruta hvor «JA» passer best

Leser, ser på fjernsyn eller annen stillesittende beskjeftigelse? 26	1
Spaserer, sykler eller beveger Dem på annen måte minst 4 timer i uka? ..... (Her skal De også regne med gang eller sykling til arbeidsstedet, søndagsturer m.m.)	2
Driver mosjonsidrett, tyngre hagearbeid e.l.? . (Merk at aktiviteten skal vare minst 4 timer i uka.)	3
Trener hardt eller driver konkurranseidrett regelmessig og flere ganger i uka?	4

E SALT/FETT

Hvor ofte bruker De salt kjøtt eller salt fisk til middag?
Sett kryss i den ruta hvor «JA» passer best

Aldri eller sjeldnere enn en gang i måneden 27	1
Opptil en gang i uka	2
Opptil to ganger i uka	3
Mer enn to ganger i uka	4

Hvor ofte pleier De strø ekstra salt på middagsmaten?
Sett kryss i den ruta hvor «JA» passer best

Sjelden eller aldri 28	1
Av og til eller ofte	2
Alltid eller nesten alltid	3

Hva slags margarin eller smør bruker De til vanlig på brød?
Sett kryss i den ruta hvor «JA» passer best

Bruker ikke smør eller margarin på brød 29	1
Smør	2
Hard margarin	3
Myk (Soft) margarin	4
Smør/margarin blanding	5

Hva slags fett blir til vanlig brukt til matlaging i Deres husholdning?
Sett kryss i den ruta hvor «JA» passer best

Smør eller hard margarin 30	1
Myk (Soft) margarin eller olje	2
Smør/margarin blanding	3

F RØYKING

Røyker De

	JA	NEI
Sigaretter daglig? (håndrullet eller fabrikkframstilte) 31		
Sigarer eller serutter/sigarillos daglig? 32		
Pipe daglig? 33		

Hvis De ikke røyker daglig nå, besvar da:

Har De røykt daglig tidligere? 34	

Hvis De svarte «JA», hvor lenge er det siden De sluttet?

Mindre enn 1 år? 35	1
Mer enn 1 år?	2

Besvares av dem som røyker nå eller som har røykt tidligere:
Hvor mange år tilsammen har De røykt daglig? ..... 36 — Antall år

Hvor mange sigaretter røyker eller røykte De daglig?
Oppgi tallet på sigaretter daglig ..... 38 (håndrullet + fabrikkframstilte) — Antall sigaretter

G KAFFE

Hvor mange kopper kaffe drikker De vanligvis daglig?
Sett kryss i den ruta hvor «JA» passer best

Drikker ikke kaffe, eller mindre enn en kopp 42	1
1 – 4 kopper	2
5 – 8 kopper	3
9 eller flere kopper	4

Hva slags kaffe drikker De vanligvis daglig?

Kokekaffe 43	
Filterkaffe 44	
Pulverkaffe 45	
Koffeinfri kaffe 46	
Drikker ikke kaffe 47	

H ARBEID

Har De i det siste året hatt:
Sett kryss i den ruta hvor «JA» passer best

For det meste stillesittende arbeid? ..... 48 (f.eks. skrivebordsarbeid, urmakerarbeid, montering)	1
Arbeid som krever at De går mye? ..... (f.eks. ekspediterarb., lett industriarb., undervisning)	2
Arbeid hvor De går og løfter mye? ..... (f.eks. postbud, tyngre industriarb., bygningsarbeid)	3
Tungt kroppsarbeid? ..... (f.eks. skogsarb., tungt jordbruksarb., tungt bygn.arb.)	4

Har De i Deres arbeid noen gang vært i kontakt med:

	JA	NEI	VET IKKE
Asbeststøv? 49			
Kvartsstøv? 50			

	JA	NEI
Har De vanligvis skiftarbeid eller nattarbeid? 51		
Er husarbeid i hjemmet hovedyrket Deres? ..... 52 (Svar: «NEI» hvis lønnet arbeid utenom husarbeid er 18 timer eller mer pr. uke)		
Har De daglig omsorg for syke eller funksjonshemmede i familien? 53		
Har De i løpet av de siste 12 måneder fått arbeidsledighetstrygd? 54		
Er De for tiden sykmeldt, eller får De attføringspenger? 55		
Har De full eller delvis uførepensjon? 56		

I ETTERUNDERSØKELSE

	JA	NEI	VET IKKE
Er to eller flere av dine besteforeldre av finsk ætt? 57			
Er to eller flere av dine besteforeldre av samisk ætt? 58			

Hvis denne helseundersøkelsen viser at du bør undersøkes nærmere:
Hvilken almenpraktiserende lege/kommunelege ønsker du da å bli henvist til?

Skriv navnet på legen her →

..... 59

Ingen spesiell lege 62

Ikke skriv her

Ikke skriv her

QUESTIONNAIRE 40 YEARS STUDY, ROUND 3

EGEN HELSE

Hvordan er helsen din nå? *Sett bare ett kryss.*

Dårlig	12	1
Ikke helt god		2
God		3
Svært god		4

Har du, eller har du hatt:

		JA	NEI	Alder første gang
Hjerteinfarkt	13			år
Angina pectoris (hjertekrampe)	16			år
Hjerneslag/hjerneblødning	19			år
Astma	22			år
Diabetes (sukkersyke)	25			år

Bruker du medisin mot høyt blodtrykk?

Nå	28	1
Før, men ikke nå		2
Aldri brukt		3

Hvis ja, hvilket merke bruker du nå? Ikke skriv her

Har du i løpet av det siste året vært plaget med smerter og/eller stivhet i muskler og ledd som har vart i minst 3 måneder sammenhengende? 33 — JA / NEI

Har du de siste to ukene følt deg:

		Nei	Litt	En god del	Svært mye
Nervøs og urolig?	34				
Plaget av angst?	35				
Trygg og rolig?	36				
Irritabel?	37				
Glad og optimistisk?	38				
Nedfor/deprimert?	39				
Ensom?	40				
		1	2	3	4

Får du smerter eller ubehag i brystet når du: JA / NEI

Går i bakker, trapper eller fort på flat mark? 41

Hvis du får slike smerter, pleier du da å:

Stoppe?	42	1
Saktne farten?		2
Fortsette i samme takt?		3

		JA	NEI
Dersom du stopper, forsvinner smertene da etter mindre enn 10 minutter?	43		
Kan slike smerter like gjerne opptre mens du er i ro?	44		

Mottar du nå noen av følgende ytelser?

Syketrygd (sykmeldt)	45	
Attføringspenger	46	
Uførepensjon (hel eller delvis)	47	
Arbeidsledighetstrygd	48	

ENDRING AV HELSEVANER

Dette gjelder din interesse for å endre helsevaner. Røykespørsmålet besvares bare av dem som røyker.

		Spise sunnere JA	Spise sunnere NEI	Trimme mer JA	Trimme mer NEI	Slutte å røyke JA	Slutte å røyke NEI
Har du de siste 12 mnd. forsøkt å:	49						
Om 5 år, tror du at du har endret vaner på noen av disse områdene?	52						

		Høyeste vekt:	Laveste vekt:
Anslå din høyeste og laveste vekt i løpet av de siste 5 år. *(Se bort fra vekt under svangerskap)*	55	kg	kg

SYKDOM I FAMILIEN

		JA	NEI	VET IKKE
Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)?	61			

Har én eller flere foreldre/søsken hatt:

		JA	NEI
Hjerteinfarkt *før* de fylte 60 år?	62		
Hjerneslag *før* de fylte 70 år?	63		

RØYKING

Hvor lenge er du vanligvis daglig til stede i røykfylt rom? 64 — Antall timer

Sett 0 hvis du ikke oppholder deg i røykfylt rom.

Røyker du selv?

		JA	NEI
Sigaretter daglig?	66		
Sigarer/sigarillos daglig?	67		
Pipe daglig?	68		

Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet? 69 — Antall år

Hvis du røyker daglig nå eller har røykt tidligere:

Hvor mange sigaretter røyker eller røykte du vanligvis daglig?	71	Antall sigaretter
Hvor gammel var du da du begynte å røyke daglig?	75	Alder år
Hvor mange år tilsammen har du røykt daglig?	77	Antall år

MOSJON

Hvordan har din fysiske aktivitet i fritiden vært det siste året? *Tenk deg et ukentlig gjennomsnitt for året. Arbeidsvei regnes som fritid.*

		Timer pr. uke: Ingen	Under 1	1-2	3 og mer
Lett aktivitet *(ikke svett/andpusten)*	79				
Hard fysisk aktivitet *(svett/andpusten)*	80				
		1	2	3	4

KAFFE/TE/ALKOHOL

Hvor mange kopper kaffe/te drikker du daglig?
Sett 0 hvis du ikke drikker kaffe/te daglig.

Kokekaffe	81	Antall kopper
Annen kaffe	83	Antall kopper
Te	85	Antall kopper

Er du total avholdsmann/-kvinne? 87 — JA / NEI

Hvor mange ganger i måneden drikker du vanligvis alkohol? *Regn ikke med lettøl. Sett 0 hvis mindre enn 1 gang i mnd.* 88 — Antall ganger

Hvor mange glass øl, vin eller brennevin drikker du vanligvis i løpet av to uker? 90

Regn ikke med lettøl.
Sett 0 hvis du ikke drikker alkohol.

Øl	Vin	Brennevin
glass	glass	glass

FETT

Hva slags margarin eller smør bruker du vanligvis på brødet? *Sett ett kryss.*

Bruker ikke smør/margarin	96	1
Meierismør		2
Hard margarin		3
Bløt (soft) margarin		4
Smør/margarin blanding		5
Lettmargarin		6

UTDANNING

Hvilken utdanning er den høyeste du har fullført?

Grunnskole 7-10 år, framhaldsskole, folkehøgskole	97	1
Realskole, middelskole, yrkesskole, 1-2 årig videregående skole		2
Artium, øk.gymnas, allmennfaglig retning i videregående skole		3
Høgskole/universitet, mindre enn 4 år		4
Høgskole/universitet, 4 år eller mer		5

ETTERUNDERSØKELSE

Hvis denne helseundersøkelsen viser at du bør undersøkes nærmere, hvilken allmennpraktiserende lege/kommunelege ønsker du da å bli henvist til? Oppgi legens navn:

Ikke skriv her

QUESTIONNAIRE 40 YEARS STUDY, ROUND 4

Spørreskjemaet er en viktig del av helseundersøkelsen. Vennligst fyll ut skjemaet på forhånd og ta det med til helseunder søkelsen. Dersom enkelte spørsmål er uklare, lar du dem stå ubesvart til du møter fram, og drøfter dem med personalet som gjennomfører undersøkelsen. *Alle svar vil bli behandlet strengt fortrolig.*

Det utfylte skjemaet vil bli lest av en maskin. Bruk blå eller sort farge ved utfylling. Det er viktig at du går fram slik:

- i de små boksene setter du kryss for det svaret som passer best for deg
- i de store boksene skriver du tall eller blokkbokstaver – NB! innenfor rammen for boksen.

Eksempler:
Avkryssing: [X] Tall: 1 2 3 4 5 6 7 8 9 0 Bokstaver: A B C

Med vennlig hilsen

Statens helseundersøkelser ♥ Kommunehelsetjenesten

1. EGEN HELSE

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

Dårlig	Ikke helt god	God	Svært god
☐ 1	☐ 2	☐ 3	☐ 4

Har du, eller har du hatt:	JA	NEI	Alder første gang	
Hjerteinfarkt	☐	☐		år
Angina pectoris (hjertekrampe)	☐	☐		år
«Hjerneslag/hjerneblødning («drypp»)	☐	☐		år
Astma	☐	☐		år
Diabetes (sukkersyke)	☐	☐		år

Får du smerter eller ubehag i brystet når du:	JA	NEI
Går i bakker, trapper eller fort på flat mark?	☐	☐

Hvis du får slike smerter, pleier du da å:

Stoppe?	Saktne farten?	Fortsette i samme takt?
☐ 1	☐ 2	☐ 3

	JA	NEI
Dersom du stopper, forsvinner smertene da etter mindre enn 10 minutter?	☐	☐
Kan slike smerter like gjerne opptre mens du er i ro?	☐	☐

2. HVORLEDES FØLER DU DEG?

Har du de siste to ukene følt deg:

	Nei	Litt	En god del	Svært mye
Nervøs og urolig?	☐	☐	☐	☐
Plaget av angst?	☐	☐	☐	☐
Trygg og rolig?	☐	☐	☐	☐
Irritabel?	☐	☐	☐	☐
Glad og optimistisk?	☐	☐	☐	☐
Nedfor/deprimert?	☐	☐	☐	☐
Ensom?	☐	☐	☐	☐
	1	2	3	4

3. SYKDOM I FAMILIEN

	JA	NEI	VET IKKE
Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)?	☐	☐	☐
Har en eller flere foreldre/søsken hatt:			
Hjerteinfarkt *før* de fylte 60 år?	☐	☐	☐
Hjerneslag/hjerneblødning *før* de fylte 70 år?	☐	☐	☐

4. MUSKEL/SKJELETT-PLAGER

	JA	NEI
Har du i løpet av det siste året vært plaget med smerter og/eller stivhet i muskler og ledd som har vart i minst 3 måneder sammenhengende?	☐	☐

Hvis NEI, gå til avsnitt 5. SOSIALE FORHOLD.
Hvis JA, svar på følgende:

Hvor har du hatt disse plagene?	JA	NEI
Nakke	☐	☐
Skuldre (aksler)	☐	☐
Albuer	☐	☐
Håndledd/hender	☐	☐
Bryst, mage	☐	☐
Øvre del av ryggen	☐	☐
Korsryggen	☐	☐
Hofter	☐	☐
Knær	☐	☐
Ankler, føtter	☐	☐

Hvor lenge har plagene vart sammenhengende?
Svar for det området hvor plagene har vart lengst.

Hvis under 1 år, oppgi antall mnd. ..... *Antall mnd.*

Hvis 1 år eller mer, oppgi antall år ..... *Antall år*

Har plagene redusert din arbeidsevne det siste året?
Gjelder også hjemmearbeidende. Sett bare ett kryss.

Nei/ubetydelig	I noen grad	I betydelig grad	Vet ikke
☐ 1	☐ 2	☐ 3	☐ 4

	JA	NEI	Ikke i arbeid
Har du vært sykmeldt pga. disse plagene det siste året?	☐	☐	☐
Har plagene ført til redusert aktivitet i fritida?	☐	☐	

5. SOSIALE FORHOLD

Mottar du nå noen av følgende ytelser?	JA	NEI
Syketrygd (sykmeldt)	☐	☐
Attføringspenger	☐	☐
Uførepensjon (hel eller delvis)	☐	☐
Arbeidsledighetstrygd	☐	☐

Er husarbeid i hjemmet hovedyrket ditt? *(Svar NEI hvis lønnet arbeid utenom husarbeid er 18 timer eller mer pr. uke)*	JA	NEI
	☐	☐

6. UTDANNING

Hvilken utdanning er den høyeste du har fullført?
Sett bare ett kryss.

