Masteroppgave

NTNU
Norges teknisk-naturvitenskapelige universitet
Fakultet for medisin og helsevitenskap
Institutt for samfunnsmedisin og sykepleie

Inger Ådnøy Ellingsen

Is heavier smoking associated with worse self-rated health?

A Mendelian Randomisation study in the HUNT Study

Masteroppgave i Master of Public Health
Veileder: Gunnhild Åberge Vie
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Sammendrag

Røyking er et stort folkehelseproblem og bidrar til mange store folkesykdommer, både i Norge og globalt. Å påvirke røykevaner har vært et viktig mål for folkehelseinitiativer over hele verden. Å finne hvilken innvirkning røykeintensitet har for selv-rapportert helse (SRH) til røykere kan kaste lys over deres egen oppfatning av hvordan helseeffektene gjelder dem selv. Utover målet SRH sin relevans for dødelighet, kan den subjektive opplevelsen av helse ha innvirkning på motivasjonen til å slutte å røyke.

Rs16969968 er en genvariant assosiert med høyere grad av røyking og sterkere nikotinsug, men ikke med SES (sosioøkonomisk status). Studien bruker rs16969968 som instrument for røykeintensitet, for å finne en sammenheng mellom grad av røyking og selvrapportert helse, og kan anta at resultatene i mindre grad vil bli forvirret av sosioøkonomiske faktorer.

Dette forskningsprosjektet bruker mendelsk randomisering for å vurdere sammenhengen mellom røykeintensitet og selvrapportert helse ved hjelp av data fra HUNT3 og HUNT2. Resultatene vil bli sammenlignet med forholdet mellom røykeintensitet og mer objektive helsemål som KOLS, hjerte- og karsykdommer eller kronisk sykdom.

Jeg har vist at rs16969968 ser ut til å øke sjansen for å gå fra sporadisk til daglig røyker, og reduserer sjansen for å lykkes med å slutte å røyke, og at effekten er sterkere med to alleler enn med en. Dette er en bekreftelse på tidligere forskning på feltet, selv om statistikken over sporadisk kontra daglig røyking ikke er eksplisitt angitt i den tidligere litteraturen studert for denne avhandlingen. Resultatet at genfordelingen blant aldri-røykere er den samme som blant befolkningen generelt er nyttig, og bidrar til å øke validiteten til rs16969968 som et instrument for røyking.

Å ha rs16969968 fører ikke til lavere SRH eller høyere forekomst av kronisk sykdom blant røykere i HUNT2 og 3. Dette er overraskende, ettersom SRH er knyttet til høyere dødelighet og sykelighet, og røyking er knyttet til dødelighet og sykelighet i mange studier som har benyttet rs16969968 for så studere sammenheng med mortalitet. Mens positive helseutfall kan være en viktig kilde til motivasjon for folk til å slutte å røyke, er den subjektive opplevelsen av helseforbedring ved å slutte å røyke kanskje ikke den samme.

Rs16969968 øker betydelig sjansene for å utvikle KOLS (RR 1,16) eller tegn på kronisk lungesykdom (RR 1,14). Begge disse reduserer livskvaliteten betydelig og øker sjansene for sykelighet for kronisk sykdom, så det er uventet at det ikke er noen signifikant endring i utfallet for lav SRH eller kronisk sykdom.

Abstract

Influencing smoking habits has been an important goal of public health initiatives around the world. Finding what impact smoking intensity has for the SRH of smokers might shed light on their own perception of how the health impacts apply to themselves. Beyond the measure's relevance for mortality, the subjective experience of health can have an impact on motivation to quit smoking.

rs16969968 is SNP associated with heavier smoking and stronger nicotine cravings, but not with SES (socioeconomic status). Using rs16969968 as an instrument for smoking intensity, in order to find a relationship between degree of smoking and self-reported health, and can assume that the results will be to a lesser degree confounded by socioeconomic factors.

This research project uses mendelian randomisation to assess the relationship between smoking intensity and self-reported health using data from HUNT3 and HUNT2. The results will be compared to the relationship between smoking intensity and more objective measures of health like COPD, cardiovascular diseases or chronic disease.

I have shown that rs16969968 seems to increase the chance of moving from occasional to daily smoker, and reduces the chance of successfully quitting smoking among, and that the effect is stronger with two alleles than with one. This is confirmation of previous research on the field, though the statistics on occasional vs daily smoking is not explicitly stated in the previous literature studied for this thesis. The result that the gene distribution among never-smokers is the same as among the general population is a useful one, and helps add to the validity of rs16969968 as an instrument for smoking.

Having rs16969968 does not lead to lower SRH or a higher incidence of chronic disease among ever-smokers. This is surprising, as SRH is tied to higher mortality and morbidity, and rs16969968 is similarly tied to mortality and morbidity in many studies. While positive health outcomes may be an important source of motivation for people to quit smoking, the subjective experience of health improvement from quitting smoking may not be the same.

rs16969968 does significantly increase the chances of developing COPD (RR 1.16) or signs of chronic lung disease (RR 1.14). These both decrease the quality of life significantly an increase the chances of morbidity for chronic disease, so it is unexpected that there is no significant change of outcome for low SRH or chronic disease.

Preface

The work for this thesis began in the autumn of 2019, almost 6 years ago now. At the time I was working part time at Helsedirektoratet and studying part time for my master's degree in public health. I received the data from HUNT in March of 2020, 3 days before the whole country shut down due to the COVID19 pandemic, and suddenly all plans were very drastically changed. My work at Helsedirektoratet changed by necessity to a full-time obligation. I am very proud of the work my colleagues and I at the department of Health Registries did to support the health care sector and the policy-makers during the upheavals in society at that time. Beyond the constraints on my time from work and homeschooling, all this left very little mental space to carry out a research project. I am incredibly grateful to NTNU, ISM and Sindre Aasheim Norås for their support in granting extensions and their effort to keep the red tape to a minimum during COVID and afterwards. I have been met with support and understanding from many teachers at the masters program for Public Health.

There were a couple of false starts in coming back to the thesis. I am incredibly grateful to my supervisor, Gunnhild Åberge Vie, for welcoming me with open arms every time I was ready to start again, and for helping me see this through to the end.

I am grateful to my supervisors and colleagues at Helsedirektoratet and NTNU who have supported me and listened to me talk about my thesis more times than I can count. Especially in times where it was difficult to meet other students the moral support from colleagues was invaluable. My family has also been a great source of support. I have to particularly thank my mother, Kristin Ådnøy Eriksen, for her help as a sounding board throughout all this and in proof-reading this thesis. While her extensive experience with qualitative methods is a far methodological leap from the work in this thesis, her work with patient participation in research is an inspiration to me. It is a steady reminder that though I have been working with rows and columns, public health research is valuable because each row has a person behind it.

The biggest thank-you goes to the two people who are most eager for me to hand in this thesis, Simen and Eivor. They have both put up with much in the last months, and in the words of Jane Austen[1] "borne the indignity with great equanimity". No amount of words can do you justice. I will have to attempt to make it up with Lego instead.

[1] Jane Austen also gives a very good explanation of confirmation bias and information bias in chapter 23 of Persuasion. I believe she would have made an excellent epidemiologist.

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Forkortelser/symboler

HUNT	The Trøndelag Health Study
NTNU	Norges teknisk-naturvitenskapelige universitet
SRH	Self-reported health status
SNP	Single Nucleotide Polymorphism
SES	Socioeconomic status
OR	Odds ratio
QALY	Quality-adjusted life years
CI	Confidence interval

1 Introduction

Influencing smoking habits has been an important goal of public health initiatives around the world. From first suspecting the negative health outcomes of smoking in the late 19th and early 20th century, tobacco was declared the likely cause of the explosive increase in lung cancer cases in the 1950s (3). Since the health authorities in Norway first advised stopping smoking as a way to prevent cancer in the mid-50s, just about every tool in the Public Health toolbelt has been used to combat the problem. Campaigns have been run to encourage quitting and reduce initiation, laws have been widely adopted to prevent passive smoking, medical and social programs have been created to combat it.

There is a large amount of research done on campaigns and interventions to influence smoking behaviour. Health issues is found to be one of the most frequent motivations for attempting smoking cessation(4).

Self-reported health status is a marker that has been increasingly used in research and cohort studies. As a measure it has been shown to have predictive value in risk of early death(5-7). This thesis uses data from HUNT2 and HUNT3 to assess smokers' experience of their own health by comparing self-assessed health status among lighter and heavier smokers and compare these finds to more objective measures of health outcomes.

1.1 Smoking and health

1.1.1 Tobacco and disease burden

The WHO lists tobacco related diseases as the second leading cause of death worldwide. According to the Global Burden of Disease study by Institute for Health Metrics and Evaluation (IHME), the global death toll due to tobacco was estimated at 7 million in 2022 and the loss of disability-adjusted life-years was estimated at 177 million(8, 9). Smoking has an established causal relationship with cancer, CVD and pulmonary diseases (10, 11). These were the three biggest causes of death in Norway in 2017 according to FHI(12). Previous studies have shown an association between higher consumption of cigarettes and higher levels of anxiety and depression(13, 14), although this association may not represent a causal effect of smoking on mental symptoms(15). Other studies suggest that higher rates of anxiety and depressive symptoms reduce the chances of success at quit attempts (14, 16). Even passive smoking has an established causal link to adverse health outcomes.

