Potential risk factors for chronic musculoskeletal complaints in a general population. The HUNT-study.

by

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LIST OF PAPERS

1. Kvalheim S, Sandven I, Hagen K, Zwart JA.

Smoking as a risk factor for chronic musculoskeletal complaints is influenced by age. The HUNT Study. PAIN 2013;154:1073-1079.

2. Kvalheim S, Sandvik L, Winsvold B, Hagen K, Zwart JA.

Early menarche and chronic widespread musculoskeletal complaints- Results from the HUNT study.

European Journal of Pain. 2016 Mar;20(3):458-64. doi: 10.1002/ejp.747. Epub 2015 Jul 1.

3. Kvalheim S, Sandvik L, Hagen K, Zwart JA. Oral contraceptives and Chronic Widespread Musculoskeletal Complaints - Cross sectional results from the HUNT Study.

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ABBREVIATIONS

ACR - American College of Rheumatology

BMI - body mass index

CI - confidence interval

HADS - Hospital Anxiety and depression scale

HPA - hypothalamic-pituitary-adrenal

HUNT - Helseundersøkelsen i Nord-Trøndelag

IASP - The International Association for the Study of Pain

MSCs - Musculoskeletal complaints

OCs - oral contraceptives

SES - socioeconomic status

WMSCs - Widespread Musculoskeletal complaints

SUMMARY

Musculoskeletal complaints (MSCs) are some of the most frequent causes for disability, work absence and long-term sick leaves and represent an important economic burden to society. The total burden of MSCs is huge and risk factors are of major interest to explore. The cause of musculoskeletal disorders is multifactorial, and some risk factors are well known. However, the causes and mechanisms remain unknown, and improved prevention and management of MSCs disability are required. Therefore, further research of potential risk factors, predictors and clinical course of MSCs is still warranted.

The aim of this study was to explore potential risk factors for chronic MSCs and chronic widespread musculoskeletal complaints (WMSCs). We used information from the health surveys in Nord-Trøndelag (HUNT), with data from HUNT 2(1995-1997) and HUNT 3 (2006-2008). We explored smoking as a potential risk factor for chronic MSCs later in life, based on the 11 years follow-up period between HUNT 2 and HUNT 3. Based on cross-sectional studies from HUNT 2, we explored the association between age at menarche and chronic WMSCs (paper 2) and the association between the use of oral contraceptives (OCs) and chronic WMSCs (paper 3). The cross-sectional studies described in paper 2 and paper 3, comprised only female participants in HUNT 2.

Regression analyses were used to assess the associations, with adjustment for potential confounders and assessment of potential effect modification.

The results in paper 1 show that smoking at baseline represents a 20% increased risk for chronic MSCs at follow-up for those less than 50 yrs.

In paper 2 there was an association between early age at menarche and chronic WMSCs later in life, but the difference in absolute risk was low (3%).

In paper 3 there was an association between previous use of OCs and chronic WMSCs, most evident in women younger than 39 yrs. Current use of OCs was not associated with chronic WMSCs.

INTRODUCTION

1.1 Background

Musculoskeletal complaints (MSCs) are highly prevalent in western communities and a major public health problem as one of the most frequent causes for disability, work absence and long-term sick leaves (1-3).

In Norway, MSCs are the most frequent medical cause for sick leave, contributing to about one third of long term work disability (http://www.formi.no/images/uploads/pdf/rapport_mussp_online.pdf). 75-80% of a Norwegian adult population experience musculoskeletal pain during a one month period (1) . There are more women than men reporting MSCs and the prevalence increases with age (1, 4, 5). Complaints of the musculoskeletal system comprise a wide range of different diseases associated with pain and varying degrees of disability. Generally, most of MSCs are minor complaints which do not affect work participation or activities of daily life to a substantial degree. However, in Norwegian health surveys, about half of the adult population reports long-lasting MSCs, i.e. lasting more than 3 months (6, 7). The most common complaints are back pain, neck and shoulder pain. Localised, single site pain, is less common and has demonstrated little impact on physical fitness and daily activities. Most of the individuals with musculoskeletal pain report pain from a number of sites. Approximately 10% have localised pain, and 40% suffers from multiple pain sites (8). There is an association between number of pain sites and the degree of disability (1), and the impact is highly dependent on how widespread the pain is and the number of pain sites (8).

Similar patterns are observed in studies conducted in other western countries, as in the Norwegian health surveys (4, 9-12). Due to ageing, the overall load of MSCs is increasing throughout the world. Over the span of 20 years from 1990 to 2010, MSCs have been among the main contributors to the disability burden in high-income countries. Consequently, MSCs represent an important economic

burden to society and the total burden of MSCs is huge and risk factors are accordingly of major interest to map and explore.

Epidemiological studies have been important to identify several potential risk factors. The cause of musculoskeletal disorders is clearly multifactorial, and some risk factors are well known and undisputable. However, the causes and mechanisms remain unknown, and improved prevention and management of disabilities due to MSCs are required. Therefore, further research of potential risk factors, predictors and clinical course of MSCs is still warranted.

In this thesis potential risk factors for MSCs were explored, based on epidemiological data from the largest population based health survey in Norway, "Helseundersøkelsen i Nord Trøndelag (HUNT)".

1.2 Diagnosis and classifications of musculoskeletal complaints (MSCs)

MSCs are not a clearly defined entity or diagnosis and there is no single case-definition. Commonly used terminology for musculoskeletal symptoms include musculoskeletal pain, disorders, complaints, conditions or diseases. MSCs comprise of a whole variety of diagnoses and discomfort in the musculoskeletal system, and are usually characterised by pain and/or stiffness in the joints or muscles and loss of function either localised or widespread.

Pain is a subjective experience and not an objectively measureable symptom. The International Association for the Study of Pain (IASP) defined pain as "an unpleasant sensory and emotional experience associated with actual or potential damage or described in terms of such damage". Chronic pain may arise from an initial injury, or there may be an ongoing cause, such as illness. There may also be no clear cause. In general, there are no specific laboratory tests or objective measures for the diagnosis of MSCs. However, underlying conditions like rheumatologic diseases, osteoarthritis, osteoporosis, and other conditions which might contribute to MSCs, are usually diagnosed and classified by objective findings and measures.

The diagnosis of MSCs is based on self-report. The frequency of MSCs in the general population has usually been assessed by use of Health Interview Survey (HIS) and Health Examination Survey (HES). As both techniques are poorly standardised, the reported occurrence of MSCs in a general population is varying substantially and, as a consequence, the comparison of data pertaining to different populations and countries is hampered. Uniform diagnostic criteria for MSCs are still warranted for the evaluation and comparability of studies.

Disease occurrence is commonly measured as incidence (first ever occurrence or onset of a condition) or prevalence (presence of a condition). Prevalence may be measured at one point of time, or over a defined period of time. There are significant variations in how prevalence and incidence are reported. It is difficult to assess the real frequency of MSCs which, in part, is a consequence of case-definition uncertainties and differences in the methods adopted in the epidemiological studies.

In the Norwegian study of HUNT 2, the incidence of MSCs lasting at least 15 days during the past month, was 7.9 % and the age-adjusted prevalence of chronic MSCs was 44.8 % (12). In HUNT 3, the age-adjusted prevalence of chronic MSCs was 47.9 %.

1.3 Diagnosis and classification of chronic MSCs and chronic widespread musculoskeletal complaints (WMSCs)

MSCs might be regarded as a continuum from localised to widespread pain (9, 13). Widespread musculoskeletal pain conditions are characterised by a gradual onset followed by a complex episodic course with remittance and recurrence of pain symptoms, and often established by early adult life (9).

Chronic MSCs and WMSCs are most commonly defined as lasting more than 12 weeks. However, the definition of chronic varies significantly. According to the definition given by Bonica, chronic pain is pain that persists beyond the time one would expect normal healing to occur (14). This definition involves different, and more or less arbitrarily, specified duration of pain. Therefore, different

(epidemiological) studies might present alternative definitions as there is discrepancy on what that duration should be. An argument has been made that the term "persistent pain" should be used in lieu of "chronic pain" (15).