- Mindre enn 7 år grunnskole ☐
- Grunnskole 7-10 år, framhaldsskole, folkehøgskole ☐ 1
- Realskole, middelskole, yrkesskole, 1-2 årig videregående skole ☐ 2
- Artium, øk.gymnas, allmennfaglig retning i videregående skole ☐ 3
- Høgskole/universitet, mindre enn 4 år ☐ 4
- Høgskole/universitet, 4 år eller mer ☐ 5

7. KOST

Hvor ofte bruker du disse matvarene?
Sett kryss i de rutene som beskriver ditt forbruk best.

	Flere g. daglig	Daglig	1-6 g. pr uke	1-3 g. pr mnd	Sjelden eller aldri
Fisk (middag, pålegg)	☐	☐	☐	☐	☐
Frukt/grønt	☐	☐	☐	☐	☐
Helmelk, kefir, yoghurt	☐	☐	☐	☐	☐
Lettmelk, lettyoghurt	☐	☐	☐	☐	☐
Skummet melk (sur/søt)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Hva slags smør eller margarin bruker du vanligvis PÅ BRØDET?
Sett kryss i den ruta som passer best.

- Bruker ikke smør/margarin ☐ 1
- Meierismør ☐ 2
- Hard margarin ☐ 3
- Bløt (soft) margarin ☐ 4
- Smør/margarin blanding ☐ 5
- Lettmargarin/lettsmør (Brelett) ☐ 6

Hva slags fett bruker du/dere vanligvis TIL MATLAGING?
Sett kryss i den ruta som passer best.

- Smør/margarin ☐ 1
- Myk (soft) margarin/olje ☐ 2
- Bare olje ☐ 3
- Vet ikke ☐ 4

8. KAFFE / TE / ALKOHOL

Hvor mange kopper kaffe/te drikker du daglig?
Sett 0 hvis du ikke drikker kaffe/te daglig.

Antall kopper daglig

Kokekaffe	Annen kaffe	Te
☐☐	☐☐	☐☐

	JA	NEI
Er du total avholdsmann/-kvinne?	☐	☐

Hvor mange ganger i måneden drikker du vanligvis alkohol? *Regn ikke med lettøl.*
Sett 0 hvis mindre enn 1 gang i mnd. ..... *Antall ganger* ☐☐

Hvor mange glass øl, vin eller brennevin drikker du VANLIGVIS i løpet av to uker?
Regn ikke med lettøl. Sett 0 hvis du ikke drikker alkohol.

Glass øl	Glass vin	Glass brennevin
☐☐	☐☐	☐☐

9. RØYKING

Hvor lenge er du vanligvis daglig tilstede i røykfylt rom? ..... *Antall hele timer* ☐☐
Sett 0 hvis du ikke oppholder deg i røykfylt rom.

Røyker du selv:

	JA	NEI
Sigaretter daglig?	☐	☐
Sigarer/sigarillos daglig?	☐	☐
Pipe daglig?	☐	☐

Aldri røykt daglig ..... (Sett kryss) ☐

Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet? ..... *Antall år* ☐☐

Hvis du røyker daglig nå eller har røykt tidligere:

Hvor mange sigaretter røyker eller røykte du vanligvis daglig? ..... *Antall sigaretter* ☐☐

Hvor gammel var du da du begynte å røyke daglig? ..... *Alder i år* ☐☐

Hvor mange år til sammen har du røykt daglig? ..... *Antall år* ☐☐

10. MOSJON

Hvordan har din fysiske aktivitet i fritiden vært det siste året?
Tenk deg et ukentlig gjennomsnitt for året.
Arbeidsvei regnes som fritid. Besvar begge spørsmålene.

	Timer pr. uke: Ingen	Under 1	1-2	3 og mer
Lett aktivitet *(ikke svett/andpusten)*	☐	☐	☐	☐
Hard fysisk aktivitet *(svett/andpusten)*	☐ 1	☐ 2	☐ 3	☐ 4

Bevegelse og kroppslig anstrengelse i din fritid. Hvis aktiviteten varierer meget f.eks. mellom sommer og vinter, så ta et gjennomsnitt. Spørsmålet gjelder bare det siste året.
Sett kryss i den ruta som passer best.

- Leser, ser på fjernsyn eller annen stillesittende beskjeftigelse? ☐ 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, søndagsturer m.m.)
- Driver mosjonsidrett, tyngre hagearbeid e.l.? ☐ 3
  (Merk at aktiviteten skal vare minst 4 timer i uka)
- Trener hardt eller driver konkurranseidrett regelmessig og flere ganger i uka? ☐ 4

11. ENDRING AV HELSEVANER

Dette gjelder din interesse for å endre helsevaner. Røykespørsmålet besvares bare av dem som røyker.

	Spise sunnere		Trimme mer		Slutte å røyke	
	JA	NEI	JA	NEI	JA	NEI
Har du de siste 12 mnd. forsøkt å:	☐	☐	☐	☐	☐	☐
Om 5 år, tror du at du har endret vaner på noen av disse områdene?	☐	☐	☐	☐	☐	☐

	Høyeste vekt	Laveste vekt
Anslå din høyeste og laveste vekt i løpet av de siste 5 år. *(Hele kg)* *(Se bort fra vekt under svangerskap)*	☐☐☐	☐☐☐

VEND!

12. MEDISIN MOT HØYT BLODTRYKK

Bruker du medisin mot høyt blodtrykk?

Nå	Før, men ikke nå	Aldri brukt
☐ 1	☐ 2	☐ 3

Hvis du bruker medisin nå, hvilke(t) merke(r) bruker du?

Ikke skriv i disse rutene

13. MEDISIN MOT HØYT KOLESTEROL

	JA	NEI
Bruker du kolesterolsenkende medisiner NÅ?	☐	☐

Hvis NEI, gå til 14. ETTERUNDERSØKELSE.

Hvor gammel var du da du begynte med kolesterolsenkende medisiner? ..... *Alder i år*

Hvis du bruker kolesterolsenkende medisiner, hva var grunnen til at du begynte med slik medisin?
(Sett kryss i de rutene som passer for deg.)

	JA	NEI
Hjerteinfarkt	☐	☐
Angina pectoris (hjertekrampe, brystkrampe)	☐	☐
Høyt innhold av kolesterol i blodet	☐	☐
Hjertesykdom i familien (foreldre, søsken)	☐	☐
Hjerneslag/hjerneblødning/ «drypp»	☐	☐
Dårlig blodsirkulasjon i bena (åreforkalkning, «røykeben»)	☐	☐
Andre årsaker	☐	☐

Skriv hvilke årsaker her:

Ikke skriv i disse rutene

	JA	NEI
Jeg er usikker på årsaken	☐	☐

Hvilke kolesterolsenkende medisiner bruker du NÅ og hvilken dose bruker du?

Hvilke(t) merke(r) bruker du? — Samlet dose på ett døgn

mg

mg

mg

Ikke skriv i disse rutene

14. ETTERUNDERSØKELSE

Hvis denne helseundersøkelsen viser at du bør undersøkes nærmere, hvilken allmennpraktiserende lege/kommunelege ønsker du da å bli henvist til?
Oppgi legens navn:

Ikke skriv i disse rutene

15. TIL KVINNER SOM DELTAR I HELSE-UNDERSØKELSEN

Hvor gammel var du da du fikk menstruasjon aller første gang? ..... *Alder i år*

	JA	NEI
Har du for tiden regelmessig menstruasjon? *Regn den for regelmessig hvis den ikke har vært borte mer enn 3 mnd. sammenhengende siste år.*	☐	☐

Til deg som svarte JA: Omtrent hvor mange dager etter starten på siste menstruasjon skjer helseundersøkelsen? *(Sett bare ett kryss)*

Under 8 ☐ 8-14 ☐ 15-21 ☐ Mer enn 21 dager ☐

Hvis du for tiden ikke har regelmessig menstruasjon, ber vi deg fylle ut nedenfor *(Sett bare ett kryss)*

Menstruasjonen sluttet av seg selv for minst 6 mnd. siden (overgangsalder)	☐ 1
Menstruasjonen sluttet etter underlivs-operasjon, strålebehandling eller cellegift	☐ 2
Usikker på om menstruasjonen har sluttet (mulig overgangsalder)	☐ 3
Gravid i mindre enn 6 måneder	☐ 4
Gravid i 6 måneder eller mer	☐ 5
Har nylig født eller ammer, og har ikke fått menstruasjonen tilbake	☐ 6
Helt uregelmessige menstruasjoner, med svært korte eller svært lange pauser	☐ 7
Ingen eller uregelmessig menstruasjon på grunn av hormonbehandling	☐ 8
Har aldri hatt menstruasjoner	☐ 9

Hvis du ikke lenger har menstruasjon, hvor gammel var du da den sluttet? ..... *Alder i år*

Hvor mange barn (levende barn) **har du født?** *Antall barn*

Hvor lenge har du ammet dine barn til sammen?
(f.eks. 3 barn: 1 + 6 + 10 = 17 måneder) ..... *Antall mnd.*

Bruker du nå, eller har du tidligere brukt	Nå	Før, men ikke nå	Aldri
P-pille (*også minipille*) eller p-sprøyte	☐	☐	☐
Vanlig spiral	☐	☐	☐
Hormonspiral (pris ca. kr. 1000)	☐	☐	☐
Østrogen/progesteron *(tabletter, plaster, sprøyte)*	☐	☐	☐
Østrogen *(krem eller stikkpiller)*	☐	☐	☐

Til deg som bruker p-pille, hormonspiral (ikke vanlig spiral) eller hormoner i overgangsalderen NÅ:
Hvilke(t) merke(r) bruker du?

Ikke skriv i disse rutene

Omtrent hvor lenge har du brukt det du bruker nå?

Antall år *Hvis mindre enn ett år: .....Måneder*

Takk for utfyllingen!
Nok en gang:
Velkommen til undersøkelsen!

IE 3213201 - 30.000 - Beyer-Hecos 11/98 (ID.NR. 1/98)

CONOR STUDY QUESTIONS ENGLISH

QUESTIONNAIRE IN ENGLISH

YOUR OWN HEALTH

1. What is your current health status? *Tick one only*

Poor
Not so good
Good
Very good

2. Do you have, or have you had?

	Yes	No	Age first time
Heart attack			
Angina pectoris (heart cramp)			
Cerebral stroke/ Brain haemorrhage			
Asthma			
Diabetes			

3. Have you during the last year suffered from pain and/or stiffness in muscles and joints that have lasted for at least 3 months ?

Yes
No

4. Have you in the last two weeks felt :

	No	A little	A lot	Very much
Nervous or worried				
Anxious				
Confident and calm				
Irritable				
Happy/Optimistic				
Down/Depressed				
Lonely				

PHYSICAL ACTIVIYY

5a. How has your physical activity during leisure time been over the last year ?

Think of your weekly average for the year. Time spent going to or fromworkk counts as leisure time

Hours per week

	None	Less than 1	1-2	3 or more
Light activity				

(*not sweating or out of breath* **)**

Hard physical activity
(*sweating/out of breath*)

5 b. Please note physical activity during the past year in your spare time.
If **activity varies between summer and wintertime,**
note a mean value.
(Tick one only)
Reading, watching TV or any other sedentary activity?

Walking, cycling, or other activity, other for at least 4 hours a week?
(Count also walking back and forth from work)

Light sports, heavy gardening?
(At least 4 thours perweek)

Hard exercise, competitive sports? *Regularly and several times a week*

SMOKING

6 . How many hours a day do you normally spend in smoke-filled rooms?
Write 0 if you don`t spend time in smoke-filled rooms
Number of hours……..

7. Did any of the adults smoke at home when you grew up?
Yes
No

8. Do you now, or have you ever lived together with a daily smoker after the age of 20 years?
Yes
No

9. Do you smoke ?
Yes No
Cigarettes daily
Cigars/cigarillos daily
Pipe daily

10. If you previously smoked daily, how long is it since you quit?
……number of years

11. If you smoke daily now or previously:
How many cigarettes do you,or did you usually smoke per day?
Number of cigarettes……..

12. How old were you when you began smoking?
……..year

13. How many years in all have you smoked daily ?

……..years

COFFEE, TEA AND ALCOHOL

14.a How many cups of coffee do you usually drink daily ?
Write 0 if you do not drink coffee daily
Boiled coffee (coarsely ground), number……
Coffee other, number……..

14.b What type of coffee do you usually drink?
Please tick
Filter/instant coffee
Boiled coffee (coarsely ground)
Other (espresso etc)
Do not drink coffee

14c. How many cups of coffee/tea do you usually drink daily?
Write 0 if you do not drink coffee/tea daily
Number of cups with coffee…….
Number of cups with tea……

15 a. How many times a month do you usually drink alcohol?
Do not count low-alcohol beer. Put 0 if less than once a month.
Number of times…….

15 b. Approximately how often during the past 12 months have you consumed alcohol?
(Do not count low-alcohol beer)
4-7 times a week
2-3 times a week
App. 1 time a week
2-3 times a month
Appr. 1 time a month
A few times last year
Have not drunk alcohol the last year
Have never drunk alcohol

16 a. How many glasses of beer, wine or spirits
do you usually drink during a two-weeks period?
Do not count low-alcohol beer. Put 0 if you do not drink alcohol.

Beer…..glasses Wine…..glasses Spirits…..glasses

For those who have consumed alcohol during the past year
16 b. When you drank alcohol, how many glasses
did you usually drink ?
Number of glasses…….

16 c. Approximately how often during the past 12 months have you consumed alcohol
corresponding to at least 5 glasses of spirits in 24 hours?
Number of times……..

16 d. When you drink alcohol, do you usually drink: *(Tick one or more).*

Beer Wine Spirits (hard liquor)

17. Are you a total abstainer from alcohol ?

Yes

No

EDUCATION

18 a. What is the highest level of education you have completed?

Less than 7 year of primary school

7-10 years primary/secondary school

Technical school, middle school, vocational school, 1-2 years senior high school

High school diploma (3-4 years)

College/university, less than 4 years

College/university, 4 or more years

18 b. How many years education have you completed all together?

(Count every year you went to school)

Number of years…….