1.1.2 Smoking prevalence

As seen in Figure 1 smoking prevalence has decreased significantly in the last decades thanks in part to awareness of ill effects(4). In Norway per 2021 9 % of the adult population in Norway are current daily smokers, and a further 8% are casual smokers(17). This is down from over 40% of the adult population reporting daily

smoking in 1960. North-Trøndelag has also had a considerable reduction in smoking rates in the past few decades similar to the national numbers. In Trøndelag the rate of daily smokers varies from 3 % to 16 % between municipalities(18).

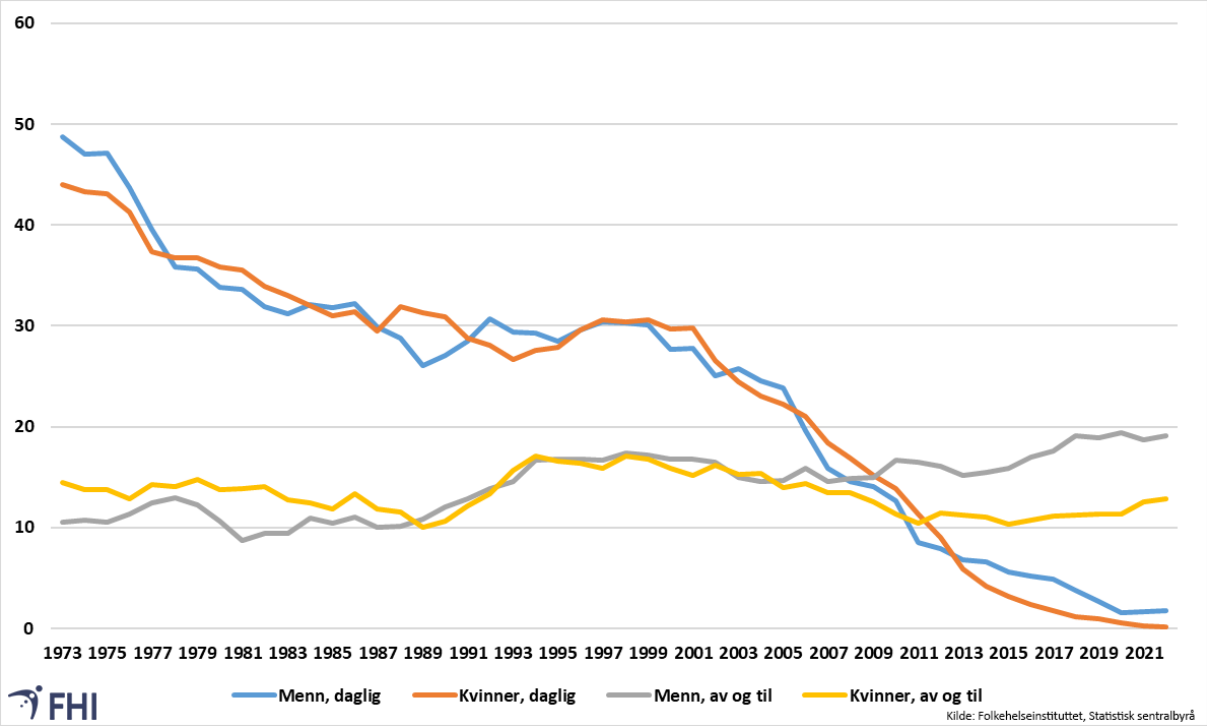

Figure 1: Occasional and daily smokers. Source: Utbredese av røyking i Norge, Tobakk i Norge (17)

Even though a substantial amount of the reduction in smoking rates can be attributed to lower rates of smoking initiation in youth, a large portion of the reduction is attributed to former smokers quitting smoking. In Figure 2 Figure 1we see the rate of smoking for 10 different cohorts over time. The graph shown here is the number for men. We can see that even though each cohort has had progressively lower rates of uptake since the 1960s, there is also reduction of smoking rates within cohorts as a result of people quitting smoking. In 1973 there were more than 2 smokers for every former smoker, but in 2009 this ratio was 1:1 (19). Smoking cessation is an important goal for public health initiatives, and can improve health outcomes for the individual, both in the short(16) and long term(20).

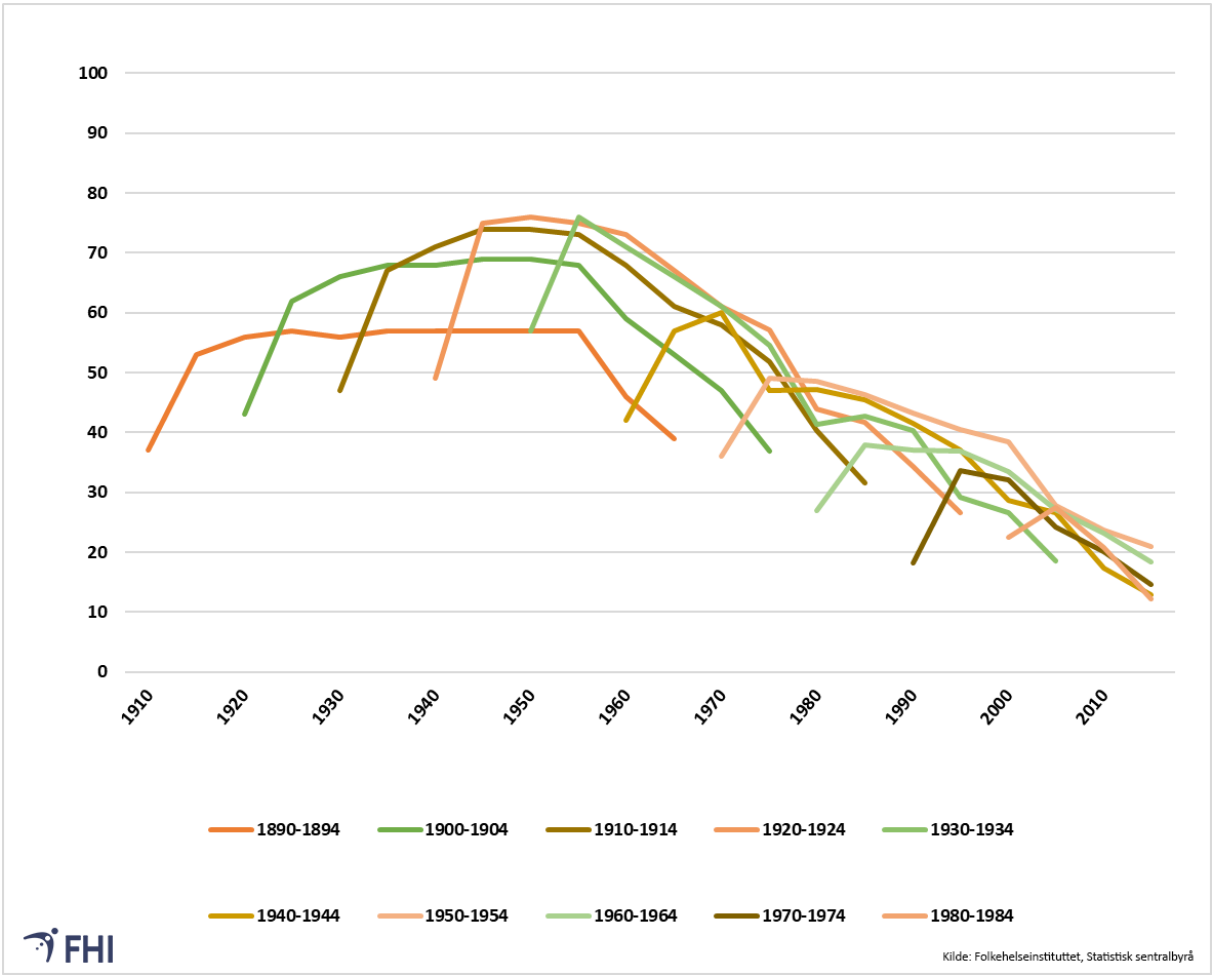

Figure 2: Smoking rates among men by age cohorts. Source: Utbredelse av røyk i Norge, Tobakk i Norge (17).

1.1.3 Health as motivation for smoking cessation

Studies have found that, along with social pressures and public policy, health benefits are one of the strongest motivations for people attempting to give up smoking (4, 21), but also that some smokers seem to be in denial about the health impact of smoking(22). For example, a review of studies evaluating the use of cancer diagnosis as teachable moment for smokers found that never-smokers and former smokers perceived the risks of smoking as much higher than current smokers(16). On the other hand, predictive testing on risk factors increased motivation to quit among those with higher chances of ischemic heart disease(23). 60-70% of smokers admitted to hospital with an acute coronary event give up smoking over the next 6 months (21). Still, the same study found that a majority of patients with mild COPD smoke, and that 38-51% of COPD patients continue to smoke despite severe disease.