Chronic widespread pain and fibromyalgia are regarded as generalised musculoskeletal pain syndromes. WMSCs are the clinical hallmark of fibromyalgia. Several argue that it is most reasonable to regard fibromyalgia as a continuum of chronic widespread pain, rather than a distinct diagnostic entity. According to the American College of Rheumatology (ACR) 1990 criteria, fibromyalgia is defined as pain that is bilateral, above and below the waist, in the axial skeleton and lasts for at least 3 months. The case definition of fibromyalgia has changed somewhat with increasing recognition of the importance of cognitive problems and somatic symptoms. These factors were not considered in the 1990 ACR classification criteria .The preliminary new ACR criteria for fibromyalgia remove the requirement for tender points and provide a measure based on a continuum of symptoms rather than a distinct cut-off point (16, 17). This might lead to a new basis for longitudinal studies in this area, and, subsequently, new estimates of the burden of generalised musculoskeletal pain syndromes. There is still controversy around the criteria of fibromyalgia.

As for many common musculoskeletal conditions, generalised musculoskeletal pain conditions have significant variations in case definitions that have been used in epidemiological studies. Therefore, the reported occurrence of WMSCs varies in different studies of general population. Prevalence is, though, the preferred measure in the context of generalised musculoskeletal pain conditions (9) as it is debatable whether measures of incidence capture initial onset of the condition or the onset of a new episode of an already prevalent condition. The prevalence of fibromyalgia in Western countries is reportedly 3-5%, with a significant female predominance. However, the prevalence of WMSCs has a range from 11.4% to 24% (11). When it comes to the reported prevalence of fibromyalgia in Norway, there is a span between 1 and 10 % (18, 19).

In HUNT 2 the age-adjusted prevalence of chronic MSCs was 44.8 % and 22.0 % for chronic WMSCs. In HUNT 3, the age-adjusted prevalence of chronic MSCs was 47.9 % and 23.6 % for chronic WMSCs.

1.4 Impact and consequences of chronic MSCs and WMSCs

MSCs are the most common cause of severe long term pain and physical disability, affecting many individuals physically and psychosocially. Chronic MSCs might lead to withdrawal from social life and work life and impose severe financial burdens on many levels: Costs of healthcare services and medication, job absenteeism and disruption in the workplace, loss of income, financial burden on family, friends and employers, worker compensation costs and welfare payments.

The impact of musculoskeletal conditions has been appreciated by the World Health Organization (WHO) and highlighted in The Bone and Joint Decade initiative (2000–2010) (20, 21). Chronic MSCs are not directly related to high mortality (22, 23) but still give a major contribution to the burden of disease and perceived health. While acute pain is by definition a brief and self-limiting process, chronic pain has a severe impact on quality of life of the pain sufferer and those around. Chronic pain patients report a lower quality of life than the general population (24). An association between chronic MSCs/WMSCs and poor health related quality of life (HRQoL) has also been clearly demonstrated (25, 26). Sleep deprivation, depression, reduced physical activity and inactivity, are common consequences of chronic pain as well as being possible risk factors and contributors to pain. These factors might be important in the explanation of increased morbidity and indirectly increased mortality as they might be common or underlying risk factor for other diseases (27, 28).

In most countries, MSCs constitute up to 10–20% of primary care consultations and are the second most common reason for consulting a doctor. MSCs are the reason for almost 20% of all health care utilization (29, 30). In a Swedish study from 1996, MSCs were the most expensive disease category,

representing 22.6% of the total cost of illness. The conclusion of a Norwegian report about MSCs says that there has been almost a doubling of the total societal costs based on a comparison of the statistical numbers from 2004 and 2009, even though the prevalence remains relatively unchanged. The greatest costs are the indirect costs related to job absenteeism and loss of productivity.

For 2014, The Statistics Norway report that diseases of the musculoskeletal system were the type of conditions that women were most often treated for in general hospitals. Among men, these diseases were the second most frequent reason for treatment, after injuries. One in six patients received treatment for a disease of the musculoskeletal system in 2014, whereof a substantial share are young women (http://www.ssb.no/helse/statistikker/pasient/aar).

The impact of chronic MSCs and WMSCs on individuals and society is expected to increase dramatically due to ageing, increased obesity and reduced physical activity of the world's population. From 1990 to 2010, MSCs have been one of the main contributors to the disability burden in high-income countries and there is a rapid increase in regions with low- and middle income. Measured by age-standardised years lived with disability (YLD), there has been more than 10% increase during this period, and MSCs cause 21.3% of the total years lived with disability, globally. There is a rapid increase in regions with low- and middle-income. Disability-adjusted life years (DALYs) count how many years of healthy life are lost due to death and non-fatal illness or impairment, and are an absolute measure of health loss. Disability-adjusted life years represent a health gap; they measure the state of a population's health compared to a normative goal for individuals which is to live the standard life expectancy in full health. In 2010, musculoskeletal disorders counted for 169624' (thousands) disability-adjusted life years globally, for all ages, both sexes combined, representing 6.7% of the total global disability-adjusted life years (3, 31, 32).

Globally, the highest incidence within MSCs has been found for low back pain. Low back pain yield the highest years lived with disability among 291 diseases and injuries evaluated in the Global Burden of Disease 2010 Study (3, 31). In Norway, low back disorders were the most common reason for

people claiming disability pensions (National Insurance Administration. Oslo: Norway; 1998 available from:

URL: http://www.trygdeetaten.no/), and MSCs in general represented 42% of all sick leave days in 2009. Chronic WMSCs/ fibromyalgia caused 5.4 % of permanent work disability in Norway in 2006.

In several regions of the world, notably in developing countries, the prevalence and impact of MSCs are not available. As a consequence of these uncertainties, the true global impact of MSCs is not known.

1.5 Epidemiological designs

Analytic (Exploratory) epidemiology

In an analytic study design, the purpose is to explicitly assess if a certain exposure is a risk factor for the outcome/disease of interest. The analytic study design can be divided into observational or interventional study designs. In an observational study, the investigator only observes the natural course of event whereas the investigator allocates the exposure in interventional study designs.

Observational studies can be divided into case-control and cohort or follow-up studies.

Cohort study

The English word *cohort* comes from the Latin word *cohors,* which meant "an enclosed area" or "a pen or courtyard enclosing a group of cattle or poultry". By extension, the word could refer to any group in general and in particular to a company of soldiers or a troop of cavalry in the army of ancient Rome. In epidemiology, a cohort is defined as “a designated group of individuals who are followed or traced over a period of time”(33). A cohort study, which is regarded as the archetype for all epidemiological studies, involves measuring occurrence of disease within one or more cohorts. The cohort comprises of persons with a common characteristic, defined by their exposure status. The

aim is to follow the defined cohort(s) through time to identify the outcome of interest and determine if the initial exposure status influences the risk of subsequent disease. There are prospective and retrospective (historical) cohort studies, defined by the timing of data collecting. In a prospective cohort study, the exposure may or may not have occurred when initiating the study, and the subjects are followed to determine the event of interest (disease/outcome).The outcome has not occurred when initiating the study with a prospective design. In a retrospective cohort study, all the relevant events are identified from recorded data i.e. both exposures and events have already occurred at the start of the study. In a retrospective cohort study, information of potentially confounding factors not already collected is very difficult or impossible to attain. The advantage is that such a study is faster, as the data has been collected, and accordingly to a lower cost. In a cohort investigation of diseases with long latency periods from exposure to disease occurrence, a retrospective study is considered particularly efficient.

A general population cohort study is feasible when common exposures are to be studied. In a study setting where a substantial proportion of a general population has been exposed to the factors of interest, the cohort does not have to be identified by the status of exposure. After a general population cohort is assembled, the cohort members can be classified according to the factors of potential interest already identified as prevalent/common exposures.

A cohort study is a longitudinal study which is defined by the data pertaining from different time points, where exposure information refers to a time point prior to the outcome/disease occurrence. The longitudinal design is therefore based on one of the premises for causality, namely temporality, where exposure has to come before the consequence/ the subsequent disease (34, 35).

In general, a cohort study has the strength of minimizing selection bias. However, if the knowledge of disease affects the selection or classification of exposed and non-exposed subjects, selection bias may be introduced to the study.

The cohort study design has the potential bias of losses to follow up which can affect the validity of the study (34, 36, 37).

Cross-sectional study

A cross-sectional study design is based on data of current disease status and exposure status and is the method of determining the prevalence of an outcome/disease. Generally, it has the advantage of being less time-consuming and may be relatively inexpensive to conduct. The main disadvantage is the lack of temporality, and consequently, a cross-sectional study is not appropriate to assess causality. However, cross-sectional data is occasionally used when they are considered to be a good proxy for longitudinal data. Sometimes, the current exposure status can be regarded as a good measurement of earlier exposure status. In cases where the exposure is a constant, i.e. tissue antigens or blood type, the study might be regarded as a longitudinal design.