ILLNESS IN THE FAMILY

19. Have one or more of your parents or siblings had a heart attack or angina pectoris?

Yes

No

Don't know

20. Tick for those relatives who have or have had:

	Mother	Father	Brother	Sister	Child
Cerebral stroke or brain haemorrhage					
Myocardial infarction before age 60					
Asthma					
Cancer					
Diabetes					
Age when diabetes was first diagnosed					

RESIDENLY

21. In which muncipality did you live at the age of 1 year*?*

If you did not live in Norway, give country of residence instead of municipality.

……..

22. What type of dwelling do you live in?

Villa/detached house

Farm

Flat/apartment

Terraced/semi-detached house
Other/institution/care home

23. How large is your home?
……m2

24. Do you have wall-to-wall carpets in the living-room?
Yes No

25. Is there a cat in your home?
Yes No

FAMILY AND FRIENDS

26 a. With whom do you live? *Tick one for each question and write the number*

	Yes	No	Number
Spouse/Partner			
Other persons older than 18 years			
Persons younger than 18 years			

26 b. Do you live with anyone?
Yes
No

If YES:

	Yes	No	Number
Spouse/Partner			
Other persons older than 18 years			
Persons younger than 18 years			

26 c (only at the questionary for the elderly)
Where do you live ? *Please tick*
Home
Institution

Do you live with?

	Yes	No
Spouse/Partner?		
Other persones?		

27. How many of the children attend day care/kindergarten/nursery school?
……..

28. How many good friends do you have with whom you can talk confidentially and who can provide help if you need it?
(Do not count people you live with, but do include other relatives)
…….

29. Do you feel that you have enough good friends?
Yes

No

30. How often do you usually take part in organised activities, e.g.
sewing circles, sports clubs, political meetings, religious or other organizations?
Never, or just a few times a year
1-2 times a month (before year 1996), 1-3 times a month (after year 1996)
Approximately once a week
More than once a week

WORK

31. What is your current work situation?
Paid work
Full-time housework
Under education, military service
Unemployed, on leave without payment

32 a. How many hours of paid work do you have per week?
…….number of hours

32 b. What is your current work situation – paid work?
Yes, full-time
Yes, part time
No

33. Do you receive any of the following?
Sickness benefit?
Old-age pension?
Rehabilitation benefit?
Disability pension?
Unemployment benefits?
Social welfare benefits?
Social benefit-single parent?

34. Do you work shifts or nights?
Yes
No

35. If you have paid or unpaid work, which statement describes your work best?
Mostly sedentary work?
(e.g. office work, mounting)

Work that requires a lot of walking?
(e.g. shop assistant, light industrial work, teaching)

Work that requires a lot of walking and lifting?
(e.g. postman, nursing, construction)

Heavy manual labour? *(e.g. forestry, heavy farmwork, heavy construction*)

36. Do you decide yourself how your work will be done? *(Tick one only)*

Not at all
Very little
Yes, sometimes
Yes, my own decision

37 a. Do you have any of the following occupations ?
(full time or part time) *Tick one for each question*

	Yes	No
Driver		
Farmer		
Fisherman		

37 b. What occupation/title did you have at this work?
(the question refers to another question (not CONOR) about the occupation where they worked the longest period during the past year)
Ex secretary, teacher, industrial worker, nursing, carpenter, l eader, salesman, driver etc)
Occupation:……

YOUR OWN ILLNESS and INJURIES

38. Have you ever had:
Tick one for each question. State age at event.
If it has happened several times, write age at the last event.

	Yes	No	Age at last time
Hip fracture			
Wrist/forearm fracture			
Whiplash			
Injury requiring hospital admission			

39. Do you have or have you ever had?
Tick yes or no for each question

	Yes	No
Hay fever		
Chronic bronchitis/emphysema		
Osteoporosis		
Fibromyalgia/fibrositis/chronic pain syndrome		
Psychological problems for which you have sought help		

40. Do you cough almost daily for some periods of the year?
Yes No

41. If yes,
do you bring up phlegm?
Yes No

42. If you cough almost daily for some periods of the year, have you had this kind of cough for as long as 3 months in each of the last two years?
Yes No

43. How often do you suffer from sleeplessness?
Never, or just a few times a year
1-2 times a month (before year 2000), 1-3 times a month (after year 2000)
Approximately once a week
More than once a week

44. Have you in the last twelve months suffered from sleeplessness to the extent that it has affected your ability to work ? Yes No

USE OF MEDICATION

45. Do you take?

	Currently	Previously	Never
Lipid lowering drugs			
Medications for high blood pressure			

46 a. Have you for any length of time in the past year used any of the following medications every day or almost daily?
Indicate how many months you have used the medication. Write 0 if you did not take the medication.

Medications:
Painkillers ……months.
Sleeping pills ……months.
Tranquilizers ……months.
Antidepressants ……months.
Allergy pills ……months.
Asthma medication ……months.
Only medication bought at pharmacy .
Do not include dietary supplements

46 b. How often during the last 4 weeks have you taken any of the following medication?
Tick one per line

	Daily	Weekly but not daily	Less than weekly	Not taken last 4 weeks
Painkillers without prescription				
Painkillers on prescription				
Sleeping pills				
Tranquilizers				
Antidepressants				
Other medication on prescription				

46.c Fill in name of medication, reason for use and time used from q 46.b

Brand name	**Reason for use**	**For how long up to 1 year/1 year or more**
1.		

2.
3.
4.
5.
6.

DIETARY SUPPLEMENTS

47 a. Have you for any length of time in the past year taken any of the *following daily or almost daily?*
Indicate how many months you have used them. Write 0 if you did not take any.
Iron tablets ……..months
Vitamin D supplements ……..months
Other vitamin supplements ……..months
Cod liver oil ……..months

47 b. Do you take any of the following?

	Yes, daily	Sometimes	No
Cod liver oil, capsules			
Fish oil capsules			
Vitamin and or mineral supplements			

THE REST OF THE FORM SHOULD ONLY BE FILLED IN BY WOMEN

48. How old were you when you started menstruating?
……..year

49. If you no longer menstruate, how old were you when you stopped menstruating?
……..year

50. Are you pregnant at the moment?
Yes No Unsure Postmenopausal

51. How many children have you given birth to?
……children

52. If you have given birth, what year was the child born and how many months did you breastfeed each child

Child	Year born	Number of months with breastfeeding
1.		
2.		
3.		
4.		
5.		
6.		

53. Do you use or have you ever used:

	Now	Previously	Never
Contraceptive pills (OC) (incl. minipill)			
Contraceptive injections			
Hormonal intrauterine device			
Estrogen (tablets or patches)			
Estrogen (cream or suppositories)			

54. If you use contraceptive pills, hormonal intrauterine device, or estrogen, what brand do you currently use?

……

Nå

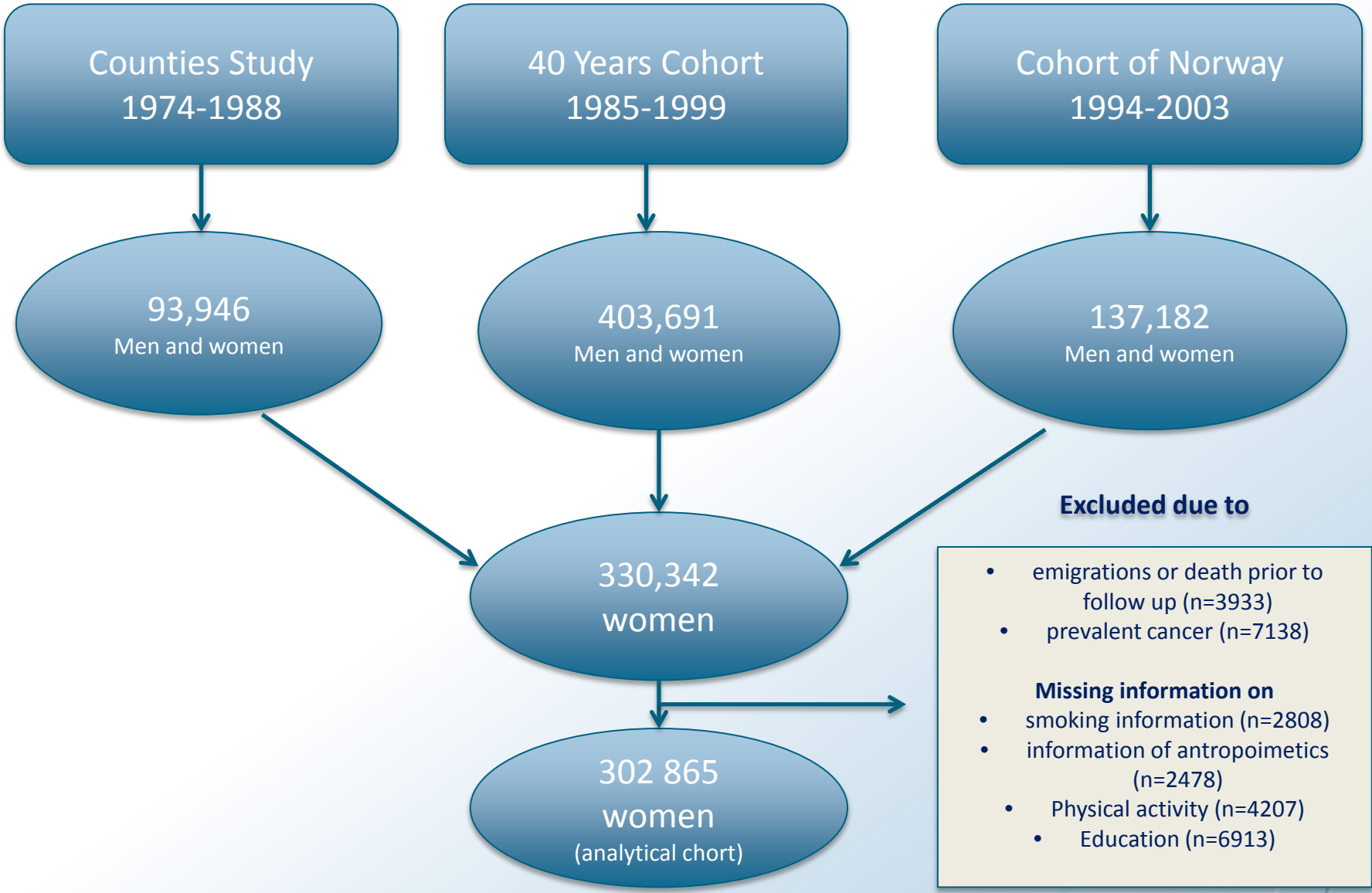
Appendix 2

Description of methodology

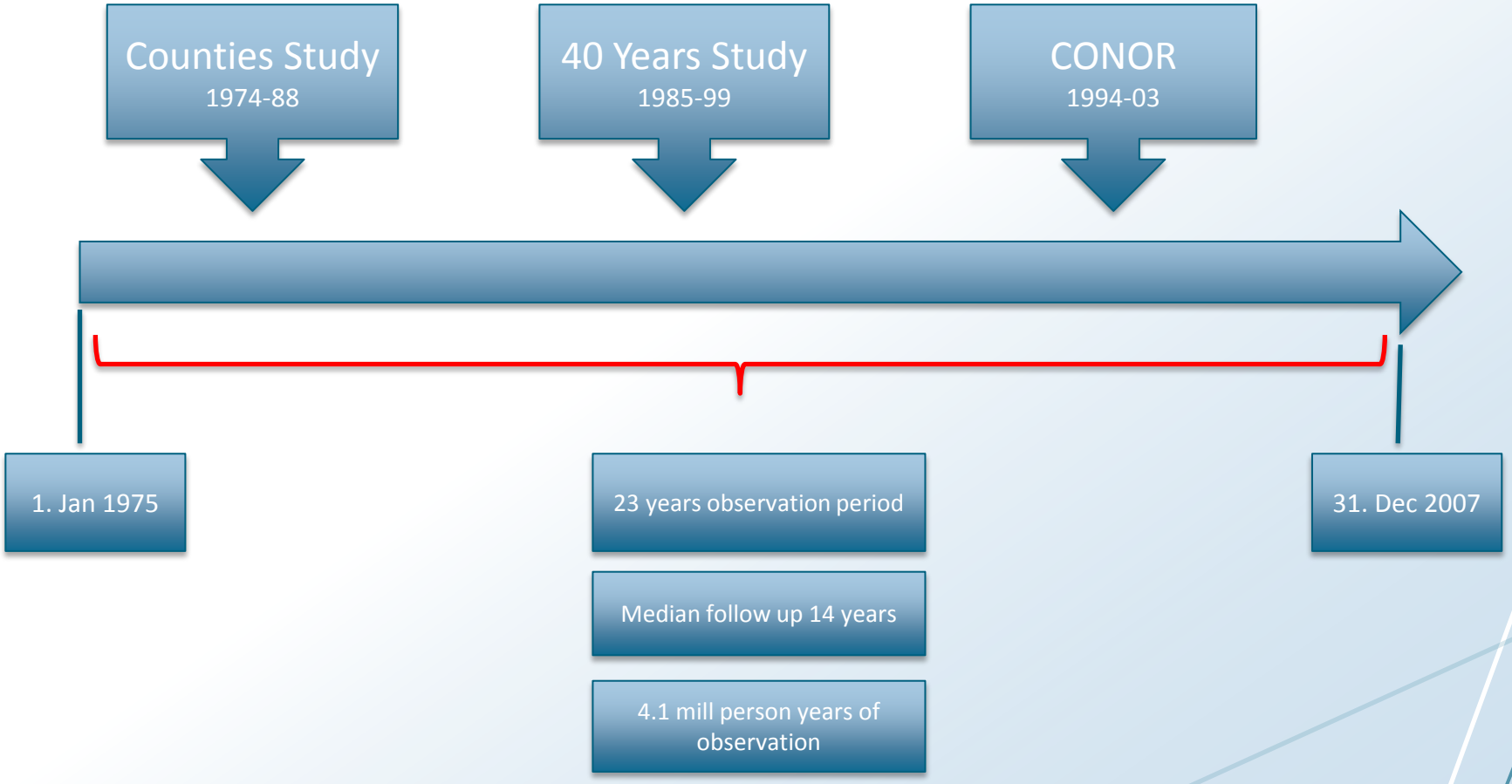
Studies included in the Pooled Cohort

Name of Survey	Year Conducted	Populations from	Total included both genders	No of Surveys	CONOR
The Three Counties	1974-88	Oppland, Sogn og Fjordane, Finnmark	Aprx. 93000	10 incl follow-up	
Follow up	2006-08		65000	(not included)	
Tromsø Health Study II	1979-80	Tromsø		1 (not included)	
Tromsø Health Study III	1986-87	Tromsø		1 (not included)	
40 years Survey	1985-99	40-42 year old	Aprx 382 000	19	
I	1985-87	Østfold, Aust-Agder, Vest-Agder, Sør-Trøndelag			
II	1988-94	All 19 counties			
III	1994-97	12 counties			
IV	1997-98	11 counties			
The Nord-Trøndelag Health Study (HUNT I)	1984-86	Nord-Trøndelag		1 (not included)	
CONOR	1994-2003		181891		
Tromsø Health Study IV	1994-95	Tromsø	26925	1	x
The Nord-Trøndelag Health Study (HUNT II)	1995-97	Nord-Trøndelag	65018	1	x
Hordaland Health Study (HUSK)	1997-99	Hordaland	25530	1	x
Tromsø Health Study V	2001	Tromsø	8077	1	
Oslo Health Study II	2001-2	Oslo	6919	1	x
Oppland and Hedmark Health Study (OPPHED)	2001-2	Oppland and Hedmark	12402	1	x
Troms and Finnmark Health Study (TROFINN)	2001-3	Troms and Finnmark	9327	1	x
Oslo Health Study (HUBRO)	2000-01	Oslo	22015		x
Oslo Immigrant Health Study (i-HUBRO)	2002	Oslo	3683		x
Romsås Study II (MoRo)	2003	Romsås (Oslo)	1995		x
Totalt 3C (89´)+ 40Y (382`) + CONOR (181`)			Aprx 652 000	Total of 38 studies	

Study population



Follow-up period



METHODOLOGY DESCRIPTION

NORWEGIAN HEALTH STUDIES

Randi Selmer 30 Nov 2007. Updated 23 June 2008.
Measurements in Health Surveys 1972-2003.