Health concerns are the main point anti-tobacco campaigns attempt to target. Such government campaigns have mixed immediate impacts, but they increase motivation to quit and increase discussions on health issues among smokers(19)

1.1.4 Self-reported health

Self-rated or self-reported health is a measure of a person's health, given by their answers to questions about their health. As such it is a subjective measure of health. This can refer to the participants in a survey answering a series of questions about various aspects of their health, but in this theses self-reported health (SRH) will be defined to be the answer to a single question in a survey, typically "how would you rate your health" The answer is usually given as a point on a Likert scale (or Likert-type scales), where the participants are asked to answer on the form "excellent", "pretty good", "poor", etc. In other words, the resulting data is ordinal. Often given on a scale from 1-5, sometimes an even number of options is given to force participants to choose "good" or "bad", by removing the "neutral" middle value. SRH has become a popular measure of health because it is very easy to obtain from a survey. At first there was some discussion as to whether these subjective measures have predictive value, especially when compared to more objective measures taken by a health professional. Since the 90s researchers have consistently found a low SRH score to have a predictive value on any-cause mortality(7, 24-26). Previous studies using HUNT data have found robust associations between low SRH and mortality, even when accounting for socio-economic status(27) and education level(28).

Finding what impact smoking intensity has for the SRH of smokers might shed light on their own perception of how the health impacts apply to themselves. Beyond the measure's relevance for mortality, the subjective experience of health can have an impact on motivation to quit smoking.

1.2 Social influences on smoking

1.2.1 Socioeconomic divides in smoking

As smoking rates are being reduced in Norway, they are increasingly becoming stratified along socio-economic lines. Smoking as a cause of ill health is well established as fact by the scientific and medical community. When smoking was being firmly established as a causal agent of cancer and other adverse health outcomes, one of the first studies that had a big impact on the medical community was one that showed doctors who smoked died earlier and had more cancer than those that did not smoke(29). Such a study could not be held in 2024, there simply aren't enough doctors who smoke. Figure 3 shows the fraction of smokers in Norway sorted by level of education, as reported by the Norwegian Institute of Public Health(17). Although smoking has decreased in all groups, this graph of smoking rates among men with university degrees(green), completed upper secondary

school (red) and no completed education after grade 10(blue) clearly shows a stark difference in proportion.

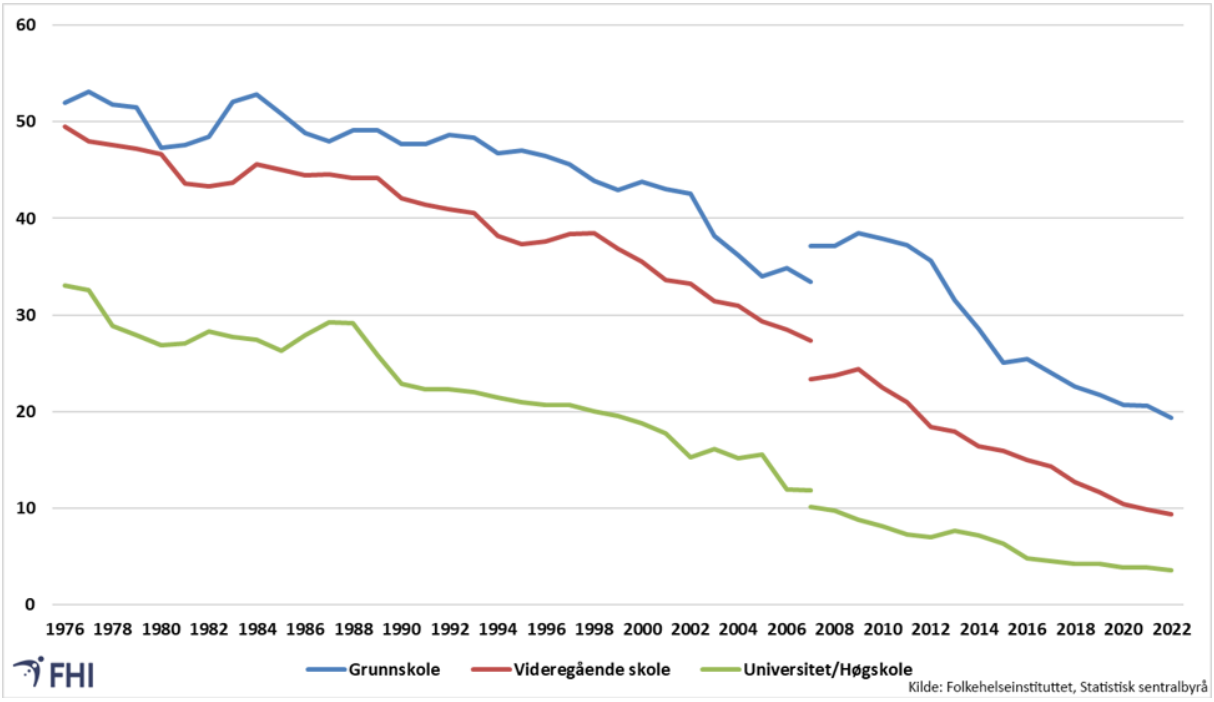

Figure 3: Percent smokers by level of education. Green: University/college education, Red: Completed upper secondary school, Blue: Did not complete upper secondary school. Source: Utbredelse av røyk i Norge, Tobakk i Norge (17). The break in the graph at 2007 is due to a reclassification of measures of education.

While someone without a university degree was slightly less than twice as likely to be a smoker in 1976 (33% vs 50% and 52%), by 2022 that has grown to over twice as likely, or four times as likely (4% vs 9% and 19%)(17). This shift changes smoking, from being a common behaviour in society, to being increasingly associated with lower Socioeconomic status (SES). SES can confound the effect smoking has on health outcomes.

As Norway is one of the countries in the world with lowest rates of smoking, another difference can be found in higher smoking rates among the immigrant population. Two extensive reports on living conditions, health and social status among immigrant populations were published by Statistics Norway (SSB) in 2016 and 2017, one looking at the immigrant population, and the other at children of immigrants (classified in the study as people born in Norway to two immigrant parents). They found that the immigrant population were lower in terms of education levels, income levels and other socioeconomic markers. Though younger immigrants tend to be healthier than the general population, this changes with age, and they fall behind in health outcomes. There is also a higher rate of smoking among men(30), though there is a large difference between different ethnic groups. Though the next generation is often closer to the Norwegian society at large both for outcomes and socioeconomic status, there are still contrasts. For example smoking rates are often very different between men and women, unlike the rates for the general population in Norway(31).

Attempting to quit smoking without any assistance has a success rate of 3-5% within a 1-year timeframe, though this increases significantly if the smoker uses therapy,

medication or nicotine products(32). It takes on average 10-30(33) (ref, (Chaiton et al 2016)) attempts before an individual succeeds in kicking the habit.

Several of the studies that(13) examine success rates in quit smoking attempts found a positive correlation between higher education and success rates. This means there is a reason to believe that, as with good nutrition and regular exercise, though the advice is the same for all inhabitants, smoking cessation is easiest to achieve for those with most resources.

1.2.2 Confounding with socioeconomic factors

As mentioned above, the closer smoking becomes associated with socioeconomic factors, the harder it becomes to isolate the effects of smoking on health outcomes, as lower SES is also strongly correlated with negative health outcomes. The Norwegian Directorate of Health suggested in a report in 2016 that smoking may be an important causal factor for the discrepancies in health outcomes between socioeconomic groups(34). Although differences in smoking patterns can contribute to these differences, there are also alternative pathways for the association between socioeconomic factors and morbidity(35). Asthma, heart disease and premature death can be confounded by socioeconomic factor or reverse causation. Socioeconomic factors could thus confound observational studies on the association between smoking and health.

1.3 Population studies and HUNT

Population studies aim to gather data on a whole population. This could either be everyone in a specific geographical area or everyone with a specific diagnosis or risk factor. Longitudinal population studies aims to follow their cohort over long periods of time, and collect data at regular intervals, sometimes lasting decades.

1.3.1 Participation and non-participation in population studies

Though population studies aim to study an entire population, these studies are based on consent from the participants, and will realistically never have 100% participation. This can introduce sampling biases if the reasons people cannot or will not participate are not randomly dispersed in the population. When looking at smoking there are two main selection biases that can affect the sample population. The first is that lower SES often reduces the chances an individual will participate in scientific studies or population surveys. An analysis by Galea and Tracy(36) covering several epidemiological studies conducted by academics, governments and private companies found a wholesale decrease in participation rates over the last decades. Among the reasons they found for non-participation, in addition to an increase in studies and reporting not having time, were a distrust of science in general and lack of saliency of the study to a potential participants own life. They also found that across every marker of SES they examined (education levels, income, employment status, marital status, functioning levels), those with lower status were less likely to participate. This is likely reflecting a higher trust in science among higher those with higher SES.

The second factor that can lead to selection bias is that engaging in risk behaviours makes people less likely to participate. Galea and Tracy speculate that marginalization or stigmatization may contribute to a lower willingness to participate, based on the fact that exposure to environments hazards increased the chances of participation, whereas

engaging in risk behaviours lowered the chances. It is a point to note, that while saliency increases the participation in scientific studies generally, engaging in risk behaviour reduced the chances of participating (36).