1.6 Validity

A measure is valid if it measures what it tends to measure. A valid association is present if it reflects a true association between the exposure and the outcome. Validity has to be assessed based on other alternative explanations to the association. The alternative explanations are chance, bias and confounding.

Chance: To assess whether the association might be due to chance, the sample size is very important as it inflicts the interpretation of a significant p-value. In large sample sizes, the confidence interval is more informative because it shows the variability of the effect estimate.

Bias: Bias is a systematic error due to difference in selection, information, reporting and exposure. Bias is to be reported but not possible to adjust for.

The design or conduct of a study might introduce a systematic error, or bias, to the study. If cases and controls are selected differently, for example related to their exposure status, a selection bias is most likely introduced. Similarly, if the way the information is obtained differs between the groups, an information bias might be introduced. Information bias (misclassification) is an important source of bias in cohort studies. To avoid differential misclassification, one have to be certain that the outcome registration is not affected/influenced by the exposure. Misclassification refers to errors in the categorization of either exposure or disease status. Such errors are inevitable in any study, but the consequences of this type of bias depend on whether the misclassification with respect to one axis is or is not dependent of the classification of the other axis. If these misclassifications are independent of each other, i.e. the exposure or disease classification is incorrect for the same proportions of subject in the groups compared; the misclassification is random or non-differential. Random misclassification always results in an underestimate of the true relative risk. Random misclassification is often believed to be a less serious problem with respect to the validity of the findings since the bias introduced is always towards the null. However, if a substantial random misclassification exists, a study can report a finding of little or no effect when in fact a true association exists.

Confounding: If not properly adjusted for, confounding might contribute to a false conclusion of the strength of an association and whether a true association is present.

Confounding derives from the Latin verb “confundere”, meaning mingle and blend, so that different elements are indistinguishable; to confuse. In medical statistics and epidemiology, a confounder is defined as a factor that is both associated to the exposure and, independently, to the outcome/disease. If presence of a confounding factor, the observed relationship between the exposure and the disease can be attributable, totally or partly, to the effect of the confounder. Confounding might lead to erroneous conclusions in a study by either overestimation or underestimation of the true association between the exposure and the effect. Confounding can even

change the direction of the observed effect. Unlike bias, which primarily is introduced by the investigator or study participants, confounding is a function of the complex interrelationships between various exposures and disease (34).

2. AIMS OF THE STUDY

The aim of this study was to explore potential risk factors for chronic MSCs and chronic WMSCs.

The aims of the individual papers were:

Paper 1: To explore smoking as a potential risk factor for chronic MSCs later in life. Paper 1 was based on the 11 years follow-up period between HUNT2 (1995-1997) and HUNT 3 (2006-2008).

Paper 2: To explore whether the age at menarche was associated with chronic WMSCs. Paper 2 was based on a cross-sectional study from HUNT2.

Paper 3: To explore whether the use of oral contraceptives was associated with chronic WMSCs. Paper 3 was based on a cross-sectional study from HUNT2.

3. MATERIAL AND METHODS

3.1 Study population

HUNT is the largest population based health survey in Norway. All inhabitants aged 20 years or more in the Nord-Trøndelag County were invited to participate in an extensive health survey, "Helseundersøkelsen i Nord Trøndelag (HUNT)". The HUNT Study has been conducted in 3 waves so far, HUNT 1 (1984-1986), HUNT 2 (1995-1997) and HUNT 3 (2006-2008). The design applied in HUNT 1 was largely repeated in HUNT 2 and HUNT 3. The target population, including participants and non-participants, has been described in detail previously (38, 39). Participation was based on informed

consent, and the study was approved by the Regional Committee for Medical and Health Research Ethics. The population is ethnically homogenous, consisting mainly of Caucasians (>95%), with a low migration rate. Two questionnaires comprising more than 200 health-related questions, including questions about MSCs, were used in both surveys (HUNT 2 and HUNT 3). An invitation letter and a first questionnaire (Q1) were mailed to all inhabitants aged 20 years or more about 2 weeks in advance and brought to a brief medical examination (M1) that included blood pressure and height/weight measurements.

In HUNT 2 the total population aged 20 years or more, which comprised 93898 persons, was eligible for participation. A total of 65 237 participated, representing 69.5% of those invited in HUNT 2. In HUNT 3, the total population of 93 860 persons aged 20 years or more was invited. The participation rate was 54 % in HUNT 3. Regarding attrition between the HUNT 2 and HUNT 3 surveys, the participation rate in HUNT 3 decreased by 15.4 percentage points. The decrease was most pronounced in men and younger adults. Among 65 237 participants in HUNT 2, 10 507 (16.1%) had died at the time of HUNT 3, 240 had emigrated and 1 had disappeared. Out of all HUNT 2 participants, 72% of women and 69% of men also participated in HUNT 3 (39).

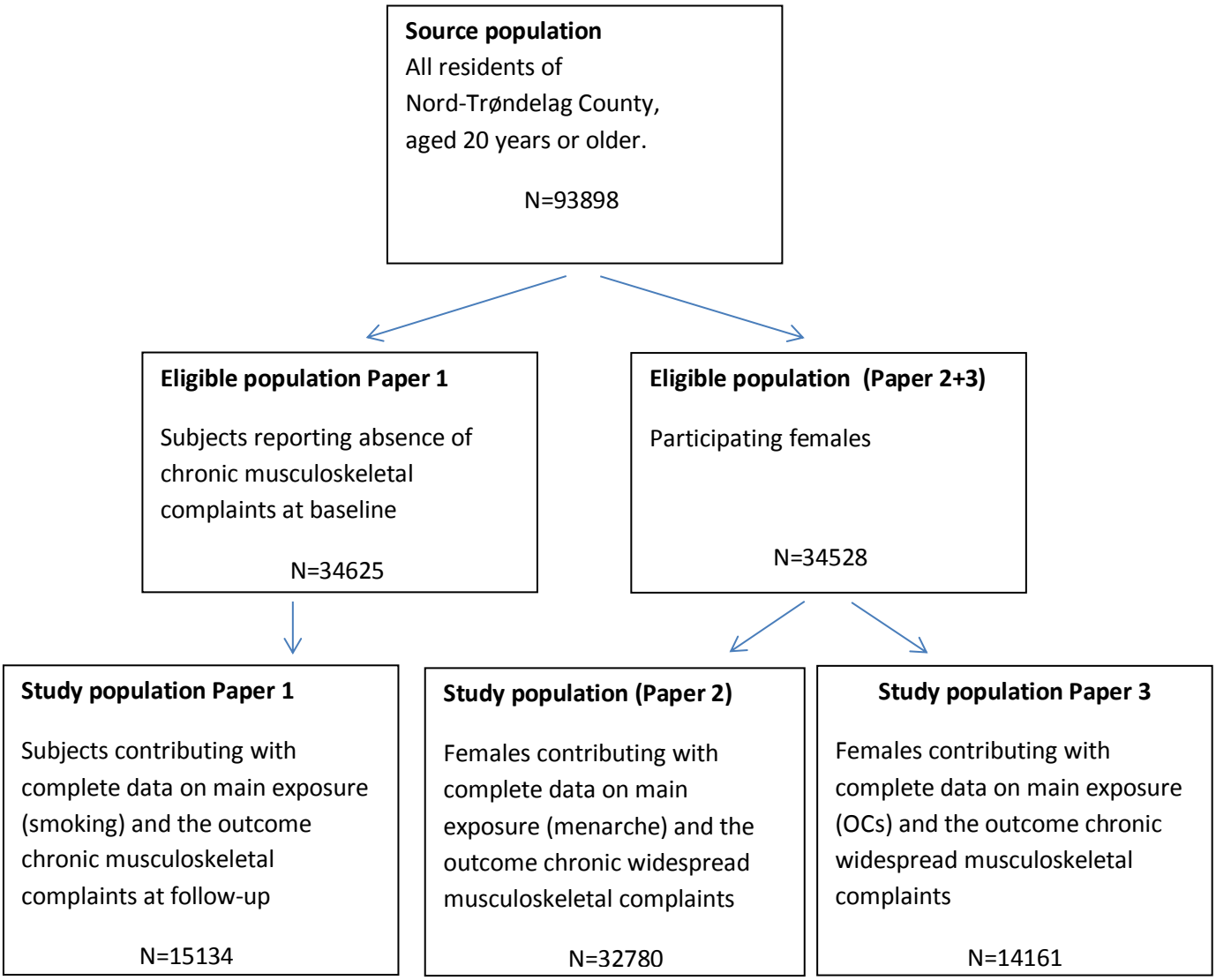
	HUNT 2	HUNT 3	HUNT 2+3
Invited (20yrs+)	N=93898	N=93860	
Participation	N=65237 (69.5 %)	N=50807 (54.1 %)	N=37071

The follow-up study (Paper 1) aimed at a cohort consisting of 15,134 participants, both men and women, without chronic MSCs at baseline (HUNT 2, 1995-1997), with valid information at follow-up (HUNT 3, 2006-2008). Persons with incomplete data on main exposure (smoking) and the outcome chronic MSCs were excluded from the study.