Blood pressure

1. 1972-84: Systolic and diastolic blood pressure were measured twice with a standard mercury sphygmomanometer after 4 minutes rest. The second measurement has usually been used in follow up studies. The interval between first and second measurement was 1 minute. Diastolic blood pressure was recorded at the disappearance of the Korotkoff sounds (phase V). When phase V was absent, phase IV was used. Standard size cuffs were used throughout. The blood pressure was measured on the right upper arm with the person sitting on a chair.
2. 1985-2003: Pulse recordings, systolic and diastolic blood pressures were measured by an automatic device (DINAMAP, Criticon, Tampa, USA), which measured the blood pressure in mm Hg automatically by an oscillometric method. After 2 minutes preceding rest, three recordings were made at one-minute intervals. The values of the mean of the second and third systolic blood pressure measurements were used in calculating the cardiovascular risk score (CVD risk score). Arm circumference of right upper arm was measured 10 cm above fossa cubiti. From these measurements small, medium or large cuff was chosen. The blood pressure was measured on the right upper arm with the person sitting on a chair.

The two methods have been compared (PG Lund-Larsen: Blodtrykk målt med kvikksølvmanometer og med Dinamap under feltforhold- en sammenligning. Norsk epidemiologi 1997; 7 (2): 235-41)

Serum analyses

Sera from the screenings were sent to the Department of Clinical Chemistry, Ullevål University Hospital, Oslo, Norway

Serum lipids

Non-enzymatic methods: Total cholesterol and triglycerides

Non enzymatic methods were used in Oslo 1972-73, first screening in Finnmark, Oppland and Sogn og Fjordane 1974-78 and second screening in Finnmark 1977-78. Enzymatic methods were used from second screening in Sogn og Fjordane 1980.

Stensvold et al. BMJ 1993:

"A blood sample was taken from non-fasting subjects and analysed for serum concentrations of total cholesterol and triglycerides, both components being measured non-enzymatically on a Tchnicon AutoAnalyzer. On later comparison with enzymatic methods, the non-enzymatic methods used gave on average 10% higher triglyceride values and 8% higher cholesterol values. The participants reported the time since last meal."

The triglyceride values included in the data set are corrected values compatible with enzymatic methods according to the formula:

(New method) = 0.90 x (Old method) - 0.11

The cholesterol values included in the data set are corrected values compatible with enzymatic methods according to the formula:

(New method) = 0.92 x (Old method) + 0.03

The formula was evolved after extensive test program comparing new and old method.

Enzymatic methods:
All measurements of HDL cholesterol were enzymatic. (Stensvold I, Urdal P, Thürmer H, Tverdal A, Lund-Larsen PG, Foss OP. High-density lipoprotein cholesterol and coronary, cardiovascular and all cause mortality among middle-aged Norwegian men and women.Eur Heart J. 1992 Sep;13(9):1155-63.)

Non-fasting serum total cholesterol, serum HDL cholesterol, glucose and serum triglycerides were measured directly by an enzymatic method (Technicon or Hitachi autoanalyzer). Seronorm Lipoprotein was used as internal quality control material for the lipid analyses and Autonorm Human Liquid for the glucose. The control material was done at the start and for every 30^{th} sample.

Stability of cholesterol measurements from 1972 has been documented (OP Foss and P Urdal: Kolesterol gjennom mer enn 25 år: kan svarene sammenliknes over så lang tid? Norsk epidemiologi 2003; 13 (1): 85-88))

Glucose
Serum glucose was measured in first screening in Finnmark, Oppland and Sogn og Fjordane 1974-78 and second screening in Finnmark 1977-78 and in a sample in second screening in Oppland 1981-83 by a non enzymatic method by Brown (ME Brown: Ultra-micro sugar determinations using 2, 9-dimethyl-1, 10-phenanthroline hydrochloride (Neocuproine). Diebetes 10:60, 1961.) The same method was used in Oslo 1972-73. The results obtained with this method were about 0.8-1.1 mmol/l higher than the true concentration defined as the value found with a specific enzymatic method.

From 1994 non fasting serum glucose was measured by enzymatic method described above. The old glucose values have not been adjusted to levels comparable with enzymatic methods.

Weight and height
Body weight (in kilograms, one decimal) and height (in centimetres, one decimal) was measured according to standard protocol with the participants wearing light clothing without shoes (manually recorded until 2000 and after that with an electronic Height and Weight scale)

Waist and hip
Waist and hip were measured from Finnmark and Akershus 1996/97 and onwards. Waist circumference was measured at the umbilicus to the nearest cm with the subject standing and breathing normally. In obese individuals, waist circumference was defined as the midpoint between the iliac crest and lower margin of ribs. Hip circumference was measured as the maximum circumference around the buttocks. Both waist and hip were measured with a measuring tape of steel – which was emphasized to be horizontal. Waist and hip circumference were used to calculate the waist-hip ratio using the formula waist (cm)/ hip circumference (cm).

Measurements of lipids in three counties 1974-1988			
	Finnmark	**Sogn og Fjordane**	**Oppland**
Name			
Screening 1			
u1kol_mg	total cholesterol mg/dl old method	total cholesterol mg/dl old method	total cholesterol mg/dl old method
u1kolest	total cholesterol old method converted to mmol/l by factor 0.02586	total cholesterol old method converted to mmol/l by factor 0.02586	total cholesterol old method converted to mmol/l by factor 0.02586
u1kolenz	total cholesterol mmol/l converted to enzymatic values from u1kolest by formulae	total cholesterol mmol/l converted to enzymatic values from u1kolest by formulae	total cholesterol mmol/l converted to enzymatic values from u1kolest by formulae
No HDL measurements			
u1trigly	triglycerides mmol/l old method	triglycerides mmol/l old method	triglycerides mmol/l old method
u1trienz	triglycerides mmol/l converted to enzymatic values from u1trigly by formulae	triglycerides mmol/l converted to enzymatic values from u1trigly by formulae	triglycerides mmol/l converted to enzymatic values from u1trigly by formulae
Screening 2			
u2kol_mg	total cholesterol mg/dl old method	total cholesterol mg/dl enzymatic method	total cholesterol mg/dl enzymatic method
u2kolest	total cholesterol old method converted to mmol/l by factor 0.02586	total cholesterol enzymatic method converted to mmol/l by factor 0.02586	total cholesterol enzymatic method converted to mmol/l by factor 0.02586
u2kolenz	total cholesterol mmol/l converted to enzymatic values from u2kolest by formulae	u2kolenz=u2kolest	u2kolenz=u2kolest
u2hdlkol	mg/dl, enzymatic*	mg/dl, enzymatic*	mg/dl, enzymatic*
u2hdlkl	converted to mmol/l by factor 0.02586	converted to mmol/l by factor 0.02586	converted to mmol/l by factor 0.02586
u2trigly	triglycerides mmol/l old method	triglycerides mmol/l enzymatic method	triglycerides mmol/l enzymatic method
u2trienz	triglycerides mmol/l converted to enzymatic values from u1trigly by formulae	u2trienz=u2trigly	u2trienz=u2trigly
Screening 3			
u3kolest/u3kolenz	All values enzymatic mmol/l . Sometimes renamed u3kolest to u3kolenz to indicate that these are enzymatic values.		
u3hdlkl	No measurements	All values enzymatic mmol/l*	All values enzymatic mmol/l*
u3trigly/u3trienz	All values enzymatic mmol/l . Sometimes renamed u3trigly to u3trienz to indicate that these are enzymatic values.		
*Eur Heart J. 1992 Sep;13(9):1155-63.			
High-density lipoprotein cholesterol and coronary, cardiovascular and all cause			
mortality among middle-aged Norwegian men and women.			

Stensvold I, Urdal P, Thürmer H, Tverdal A, Lund-Larsen PG, Foss OP.

The cardiovascular surveys in Finnmark, Sogn og Fjordane and Oppland 1974-78, 1977-83 and 1985-88. Sources: Final reports from each survey in each county

County	Period	Age groups invited	Number invited	Number attending	% attendance, fully invited ages
Finnmark	1974-75	All residents in age 35-49 by Dec 1974 (born 25-39). Age 20-34: 10% random samples	17401	14340	82.4 Men: 78.8, women: 86.2
	1977-78	All residents born 1925-42, samples in younger ages from 20 years.	20647	17145	83.0 Men: 79.2 women: 87.3
	1987-88	All residents in age 40-62 by Dec 1987 (born 1925-47) + those aged 30-39 and invited in 1977-78 + 10 % of non-invited in age 20-39. All residents 18 years or older in Bugøynes.	22994	17852	77.6 Men: 73.4, women: 82.6
Sogn og Fjordane	1975-76	All residents in age 35-49 by Dec 1975 (born 1926-40) + 10 % random sample in age 20-39.	16603	14966	90.1 Men: 87.4, women:93.1
	1980-81	All residents born 1926-40 + samples in younger ages from 17 years.	19506	17473	89.6 Men: 86.8, women:92.6
	1985-86	All residents in age 40-54 by Dec 31 1985 (born 1931-45) + those younger than 40 years and invited in 1980-81 + 5-% sample of those in age 20-39 not invited in 1980-81 +10 % sample of invited in 1980-81 in age 55-59. A few older subjects in a hypertension register.	21423	18669	87.1 Men: 83.9, women: 90.7
Oppland	1976-78	All in age 35-49 by Dec 1976 (born 1927-41) +10- % random sample in age 20-39.	31620	28399	89.8 Men: 87.8, women: 91.8
	1981-83	All residents born 1927-41 + samples in younger ages from 20 years.	31581	28437	90.0 Men: 88.1, women: 91.9
	1986-88	All residents aged 40-54 on Dec 1986 (born 1932-46) + all residents below 40 years and a 10 % sample in age 55-59 if invited in 1981-83 + 5-% of not invited in 1981-83 in age 20-39. A few older subjects in a hypertension register.	37270	32124	86.2 Men: 83.5, women: 88.9

CONOR STUDY
MATERIALS AND METHODS
DESCPRIPTION

Cohort Norway (CONOR): Materials and methods

Anne Johanne Søgaard, Norwegian Institute of Public Health, April 2006

CONOR (COhort NORway) is a large collaborative project between epidemiological centres at the University of Tromsø, the Norwegian University of Science and Technology in Trondheim, the University of Bergen, the University of Oslo, and the Norwegian Institute of Public Health.

Data from 10 regional studies

In CONOR, regional data from 10 different epidemiological studies have been merged into a national database, which is more representative of the Norwegian population than each of the individual sites.

The database consists of information obtained from questionnaires, a simple physical examination, analyses of blood samples, and frozen stored blood and/or DNA. The main purpose of CONOR is to study the aetiology of rare diseases by testing environmental, inheritable, cultural and social factors in order to describe the dispersion of diseases and risk factors by time, place and socio-demographic factors.

CONOR is particularly suitable for studying gene-environment interactions and for linkages to various national registers (eg. cancer-, cause of death-, hospital- and medical birth registers).

Invitation and procedures

Altogether 309,832 individuals were invited in the 10 studies based on addresses from the Population registry of Norway (Hammer, 2002). Some of the individual studies invited all subjects above a specific age (for example all above 19 years in HUNT II), whereas others invited all subjects in selected age groups (for example all 30-, 40-, 45-, 60 and 75 years in OPPHED and TROFINN). The web site for each study contains more detailed information (see Table 1).

In all CONOR surveys, the data collection followed a standard procedure. Letters of invitation were mailed about 2 weeks before the time of appointment and included a

questionnaire and a booklet with the aims of the study and information about the examinations and procedures. At the screening, the main questionnaire was collected from the attendees, they went through a physical examination and a non-fasting blood sample was drawn for analyses in fresh serum. Another sample was stored at minus 80 degrees. In most studies, the participants were given one or two supplementary questionnaires, which they were instructed to fill in at home and to return by mail in pre-addressed envelopes.

About four weeks after attending the examination, a letter with some results from the examination and blood tests was sent to all participants. Those with the highest scores of cardiovascular risk were offered a new clinical examination at the regional University Hospital - or, in some of the studies, were asked to visit their own general practitioner.

Measures

All surveys have been carried out in collaboration with the National Health Screening Service, Oslo (now Norwegian Institute of Public Health). Experienced and trained personnel conducted all procedures. Non-fasting serum total and HDL cholesterol, glucose and triglycerides were measured directly by an enzymatic method (Boehringer 148393, Boehringer-Mannheim, Federal Republic of Germany – from 2000 Hitachi 917 auto analyzer, Roche Diagnostic, Switzerland).

The Department of Clinical Chemistry, Ullevål University Hospital, Oslo, performed all laboratory assessments except for HUNT II where the analyses were performed at the Department of Clinical Chemistry, Innherad Hospital, Levanger. Comparisons of blood-samples were performed between the laboratories, and small differences were found (Tverdal A et al 1997). Calibration procedures were carried out between these laboratories in connection with the surveys (Dr. Lund-Larsen PG, National Health Screening Service, personal communication). An acceptable stability of the laboratory analyses over time in the population surveys has been reported (Foss & Urdal, 2003).