1.3.2 HUNT and non-participation in HUNT

North-Trøndelag Health Study (HUNT) consists of 4 population surveys conducted in the county of Nord-Trøndelag between 1984 and 2019. HUNT1 was performed from 1984-1986, HUNT2 in 1995-1997, HUNT3 in 2006-2009 and HUNT4 was conducted from 2017-2019. The purpose of HUNT is to give an overview of living conditions and health status among the population and has informed public health policy as well as provided data for researchers (37).

Participation rates have fallen significantly since it was introduced in the 80s, following the pattern described by Galea and Tracy (36). A study was done on non-participants of HUNT3 by Langhammar et. al using questionnaires, data from general practitioners in the region and register data(38). They found that non-participation carried a higher mortality rate and higher rate of several chronic diseases (e.g. cardiovascular disease or diabetes), but lower rates of several other common problems (e.g. musculoskeletal pain) (38, 39).

This means that people with lower SES are less likely to participate in HUNT3. This holds true for education levels, income levels, employment status and disability status(38).

1.4 Genetic influences on smoking

In recent years genome Wide Association Studies have attempted to find associations between genes and behaviours. The fact that genes influence smoking has been established knowledge for a long time. Before genome-wide studies to find specific genetic causes for nicotine addiction twin studies and familial studies had shown that genes played a role in people becoming smokers and remaining smokers (40, 41)

1.4.1 Why use genes to study smoking?

Randomized controlled trials (RCT's) are held up as the gold standard of medical research in terms of establishing causative pathways(42). In RCT's the participants are randomly assigned to be in the exposure (treatment) group or control group. The important thing about the random assignment of exposure is to also randomly assign the confounding factors (hopefully) equally to each group, thus isolating the effect of the exposure or treatment as the difference between the results of the two groups. However, this is impossible or wildly unethical to do for many exposures such as cigarettes, career path, alcohol etc. As the human genome has been studied and mapped over the last few decades several genes have been shown to have different varieties (SNP's or alleles, se insert below) that increase or decrease the chance of certain conditions or behaviours. As genes are randomly passed down from ones parents, and not changed later in life by lifestyle choices, using genes that influence behaviours as proxy for those behaviours can help to uncover causal pathways(43).

Several studies have been done over the last decade to establish association between an SNP rs16969968 (or similar alleles) and health outcomes. The studies have shown a very

clear causal association with COPD, lung cancer, and cardiovascular issues. Genes that increase smoking consumption are associated with higher all-cause mortality (44). It has also been used to try to uncover causative effects in cases where the role of smoking is more unclear. For example, previous studies using HUNT data found no clear causal effect on anxiety and depression, even though smoking is correlated with these conditions(45, 46). Similarly, smoking seems to have no causal effect on increased alcohol consumption even though the two are strongly associated with each other (47)In addition to confounding factors, reverse causation can also make it hard to find the causal pathways in health outcomes. Sometimes referred to as the "healthy smoker effect", if people are more likely to quit smoking after health problems emerge the pool of current smokers may be healthier than the pool of former smokers, or even never-smokers (48).

1.4.2 Basic genetics

DNA (Deoxyribonucleic acid) is an extremely complex molecule organised in a double helix. DNA consists of 4 nitrogenous bases, adenine (A), thymine (T), cytosine (C) and guanine (G) where A binds to T and G binds to C, and vice versa. These binding s are called base pairs, and the human DNA contains about 6 billion base pairs divided into 23 pairs of chromosomes.(43)

DNA is sometimes described as the instruction manual and is the basis for all living plants and animals on the planet. Various sequences of DNA form the instructions that allow organisms to assemble into our forms, grow into lager versions, maintain and repair ourselves and, ideally, replicate into new generations. DNA can be coding (i.e. provide instructions for building cells or structures) or non-coding(49). Non-coding DNA also has an effect, but this is not fully understood by science yet. Genome-wide association studies often find associations between outcomes and non-coding areas of DNA.

SNPs and alleles

A single nucleotide polymorphism (SNP) is variation of a single nucleotide at a specific point of a genome in a significant part of the population.(1) E.g. if most of the population has an A in a specific place but a significant minority have a T, this is a SNP. A and T are called alleles. A significant minority is generally taken to mean 1% or more.

A SNP can happen in the coding-or non-coding regions of genes, and within coding regions the substitution of one allele for another can have a range of effects on resulting gene expression of proteins. The difference in protein can mediate the effects of the cell it's a part of or result in a nonsense-protein that is not functional or even variants that cause diseases.

Though there is no universal naming convention for SNP's, various databases with identified and named SNP's exist (2). In this study we are looking at rs16969968, the name taken from the the Single Nucleotide Polymorphism Database hosted by the National Library of Medicine.

When DNA is replicated in conjunction with cell division, one base pair can be switched for another. We call this a mutation. If this happens when a gamete (sperm or ovum) is formed the mutation will be passed on.

1.4.3 Influence of rs16969968 (and other genes) on smoking

In this study we are using rs16969968, which is a SNP associated with a higher intensity of smoking among daily smokers(50) and with lower quitting rates. This SNP is found on the gene cluster CHRNA5/A3/B4 that is responsible for encoding the nicotinic receptors in the brain(51). Several genes in this gene cluster can affect smoking behaviours, but rs16969968 has the strongest association and is identified in several studies as the main risk factor(52). The plausible mechanism for the effect is through number or functioning of nicotinic acetylcholine receptor (nAChR) in individuals with one or two copies of the SNP. Nicotine binds to the nAChR and produces both euphoria and relaxation, and these feelings of well-being seem to be increased for people with this allele(53). It has both an excitatory and inhibitory effect, producing a state where the user feels more focused and more relaxed at the same time. The receptors are intended for the neurotransmitter acetylcholine, a neurotransmitter that plays an important role in attention and cognitive tasks. Nicotine mimics acetylcholine and causes many of the same effects, but at a much higher rate(54).

The effect of having the allele is estimated at around 1 cigarette per day(48, 55, 56). A previous analysis of 12 178 current smokers from HUNT2 found the effect to be 0.66 cigarettes per day (CI: 0.52, 0.80)(48)[2]. However, these effects were calculated based on data collected in population studies and rely on self-reported estimates from smokers. If we instead look at studies examining objective measures of nicotine consumption like cotinine levels in blood serum the associations between rs16969968 and cigarette consumption is even stronger than the self-reported data suggests (57). This could be due to mistakes typical of self-reported data like faulty recall, ambiguously worded questions, or under-reporting of risk behaviours. Another possibility is that higher dependence leads to taking more puffs of the same cigarette than someone without a copy of the allele or smoking closer to the filter before extinguishing the cigarette.

A person can have 0, 1 or 2 of this allele in their genome. The effect seems cumulative, meaning someone with 2 rs16969968 alleles in their genome will (on average) have a higher smoking intensity than someone with 1 (50).

1.5 Research question

With these, sometimes contradictory, studies on how smokers perceive their own health risks and how smoking effects these, and knowing ill health can be a motivator to quit smoking, it seems valuable to look at how smokers evaluate their own health status. Since rs16969968 is associated with smoking, but not with SES we will be using the allele as an instrument for smoking intensity, in order to find a relationship between degree of smoking and self-reported health, and can assume that the results will be to a lesser degree confounded by socioeconomic factors.

This research project uses mendelian randomisation to assess the relationship between smoking intensity and self-reported health using data from HUNT3 and HUNT2. The results will be compared to the relationship between smoking intensity and more objective measures of health like COPD, cardiovascular diseases or chronic disease.

[2] Number taken from figure S8 in the supplementary material of Skaaby et al 2017

2 Methods

2.1 Mendelian randomization

Mendelian randomization is a method that has been widely used in the last decade to attempt to counter problems of confounding and reverse causation in epidemiological research.

2.1.1 Approximating randomized control trials (RCTs)

As mentioned, Mendelian randomisation is a way to approximate RCTs in observational studies. RCT is the gold standard for assessing causality and effectiveness of treatments in medical research. However, in epidemiological research observational studies are much more accessible(58), and often the only realistic option. This leaves the conclusions drawn open to confounding variables, e.g. SES, in relation to smoking. Instrumental variables (IV) are variables that can be used as unbiased estimators for the effect of smoking. To avoid confounding, the instrumental variable must be associated with the outcome only through the treatment and must be randomly distributed. Mendelian randomization is defined as "instrumental variable analysis using genetic instruments"(42).

2.1.2 Instrumental variable analysis

A confounding variable is one that affects both the exposure and the outcome, making it difficult to isolate the effect the exposure has on the outcome. This is illustrated in Figure 4, showing the confounder C affecting both the exposure E and the outcome D. This masks the effect E has on D. To combat this Mendelian randomization introduces an instrumental variable(59). An instrument has three properties; i: it influences E. ii: It influences D ONLY through its influence on E. I.e. it is not associated with any confounder that influences D. iii: Assumption of independence requires that there is no arrow in either direction between I and C. This assumption is maintained if the IV is randomly assigned(60).

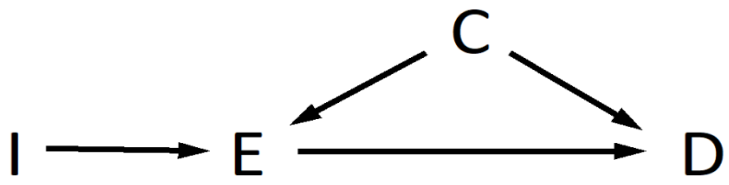

Figure 4: Directed Acyclic Graph showing an instrumental variable I working on the exposure, E, unaffected by the confounder, C. It affects the outcome, D, only through the impact it has on E.