The cross-sectional studies described in paper 2 and paper 3, comprised only female participants in HUNT 2. Among the 46709 eligible women in HUNT 2, 35280 participated (75.5%) whereof 34,528 (73.9%) filled in the questionnaire (Q1) and participated in a brief medical examination that included blood pressure, height and weight measurements (M1). Females with incomplete data on main exposure (menarche or use of OCs) and the outcome MSCs were excluded from the study.

	HUNT 2
Invited women(20yrs+)	N= 47312
Eligible women	N= 46709
Participation	N= 35280 (75.5 %)
Participation (Q1+M1)	N= 34528 (73.9 %)

Flow chart of the study populations for the 3 studies:



3.2 Outcome measure

The outcome variable was defined as the presence of self-reported chronic MSCs/WMSCs. Firstly, chronic MSCs were identified, in accordance with the definition of chronic pain given by The International Association for the Study of Pain (IASP), by the screening question “During the last year have you had continuous pain and/or stiffness in muscles and joints for at least 3 months”? The screening question was identical in HUNT 2 and HUNT 3.

Secondly, those answering "yes" were asked to mark the location of pain on a drawing where one or more of the following areas could be chosen: neck, shoulders, elbows, wrist/hands, upper back, low back, hips, knees, and/or ankles/feet. According to the 1990 criteria of the American College of Rheumatology (ACR), chronic WMSCs are defined as chronic MSCs of the following three regions: axial skeleton (neck, upper back or lower back), above the waist (neck, shoulders, elbows, wrist/hands or upper back), and below the waist (lower back, hips, knees or ankles/feet). The side localisation was only assessed in HUNT 3.

3.3 Confounders and risk factors

The assessed factors associated with chronic MSCs/WMSCs include age, gender, smoking, increased BMI, low education, low family income, low physical activity, depression and anxiety (9, 11).

Age: The prevalence of MSCs/WMSCs increases with age, showing a flattening or decreasing curve after 70-80 yrs. (4, 32).

Gender: Women report more pain in general and are at higher risk for MSCs than men (4, 9, 11). Since pain is a subjective measure, based on self-report, the sex differences might at least partly be explained by psychosocial or cultural mechanisms (40). There is an abundant evidence of hormonal contributions to common pain conditions (40), and subsequently a possible explanation for the female predominance. The pain mechanisms are complex interactions of psychological and biological pathways.

BMI/Obesity: Body Mass Index (BMI) is a simple index of weight-for-height that is commonly used to classify underweight, overweight and obesity in adults. It is defined as the weight in kilograms divided by the square number of the height in meters (kg/m^2). The WHO's International Classification

of adult underweight, overweight and obesity according to BMI defines underweight as BMI<18.5, normal weight as BMI 18.5-24.99, overweight as 25.00-29,99, and obesity as BMI>30.00.
As concluded in systematic reviews and longitudinal studies, increased BMI and obesity are identified as risk factors for MSCs (41-44). The mechanisms for a relationship between BMI and MSCs are not fully understood, and several pathways have been discussed. There might be mechanical, structural, physiological or behavioural mechanisms to explain the association between BMI and MSCs.

Socioeconomic status (SES)/educational level: Low education, which reflects low SES, is associated with chronic MSCs and, more strongly, to chronic WMSCs (45, 46). Low SES is associated to poor health in general and has been shown for self-reported health and for overall mortality (47, 48). Inequalities in health are determined by socioeconomic differences in lifetime exposure to various factors, but comparative studies have methodological drawbacks (49). The relationship between socioeconomic status and morbidity and mortality is well known from a number of studies (49, 50). Educational level, occupation and income might all be regarded as different aspects of socioeconomic status (46). Data from the HUNT Study have shown a consistent pattern of increasing self-reported health problems with decreasing educational level (51).
A high level of education was defined in our papers as college or university.

Physical activity: There is evidence of physical inactivity being both a consequence and a risk factor for chronic MSCs (52-55). There are methodological problems in measuring physical activity. In epidemiologic studies, information about physical activity is often collected using questionnaires, through self-reporting or by interviewing, and the reliability and validity of questionnaires are important. Studies have shown moderate to fair validity and reliability for moderate to light physical activity, and somewhat better for more rigorous physical activity and occupational physical activity (56, 57).

Due to the high proportion of missing, physical activity could not be assessed as a potential confounding factor in paper 2 and 3. In paper 1, light physical activity (defined as high when ≥1 hour per week and low when less than 1 hour per week), was assessed as a potential confounder with the awareness of 11.5% missing data. Physical activity did not confound the association and accordingly not included in the final analysis.

Psychological distress: There is abundant evidence of an association between psychological distress or poor mental health and chronic MSCs (58-61).

Psychological distress has been reported to precede musculoskeletal pain and to be a consequence of such conditions (26, 45, 62-65). A large proportion of pain and dysfunction in the musculoskeletal system is considered to be non-specific (66, 67). Non-specific pain has a high degree of association with personal and psychosocial factors (66). Psychological and sociocultural factors are important risk factors for musculoskeletal pain syndromes, especially in the adult population that reports WMSCs (66, 68).

Anxiety and depression were measured by HADS (Hospital Anxiety and Depression Scale). To achieve a high level of specificity a cut-off value of ≥11 was chosen for both subscales in the present study (69-71). HADS is a reliable and valid instrument for assessing the separate dimensions, symptom severity and caseness of anxiety and depression in the general population (72) and in patients with acute low back pain (73).

Smoking: According to WHO, tobacco is the leading cause of death, illness and impoverishment. The tobacco epidemic is one of the biggest public health threats the world has ever faced, killing around 6 million people a year. Tobacco use is one of the main risk factors for a number of chronic diseases. Despite this, it is common throughout the world. A number of countries have legislation restricting tobacco advertising, and regulating who can buy and use tobacco products, and where people can

smoke (74).Tobacco smoke contains tare, carbon monoxide and the highly addictive psychoactive ingredient, nicotine. Additionally, 7000 different chemical components have been identified whereof 70 might cause serious diseases. Carbon monoxide is identified as the leading cause of cardiovascular disease among smokers (74), (www.who.int/mediacentre/factsheets/fs339/en/, www.cancerresearchuk.org/).

A study on global trends and projections for tobacco use found that the prevalence of tobacco smoking has fallen between 2000 and 2010, for both women and men (www.who.int/mediacentre/news/releases/2015/trends-tobacco-use/en/). Cigarette smoking prevalence among adults (aged 16 and over) in European countries has decreased since the early 1970s, and the sex gap in cigarette smoking prevalence has narrowed in recent years. The trends are the same for Norway, where 13 % of the population were daily smokers in 2014, compared to 21 % in 2010 and 42% in 1973. In HUNT 2 (1995-1997) 22.7% were daily smokers, whereas in HUNT 3 (2006-2008) 11.7% were smoking cigarettes daily.

An association between smoking and MSCs has been studied in meta-analyses (75-77) , mostly based on restricted population samples, and only a few prospective studies of a general population (78, 79).

These meta-analyses conclude that there is an association between smoking and low back pain, and being an ex-smoker predicts the onset of neck pain, but there is a fairly modest association and possibly due to statistical artefacts.

Self-reported smoking has been evaluated and is a valid indicator of current smoking (80, 81).

Menarche: Menarche is defined by the onset of menstruation in girls, is due to increased estradiol production in puberty. The age of menarche depends on the interaction between genetic and environmental factors and, in some cases, lifestyle factors (82). It is partly a heritable trait defined by

a complex genetic pattern. 106 genomic loci have been identified through a study comprised of 182,416 women of European descent. Many of these genomic loci were implicated in body mass index and various diseases. The mechanisms that determine menarche and it's links to disease risk remain unclear (83). Obese girls tend to enter puberty earlier (84).