Heart rate, systolic and diastolic blood pressures were measured by an automatic device (DINAMAP, Criticon, Tampa, USA), which measured the blood pressure in

mm Hg automatically by an oscillometric method. After 2 minutes of preceding rest, three recordings were made at one-minute intervals. Mean values of the second and third systolic blood pressure measurements were used in calculating the cardiovascular risk score (CVD risk score) (Tverdal et al., 1989). The stability of the blood-pressure measures have been evaluated and deemed acceptable (Lund-Larsen, 1997).

Body weight (in kilograms, one decimal) and height (in cm, one decimal) was measured according to a standard protocol with the participants wearing light clothing without shoes (manually recorded until 2000 and after that with an electronic Height and Weight Scale). Body mass index (BMI) was calculated as kg/m^2. Waist circumference was measured at the umbilicus to the nearest cm and with the subject standing and breathing normally. In obese individuals, waist circumference was defined as the midpoint between the iliac crest and lower margin of ribs. Hip circumference was measured as the maximum circumference around the buttocks. Both waist and hip were measured with a measuring tape of steel – which was emphasized to be horizontal. Waist and hip circumference were used to calculate the waist-hip ratio using the formula waist (cm)/ hip circumference (cm).

Most of the studies consist of a central core and several supplementary projects – for example extra samples of blood, ECG, ultrasonographic examination of carotid artery and abdominal aorta, and bone mineral densitometry (BMD). The web site for each study contains more detailed information (see Table 1). Only a limited and mutual core of each study constitutes CONOR. Most of the studies have published reference papers with more detailed information about their own study (Table 2).

The CONOR-questions

All surveys used 50 common CONOR-questions agreed upon before the first CONOR survey in Tromsø in 1994. The exact wording of the questions is available at the CONOR web site (http://www.fhi.no/dav/CA11310499.doc). Some of these questions were placed on the second questionnaire handed out at the screening station – and thus have lower response rate.

The CONOR-questions cover the following main topics: Self-reported health and diseases such as diabetes, asthma, coronary heart disease, stroke and mental distress, musculo-skeletal pains, family history of disease, risk factors and lifestyle, environment while growing up, social network and social support, education, work and housing, some types of occupation, use of medications and reproductive history (women).

Several of these questions have been evaluated or validated previously and were deemed acceptable (Tretli et al., 1982; Jacobsen & Thelle, 1987; Løchen & Rasmussen, 1992; Thune et al., 1997, Joakimsen et al., 1998; Saltin & Grimsby, 1968; Derogatis et al., 1974; Ainsworth et al., 1996; Brugha et al., 1985; Strand et al., 2003; Søgaard et al 2003). The Population registry of Norway, which was used for invitation, contains information about gender, birth date, marital status, address and country of birth.

Participation in the CONOR studies

Altogether 181,891 subjects accepted to participate and provided a declaration of consent – 7,460 of these participated in more than one survey. The age distributing of these 174 430 participants is shown in table 3. The participation rate varied among the surveys. The participation was slightly reduced throughout the study-period 1994-2003 - and was higher in rural as compared to urban areas.

Ethics and approvals

All participants of the studies included in CONOR, have given their written consent. The participant's names and personal ID numbers are omitted when data are used for research purposes. The Norwegian Data Inspectorate has approved - and the Regional Committees for Medical Research Ethics has evaluated each individual study. The studies have been conducted in full accordance with the World Medical Association Declaration of Helsinki.

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TABLE 1. Number of invited and participating subjects in Cohort Norway (CONOR) 1994-2003.

Name of the study	Year of survey	Number invited†	Invited age-groups in years‡	Number of participants *			Web address
				Men	Women	Total	
Tromsø IV (The fourth Tromsø Study)	1994-1995	37,558	25 +	12,797	14,128	26,925	http://uit.no/tromsoundersokelsen/tromso4/2
HUNT II (The second North-Trøndelag Health Study)	1995-1997	94,196	20 +	30,442	34,576	65,018	http://www.hunt.ntnu.no/
HUSK (The Hordaland Health Study)	1997-1999	38,587	40-44, 46-47, 70-72	11,678	13,852	25,530	http://www.uib.no/isf/husk/
Oslo II (The second Oslo Study)	2000	14,209§	48-77	6,919		6,919	http://www.fhi.no/artikler/?id=54685
HUBRO (The Oslo Health Study)	2000-2001	58,660#	30, 31, 40, 45, 46, 59/ 60, 75/ 76	9,751	12,264	22,015	http://www.fhi.no/artikler/?id=54464
OPPHED (The Oppland and Hedmark Health Study)	2000-2001	22,327	30, 40, 45, 60, 75	5,650	6,752	12,402	http://www.fhi.no/artikler/?id=28233
Tromsø V (The fifth Tromsø Study)	2001	10,353	30 +	3,491	4,586	8,077**	http://uit.no/tromsoundersokelsen/tromso5/2
I-HUBRO (The Oslo Immigrant Health Study)	2002	12,088††	20-60	1,915	1,768	3,683	http://www.fhi.no/artikler/?id=28217
TROFINN (The Troms and Finnmark Health Study)‡‡	2002	16,229	30-77	4,318	5,009	9,327	http://www.fhi.no/artikler/?id=28261
MoRo II (The second part of the Romsås in Motion Study)	2003	5,535	34-70	899	1,096	1,995	http://www.fhi.no/artikler/?id=28254
CONOR (Cohort Norway)	1994-2003	309,742	20-103	87,157	92,928	181,891*	http://www.fhi.no/artikler/?id=28138

* Number of participants equals those who attended the survey and/or answered at least one questionnaire and signed a written consent. 7,460 persons participated in a second CONOR survey and 1 person participated in a third. Thus, the total numbers of participants with consent were 174,430.

† The numbers include all individuals invited. The individual surveys could have published papers with slightly different total numbers.

‡ HUSK: All 40-44 years and those participating in a study in 1992-93 born 1950-51 and 1925-27; Oslo II: All those invited to the Oslo Study 1972-73, except those invited to HUBRO and MoRo I (Invited in 1972/73: all men born 1923-32 and 7% random sample of those born 1933-52); Tromsø V: All 30, 40, 45, 60, 75 years and all those participating in phase II in Tromsø IV - which included: all born 1920-1939, 5-10% sample of other age groups attending phase I, all women born 1940-44; I-HUBRO: 30% random sample of people born in Pakistan, all born in Turkey, Sri Lanka, Iran, Vietnam - except those invited to HUBRO; MoRo II: All those participating in a study in 2 local districts in Oslo in 2000 (MoRo

I) born 1933-1969 – except those participating in HUBRO; TROFINN: All 30, 40, 45, 60, 75 years and all those participating in three Finnmark studies in the period 1974-1988 – which included: All born 1925-1947, all born 1948-1968 invited to Finnmark I, II or III.
§ 2,515 more men who belonged to the Oslo II cohort, also belonged to the HUBRO cohort, and were only invited to HUBRO. Of these 1,320 men participated. They are only counted as invited to HUBRO. 50 more men belonged to the MoRo-cohort, and are only counted as invited there.
# Include 17,308 invitees (31 and 46 years – additional cohorts) who were not reminded. The attendance-rate of these was low.
** 7,166 of these participated also in Tromsø IV.
†† Include 4,116 persons (20-30 years – additional cohort) who were not reminded. The attendance-rate of these was very low.
‡‡ Include 18 of 25 municipalities in Troms and 10 of 19 municipalities in Finnmark. The other municipalities participated in Tromsø V and in SAMINOR, i.e. a health survey in communities with Sámi and Norwegian population, at the same time.

Table 2. Reference papers to the 10 participating CONOR studies.

Tromsø IV: Wilsgard T. Longitudinal analyses of cardiovascular risk factors. The Tromsø study 1974-1995. ISM skriftserie nr. 65. Tromsø, Norway: Institute of Community Medicine, University of Tromsø, 2002.

HUNT II: Holmen J, Midthjell K, Krüger Ø, Langhammer A, Lingaas Holmen T, Bratberg GH, Vatten L, Lund-Larsen PG. The Nord-Trøndelag Health Study 1995-97 (HUNT 2): Objectives, contents, methods and participation. Nor J Epidemiol 2003; 13: 19-32.

HUSK: Bjelland I, Tell GS, Vollset SE, Refsum H, Ueland PM. Folate, vitamin B12, homocysteine, and the MTHFR 677C->T polymorphism in anxiety and depression: the Hordaland Homocysteine Study. Arch Gen Psychiatry 2003 Jun;60(6):618-26 - and

Sanne B, Mykletun A, Dahl AA, Moen BE, Tell GS; Hordaland Health Study. Occupational differences in levels of anxiety and depression: the Hordaland Health Study. J Occup Environ Med 2003;45:628-38.

Oslo II: Lund Håheim L, Holme I, Hjermann I, Søgaard AJ, Lund-Larsen PG, Leren P. Resultater fra Oslo-undersøkelser blant de samme menn i 1972/3 og i år 2000. Endring i risikofaktorer for hjerte- og karsykdom. Tidskr Nor Laegefor (Cond accepted)

HUBRO: Søgaard AJ, Selmer R, Bjertness E, Thelle D. The Oslo Health Study. The impact of self-selection in a large, population-based survey. Int J Equity Health 2004:3: 1-24. Online: http://www.equityhealthj.com/content/3/1/3

OPPHED: Only web-site - http://www.fhi.no/artikler/?id=28233

Tromsø V: Johnsen SH, Fosse E, Joakimsen O, Mathiesen EB, Stensland-Bugge E, Njølstad I, Arnesen E. Monocyte count is a predictor of novel plaque formation: a 7-year follow-up study of 2610 persons without carotid plaque at baseline the Tromso Study. Stroke. 2005;36(4):715-9.

I-HUBRO: Holvik K, Meyer HE, Haug E, Brunvand L.Prevalence and predictors of vitamin D deficiency in five immigrant groups living in Oslo, Norway: the Oslo Immigrant Health Study. Eur J Clin Nutr. 2005;59:57-63.

TROFINN: Only web-site - http://www.fhi.no/artikler/?id=28260

MoRo II: Jenum AK,. Anderssen SA, Birkeland KI, Holme I, Graff-Iversen S, Lorentzen C, Ommundsen Y, Raastad T, Ødegaard AK, Bahr R. Promoting physical activity in a low-income multi-ethnic district: behavioural, psychological and biological effects of a pseudo-experimental community intervention study to reduce risk factors for diabetes and cardiovascular disease (submitted)

CONOR: Engeland A, Søgaard AJ. CONOR (Cohort NORway) – en oversikt over en unik forskningsdatabank. Nor J Epidemiol 2003;13:73-7 - and Magnus P, Arnesen E, Holmen J, Stoltenberg C, Søgaard AJ, Tell GS. CONOR (Cohort NORway): historie, formål og potensiale. Nor J Epidemiol 2003;13:79-82.

Table 3 Number of participants in Cohort Norway (1994-2003) according to gender and age-groups (at the time they attended the screening station). If participating in more than one study, only the last one is counted.

	Men	Women	Total
Age	N	N	N
<20	116	148	264
20-29	5 884	7 236	13 120
30-39	13 322	15 547	28 869
40-49	27 969	32 148	60 117
50-59	10 517	10 176	20 693
60-69	12 229	10 373	22 602
70-79	13 119	11 883	25 002
80+	1 460	2 303	3 763
Total	84 616	89 814	174 430

Int. J. Epidemiol. Advance Access published November 4, 2007

Published by Oxford University Press on behalf of the International Epidemiological Association. *International Journal of Epidemiology* 2007;1–5
 doi:10.1093/ije/dym217

COHORT PROFILE

Cohort Profile: Cohort of Norway (CONOR)

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Accepted 1 October 2007

How did the study come about?

A number of large population-based cardiovascular surveys have been conducted in Norway since the beginning of the 1970s. The surveys were carried out by the National Health Screening Service in cooperation with the universities and local health authorities. All surveys comprised a common set of questions, standardized anthropometric and blood pressure measurements and non-fasting blood samples that were analysed for serum lipids at the Ullevål Hospital Laboratory. These surveys provided considerable experience in conducting large-scale population-based surveys, thus an important background for the Cohort of Norway (CONOR). In the late 1980s the Research Council of Norway established a programme in epidemiology. This also gave stimulus to the idea of establishing a cohort including both core survey data and stored blood samples. In the early 1990s, all universities, the National Health Screening Service, The National Institute of Public Health and the Cancer Registry discussed the possibility of a national representative cohort.[1] The issue of storing blood samples for future analyses raised some concern and it was discussed in the parliament. In 1994, the Ministry of Health appointed the Steering Committee for the CONOR collaboration. In 1994–95, the fourth round of the Tromsø Study was conducted, and became the first survey to provide data and blood samples for CONOR. During the years 1994–2003, a number of health surveys that were carried out in other counties and cities also provided similar data for the network. So far, 10 different surveys have provided data and blood samples for CONOR (Figure 1). The administrative responsibility for CONOR was given to the Norwegian Institute of Public Health (NIPH) in 2002. The CONOR collaboration is currently a research collaboration between the NIPH and the Universities of Bergen, Oslo, Tromsø and Trondheim.

The purpose of CONOR

The CONOR cohort has not been established on the basis of any single hypothesis but is rather a multipurpose study. The ambition was to set up a sufficiently large enough cohort to study aetiological factors for a wide range of diseases. Additionally, this cohort should make it possible to describe Norwegian men and women in terms of distribution of exposures and health status according to time, place and socio-economic factors.

In 2002, CONOR and the Norwegian Mother and Child study (MoBa),[2] received a 5-year grant from the Norwegian Research Council to build a technology platform under the Functional Genomics programme (FUGE), called the Biobanks for Health in Norway (Biohealth) platform.[3] The overall aim was to investigate separate and combined effects of genes and environment on the risk of disease.

Who is in the sample?