If these assumptions hold, then a change in instrument would affect the outcome D. It is then possible to compare the outcome of groups with different levels of the instrument to ascertain the true causal effect of the exposure, E, on the desired outcome.

In addition to these assumptions an instrument should be something easy to measure, both in the sense of the difficulty involved in getting the measurement and in terms of how precise the measurement of the instrument can be. At any rate it should be easier to obtain and ascertain than the difficulty involved in measuring the confounding factors C.

Presence or absence of an instrumental variable and it's effect on the outcome is enough to suggest causality. A full instrumentation would be to use an estimate of how many extra cigarettes a day each allele represents. If we say in this case that each allele is 1 extra cigarette per day per allele, we would use this to estimate the effect of one extra cigarette per day on the outcome.

2.1.3 Using genes as IV

Using genes as IV that impact the treatment (behaviour), but not the outcome in other ways has many advantages but requires some assumptions we must examine closer before proceeding.

2.1.3.1 Assumption i

The first assumption is that the gene variant influences the behaviour. In the case of rs16969968 there are not only numerous studies documenting the effect on smoking behaviour, there is also a clear pathway showing how the gene would physiologically affect how the brain responds to nicotine(51, 52). Studies suggest that the effect is 1 cigarette per day per allele in most studies (48), though as mentioned above, the similar result for data from HUNT is 0.66(45). There is also an impact on the difficulty in quitting smoking(52), and presumably on the transition from occasional smoking to daily smoking, though I was unable to find this particularly in the literature. In a full instrumentation we would use the allele as an equivalent of 1 extra cigarette per day for the length of time they have smoked to find out how much each extra cigarette impacts the outcome. However, as mentioned in 1.4.3 studies have shown that this estimate of effect seems likely to be inaccurate(57). Doing a full instrumentation would also not fully include the effect the allele has on current smoking status, and the reduced rate of quitting among those with the allele. Instead we will divide into smokers and never-smokers and see how the allele influences the outcomes in both groups. This will simplify the analysis compared to a full instrumentation.

Dividing into smokers and never-smokers means making the assumption that having one or two copies of the allele does not influence who tries smoking in the first place (smoking uptake). It seems a reasonable idea that a person with the allele would need to be exposed to nicotine to realise they found it addictive. This is an important assumption, because SES is a strong component in smoking habits, and has a documented effect on smoking uptake. If using the gene as an instrument is supposed to circumvent the effect SES has on smoking, the gene cannot have the same effect or there will be a confounding. We can test this assumption by checking if the distribution of alleles in the participants who have never smoked is the same as in the general population.

2.1.3.2 Assumption ii – No horizontal pleiotropy

The second assumption, that it affects the outcome only through the exposure we wish to study, is difficult to make with 100% certainty. The human brain and body are an incredibly complex system, and it is hard to say with 100% certainty that one thing absolutely does not affect another. Pleiotropy is when a single genetic variant influences multiple traits, and this is likely very common in DNA (61). Hemani, Bowden and Smith explain in their article on the role of pleiotropy in Mendelian Randomization that

> If pleiotropy arises because the single nucleotide polymorphism (SNP) influences one trait, which in turn influences another ('vertical pleiotropy'), then Mendelian randomization (MR) can be used to estimate the causal influence between the traits. […] Among the many limitations to MR is the unprovable assumption that apparent pleiotropic associations are mediated by the exposure (i.e. reflect vertical pleiotropy), and do not arise due to SNPs influencing the two traits through independent pathways ('horizontal pleiotropy'). (61)

There are methods made to try to uncover horizontal pleiotropy in the analysis and correct for it, as it poses a real limitation in the method (62). Such analysis require availability of multiple genetic instruments for the exposure(63) and is beyond the scope of this thesis. Rs16969968 is furthermore well studied and established as an instrument for smoking in research(41, 64), which means the validity of using it as an instrument can rely on previous research(63).

However, we can take advantage of the fact that in people who have never been exposed to smoking the SNP should not have an effect on the outcome. This gives us a negative control group to run the same analysis and hopefully find no effect of the allele on the outcome(65). The use of negative controls is described further in chapter 2.1.5. This relies on the assumption mentioned in the previous paragraph that having one or two copies of the allele does not influence uptake of smoking. Since we also assumed the SNP may influence transitioning from occasional smoking to daily smoking, and may also affect success in quitting smoking, we separate between ever-smokers and never-smokers rather than between current, former and never-smokers.

2.1.3.3 Assumption iii – Random distribution

The third assumption is that is that the genes are randomly distributed in the study population. Genes are always randomly assigned in the sense that they are passed on by parents at random. Your genes as they are handed out in the birth lottery are not affected by any diseases you have later in life, the profession you chose etc. In this sense the genes are randomly distributed and are not confounded.

This is not necessarily the case for alleles in the population. If smokers are more likely to pair up with other smokers, and smokers are more likely to have the allele the result would be a bias known as assortative mating bias(66). There could also be population stratification, where subpopulations end up with different SNP distributions(65). Other reasons a gene might not be randomly distributed would be if there was a recently arrived immigrant population where a SNP was more widespread. In this case the results would be confounded by the socioeconomic factors associated with immigrants mentioned earlier. To test the assumption that the SNP is randomly distributed we will compare the distributions of alleles in the population with an imagined idealized population as predicted by the Hardy-Weinberg equilibrium.

2.1.4 Hardy-Weinberg equilibrium

The Hardy-Weinberg equilibrium states that the genetic distribution in a population will remain constant from one generation to the next in the absence of disturbing factors, such as the above mentioned assortative mating(43). The Hardy-Weinberg equation, $p^2 + 2pq + q^2 = 1$ gives the expected level of each allele in a hypothetical ideal population, where p^2 is the proportion of the population with 0 of the SNP in question, $2pq$ represents the proportion of those with one copy of the SPN and q^2 represents the proportion of those with 2. By comparing the distribution in the general population with the ideal values in a Chi-squared test we can find out how close to completely random the SNP distribution in the population is.

2.1.5 Negative controls

As mentioned in 2.1.3.1 the instrument used should only affect the outcome through its effect on the exposure. This assumes the allele rs16969968 only affects smoking behaviour once the person tries smoking, but that whether or not the person tries smoking in the first place is not associated with the SNP. This is an important assumption, because SES is a strong component in smoking habits, and has a documented effect on becoming a daily smoker. If using the gene as an instrument is supposed to circumvent the effect SES has on smoking, the allele cannot have the same effect or there will be a confounding. For example, if the allele makes it less likely to quit smoking a person with the allele would have a greater chance of having close family members who smoke. This could have an effect on health outcomes through childhood exposure to smoking. If having family members who smoke also increase the chance of trying the first cigarette then the effect of the smoking habits of the individual could be confounded by the effects of exposure to cigarette smoke as a child. I can test this assumption by checking if the distribution of alleles in the participants who have never smoked is the same as in the general population. If people without any copies of rs16969968 are over-represented among the never-smokers this could indicate a problem.

To ensure that any association between the SNP and the outcome is mediated through smoking intensity an analysis will be performed on the never-smokers to see if the SNP affects their health outcomes(43). If the SNP is associated with outcomes also among never-smokers, this would indicate that the association between health outcomes and smoking is confounded by other pathways(65, 67).

2.2 Study sample and variables

As introduced in chapter 1.3 the entire adult population of Nord-Trøndelag is invited to participate in the HUNT-studies, and all participation is voluntary. All participants are invited to fill out questionnaires and all in HUNT2, HUNT3 and HUNT4 were asked to contribute biological material to the HUNT Biobank, where the genetic information is taken from(37).

2.2.1 Participation rates in the HUNT surveys

Table 1 shows participation in the HUNT surveys. The numbers show a decrease in participation rates, consistent with observations mentioned in 1.3.

HUNT study	HUNT1 (84-96)	HUNT2 (95-97)	HUNT3 (06-09)	HUNT4 (17-19)
% Participated (adults 20+)	89,4	69,5	54,1	54
Number participated	77 212	65 237	50 807	56 078

Table 1: Numbers are taken from Cohort Profile Update: The HUNT Study, Norway (30).

Studies on the population that did not participate (nonparticipation studies) were carried out after HUNT1 and HUNT2, both limited in scope to a few topics, and both indicating "only minor potential nonparticipation bias" according to Langhammer A, et al 2013. (38).

For HUNT3 the non-participation questionnaire (NPQ) uncovered that more non-participants had reported poor or very poor health compared to the participants. The

youngest and oldest are underrepresented in the study, with lowest rates of participation among those over 80 and those between 20-39. The same article found that when comparing participants to non-participants there was no significant difference in daily smoking rates for women (20.6% vs 20.2%), but a significant difference for men (16.9% vs 18.7%). For a disease we are looking at, such as COPD, the non-participation study found lower rates among the general population than in the study population for those under 60, and the opposite for those over 60. For diseases caused by lifestyle it is the older age groups that are most interesting for the analysis. In this case the most common reason given for not participating among the oldest potential participants was their health being too bad(38).