In western countries, the age at menarche has been decreasing the last decades. Studies have shown that up to 60% might be explained by the genetic variances, and environmental factors such as overweight and the widespread presence of endocrine-disrupting chemicals is suspected to contribute to the trend of earlier pubertal onset (85), but there is still inconsistent findings of the influence of non-genetic factors of age at menarche. Early menarche (<12yrs) is consistently associated with higher risk of death from all causes (86), and an association between menarche ≤12yrs and headache is reported (87). When it comes to MSCs, an association between age at menarche and pelvic pain in pregnancy has been reported (88). There is little evidence of the associations between menarche and MSCs in general.

Oral contraceptives (OCs): OCs are used primarily for birth control and are commonly used in Norway and other Western countries. OCs prevent ovulation and are usually composed of a synthetic estrogen, ethinyl estradiol, and a progestin (89). OCs were introduced to the Norwegian market in 1967. The dosage of estradiol was initially very high (150µg), but nowadays there is a lower dosage of estradiol (20-35µg). The use of OCs increases the risk for deep venous thrombosis (90) and reduces certain types of cancer (91) and possibly osteoporosis (92-96). The risk of ovarian, endometrial and colon cancer is reduced with OCs use (91, 97) , while data on breast cancer are conflicting (98, 99). The use of OCs in women over age 35 years who smoke is associated with an increased risk of death from cardiovascular events (100). However, overall mortality rates are not increased, and may actually be decreased, among ever users of OCs compared with never users (101, 102).

There is sparse evidence of an association between OCs and MSCs, but duration of OCs use might have an association to low back pain (103). A study of use of OCs and rheumatoid arthritis (RA) concluded that there is no cumulative effect between use of OCs and the risk of RA (104).

3.4 Statistics and data processing

	Research Question	Study design	Method	Confounding	Effect modification
Paper 1	Risk/Association Smoking-MSCs	Follow-up	Poisson regression	Mantel Haenszl	Breslow and Day
Paper 2	Association Menarche-WMSCs	Cross-sectional	Logistic regression	Logistic regression	Logistic regression Interaction factor
Paper 3	Association OCs- WMSCs	Cross-sectional	Logistic regression	Logistic regression	Logistic regression Interaction factor

We used a longitudinal design with an explanatory strategy in paper 1 and cross-sectional design with descriptive strategy in paper 2 and 3. Our major hypothesis was that the exposure variables were associated with occurrence of chronic MSCs/WMSCs. The other variables were of interest as potential confounders or effect modifiers of this association.

A significance level of 5% was used throughout.

We used the STROBE (Strengthening the reporting of observational studies in epidemiology) statement guidelines in reporting our study (105).

Paper 1:

In the follow-up study in paper 1, we used Poisson regression analysis to assess the association between smoking and chronic MSCs. Total cumulative observation time was 171328 person years with a median observation time of 11.3 years.

Confounders were identified and controlled univariate using the Mantel-Haenszel method for pooled relative risk estimates (34, 106). The confounding effect was quantified by comparing the adjusted Mantel-Haenszel incidence rate ratio (IRR) to the crude IRR. A Breslow and Day test of heterogeneity was done to pinpoint effect modification. Assessment of effect modification was done also at the additive scale, as it is important in public health (36). Because of variability in observation time of subjects, the Poisson regression model was used to estimate the incident rate ratio (IRR) of daily smoking as the exposure and chronic MSCs as the outcome controlling for the presence of interactions. The significance of interactions was highlighted by the log – likelihood ratio test, comparing the model with interactions versus the model without interactions (107). A Mantel-Haenszel test of linear trend was applied to pinpoint a dose response effect for different exposure levels of smoking (106). The etiological fraction (EF) was estimated $EF = \frac{P_E(IRR-1)}{P_E(IRR-1)+1)}$ where P_E is the follow-up time in exposed divided by the total follow-up time.

We adjusted for the interaction between age and smoking.

Statistical analyses were performed using STATA version 11.0.

Paper 2:

Logistic regression analysis was used to estimate the odds ratio (OR) with menarche ≤12yrs as the exposure, and chronic WMSCs as the outcome in a cross-sectional design. Initially, a crude association between age at menarche and chronic WMSCs was analysed. The association between

potential confounders and chronic WMSCs was investigated using univariable logistic regression, with only those significantly associated ($p< 0.05$) with both exposure and outcome taken forward in the multivariable model as confounders of the association between age at menarche and chronic WMSCs.

Interaction analyses between all independent variables and the exposure of interest were performed by introducing interaction terms and were included in the final analyses if statistically significant (with $p< 0.05$).

Statistical analyses were performed using IBM SPSS version 21, Armonk, N.Y, USA.

Paper 3:

Logistic regression analysis was used to estimate the odds ratio (OR) with use of OCs as the exposure, and chronic WMSCs as the outcome in a cross-sectional design.

The association between use of OCs and chronic WMSCs was controlled for potential confounding using logistic regression analysis, first introducing potential confounders one at a time, and then using only those significantly associated with WMSCs (with p-level < 0.05) in the multivariable model.

Analyses for effect modification of all independent variables, on the association between exposure and outcome, were performed by introducing an interaction term, and selected by statistical significance (with p-level<0.05). Stratified analyses were performed as a supplementary assessment of the confounding and effect modification, using the Mantel-Haenszel method to identify confounding effect, and a Breslow and Day test of heterogeneity to identify any effect modification (34, 106). Logistic regression analysis was used to estimate the OR of previous or current use of OCs as the exposure, and chronic WMSCs as the outcome.

We adjusted for the interaction between age and previous use of OCs.

Statistical analyses were performed using IBM SPSS version 21, Armonk, N.Y, USA.

4. SUMMARY OF RESULTS

4.1 Paper I

Smoking as a risk factor for Chronic Musculoskeletal Complaints is influenced by age. The HUNT Study.

Abstract:

Chronic musculoskeletal complaints (MSCs) are among the major health problems, and cross-sectional studies suggest an association between smoking and MSCs. The causal relationship, however, is not known. The present study is designed to assess the association between smoking and chronic MSCs and is based on data from a large longitudinal cohort study of all inhabitants ≥20 years in Nord-Trøndelag County (Helse Undersøkelsen i Nord-Trøndelag -HUNT), conducted in 1995-1997 (HUNT 2) and 2006-2008 (HUNT 3). The study population consisted of 15,134 subjects without chronic MSCs and valid exposure data on smoking at baseline (HUNT 2). The outcome was defined as presence of chronic MSCs at follow-up (HUNT 3). The results show that smoking at baseline represents a 20% increased risk (IRR=1.20, 95% CI: 1.14 – 1.27, p=0.0001) for chronic MSCs at follow-up. The risk for chronic MSCs by daily smoking decreased with increasing age up to 50 years, which after there was no significant association. The results show that modifiable risk factors like smoking should be included in public health intervention programs for MSCs.

4.2 Paper II

Early menarche and chronic widespread musculoskeletal complaints. Results from the HUNT study.

Abstract:

Background: There is a predominance of chronic widespread musculoskeletal complaints (WMSCs) among females. Previous studies suggest an association between hormonal factors and pain. However, it is not known whether earlier age at menarche is associated with higher prevalence of chronic WMSCs.

Aim: To investigate the association between age at menarche and chronic WMSCs.

Methods: Data from a cross-sectional study of inhabitants≥20 years in Nord-Trøndelag County (Helseundersøkelsen i Nord-Trøndelag -HUNT), conducted in 1995-1997 (HUNT 2) were used. The study population comprised 32,673 women with valid information of age at menarche (exposure) and chronic WMSCs (outcome data).

Results: In total, 8,986 (27.5%) women reported WMSCs. The overall prevalence of WMSCs was 29.7% among those with menarche ≤12yrs and 26.7% among those with menarche >12yrs. The prevalence of chronic WMSCs was consistently higher for those with early age at menarche in all age groups. The crude odds ratio for chronic WMSCs, when comparing women with age at menarche ≤12yrs to women with age at menarche >12yrs, was 1.16 (95% CI: 1.10-1.22). The corresponding odds ratio was 1.26 (95%CI: 1.19-1.34) when adjusted for age, education, body mass index (BMI), smoking, alcohol consumption, depression, systolic blood pressure (SBP), and parity.

Conclusion: In this cross-sectional study there was an association between early age at menarche and chronic WMSCs later in life, but the difference in absolute risk was low (3%).

4.3 Paper III

Oral contraceptives and chronic widespread musculoskeletal complaints. Results from the HUNT study.