Altogether 309 742 individuals were invited to the 10 surveys based on the 11-digit personal identifier and addresses from the Population Registry of Norway.[4] The goal is to include 200 000 participants. We defined those who attended the survey and/or answered at least one questionnaire and signed a written informed consent as participants. The numbers in Table 1 include individuals who participated and had given their written consent for research and linkage to health registries. A total of 7309 persons participated in two CONOR surveys, and one person participated in three. Thus, the total number of

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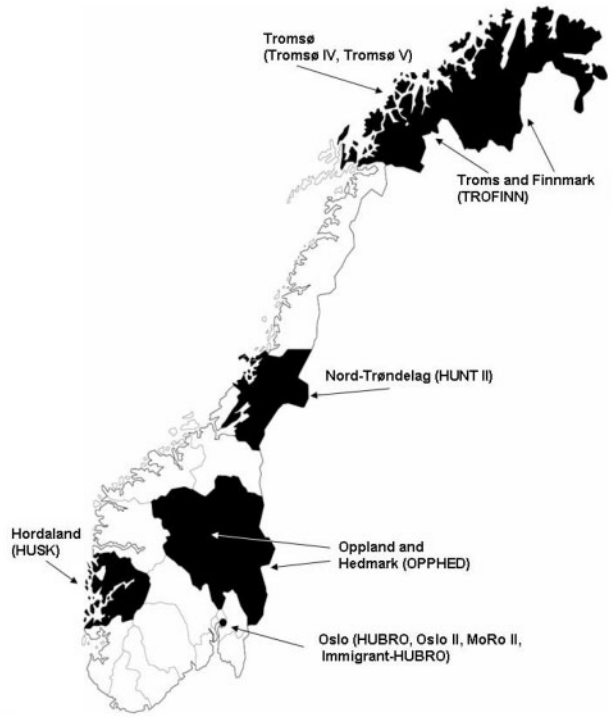

Figure 1 Map of Norwegian counties with location of each sub-study included in cohort of Norway (CONOR)

individuals in the CONOR cohort is 173 236. The distribution of age at the first examination and the number of deaths during follow-up through 2003 is given in Table 2. The individual surveys may have published papers with slightly different total numbers. Sampling procedures differed somewhat between the individual studies. The web site for each study contains more detailed information (Table 1).

What has been measured?

In all the CONOR surveys, the data collection followed a standard procedure. Letters of invitation were mailed about 2 weeks before the time of appointment and included a questionnaire and a brochure with the aims of the study and information about the examinations and procedures. At the screening, this initial questionnaire was collected from the attendees, participants underwent a physical examination and a non-fasting blood sample was drawn. In most studies, the participants were given one or two supplementary questionnaires, which they were instructed to fill in at home and return by mail in pre-addressed stamped envelopes.

About 4 weeks after attending the examination, a letter with selected results from the examination and blood tests was sent to all participants. Those with the highest scores of cardiovascular risk (a modified Framingham risk score based on multiplying the relative risks attributable to the subject's gender, serum cholesterol, systolic blood pressure the number of cigarettes currently smoked per day and family history of

Table 1 Number of invited and participating subjects in cohort of Norway (CONOR) 1994–2003

Name of the study	Year of survey	Number invited	Invited age-groups in years	Number of participants[a]			
				Men	Women	Total	Web address
Tromsø IV (The fourth Tromsø Study)	1994–1995	37 558	25+	12 797	14 128	26 925	http://uit.no/tromsoundersokelsen/tromso4/2
HUNT II (The second North-Trøndelag Study)	1995–1997	94 196	20+	30 441	34 576	65 017	http://www.hunt.ntnu.no/
HUSK (The Hordaland Health Study)	1997–1999	38 587	40–44, 46–47, 70–72	11 678	13 851	25 529	http://www.uib.no/isf/husk/
Oslo II (The second Oslo Study)	2000	14 209	48–77	6919		6919	http://www.fhi.no/artikler/?id=54685
HUBRO (The Oslo Health Study)	2000–2001	58 660	30, 31, 40, 45, 46, 59/60, 75/76	9509	11 852	21 361	http://www.fhi.no/artikler/?id=54464
OPPHED (The Oppland and Hedmark Health Study)	2000–2001	22 327	30, 40, 45, 60, 75	5602	6661	12 263	http://www.fhi.no/artikler/?id=28233
Tromsø V (The fifth Tromsø Study)	2001	10 353	30+	3440	4457	7897	http://uit.no/tromsoundersokelsen/tromso5/2
I-HUBRO (The Oslo Immigrant Health Study)	2002	12 088	20–60	1877	1737	3614	http://www.fhi.no/artikler/?id=28217
TROFINN (The Troms and Finnmark Health Study)	2002	16 229	30–77	4196	4836	9032	http://www.fhi.no/artikler/?id=28261
MoRo II (The second part of the Romsås in Motion Study)	2003	5535	34–70	896	1093	1989	http://www.fhi.no/artikler/?id=28254
CONOR (Cohort Norway)[a]	1994–2003	309 742	20–103				
Sum of participants				87 355	93 191	180 546	http://www.fhi.no/artikler/?id=28138
Sum of individuals				84 153	89 083	173 236	

[a]Number of participants equals those who attended the survey and agreed that information from the CONOR survey and blood samples can be linked to other registers and used in research. A total of 7310 individuals participated in more than one survey. Thus, the total number of individuals equals 173 236.

coronary heart disease) were advised to visit their own general practitioner, and in some cases offered a follow-up examination at the local hospital.[5]

Measures

Only a restricted core set of measurements and questionnaire responses constitute the CONOR data. Most individual studies that contribute to CONOR have more detailed measurements and questionnaire data. In the following section we describe the key core measurements that all studies contribute to CONOR; at the end we briefly describe some of the additional measurements that are in some of the contributing individual studies. All surveys were carried out in collaboration with the National Health Screening Service, Oslo (now the NIPH). Experienced and trained personnel conducted all procedures. Non-fasting serum total- and HDL-cholesterol, glucose and triglycerides were measured directly by an enzymatic method (Boehringer 148393, Boehringer-Mannheim, Federal Republic of Germany—from 2000 Hitachi 917 auto analyzer, Roche Diagnostic, Switzerland).

The Department of Clinical Chemistry, Ullevål University Hospital, Oslo, performed all laboratory assessments except for HUNT II (The second North-Trøndelag Study) where the analyses were performed at the Department of Clinical Chemistry, Levanger Hospital, Levanger. In Tromsø IV and V, cholesterol and triglycerides were measured at the Department of Clinical Chemistry, University Hospital North-Norway, Tromsø. Calibration procedures were carried out between these laboratories in connection with the surveys (Dr P.G. Lund-Larsen, National Health Screening Service, personal communication). An acceptable stability of the laboratory analyses over time in the population surveys has been reported.[6]

Heart rate, systolic and diastolic blood pressures were measured by an automatic device (DINAMAP, Criticon, Tampa, FL,USA). After 2 min of seated resting, three recordings were made at 1-min intervals. Mean values of the second and third systolic blood pressure measurements were used in calculating the cardiovascular risk score (CVD risk score) (Tverdal, 1989 5/id). The stability of the blood pressure measures has been evaluated and deemed acceptable.[7]

Body weight (in kilograms, one decimal) and height (in centimetres, one decimal) was measured according to a standard protocol with the participants wearing light clothing without shoes (manually recorded until 2000 and after that with an electronic Height and Weight Scale). Body mass index (BMI) was calculated as kilograms per square metre. Waist circumference was measured at the umbilicus to the nearest centimetre and with the subject standing and breathing normally. In obese individuals, waist circumference was defined as the midpoint between the iliac crest and lower margin of ribs. Hip circumference was measured as the maximum circumference around the buttocks. Both waist and hip were measured with a measuring tape of steel—which was emphasized to be placed horizontally. The waist–hip circumferences were used to calculate the waist–hip ratio.

Most individual studies that contribute to CONOR have several additional measurements—for example, extra samples of blood, ECG and ultrasonographic examination of carotid artery and abdominal aorta. Four of the study sites measured bone mineral density (DEXA and/or SXA) and have established a research group called Norwegian Epidemiologic Osteoporosis Studies (NOREPOS).[8] Altogether, around 28 000 individuals have had their bone mineral density measured and currently a number of collaborative studies are carried out.

The CONOR questions

All surveys used about 50 core CONOR questions agreed upon before the first CONOR survey in Tromsø in 1994. The exact wording of the questions is available at the CONOR website (http://www.fhi.no/dav/CA11310499.doc). Some questions have been slightly modified over the years.

The CONOR questions cover the following main topics: self-reported health and diseases such as diabetes, asthma, coronary heart disease, stroke and mental distress, musculo-skeletal pains, family history of disease, risk factors and lifestyle, social network and social support, education, work and housing, some types of occupation, use of medications and reproductive history (women).

Several of the questions have been evaluated or validated and deemed acceptable.[9–18] The Population Registry of Norway that was used to identify eligible subjects, contains information about gender, date of birth, marital status, address and country of birth.

Blood samples

Blood samples were drawn from the CONOR participants. EDTA blood for CONOR and the other sub-surveys have normally been collected in 7 or 5 ml vacutainers. These vacutainers were made by different manufacturers but were normally made of polypropylene. DNA has been extracted from more than 90 000 specimens to medio 2007, and Biohealth intends to extract DNA from all samples by Spring 2008. The extracted DNA and an additional sample of 1.25 ml EDTA-blood will be stored at a national biobank storage site at HUNT/NTNU biobank in Levanger (Mid-Norway).

What has been found?

Although a number of analyses from each participating study have been conducted, the CONOR file has only recently been compiled and made available for research. The first CONOR project was anchored in NOREPOS describing urban–rural differences in forearm fractures.[19] Other methodological and validation studies have been completed as described above.

What are the main strengths and weaknesses?

The CONOR database has several strengths: it is population based including populations from various parts of Norway, both rural and urban. The 11-digit personal identification number makes it possible to link cohort participants to national health registries. At present, several large linkages to other registers have been or are in the process of being conducted. These include linkages with census-based data for the whole population and the Medical Birth Registry of Norway, Disability Registry, Cancer Registry of Norway. Tables 2 and 3 present number of deaths and new cases of cancer in CONOR since date of examination by linkage to the death and cancer registries. Other large linkages include data from the Norwegian Drug Prescription Database and information from

Table 2 Number of participants (*n*) and number of deaths until December 31, 2003 in the cohort of Norway (CONOR) by age at inclusion in the surveys

	Men		Women	
Age (years)	*n*	Deaths	*n*	Deaths
<25	2037	15	2512	6
25–34	12 028	56	14 658	22
35–44	21 544	158	24 399	123
45–54	17 009	296	18 474	218
55–64	11 698	604	11 903	325
65–74	13 654	2008	9399	991
⩾75	6183	2138	7738	2141
Total	84 153	5279	89 083	3826

Table 3 Follow-up 1994–2006[a] of the CONOR cohort members. Number of cases of first cancer diagnosis in the Norwegian Cancer Registry after initial CONOR examination

	Men		Women	
	<70 years	⩾70 years	<70years	⩾70 years
Cancer site (ICD-7)				
Colorectal cancer (152-4)	582	631	528	476
Trachea, bronchus and lung (162)	191	300	133	110
Breast (170)	1	4	936	271
Prostate (177)	607	995	0	0
Bladder and other urinary organs (181)	102	235	33	51
Melanoma of skin (190)	170	89	238	82
All sites (including basal cell carcinoma of skin)	3180	3971	5411	2515

[a]Follow-up approximately through March 2006.

health surveys in several counties in the 1970s. There are also a number of disease registers that may be linked to the CONOR database. Earlier this year, the government passed a new legislation to make the national hospital discharge register personal identifiable, which would be possible to link to CONOR in the near future.

A major strength of CONOR is its sample size that means it would be able to make a unique contribution to establish main genetic effects and gene–environmental interactions, since precise and robust estimation of these effects requires very large sample sizes.[20,21] Our aim is to reach 200 000 individuals with blood samples and extracted DNA and we anticipate reaching this sample size by Spring 2008. For some hypotheses, it would be most efficient to employ a nested case control study design within CONOR, and we anticipate several such studies in the future. This comparatively large sample size means cases for a number of common and less common diseases may be identified from various sources.

There are some important weaknesses: the overall participation rate is 58% and is lowest in the surveys in Oslo and other urban areas and became lower throughout the study period. However, the overall participation rate is influenced by low participation rate in those aged ⩽30 years. The study population is somewhat heterogeneous as it includes sampling from 10 geographical areas with various age groups included over a 10-year period. The number of core variables is limited, and in some cases the wording of questions is slightly changed over the years.

Can I get hold of the data? Where can I find out more?

Guidelines have been developed for projects using data from CONOR (www.fhi.no). These shall ensure that projects will have a high scientific quality, facilitate quick publication of results from CONOR and make the data accessible for research. Research groups may apply for access. A project leader must be appointed. Researchers not residing in Norway are advised to seek contact with Norwegian counterparts. The study objectives should be within the broader aims of CONOR. Further details of these guidelines are provided at the CONOR website.

Applications and enquiries can be sent electronically to the Norwegian Public Health Institute (email: conor@fhi.no). Applications will be evaluated by the CONOR Steering Committee.

Acknowledgements

The authors would like to thank Kjell Bjartveit, Yngve Haugstveit, Per G Lund Larsen and Arve Sjølingstad for coordination of the blood samples, preparation and management of the CONOR cohort data file. The authors would also like to thank all those who have been involved in collecting the data at the Universities of Bergen, Oslo, Tromsø and Trondheim and the Norwegian Institute of Public Health.