2.2.2 Genetic data

Genetic data was collected as part of HUNT2 and HUNT3 from whole blood. In total 71860 participants have contributed genetic data to HUNT Biobank. The participants have all consented to the use of data from the genetic material and questionnaires. I have genetic data available on 69421 participants. Some samples are excluded because of technical issues or contamination, and some are excluded because they are not of recent European ancestry. To work as an unconfounded instrumental variable, genetic variance due to recent immigrant populations having different levels of an allele cannot be included. See appendix 3 for more information.

2.2.3 Definition of the study sample

To be included in the analyses, participants needed to have available genetic data and valid outcome variables in either HUNT2 or HUNT3. Thus, the number of individuals included in each analysis differ for different outcomes, and the number of included and excluded individuals will be specified at the beginning of each section in the results. In the analysis only one data point for each individual will be used, to avoid issues related to repeated measurements. Where there is relevant data from both HUNT2 and HUNT3 the most recent will be selected.

2.2.4 Important differences from HUNT2 to HUNT3

There were some changes in the questions and the wording of the questions between HUNT2 and HUNT3. There were also differences in the layout and grouping of the questions asked. The questionnaires can be found in appendix 1.

2.2.4.1 Smoking status

One of the most relevant differences that impact the research at hand is a difference in wording of smoking status questions. In HUNT2 the question of smoking is "have you ever smoked daily" with the possibility to select "Never smoked daily". They also ask about age at smoking initiation, time since smoking cessation and daily consumption of cigarettes. HUNT databank has used a combination of these questions and answers to assign people to the categories "Never-smoker", "Former smoker" and "Daily smoker" in the variable "smoking status" for each HUNT wave(68, 69).

In HUNT3 on the other hand, the question is "have you ever smoked" with response options "no", "daily", "formerly" or "occasionally". This means there is an extra layer of stratification, as no information on occasional smoking was included in the HUNT2 questionnaire. This has some impact on how we can define never-smokers, as we assume that RSrs16969968 makes it more likely to develop a daily smoking habit if

exposed to smoking. The group in "never-smoker" will not include those who were occasional smokers only and never progressed to be daily smokers.

In addition to constructing new variables for smoking status, HUNT databank has refined the information from each of the questions on smoking. Doing this, they also considered information provided in other study waves. Where a participant has reported to never have smoked, but nevertheless indicated current or former smoking through their response to other questions, HUNT databank has recoded the never-smoking variable to missing. Similarly, if the participant reported smoking in an earlier study wave, the response on never smoking has been changed to missing.

2.2.4.2 Defining never-smokers and ever-smokers

For the current research project, separating between current and former smokers is not of interest, we only need to know whether participants are ever-smokers or never-smokers. If I use the information in the variable "smoking status" I would lose ~1300 participants with missing values in HUNT3 and ~1100 in HUNT2 from the study sample. I therefore initially used all the available information about smoking, such as given an age for start or cessation, information from HUNT2 to identify ever-smokers in HUNT3. After considering all available information, only 19 participants were categorized as missing for smoking status in HUNT3. Doing the same for HUNT2 would be more difficult, as I do not have information from HUNT1, and participants who gave a different answer from HUNT2 to HUNT3 may have begun smoking in the interim.

The never-smoking variable as provided from HUNT databank contained values 1 for never-smokers and missing for anyone else. As the ascertainment of smoking status was complex and depended on the study wave from which information would be used, which differed between outcomes, and because the result was almost identical to the information contained in the one variable on never-smoking, I chose to use only the information on this variable from each study wave.

In short, those who have value 1 on this variable are considered to be never-smokers, while those who are missing data on this question are considered to be ever-smokers. This means that a few participants who were truly have no information on smoking will be assigned to the "ever-smokers"-group, instead of being discarded as missing. One argument in favour of this simplified definition is that HUNT has done a substantial amount of work on the variable that is useful here(68).

Such a small number of participants are falsely changed from missing to ever-smoking compared to the total number, they are unlikely to make a difference to the analysis. However, I performed additional analysis using the more restrictive smoking-status provided by HUNT databank for the main result (SRH).

Where there are two data points for one participant the data for HUNT3 will always be selected, meaning I will have the most precise category for as many participants as possible.

The control group will consist of those who report that they have never smoked from HUNT3, and those who say they have never smoked daily from HUNT2. It is hard to completely avoid the issues that stem from the difference in the way these questions are asked. In the analysis care must be taken to make sure the selection of the non-smoking group is checked against the smoking data available from HUNT3. This is particularly

important as we have hypothesized that a difference in smoking uptake (moving from occasional to daily smoker) is higher for those with the allele than without the allele.

It is possible to check those who have the status "occasional smoker" in HUNT3 against those who have never smoked daily in HUNT2 to see how large the overlap is. As we are measuring a relatively small effect it is useful to have a population that is as large as possible to find if the SNP has a significant influence on the outcome.

2.2.4.3 COPD

The question "Do you have COPD" is not included in HUNT2. COPD did not exist as a diagnosis at the time of HUNT2. COPD shows up in the library of MESH-terms for the first time in 2002. Instead, I will use the questions asked about daily coughing and heaviness of breath as a sustained problem over longer periods (3 months and 12 months respectively). This is a more subjective measure than asking whether one has received a diagnosis of a specific disease. This study makes the assumption that yes to either or both of these questions indicates presence of chronic lung problems and no or empty answers indicate absence of chronic lung problems.

2.2.5 Variables used in the analysis

2.2.5.1 Genetic instrument

The instrument to represent heavier smoking is the SNP (rs16969968). The number of the relevant allele each participant can have is 0, 1 or 2. Due to the way the genome is sequenced there are some participants that have allele numbers that fall between these values. For numbers and tables presented here the numbers have been rounded to the nearest integer. For analysis purposes they are kept as they are. In total 237 values fall in the intervals 0.001-0.999 and 1.001-1.999.

2.2.5.2 Confounders

Age and sex will be included as exposures in the analysis, as both have impact on the outcomes. As mentioned, participants are identified by their personal identification number by HUNT, which are recoded in the dataset to protect the identity of the participants. The Norwegian PID includes information on date of birth and gender of the person hardcoded into the number. The date the participant attended was also recorded by HUNT. This means that the categories age and sex are complete in the dataset, as they can both have been extrapolated from the personal identification number and the date of participation.

2.2.5.3 Outcomes

I will be looking at seven outcomes; Self-reported health, COPD (HUNT3 only), signs of chronic lung disease (HUNT2 only), heart disease, chronic illness, cancer and stroke.

Self-reported health (SRH) is framed as a question "how is your health in general?" and the possible answers are listed as "very poor", "poor", "good" and "very good", which is assigned a number value 1-4 respectively. These responses will be recoded to Low SRH (1 and 2) or good SRH (3 and 4).

In questionnaire 1 (Q1) in HUNT2 and HUNT3 participants are asked about a range of diseases or conditions, asked as "do you have or have you ever had x?" and have the response values no (0) and yes(1). From these questions I will be looking at COPD (only

in HUNT3), Cancer, Stroke/Cerebral haemorrhage, Heart attack and Angina pectoris. The first four of these are outcomes on their own. Heart attack and angina pectoris will be combined into one outcome, "heart disease". Heart disease will have the value 1 if the participant has answered yes to either or both of the original variables, and 0 if they answered no to both, or answered "no" to one and did not answer the other.

In HUNT2 participants are asked "Have you had daily coughing that brings up phlegm for at least 3 months?" and "Have you had attacks of wheezing or breathlessness during the last 12 months?". As was done for heart disease, these will be recoded to 0 if they answered "no" to both, or "no" to one and refrained from answering the other, and 1 if they answered "yes" to either or both.

For chronic disease the question is framed as "Do you suffer from any long-term illness or injury of a physical or psychological nature that impairs your functioning in your everyday life?"

2.3 Statistical analysis

The statistical analysis was performed using R version 4.1.2.

2.3.1 Logistic regression

I used binomial logistic regression to estimate the association between rs16969968 and each outcome. This means that the response variable must be a categorical variable with two possible values, here 0 and 1, where 0 indicates not having the outcome and 1 indicate having the outcome. Each outcome was assessed in a separate model, adjusted for age as a continuous variable and sex.

Under the assumptions outlined in 2.1.3, the association between rs16969968 and each outcome can be interpreted as an estimate of the causal effect of smoking with a higher intensity. However, as I did not perform full IV analysis, the estimated effect sized are given per allele of the smoking associated SNP and not readily translated to units of measured smoking, e.g. effect per cigarette smoked.

3 Results and Analysis

3.1 Describing the study sample

We received data from all participants of HUNT2 and HUNT3, which is a total of 78959 individual participants. Of the 78959 participants we have information on the rs16969968 for 69421 individual participants. (See Figure 5). 1850 participants of HUNT3 and 8647 participants of HUNT2 either did not give a sample, or did not give consent for their sample to be used. There is no genetic information for 9538 participants in total. For the rest of the thesis 69421 is the total unless stated otherwise.

Of the 69421, 56581 have participated in HUNT2 and 48950 have participated in HUNT3, meaning 12 840 have only participated in HUNT3 and 20 471 have only participated in HUNT2. 36110 have participated in both studies. Where we have two valid datapoints for the participant the most recent is selected.