Abstract:

Background: There are studies which suggest an association between musculoskeletal complaints (MSCs) and sex hormones. Sex hormones may be affected by use of oral contraceptives (OCs). The aim of this study was to assess the association between the use of OCs and chronic widespread musculoskeletal complaints (WMSCs).

Methods: Data from a large cross-sectional population-based study of inhabitants aged ≥ 20 yrs in Nord-Trøndelag County (Helseundersøkelsen i Nord-Trøndelag -HUNT), conducted in 1995-1997 (HUNT 2) was used. The study population consisted of 14161 women aged 20-55 yrs with valid exposure and outcome data. The outcome was defined as presence of chronic WMSCs.

A logistic regression model was used to estimate the odds ratio (OR) of previous or current OCs use as the exposure, and chronic WMSCs as the outcome.

Results: 3053 (21.6%) women reported chronic WMSCs, 2917 (20.6%) had chronic non-WMSCs, and 8191 (57.8%) had no MSCs. In age-adjusted analyses no significant association with chronic WMSCs was found when comparing women who currently used OCs to those who had never used OCs (OR 0.99, 95% CI 0.90-1.09). The corresponding OR was 1.27 (95%CI: 1.15-1.39) for women who had previously used OCs, and the association between previous use of OCs and chronic WMSCs was more evident in women ≤ 39 yrs (OR 1.41, 95% CI: 1.18-1.68) than women > 39 yrs (OR 1.16, 95% CI 1.03-1.30).

Conclusion: In this cross-sectional study there was an association between previous use of OCs and chronic WMSCs, most evident in women younger than 39 yrs. Current use of OCs was not associated with chronic WMSCs.

5. METHODOLOGICAL CONSIDERATIONS

5.1 Designs

A general population cohort study is feasible when common exposures are to be studied. Paper 1 is based on a general population cohort study where smoking, a common exposure in a general population, was assessed as a risk factor for subsequent chronic MSCs.

A longitudinal cohort study which might be classified in different ways: a historical cohort study, a retrospective cohort study or a retrospective follow-up study. Some would argue that all follow-up studies have a prospective design and subsequently classify it as a prospective cohort study. As the study in paper 1 is based on data that already exists, both for the exposure and the outcome, one might argue that this cohort study is historical/retrospective and not prospective.

Paper 2 and 3 are cross-sectional studies based on data from HUNT 2. In paper 2, we could argue that the study could be considered as a proxy for longitudinal data as age at menarche is an exposure reported retrospectively in a cross-sectional study. As all the participants in the study are 20 yrs. or more, age at menarche is a prior and well-defined event.

In paper 3, however, it is not reasonable to argue that the cross-sectional data give a proxy for a longitudinal design. The exposure “previous use of OCs” is not as well-defined event as the exposure in paper 2.

Paper 2 was originally designed as a follow-up study with baseline data from HUNT 2 and the outcome data from HUNT 3, but the editor/reviewer did not find the rationale for associating early

menarche specifically with WMSC onset during an arbitrary 11-year period at some later time of life. As this was a major concern, the design was changed to a cross-sectional study.

Applying a longitudinal design for paper 3 raises somewhat the same concerns as for the design in paper 2, and was accordingly designed as a cross-sectional study.

5.2 External validity

External validity, or generalisability, refers to the extent to which results from a study can be generalised outside of the study population. A prerequisite for external validity is internal validity, i.e. that the results hold true for its study population itself. The representativeness of the study sample is often the focus when evaluating the external validity in epidemiological studies.

The present study is questionnaire-based from a general population in the county of Nord-Trøndelag in Norway. We do have reasons to believe that this population is representative for the Norwegian population and as well for most of the European population. The population is ethnically homogenous, consisting mainly of Caucasians (>95%), with a low migration rate. However, the habitation is mostly rural with little urbanization which might be argued to give somewhat less generalisability as we know that half of the world's population lives in urbanized areas.

5.3 Internal validity

Participation and Selection bias

Selection bias reduces the external validity. Low participation rate is most problematic if the cohort is to be used in surveillance or cross-sectional studies. Follow-up studies to assess the association between exposure and outcome, does not necessarily get influenced by a low participation rate as long as the cohort is representative.

Generally, the strengths of the HUNT Study is the large population with a large age span, covering groups of people with different cohort exposures, within a defined geographical area covering one county in Norway, and that all data are linked to the unique personal identification number enabling linkage of data for each individual. The participation rate has been reported as very good or acceptable in most age groups in HUNT 2 and HUNT 3 (39).

The major potential source of selection bias in paper 1 is related to a large proportion of losses to follow- up (56 %). Baseline information in the eligible population made it possible to examine whether there were systematic differences in main exposure status or other risk factors between the group in which the disease status was known and unknown. Those with unknown disease status were more frequently daily smokers as compared to those with known disease status, males and less highly educated. These figures indicate that estimation of the exposure-disease association could be affected of bias due to losses of follow-up in this cohort, but we neither know the magnitude nor the direction in which the effect measure is biased.

Information bias

Information bias is a very important source of bias in cohort studies. The possibility of misclassification of exposure and disease status cannot be excluded in our study. Information was obtained using the same questionnaire for all participants, and the effect of misclassification will dependent on the sensitivity and specificity of the questionnaire. The answers obtained by a questionnaire may not represent the true state of the individual.

To avoid differential misclassification, one have to be certain that the outcome registration is not affected/influenced by the exposure. The outcome, chronic MSCs, was classified according to self-reported symptoms and misclassification of disease status could have occurred. However, as the respondents were unaware of our research hypothesis we believe that misclassification of disease status is non-differential. Non-differential misclassification of both exposure status and disease

status dilute the association between exposure and disease (107), and therefore the observed association between the exposure and chronic MSCs is expected to represent a diluted, not inflated effect.

Recall bias is especially problematic in case-control and retrospective cohort studies. Recall bias can lead to either over- or underestimate of an association between exposure and disease/outcome. In paper 2 and 3, there could be a recall bias for the exposure, but equivalent to paper 1, the respondents were unaware of our research hypothesis.

Confounding:

In the epidemiology of MSCs, several confounding factors are known and several discussed and proposed as possible confounders. In different epidemiological studies, the confounders that have been assessed and included might differ. Therefore, the comparison between studies might be difficult and somewhat hampered. However, age, gender, socioeconomic status, and psychological factors, are usually considered as well-established confounders when assessing an association to MSCs. Occupational data in the HUNT Study were reclassified according to the international Erikson Goldthorpe Portocarero (EGP) social class scheme, but due to a high proportion of missing data (>25%), we were unable to use the occupational data in our papers. However, education had a very low proportion of missing data (<1%) and could accordingly be included.

Exposure variables:

Paper 1: The main exposure variable was smoking status at baseline (HUNT 2). The unexposed (non-smoker) was defined as “never”, “passive” or “previous smoker”. Exposed subjects included all current smokers regardless of the number of cigarettes smoked per day.

Paper 2: The exposure variable was age at menarche reported in HUNT 2. Unexposed participants were defined as females with menarche >12yrs and exposed participants as those with menarche ≤12yrs, the latter group representing the lower quartile of age at menarche in our study. The same cutoff for defining early age at menarche has been used in previous studies (108-110).

Age at menarche was self-reported in this study. We considered this to be a reliable measure, as menarche is a milestone in a woman's life. Previous studies have found good validity (111) and reproducibility (112) for this self-reported measure. However, two more recent studies throw some doubt on whether it is justifiable to use age at menarche self-reported in middle age as there might be reporting errors and limitations in the interpretations (113, 114).

Paper 3: The main exposure variable was use of OCs. Q2 included questions about menstruation, pregnancy and use of OCs. Women aged <56 yrs who answered "yes" to the question "Are you still menstruating?" were sub-classified according to their response to two different questions regarding use of OCs "Did you ever take the pill, the mini-pill included?" and "Do you take the pill now?" Women who had never used OCs were defined as unexposed, and exposed, those who had used OCs, were divided into 2 groups comprised of either current or previous use of OCs.

Information about duration of OCs use was necessary for the estimation of a potential dose-response relationship. We would prefer to assess the duration of OCs use, for both current and previous users, but this variable was too often missing (34.8%).

It appears reasonable to assume that parity is associated with use of OCs. Parity might be associated with musculoskeletal pain (115). We did not find studies of the associations between parity and WMSCs to support an assessment of parity as a potential confounder. Nevertheless, we did control for parity in the present study leading to no change in the effect estimate.