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Appendix 3

Summary of cohort studies examining the association between smoking and breast cancer incidence and mortality published after 2004

Summary of some cohort studies examining the association between smoking and breast cancer incidence and mortality published after 2004

*** Incidence**

First author, year	Population	Length of follow up (years)	Cases/ Cohort	Main results (mulitvariate)	Highest sig risk estimate	Longest duration before first birth	Comments	Education
Al-Delaimy (2004)	Nurses Health II	10	1009/112844	Current 1.12 (0.92-1.37) Former 1.18 (1.02-1.36)	Longest duration 1.21 (1.01-1.45)	1.10 (0.80-1.52)		Not in main model
Reynolds (2004)	California Teacher Study	5	2005/ 116544	Current 1.32 (1.10-1.57) Former 1.08 (0.98-1.19)	Young age at initation 1.17 (1.05-1.30). Higest PY 1.25 (1.06-1.47)	1.13 (1.00-1.25)	Analysis for pre and postmenopausal	Not in main model
Lawlor (2004)	UK	3	139/3047			1.06 (0.72-1.56) for smoking BFC	Smoking before first childbirth only. Cohort study and meta-analysis. Cohort study has 3 years follow up. Non significant findings.	Not in main model
Gram (2005)	Norwegian Sweedish cohort	9	1240/102098	Current 1.17 (0.95-1.45) Former 1.05 (0.94-1.41)	Young age 1.48 (1.03-2.13) Higest PY 1.46 (1.11-1.93)	1.27 (1.07-1.37)	No modification by alc use. Risk estimate by ever/never.	Not in main model
Hanaoka (2005)				Current 1.7 (1.0-3.1) Former 1.4 (0.4-3.5)			Not incl due to low number of cases (14 current, 4 former). Prevalence current smokers 5,7%. Japan.	
Olson (2005)	Iowa Women Health (US)	14	2017/41836	Current 1.19 (1.03-1.37) Former 1.08 (0.95-1.22)	Duration before first preg 1.21 (1.01-1.25)	1.21 (1.01-1.25)	Positive associtaion with post-menopausal BC, but no dose-reponse.	Edu in main model
Cui (2006)	Canadian National Breast	16	4445/89835	Current 1.18 (1.09-1.27)	Longest duration >40	1.13 (1.01-1.25) > 5	No modification by alc use	Edu in main model

Cui (2006)	Screening Study (CAN)	10	4445/89855	Former 1.00 (0.93-1.08)	years 1.50 (1.19-1.89)	years before	No modification by alc use.	Edu in main model
Ha (2007)	US Radiol Technologists	15	906/ 56042	Current 1.13 (0.96-1.32) Former 1.17 (0.99-1.38)		1.39 (0.82-2.35) ≥ 10 pack years before	Focus: smoking before first childbirth. Higher risk among postmenopausal. No risk for smoking *after* FCB.	Not in main model
Luo (2011)	Women Health Initiative (US)	10	3520/79990	Current 1.16 (1.00-1.34) Former 1.09 (1.02-1.17) Passive 1.32 (1.04-1.67)	Smoking >50 years: HR 1.35 (1.03-1.77)	1.21 (1.11-1.33)	Active (and passive) smoking in postmenopausal women only. Also reference for passive smoking.	In model but not commented elsewhere
Xue (2011)	Nurses Health Study	(-)	8772/111140	Current 1.09 (1.02-1.17) Former 1.06 (1.01-1.11) Ever 1.07 (1.02-1.12)	Highest PY 1.27 (1.16-1.38). Smoking from menarche to first birth: 1.18 (1.10-1.27) for every increase in 20 PY.	1.25 (1.11-1.40)	Large no of cases. Analysis for pre- and postmenopausal (no difference). Not used as reference for passive (no association). Biannual collection of smoking data.	Not mentioned
DeRoo (2011)	Meta-analysis of 23 prospective studies	(-)		(-)		1.10 (1.07-1.14)	Only focus: first pregnancy. Meta-analysis. Similar risks smoking only before and only after FCB. Concludes negativelly.	
Bjerkaas (2013)	3 Norwegian Cohorts	14	7490/302865	Current 1.14 (1.08-1.20) Former 1.17 (1.10-1.24) Ever 1.15 (1.10-1.21)	≥16 PY: 1.34 (1.25-1.45)	1.60 (1.42-1.80)		Incl in main model and discussed
Dossus (2013)	EPIC - 10 European Countries	11	9822/322988	Ever 1.06 (1.01-1.10) Former 1.05 (1.00-1.10) Current 1.06 (1.00-1.12) - passive in reference group.	1.73 (1.29-2.32) for every PY before 1 first childbirth.		Largest study to date (cases). Found strong association for increase 20PY before first childbirth. Mostly no ass for high PY ! Increased risk among non-drinkers only. Passive excluded from reference group in some analysis.	Included and discussed. Stronger ass for current smokers with low edu HR=1.21 comp with high edu HR=1.12 NS.
Gaudet (2013)	Meta-analysis and prospective cohort	14	97786	Current 1.14 (1.07-1.42) Former 1.13 (1.06-1.42)	45% increased risk when smoking 11 or more years before first birth: 1.45 (1.21-1.74)		*8.2% current smokers at enrollment. Meta-analysis of 14 studies- concludes positivelly.No alc association but no info of amount(dose).*	Incl in main model

Rosenberg (2013)	The Black Women`s Health Study	14	1377/52425	Current 1.05 (0.83-1.31) Former 1.10 (0.90-1.35) Ever 1.08 (0.89-1.31)		Premonp 2.01 (1.10-3-65) Postmenop 0.88 (0.55.1-39)	Increased risk for premonopausal cancer when smoking before frist childbirth. No increase for postmenopausal. NS for overall (current, former, ever).	Incl in main model.
Glantz and Johnson (2014)							Commentary paper on 2014 Surgeon General Report.	
Nyante (2014)	American Assiciation of Retired Persons	10	7481/186150	Current 1.19 (1.10-1.28) Former 1.07 (1.01-1.13)	1.22 (1.11-1.35) for smoking 11-20 cig/day		Poor dose-responce. Stronger ass for family history and late menarche. Adj for age at enrollment.	Incl in main model
*** Mortality**								
Calle (1994)	Cancer Prevention Study II	6	604412	Current 1.26 (1.05-1.50) Former 0.85 (0.70-1-03)	>40 cig per day 1.74 (1.15-2.62)		Stricly mortality and breast cancer	
Manjer (2000)	Malmø Mammograhic Screening Trial	12	792	Current 1.44 (1.01-2.06) Former 1.13 (0.66-1.94) unadjusted				
Holmes (2007) - survival + mortality (prediagnosis)	Nurses Health	8	5056	Current 1.00 (0.83-1.19) Prediagnosis smoking status: Current 1.03 0.87-1.22			Main analysis done on prediagnostic smoking status. Increased risk for total mortality, no risk for BC mortality.	
Sagiv (2007)	Long Island Breast Cancer	6	1273	Current 1.04 (0.63-1.71) Former 0.89 (0.57-1.40)			No effect even for all cause survival and smoking. Confusing use of terms.	

Braithwaite (2012) review + cohort	Life after Cancer Epidemiology LACE	12	2265	Current (survival): 2.01 (1.27-3.18)		Review on survial. Confusing assessment of mortality and survival. But strong association found for survival (NB low no of cases:16) in both prosp analysis and review with current, NOT former. Nice overview of surveys. Smoking assessment 2 years post diagnosis.
Pirie (2012)	Million Women Study	12	1.3 mill	Mortality for breast 1.13 (1.04-1.22)		Lancet. Smoking and disease spesific mortality, and overall mortality. Analysis on non-drinking women changed results to non-significant 1.06 (0.95-1.18).
Warren (2013)	Roswell Park	12		Current survival: 1.71 (1.28-2.29)		Stricltly survival, most cancer sites. Premenopausal most affected.
Saquib (2013)	Women`s Healthy Eating and Living (WHEL) US	7	245/2953	Current survival: 1.12 (0.67-2.24), former 1.08 (0.82-1.40).	Lifetime exposure 20+ PY (mortality): 1.54 (1.07-2.32)	Discussing the benefit of assessing llifetime smoking exposure instead of current or former smoking at diagnosis. of mortality before survical. For survival: no significant results. NB Less than 5% current smokers, one third of those with >20 pack-years history.
Pierce (2013)	3 US cohorts (WHEL, LACE, NHS)	11	1059/9975		Former >=35 pack years: 1.54 (1.24-1.91)	JNCI. Compare with Saquib (2013). Lifetime exposure assessed for former smokers at diagnosis. NB very high exposure (mean 39 PY).
Bjerkaas (2013)	3 Norwegian Cohorts	14	1106/302865	Current: 1.15 (1.01-1.32) Former: 1.14 (0.97-1.34) Ever: 1.15 (1.02-1.30)		

Braithwaite (2012) review + cohort	Life after Cancer Epidemiology LACE	12	2265	Current (survival): 2.01 (1.27-3.18)		Review on survial. Confusing assessment of mortality and survival. But strong association found for survival (NB low no of cases:16) in both prosp analysis and review with current, NOT former. Nice overview of surveys. Smoking assessment 2 years post diagnosis.
Pirie (2012)	Million Women Study	12	1.3 mill	Mortality for breast 1.13 (1.04-1.22)		Lancet. Smoking and disease spesific mortality, and overall mortality. Analysis on non-drinking women changed results to non-significant 1.06 (0.95-1.18).
Warren (2013)	Roswell Park	12		Current survival: 1.71 (1.28-2.29)		Stricltly survival, most cancer sites. Premenopausal most affected.
Saquib (2013)	Women`s Healthy Eating and Living (WHEL) US	7	245/2953	Current survival: 1.12 (0.67-2.24), former 1.08 (0.82-1.40).	Lifetime exposure 20+ PY (mortality): 1.54 (1.07-2.32)	Discussing the benefit of assessing llifetime smoking exposure instead of current or former smoking at diagnosis. of mortality before survical. For survival: no significant results. NB Less than 5% current smokers, one third of those with >20 pack-years history.
Pierce (2013)	3 US cohorts (WHEL, LACE, NHS)	11	1059/9975		Former >=35 pack years: 1.54 (1.24-1.91)	JNCI. Compare with Saquib (2013). Lifetime exposure assessed for former smokers at diagnosis. NB very high exposure (mean 39 PY).
Bjerkaas (2013)	3 Norwegian Cohorts	14	1106/302865	Current: 1.15 (1.01-1.32) Former: 1.14 (0.97-1.34) Ever: 1.15 (1.02-1.30)		

Appendix 4

Variable descriptions

Project name	The role of smoking and socio-economy in explaining health disparities in breast cancer and colorectal cancer incidence and mortality
	Variables Description
Authors	Eivind Bjerkaas and Ranjan Parajuli
Finalized	
Date of masterfile	16 March 2012
Name of masterfile	master_sc_v_112.zip

Inclusions selected on survey from data manager:

3 Counties I	62 220
3 Counties II	9 188
3 Counties III	22 538
CONOR	137 182
40 Years (total)	403 691
Oslo I	17 973
Sum	652,792

Analytical cohort: 602, 242(m=299,376, f=302,866)

Cancer cases in cohort by smoking status

	Never-smokers	Former-smokers	Current-smokers	Total
Breast cancer	3,028	1,581	2,881	7,490*
Colon cancer	1,368	1,099	1,531	3,998
Rectal cancer|	648	602	926	2,176

*Only among women

Cancer Mortality in cohort by smoking

	Never-smokers	Former-smokers	Current-smokers	Total
Breast cancer	459	216	431	1,106*
Colon cancer	1,607	443	642	1,607
Rectal cancer|	202	181	343	726

*Only among women

Daily smokers

The daily-smokers variable in CONOR was based on question "Do you smoke daily?" (In CONOR, this question includes cigarettes, pipe and cigar daily smokers, according to CONOR documentation (variable a8_0)).

In Oslo health study I, the question "Do you smoke daily?" is used for current smokers. Answering "yes" to this question will be current smokers.

In the Norwegian counties study (I, II and III), this was based on the question "Do you smoke daily now?" A positive answer will give a categorization of daily smoker. (We do not consider other answers regarding smoking to classify the current smokers.)

40 years I was based on the question "Do you smoke daily now?" Answering "Yes" will be current smokers.

40 years II was based on the questions "Do you smoke cigarettes daily? Or "Do you smoke cigar daily?" "Do you smoke pipe daily?" answering "Yes" to any of these questions gives daily-smokers.

The 40 years III and IV was based on "Do you smoke cigarettes daily?" or "Do you smoke cigar daily?" or "Do you smoke pipe daily?" If participants have answered "Yes" on any of the above questions, then they are categorized as current smokers.

Former smokers

After we got all current smokers, then we categorized remaining participants in the former-smokers category as below:

In CONOR if participants have valid answer (greater than 0) in questions "How long time since quit smoking (a_9)?" or numbers of cigarettes smoking daily (a_10) or "How old were you when you start smoking (a_11)? or "How many years of smoking in total(a_12_1).?" ,then categorized as former- smokers.

Oslo study I: Those who answered "Yes" to the question "Have you smoked cigarettes daily previously" (tidlrok) in Oslo health study were classified as former smokers. In addition, we check if a valid value on (tidsidsl) "How long since quitting?!", if there is a valid value then we categorized them as former smokers.

In the Norwegian counties those answering "Yes" to the questions "Have you smoked cigarettes daily previously?" were categorized as former-smokers. If answering any value (except zero) to the question "How long since you quit smoking?", and "How many years have you smoked daily?" and "how many cigarettes do you or did you smoke daily?", and <u>not</u> a current smoker, then categorized as a former smoker.

40 years I and II is done similar as the Norwegian Counties. Those answering "Yes" to the questions "Have you smoked cigarettes daily previously?" were categorized as former-smokers. If answering any value (except zero) to the question "How long since you quit

smoking?", and "How many years have you smoked daily?" and "how many cigarettes do you or did you smoke daily?", and not a current smoker, then categorized as a former smoker.

(Please note the comment from Randi about classification this question in 40 years II.)

40 years III and IV: any answer more than zero in the question "if you have smoked previously, how long since you quit?" then a former smoker. (As answering option is in years, we might misclassify those answering zero because they have quit less than 1 year ago.) Also, answering any value more than zero to the questions "how many cigarettes do you smoke or did you smoke daily", "how old were you when you started to smoke daily?" or "how many years have you smoked daily?", then classified as former smoker, if not already classified as a current smoker.

After we have categorized current and former-smokers, from the remaining group of participants, we categorized never-smokers in the following ways:

Never smokers

CONOR: Answering "No" to the question "Do you smoke daily (a8_0)?" then never smokers.

In the Norwegian counties study, participants answering "No" in the questions "Do you smoke cigarettes daily?" or Do you smoke cigars daily?" or Do you smoke pipes daily?" and if answering "No" to the question "Have you smoked cigarettes daily previously?" were categorized as never smokers.

In the 40 years I and II we did the same in the Norwegian counties. Participants answering "No" in the questions "Do you smoke cigarettes daily?" or "Do you smoke cigars daily?" or "Do you smoke pipes daily?" and if answering "No" to the question "Have you smoked cigarettes daily previously?" were categorized as never smokers.

40 years III: Participants answering "No" to the question "Do you smoke cigarettes daily?" Do you smoke cigars daily?" or "Do you smoke pipes daily?" and not answering the question "if you have smoked previously, how long since you quit?", then categorized as never smoker.

40 years IV: Participants answering "No" to the questions "Do you smoke cigarettes daily?" or "Do you smoke cigars daily?" or "Do you smoke pipes daily ?" and not answering the question "if you have smoked previously, how long since you quit?", then they are categorized as a never smoker. In addition we include the question unique for IV: "Never smoked daily?", then a never smoker. (Brings any records from missing to never, not from daily or former.)

Oslo: Those answering "No" to the both questions "Do you smoke daily?" and answering "No" to the question "Have you smoked cigarettes daily previously?" were categorized as never-smokers.

Ever-smokers (daily+ former- smokers)

Duration of smoking

The duration of smoking variable was based on two questions. In the CONOR and the Oslo health study I, daily and former smokers answered the questions "Numbers of years smoked?" In the Norwegian counties study and the 40 years cohort, subjects answering that they were ever smokers were asked "How many years all together have you smoked daily?" Duration of smoking will be further categorized into three groups (1-29, 30-39 and >40)(Ref: Cigarette smoking and risk of colorectal cancer among Norwegian women). Suggestion: Look in EPIC article for different categories which can be appropriate to use in our cohort)

Age at smoking initiation

The age at smoking initiation variable in CONOR and 40 years III+IV was based on question "How old were you when you started smoking"?