Source	Participants	Mean age	St dev age	Men	Women
HUNT2	20471	54.46	20.43	10368	10103
HUNT3	48950	53.30	15.95	22319	26631
Total	69421	53.64	17.40	32687	36734

Table 2: Study population.

Table 2 represents the total possible study sample, using all participants from HUNT3 and all participants who only participated in HUNT2. For each analysis participants will be selected based on available data for the outcome of interest. In our analysis we will be selecting for various outcomes, and as such the selection for each outcome will be slightly different.

	Ever-smokers		Never-smokers		Total
HUNT2*	13139	64%	7332	36%	20471
HUNT3	28682	59%	20268	41%	48950
Study population	41821	60%	27600	40%	69421

*Table 3: Ever-smokers and never-smokers in the potential study population. *Selection of HUNT2 after those who also participated in HUNT3 are removed*

In Table 3 never-smokers were selected as those who ticked "I have never smoked" in HUNT3 and "I have never smoked daily" for HUNT2.

In Table 2 and Table 3 we see the total using all participants from HUNT3 and the participants who only participated in HUNT2. For each outcome the selection will be slightly different. Where participants have missing values for the outcomes in HUNT3 their values from HUNT2 are used instead if possible.

3.2 Gene distribution

The analysis is built on an assumption that the genetic distribution if the allele is random in the population, and that smoking uptake is random and not predicted by presence of absence of the allele.

3.2.1 Comparing gene distribution to "ideal values"

The table below shows the distribution of the allele in the total study population

	Total study sample		Ideal* population distribution	HUNT2 study sample		HUNT3 study sample	
Number of alleles	Number	Percent	Percent	Number	Percent	Number	Percent
0	30716	44.25	43.95	8910	43.52	21806	44.55
1	30816	44.39	44.69	9201	44.95	21615	44.16
2	7889	11.36	11.36	2360	11.53	5529	11.30
Total	69421	100		20471	100	48950	100

*Table 4: Gene distribution, all data. *Ideal distribution refers to equilibrium in population according to the Hardy-Weinberg-principle*

Recalling the Hardy-Weinberg principle for an ideal (hypothetical) population and calculating based on $q^2 = 0.1136$, (i.e. the observed prevalence of homozygosity for the rs16969968 x allele) we get expected values $2pq = .4469$ and $p^2 = 0.4395$ for heterozygosity and homozygosity of the x allele, respectively. The gene levels in the study population are very close these values, and a chi-squared test between our sample and the hypothetical ideal population is not significantly different (p-value .498).

3.2.2 Comparing gene distribution in smokers vs never-smokers

As mentioned above "occasional smoker" was an option in HUNT3, though not in HUNT2. Of the 3484 that stated they were "occasional smokers" in HUNT3 2171 also participated in HUNT2. Of these 494 gave their status as "never smoked daily", 828 as "former smoker" and 747 gave their status as "daily smoker" in HUNT2.

	Alleles	Never Smoker	Former smoker	Daily smoker	Occasional smoker	total(100%)
HUNT2 (%)	0	10666(43.5)	6953(28.4)	6882(28.1)		24501
	1	10566(42.7)	6738(27.3)	7415(30.0)		24719
	2	2686(42.8)	1634(26.1)	1951(31.1)		6271
	Total HUNT2	23918(43.1)	15325(27.6)	16248(29.3)		
HUNT3 (%)	0	9047(42.7)	7064(33.3)	3461(16.3)	1629(7.7)	21201
	1	8897(42.3)	6853(32.6)	3783(18.0)	1488(7.1)	21021
	2	2298(42.7)	1689(31.4)	1026(19.1)	367(6.8)	5380

	Total HUNT3	20242(42.5)	15606(32.8)	8270(17.4)	3484(7.3)	47628

Table 5: Gene distribution vs smoking status in HUNT2 and HUNT3. The category "occasional smoker" did not exist for HUNT2.

In table 4 we see that the number of never-smokers in HUNT2 with 0 of the allele is slightly higher than for the ever-smokers. As mentioned in 2.2 the category "never-smoker" in HUNT2 is less precise, or less stratified than in HUNT3. If we isolate the participants in HUNT3 where we have an extra layer of stratification in the data the difference between the general population and the never-smokers is not statistically significant in a chi-squared test (p-value 0.500). In a chi-square test comparing the whole study sample of never-smokers to the general population the difference between them is significant with a p-value of 0.048.

3.3 Flow charts

3.3.1.1 Self-reported health

Of the 69421 participants with available genetic data 490 had no information about self-reported health from either HUNT2 or HUNT3. This left 26901 in the never-smokers and 42030 in the ever-smokers group, as illustrated in Figure 5.

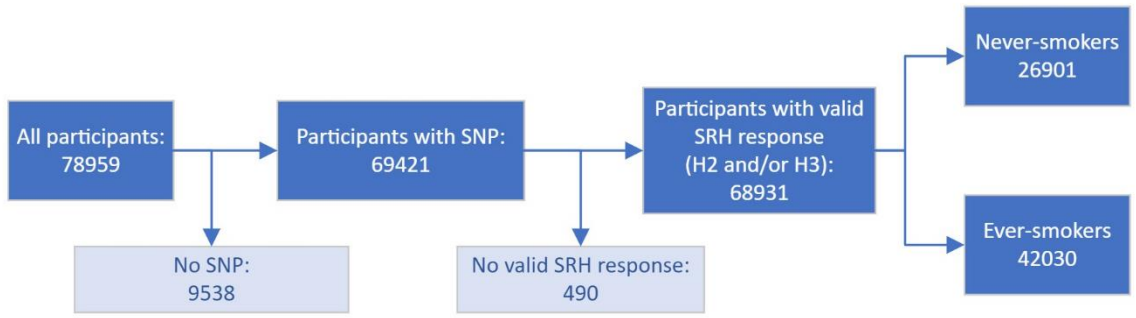

Figure 5: Flow chart for SRH (Self-Reported Health).

The study sample for SRH consists of 47 467 participants from HUNT3 and 21 464 participants from HUNT2.

For the sensitivity analysis all participants who had missing data for smoking status in both HUNT2 and HUNT3 were excluded. This resulted in a sample of 39718 participants, 2312 fewer than the sample used in the main analysis.

3.3.1.2 Chronic disease

The study sample for chronic disease consisted of 47 911 participants from HUNT3 and 20 106 participants from HUNT2.

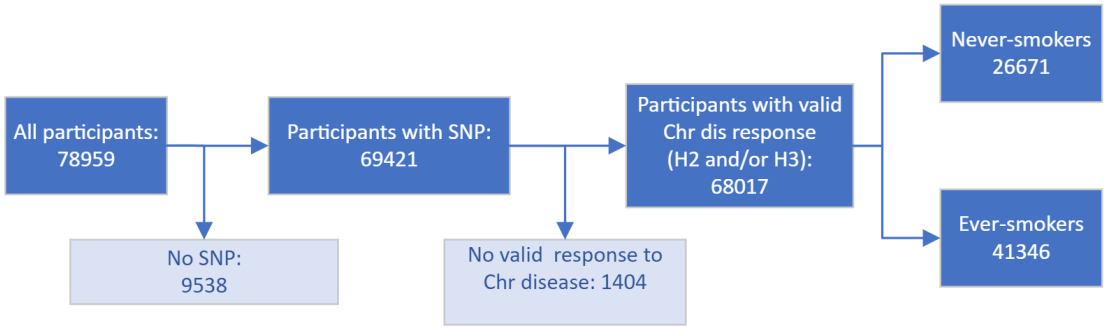

Figure 6 Flow chart for answers to "Do you suffer from any long-term illness or injury of a physical or psychological nature that impairs your functioning in your everyday life?"

3.3.1.3 COPD

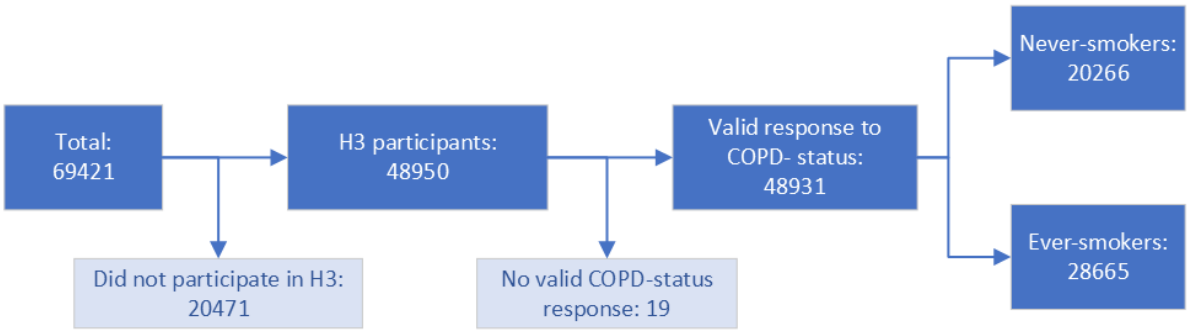

Figure 7: Flow chart for "Do you have COPD/chronic emphysema" HUNT3.

The study sample for COPD consisted of 48 931 participants from HUNT3.