Outcome measures:

The outcome definition in all 3 papers might include complaints where chronic stiffness in muscles and joints acts as a separate condition, but the prevalence of stiffness without pain is unknown and a possible bias could not be ruled out. However, as the respondents were unaware of our research hypothesis, we believe that misclassification of the outcome is non-differential.
Chronic MSCs were the outcome variable in paper 1. The outcome variable includes both widespread and non-widespread MSCs.

The outcome definition in HUNT 2 did not include a question regarding whether participants had pain in both sides of the body, one criterion for WMSCs according to the ACR 1990 criteria.
The reliability of the screening question for chronic MSCs and chronic WMSCs was respectively good (kappa value 0.63, 95% CI: 0.53-0.73) and moderate (kappa value 0.48, 95% CI: 0.38-0.64) (4). Note that the definition of chronic WMSCs differs slightly between HUNT 2 and HUNT 3. In HUNT 3, all individuals with chronic widespread MSCs confirmed that they had pain in both sides of the body, whereas participants in HUNT2 were not asked to distinguish between pain in the left and right side of the body.

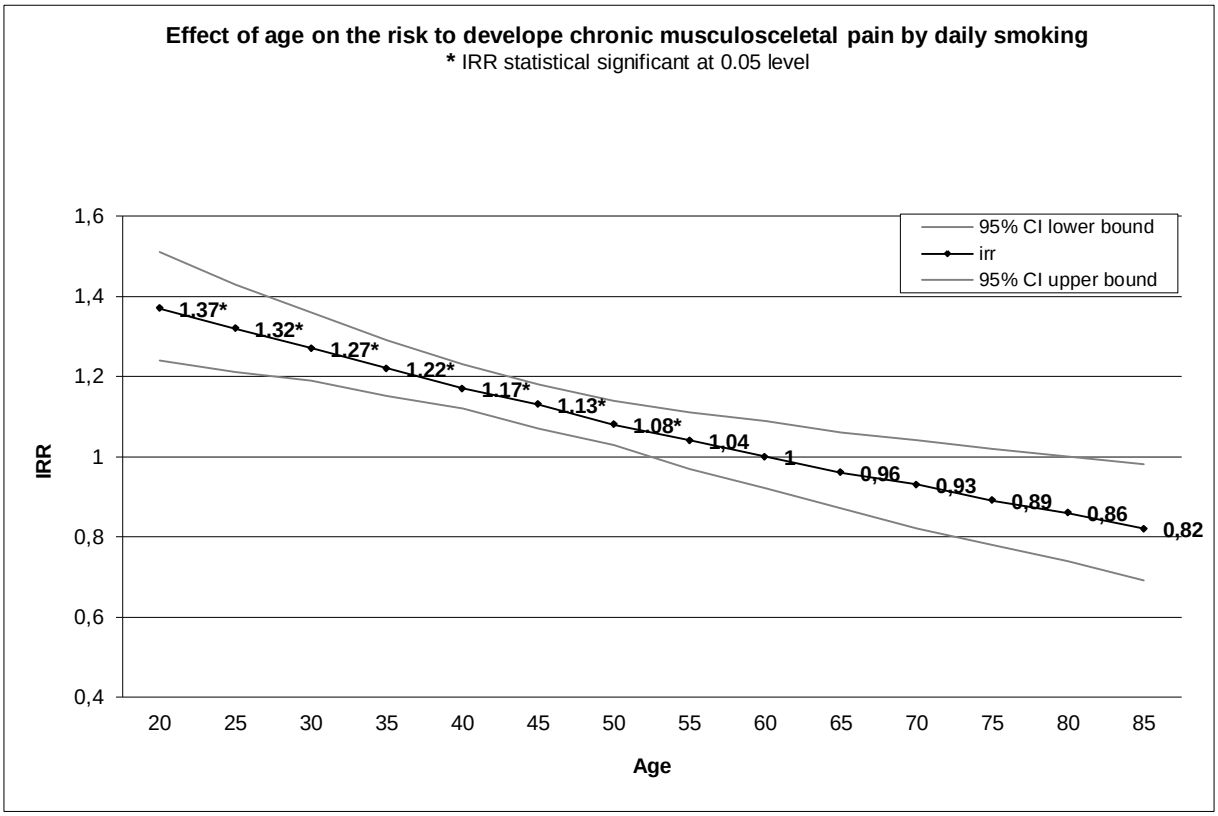
5.4 Statistical approach

As a general rule, variables that are known a priori to be important confounders, based on previous work should be controlled for in the analysis. In addition, other possible confounders may be selected as a result of exploratory analysis based on the data present and external knowledge, and restricted to those variables that are associated to both the outcome and the exposure without being on the causal pathway. In paper 1 we identified confounders accordingly and controlled univariably using the Mantel-Haenszel method for pooled estimate of effect in a stratified analysis. The

confounding effect was quantified by comparing the adjusted Mantel-Haenszel incidence rate ratio (IRR) to the crude IRR (34). Confounding effect was quantified using the formula $\frac{IRR_{MH} - IRR_{crude}}{IRR_{crude}}$

The confounding effect was minimal (<1%) and hence no confounders were included in the final analysis. Our main finding was that there was a significant interaction (effect modification) with age between the exposure and the outcome, and hence the final analysis was done for the two strata, i.e. under and over 50 yrs. There are different approaches to how interaction should be interpreted, and there are pitfalls in the analysis and interpretation. With multiple comparisons, we would expect one in twenty comparisons to be statistically significant at the 5 % level. Therefore, in studies where the effect of many exposures is measured, a more cautious interpretation of associations is needed as opposed to a study with a specified a priori hypothesis. Accordingly, some epidemiologists argue that interactions between the exposure and the outcome should be identified a priori. However, there are arguments to support the importance of a statistical approach to identify interaction as there might be effect modifications that are not obvious from previous studies or by eyeballing the present data. Previous studies gave contradictory results on the interaction between smoking and age on the outcome (116, 117). In the presence of substantial interaction, the stratum-specific effects of the exposure should be reported (118). The tests for interaction lack power, and sample size is therefore important. In our paper, we argue that with the large sample size should be ample to support our interaction analysis. The purpose of a statistical test is to provide a simplified but useful picture of reality. In assessing the evidence for interactions, it is important to assess meaningful trends in the effect estimates over the strata. A finding of weak interactions is probably of little interest (118).

In paper 1, we found a consistent trend of decreasing IRR with age, and no significant association between exposure and outcome after the age of 50 yrs, as shown in the figure:



We used Poisson regression analysis in paper 1. The general form of the Poisson regression model is similar to that for logistic regression. Poisson regression is used to estimate rate ratios comparing different exposure groups in the same way that logistic regression is used to estimate odds ratios comparing different exposure groups.

Previous studies that are comparable to our study have used both Poisson and logistic regression models (4, 44, 45). Incidence rate ratio (IRR) is the effect estimate of a Poisson regression analysis and Odds Ratio (OR) from a logistic regression analysis. If the outcome is common, i.e. high prevalence like in our studies, the OR is higher than the RR/IRR. This might be an argument for using Poisson regression analysis together with the statement from many researchers that RR/IRR is intuitively more comprehensible than OR. On the other hand, the use of logistic regression analysis is

somewhat more common and could be argued for as to simplify the direct comparison of other studies and their effect estimates.

In paper 2, logistic regression analysis was used for the cross-sectional study. A cross-sectional study cannot measure disease incidence because risk or rate calculations require information across a period of time. The association between potential confounders and WMSCs was investigated using univariable logistic regression, with only those significantly associated ($p< 0.05$) with both exposure and outcome taken forward in the multivariable model as confounders of the association between age at menarche and WMSCs. In a large sample size, it is more likely to get a statistically significant association and we could have chosen to assess the potential confounders as in paper 1 by estimating the confounding effect. However, the final analysis showed small differences between the age-adjusted analysis and the fully adjusted analysis. We have used two different statisticians who prefer somewhat a slightly different approach.

In paper 3, we have used the same method as in paper 2. However, stratified analyses were performed as a supplementary assessment of the confounding and effect modification, using the Mantel-Haenszel method to identify confounding effect, and a Breslow and Day test of heterogeneity to identify any effect modification. In both paper 2 and paper 3 , analyses for effect modification of all independent variables, on the association between exposure and outcome, were performed by introducing an interaction term, and selected by statistical significance (with p-level<0.05).

In paper 2, the interaction analysis identified a statistically significant interaction between age and age at menarche ($p<0.001$), but the prevalence of chronic WMSCs was consistently higher in those with early age at menarche in all age groups. Subsequently, the interaction found statistically did not seem clinically relevant.