In the Norwegian counties study, 40 years I and II cohort and Oslo health study I, this variable is constructed. We subtracted total years of smoking from age at enrollment to construct the age at smoking initiation. This variable was available for both daily and former smokers.

Numbers of cigarettes

The numbers of cigarettes variable was based on question "Numbers of cigarettes smoked daily?" in CONOR and Oslo health study I. In the Norwegian counties study(I, II and III) and 40 years cohort(I,II,III and IV) , ever-smokers were asked "How many cigarettes do you smoke/smoked daily?" to extract information on numbers of cigarettes. We will further categorized it into three groups (1-9, 10-14 and > 15) (Ref: Gram et al: Cigarette smoking and risk of colorectal cancer among Norwegian women). This can be modified during the analysis by other categorizations if more groups needed.

Time since quitting smoking (former smokers only)

The time since quitting smoking variable was based on question "How long since you have quit smoking?" in CONOR, 40 years III and IV.

Answering option in CONOR and 40 years III and IV was "time in years" continuous variable. (rokslutp3 roykslutp4)

In the Norwegian counties study, Oslo health study I and 40 years I there were four different answering options:

a. Quit since 3 months
b. Quit since 3 months to 1 year
c. Quit since 1 to 5 years
d. Quit for more than 5 years

In 40 years II the question was "If you have smoked previously, how long since you quit" with answering options "less than one year" and "more than one year". (roykslutp2)

Answers > 60 years is set to missing as outlier (n=4).

Conclusion:

- For *current* smokers "time since quitting smoking" can be handled ok.
- For former smokers it is a problem for 40 years II because we can only differ between <1 year and > 1 year.
- We decide that *former smokers* from Norwegian Counties, 40 years I and II and Oslo I will be called missing in the continuous variable, but can still be handled as categorical variable with four options.

Latency

We have used information from several variables (see below.). For current smokers the information is good. For former smokers, we have information from CONOR and 40 years III and IV. The others are set to missing.
Latency is a constructed variable
Latency for current smokers:

a. Years between smoking initiation and cohort enrollment(latency 1)
   or
b. Years between smoking initiation and censoring/failures(latency 2)

For former-smokers

a. Years between smoking initiation and time since quitting

In some of the surveys, like in the Norwegian counties study 40 years I+II and Oslo health study I, we have "time since quitting" variable which was used for constructing latency for former-smokers was available only in four different options as:

1. Less than three months
2. Three months to 1 year
3. 1 year to 5 years
4. 5 years to more

Our main goal was to create a continuous latency variable which was not possible for former-smokers in these surveys.

a. Latency
   Latency 1 (Total years from smoking initiation and quitting or cohort enrollment – current smokers only)

b. Latency 2 (Total years between smoking initiation to failure/censoring – current smokers only)

c. Latency 3 (Total years between smoking initiation and quitting or cohort enrollment- former smokers only)
   "Only for CONOR, 40 years III and IV"

   # missing here includes if participants are from other surveys rather than CONOR, 40 years III and IV".

d. Latency 4 (Total years between smoking initiation to failure/censuring – former smokers only)
   "Only for CONOR, 40 years III and IV"

Pack- years of smoking

This is calculated as number of cigarettes smoked per day, divided by 20 and multiplied by the number of years smoked.

Pipe smokers

The “pipe_smoker_sc” variable yes/no comes from all our surveys.

The amount of pipe smoking *(packs pr week)* will come from 3C I, II, III, 40Y I, II, and Oslo I. Variable name “number_pipetobacco_sc”.

In Oslo 1 they only ask about nr of packs in 3 categories. We have estimated that if answering 0-0,5 pack will be 0,25 pack, 1-2 packs will be 1,25 and 2 packs will be 2 packs. Then they are categorized in the variable “number_pipetobacco_sc”.

Further, if any answer then considered “yes”, if no answer then considered “no”, in the “pipe_smoker_sc” variable.

(For BC analysis pipe smokers are disregarded due to very low number of female pipe smokers.)

Alcohol Variables

The alcohol variables are from the CONOR and the 40 years study III and IV. The 40 years study I and II, the Oslo study and the Norwegian county study has no alcohol information.

Teetotalers

In CONOR and 40 years study III and IV the question was “are you a teetotaler?” and there was a “yes/no” answering option.
We have added the persons who are light/moderate/heavy drinker from the “alcohol frequency” variable into the non-teetotalers group, to increase the numbers of non-teetotallers.

Alcohol frequency

Our alcohol frequency variable is constructed to become a light, moderate and heavy (n=42, drinker as categorical variable. In general, we have considered a heavy drinker to drink more than once a week, a moderate drinker once a week, and a light drinker to drink less than once a week.

CONOR
In the CONOR study the variable “drinking pattern” is a 1 to 5 categorical variable: 1. Drinking more than once a week 2. Drinking once a week. 3. 2-3 times pr month 4. Once a month. 5. Less than once a month. The following categorization has been made: if answering 1 in CONOR, then categorized as heavy drinker. If answering 2 in Conor, then categorized as a moderate drinker. In answering 3,4 or 5 in CONOR, then categorized as a light drinker.

40 years
There is no information about alcohol consumption in 40 years I and II. In 40 years III and IV the question was “how many times pr month do you drink alcohol?”. If drinking 5 times or

more pr week, then categorized as a heavy drinker. If drinking 4 times pr month (once a week) then categorized as a moderate drinker. If drinking less, then categorized as a light drinker.

The Norwegian counties study and Oslo health study I
No information.

Alcohol grams pr day

This variable has been constructed from information about drinking frequency and type of drink. According to the (ref: www.fhi.no), one glass of wine equals 14,4 grams of pure alcohol, one glass of beer equals 11,9 grams of pure alcohol, and one glass of spirits equals 12,8 grams of pure alcohol. Values larger than 100 grams pr day has been considered extreme, and have been set to missing (n=12).

CONOR
In CONOR the question was "how many glasses of wine / beer / spirits do you drink in a two weeks period?" The calculated amount of grams was divided on 14, to get the alcohol consumption per day.

40 years
In 40 years III and IV the question was "how many glasses of wine / beer / spirits do you drink in a two weeks period?" (Calculation as above).

BMI

Height and weight were recorded at the health station for all participants, and body mass index (BMI) was calculated by standard formula (ref). Observations with extreme values for height and weight were set to missing as follows: height <100 or >250 cm, weight <35 or >250 kg, BMI <15 or >60 kg/m2.(Ref: T Stocks Me-Can Cohort Profile 2009).

BMI is categorized in 4 different groups according to WHO classifications in following order:

1. <18.5
2. 18.5-24.9
3. 25-29.9
4. >30

In the analysis we will collapse category 1 and 2 due to low number in category 1 (1.17%) giving BMI as a 1-3 category.

Other variables

Menopause assessment (women only)

Women were categorized as pre-, peri- or postmenopausal. Only 10 per cent of our cohort was equal to, or older than 48 years old at inclusion, therefore most in our cohort was premenopausal at inclusion.

Questions about menopause were present in CONOR and 40 years III and IV as a continuous variable "age at menopause". In the County Study and in 40 years I and II, this was a question with 6 options: "

1=Ja, menopause inntrådt

2=Nei, menopause ikke inntrådt

3=Usikker om menopause

4=Gravid

5=primær amenorrhoe

6=Hysterectomy

Answering 1 and 6 were classified as postmenopausal, 2 and 4 were premenopausal, 3 and 5 were uncertain and classified as the other missing according to age (see below):

If missing information, women were classified as premenopausal if they were less than 46 years of age. If they were older than 55 years of age, they were classified as postmenopausal. Women who were between 46 and 55 years of age were classified as perimenopausal / unknown. (Ref: EPIC).

Oral contraceptive use (woman only)

We made the variable "oral contraceptive use" a binary variable (ever / never). In CONOR it was reported in questionnaires as current, former or never user, and the current and former category were collapsed into ever user by us. There is no information about OC in the County Study.
In the 40 years study, this information was initially collected through interviews, later from questionnaires. Due to inconsistent information from several of these studies, we have only used information from 40 year III in our study. This is in accordance with advice from tex. Anders.

Post- menopausal hormonal therapy (PMHT) (women only)

Post-menopausal hormonal therapy (PMHT) in CONOR was 5 category options, with different answering options for never users, former users, and for users of PHT with or without prescriptions. In the 40 years study, the answering options were ever, former, never. There is no information about PHT in the Norwegian counties study.

Menarche (women only)

Age at menarche was categorized as a continuous variable. Information about menarche is in CONOR and 40 years III and IV.

Comment from Anders: use average age for menarche?

Women reporting menarche at age 6 years old or less (n=9), or 22 years old or more (n=31), were set to missing.

Parity (women only)

Information about parity was provided by the Statistics Norway, and is the reported number of live born children at 31. December 2001. This is the official data and is more updated than the questionnaire.

Age at first childbirth (women only)

Variable created from information provided by the SSB, which provided the year for the persons first child, and birth year.
Year first childbirth – year born = age at first childbirth

Smoking exposure before first childbirth (woman only)

Year at first childbirth was given by the SSB.
Age at smoking initiation is a continuous variable in CONOR and 40 years III and IV.

The age at smoking initiation variable in CONOR and 40 years III+IV was based on question "How old were you when you started smoking"?

In the Norwegian counties study, 4o years I and II cohort and Oslo health study I, this variable is constructed. We subtracted total years of smoking from age at enrollment to construct the age at smoking initiation. <u>This variable was available for both daily and former smokers.</u>

We therefore have good information about smoking exposure before first childbirth, for both former and current smokers.

Formulas:

1. Year of survey assessment – total years of smoking = year of smoking initiation
   Year of smoking initiation – year of birth = age at smoking initiation

2. Age at enrollment - total years of smoking = age at smoking initiation

<u>Total: Age at smoking intiation</u>

<u>Year first childbirth – year smoking initiation = years of smoking before first childbirth</u>

Excluded:

- Male sex
- Non-smokers

- Smokers initiating after first childbirth
- No parity

In the variable exposure_before_first_childbirth are those with negative number (ie those initiating *after* first childbirth) not included.

Physical activity

The physical activity variable was created as a 1 to 4 categorical variable, with the variable description from CONOR as a reference: 1. Reading, watch TV, other sedentary activity, etc. 2. Walking, bicycling, etc. 3. Light sports, heavy gardening > 4 hours pr week. 4. Hard exercise, competitive sports regularly. In all the included studies except 40 years III, there were a 1 to 4 categorical variable.

In the 40 years III, there were two questions for physical activity: "how much light activity do you do pr week?", and "how much heavy activity do you do pr week", with a 1 to 4 answering option for both questions.

If answering 1 or 2 to I aktiv then 1
3 or 4 to Iaktiv then 2
1 or 2 to h_aktiv then 3
3 or 4 to h_aktiv then 4

Group 1: Light physical
Group 2: Mild physical activity
Group 3: Moderate physical activity
Group 4: Hard physical activity

Education

We have information about education level from SSB, and the 1970, 1980 and 1990 census. By consensus, we decide to use the highest level of education from the 1980 or 1990 census. If the information is missing, then we use the 1970 census. If no information from any census, then real missing.

Educational level was given in 1-8 categorical variables from SSB. Value 9 is not answered or unknown level of education:

1. 7 years primary school
2. 9-10 years primary/secondary school
3. Technical school, middle school, vocational school, 1-2 years senior school
5. University or university college level 1
6. University or university college level 2
7. University or university college level 3

8. University researcher level

9. Not answered or unknown level of education

These were merged into four levels of education as follows:

1: 1 and 2 low education level
2: 3 and 4 low/medium education level
3: 5 and 6 medium/high education level
4: 7 and 8 high education level

This made four education categories (new_ses4groups_NEW).

Income

As for education, information provided by SSB from the 1970, 1980, 1990. Information about income was categorized in different ways in the different census, which makes it difficult to compare the different time periods.

Income was categorized as follows: Distribution of all incomes at one census was categorized in quartiles. The first quartile was given value 1, the second quartile was given value 2, the third quartile was given 3, and the fourth quartile was given 4. This was done for all three census independently.

The highest quartile registered at either census counted for that individual. The income files were organized by Knut Hansen in the master file (income_max_quart).

SES

To create four groups for socioeconomic status (SES), income and education categories were added. The sum classified the individuals as follows:

A) 2 score= SES group 1
B) 3 and 4 score = SES group 2
C) 5 and 6 score= SES group 3
D) 7 and 8 score= SES group 4

Comment: we suggest creating 3 SES groups instead of 4. The reason for this is that the groups 2 and 3 will be very homogenous, if we create 4 categories.

If we create 3 categories, we will have a low, middle and high SES category, which is a common way of classifying social groups. It probably gives a more correct picture of the data, as the most important issue about SES will be to differ between low and high SES. We therefor also create a variable (ses3groups_NEW), where the above group 2 and 3 is merged.

eb
rp

Appendix 5

Other publications during the PhD period

1.

Cigarette smoking and colorectal cancer mortality among 602,242 Norwegian males and females.

Parajuli R, **Bjerkaas E**, Tverdal A, Le Marchand L, Weiderpass E, Gram IT.

Clin Epidemiol. 2014

2.

Active and passive cigarette smoking and breast cancer risk: results from the EPIC cohort.

Dossus L, Boutron-Ruault MC, Kaaks R, Gram IT, Vilier A, Fervers B, Manjer J, Tjonneland A, Olsen A, Overvad K, Chang-Claude J, Boeing H, Steffen A, Trichopoulou A, Lagiou P, Sarantopoulou M, Palli D, Berrino F, Tumino R, Vineis P, Mattiello A, Bueno-de-Mesquita HB, van Duijnhoven FJ, Bakker MF, Peeters PH, Weiderpass E, **Bjerkaas E**, Braaten T, Menéndez V, Agudo A, Sanchez MJ, Amiano P, Tormo MJ, Barricarte A, Butt S, Khaw KT, Wareham N, Key TJ, Travis RC, Rinaldi S, McCormack V, Romieu I, Cox DG, Norat T, Riboli E, Clavel-Chapelon F.

Int J Cancer. 2014

3.

The increased risk of colon cancer due to cigarette smoking may be greater in women than men.

Parajuli R, **Bjerkaas E**, Tverdal A, Selmer R, Le Marchand L, Weiderpass E, Gram IT.

Cancer Epidemiol Biomarkers Prev. 2013

4.

Smoking increases rectal cancer risk to the same extent in women as in men: results from a Norwegian cohort study.

Parajuli R, **Bjerkaas E**, Tverdal A, Le Marchand L, Weiderpass E, Gram IT.

BMC Cancer. 2014