As in paper 2, a statistical interaction with age was found in paper 3, but did not appear clinically important.

5.5 Ethical considerations

The Data inspectorate of Norway and the Regional committee for medical Research Ethics approved the HUNT study. All information from the HUNT-study was treated according to the guidelines of The Data inspectorate of Norway.

The participation in HUNT was based upon a written informed consent from each participant.

6. DISCUSSION

Results, findings, compared with current evidence.

In paper 1, we found an association and a dose-response relationship between smoking and chronic MSCs, but only among those less than 50 years of age.

An association between smoking and MSCs has been studied on several occasions. However, the majority of the studies that have been carried out are cross-sectional of which several have been inconclusive. There are few follow-up studies of a general population (78, 79). The meta-analyses in this field have been based on a majority of studies with a restricted population, and subsequently less generalisable (75-77). Follow-up studies, RCTs and case-control studies are the designs which enable the assessment of causal effects. Given the facts that smoking is well documented as a risk factor for many diseases, and that smoking and MSCs both have a rather high prevalence with implications in the general population, there is obviously a need for follow-up studies.

A dose-response relationship between smoking and MSCs suggests a causal mechanism and has been reported in some of the studies carried out (119-122), but not in other studies (123, 124). It has been concluded that it is not feasible to do a meta-analysis of the dose-response relationship due to the limited number of prospective studies and different cut-off points for number of cigarettes smoked per day applied in the studies identified (75).

The negative effect of tobacco smoking on the musculoskeletal system might be caused by poorer vascularization, local hypoxia and cytokine release in connective tissues leading to pain or degenerative changes. From this perspective, it is plausible with a dose-response relationship between smoking and MSCs based on an expected increase in pack-years by increasing age. Given this, it is difficult to explain why a dose-response relationship was not observed after the age of 50 yrs in our study (Paper 1) where the observed association and dose-response relationship were strongest between young smokers and MSCs. Two previous studies gave contradictory results on the interaction between smoking and age (116, 117). The reason for the interaction between smoking and age in our study is not obvious. Some argue that age frequently interact with other factors (117).

Another study observed an interaction between smoking and age, with a higher prevalence of headache among smokers when compared to non-smokers, but only for those less than 40 years of age (125). As in our study, the possibility of a cohort effect leading to such results is difficult to rule out.

We know that daily smoking in adolescents is associated with multiple somatic and psychological health problems (126). Smoking might act as a relaxant, stress reliever and pain moderator. People with a low threshold for reporting pain and disability could be more likely to take up and continue smoking (127), and it is possible that smoking is a consequence of painful conditions.

Nicotine is a psychostimulant which affects both cortical and autonomic arousal. Thus, it could affect the pain processing both in the peripheral and central nervous system (128). Chronic cigarette smoking is associated with alterations in the hypothalamic-pituitary-adrenal (HPA)-axis and there is evidence for higher HPA-axis activity as a predictor of smoking in early adolescence (129). The HPA-axis is involved in acute and chronic pain (130). Accordingly, an effect from smoking due to a higher susceptibility and reactivity in the HPA-axis in younger people could be one theory.

Possibly there are neuropsychological or sociocultural differences that varies systematically between those who become smokers and those who do not. There might be indirect effects of smoking on musculoskeletal pain which are mediated through psychological aspects, or there might be a common underlying factor. Lower socioeconomic status is associated to smoking, MSCs and self-assessed/perceived general health (5, 45, 49, 131-133). One possible explanation for the findings in our study might be that the classifications of socioeconomic status do not capture the social dimensions that influence the association between pain and smoking.

In paper 2 we found that early menarche (≤ 12 yrs) was associated with chronic WMSCs later in life, but the difference in absolute risk was small (3%).

Other studies have shown that early age at menarche is associated with increased risk for obesity, type 2 diabetes, cardiovascular disease, breast cancer, and all-cause mortality (109, 134, 135). Early menarche age is also associated with pain conditions like headache (110) and pelvic girdle pain in pregnancy (88).

Age at menarche has been decreasing over the last decades (136-139), implying that the younger cohort will have lower age at menarche. In the HUNT study, there was a significant increase in the prevalence of MSCs, and most prominent in the younger age groups. Accordingly, in the Norwegian report based on a comparison of the statistical numbers from 2004 and 2009, the conclusion states that the prevalence of MSCs remains relatively unchanged but an increase in the young population is observed. One possible explanation for this higher prevalence is that young people have an increased awareness of musculoskeletal pain or that they are more willing to report MSCs. One cannot exclude the possibility that the observed associations might be due to a cohort effect.

In paper 3, we found an association between previous use of OCs and chronic WMSCs, most evident for women younger than 39yrs. Current use of OCs was not associated with chronic WMSCs.

We were not able to find any other studies on the association between use of OCs and chronic WMSCs, but there are studies which have assessed the association between OCs and low back pain (103), carpal tunnel syndrome (140), and pain tolerance throughout the menstrual cycle (141). Scientific evidence for the association between use of OCs and low back pain is scarce (142) or not supportive (143, 144). Subjects with low back pain often report other MSCs (8, 145). The tendency of MSCs from different sites may reflect the existence of a more general musculoskeletal pain syndrome. Hormonal and reproductive factors associated with low back pain may be related to musculoskeletal pain in other anatomic locations as well. As some women experience variations of muscular pain throughout the menstrual cycle, theories regarding a beneficial effect of OCs use, through regulation of the hormonal fluctuations, have been formed (146). There is evidence for hormonal influence on pain susceptibility (147). Sex hormones might alter the pain processing through the neuroendocrine system. Sex hormones like estrogen and progesterone have potent modulating effects on central serotonergic and opioid neurons, and on both neuronal activity and receptor density (148). Administration and withdrawal of estrogens may increase the risk of pain (40, 149, 150).

A common explanation for chronic MSCs/WMSCs is based on a biopsychosocial model where the total burden of genetic, physical, psychological and social factors are modified negatively through stress, lack of coping strategies and comorbidity with anxiety and/or depression which lead to sustained activation of the HPA-axis . The sustained activation and dysregulation of the HPA-axis is thought to lead to, or be a part of, sensitization of central or peripheral nervous system. There is some evidence of OCs reducing the HPA-axis activity (151) and the current hypothesis of the aetiology of WMSCs includes inflammatory and neuroendocrine disorders. Genetic variation in HPA-

axis genes is associated with musculoskeletal pain; however, some of the associations were explained by comorbidities (152).

The large proportion of health problems due to pain and dysfunction in the musculoskeletal system could be considered to be non-specific, with no obvious pathology observed. Non-specific pain has a high degree of association with personal and psychosocial factors. This seems to especially be the case for chronic WMSCs. A recent study showed that the onset of WMSCs might be a result of a combination of the risk factors obesity, mental distress, poor sleep quality and poor physical fitness (153). A heritability of 48–52% has been shown for WMSCs in twin studies and a shared genetic component with other functional disorders and with anxiety and depression (154) .

7. CONCLUSIONS

Chronic MSCs/WMSCs are common and costly health problems, and it is important to identify risk factors in order to find prevention or treatment. In this thesis, epidemiological data were used in an explanatory strategy. An association between smoking and chronic MSCs was found in a follow-up study, and an association between early age at menarche, earlier use of OCs and chronic WMSCs was found in cross-sectional studies. Smoking and use of OCs are factors which are modifiable by the individual, while age at menarche is not.

Under the assumption that the observed association between smoking and chronic MSCs is causal, chronic MSCs might be prevented if smoking is ceased. As smoking is prevalent in the general population and a modifiable risk factor, these findings could have a public health impact.

The two cross-sectional studies, for the association between age at menarche and chronic WMSCs and for the association between use of OCs and chronic WMSCs, cannot address any causal effect.

Future perspectives:

The goal for future studies is to explore more risk factors and prognostic factors for the development of chronic MSCs. The HUNT study will start the fourth wave in 2017. The aim is to use the potential of follow-up studies by using the different waves of the HUNT study, but some of the potential risk factors will probably still be most suitable for cross-sectional studies due to the limitations of questionnaire-based epidemiological studies.

In future studies, it would be interesting to explore if there is an effect modification between several risk factors and age as to try to elaborate on the theory of a higher susceptibility in the younger age groups or if this could be merely a cohort effect. To look for underlying genetic predisposition, there would be a need for genetic studies in combination with other clinical studies.

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