3.3.1.4 Lung disease symptoms

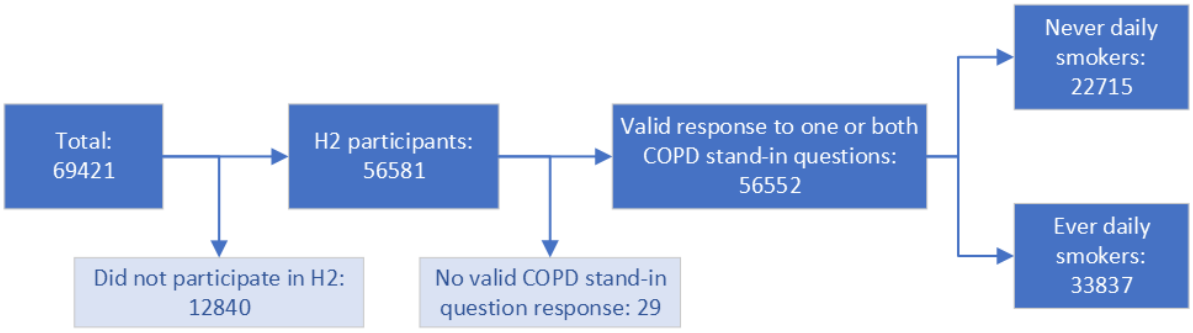

Figure 8: Flow chart for answers to questions on symptoms of lung problems from HUNT2 only.

No valid response to the COPD-stand in should be read as no response to both questions on lung health used ("daily coughing with phlegm for 3 consecutive months" and "shortness of breath for the last 12 months"). In addition to the 29 who had no valid response to either question a further 22 had not responded to one of them. In these cases the given answer was used on its own. As a binomial logistic regression requires the outcome to be expressed binomially (0 or 1) no distinction was made between those who responded yes to both (1201) and those who responded yes to only one or the other (7373).

3.3.1.5 Cancer

Cancer had a very high number of missing values from HUNT2 (see Table 6), especially considering a very small amount of participants answered "yes" to the question.

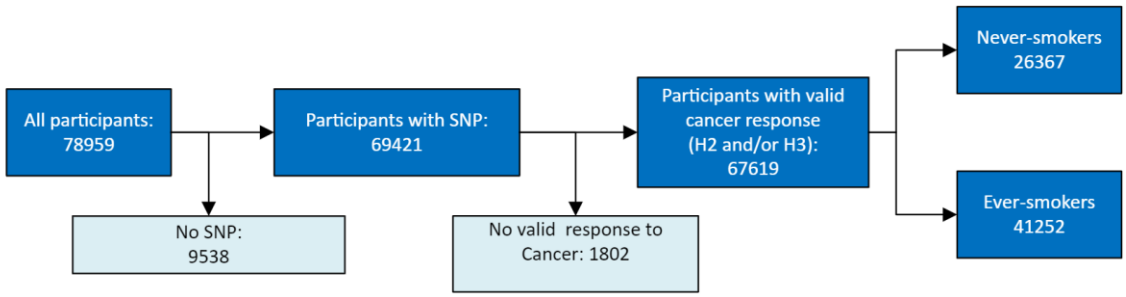

Figure 9: Flow chart for "Do you have or have you ever had Cancer?"

The study sample for cancer consisted of 48 937 participants from HUNT3 and 18 682 participants from HUNT2.

3.3.1.6 Heart disease

No valid response to heart disease in should be read as no response to both questions on heart disease used ("do you have or have you ever had a heart attack" and "Do you have or have you ever had angina pectoris"). In addition to the 27 who had no valid response to either question a further 27 had not responded to one of them. In these cases the

given answer was used on its own. As a binomial logistic regression requires the outcome to be expressed binomially (0 or 1) no distinction was made between those who responded yes to both and those who responded yes to only one or the other.

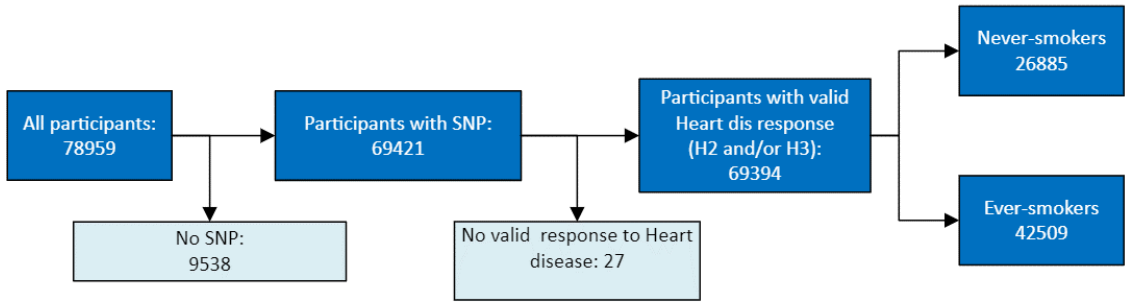

Figure 10: Flow chart for myocardial infarction or angina, combined here to "heart disease"

The study sample for heart disease consisted of 48 943 participants from HUNT3 and 20 451 participants from HUNT2.

3.3.1.7 Stroke/cerebral hemmorhaege

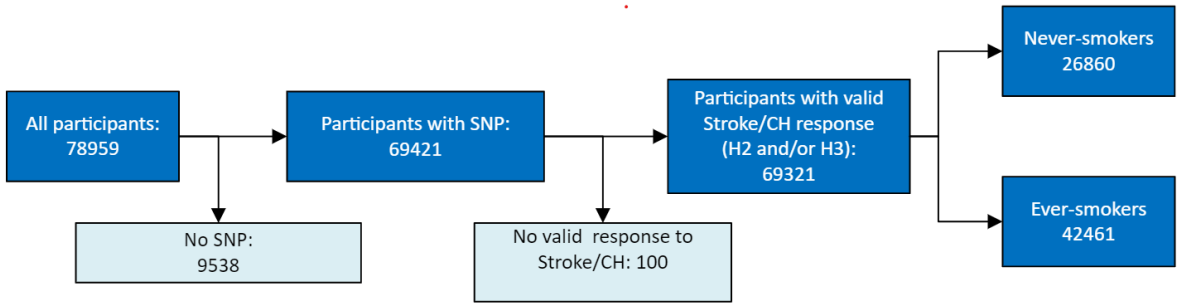

Figure 11: Flow chart for stroke or cerebral haemorrhage.

The study sample for stroke or cerebral haemorrhage consisted of 48 942 participants from HUNT3 and 20 379 participants from HUNT2.

3.3.2 Table over missing values by outcome

For each analysis the data was first divided into those with valid outcomes in HUNT2 and HUNT3, then divided into ever-smokers and never-smokers. For all cases the most recent data point was included where there was data from both surveys available. To see how many were grouped into the exposure group (ever-smokers) vs control group (never-smokers) see the flow charts, figures 5-11.

Outcome		**Study sample** (n)	**%**	**HUNT2** (n)	**HUNT3** (n)
Total		69421	100	56581	48950
Low SAH	Yes	19714	28.40	14966	12325
	No	49217	70.90	41181	35142
	Missing	490	0.71	434	1483
COPD	Yes	1676	3.42	-	1676
	No	47255	96.54	-	47255
	Missing	19	0.04	-	19
Lung symptoms	Yes	8574	15.15	8574	-
	No	47978	84.80	47978	-
	Missing	29	0.05	29	-
Stroke/CH	Yes	2105	3.03	1040	1339
	No	67216	96.82	55436	47603
	Missing	100	0.14	105	8
Heart disease	Yes	5408	7.79	3593	2924
	No	63986	92.17	52960	46019
	Missing	27	0.04	28	7
Chr disease	Yes	28791	41.47	18793	19837
	No	39226	56.50	35604	28074
	Missing	1404	2.02	2184	1039
Cancer	Yes	3728	5.37	1997	2701
	No	63891	92.03	51608	46236
	Missing	1802	2.60	2976	13

Table 6: Missing variables for each outcome.

In Table 6 we see the missing values for each outcome variable. There was no data lost to missing values in any of the other columns used (smoking status, sex, age). There is a marked difference in missing between HUNT2 and HUNT3, with many more being missing in the former. It is particularly notable that for cancer the number of missing values for HUNT2 (2976) is higher than the number who responded that they had had cancer

(1997). In contrast 2701 said they had had a cancer diagnosis in HUNT3 and only 13 didn't respond.

3.4 Results of logistic regression

Table 7 shows the results of the logistic regression. In all analyses sex and age were corrected for at once

	Ever-smoker			Never-smoker		
Outcome	OR	95% CI	p-value	OR	95% CI	p-value
Self-reported health	1.01	0.98-1.04	0.65	1.01	0.97-1.06	0.6
Chronic disease	1.01	0.98-1.04	0.42	1.00	0.96-1.04	0.9
COPD HUNT3	1.16	1.07-1.25	0.0004	1.00	0.84-1.20	0.97
Lung symptoms HUNT2	1.14	1.09-1.18	1.57E-09	0.99	0.93-1.06	0.80
Stroke/ CH	1.07	0.99-1.16	0.10	0.93	0.83-1.05	0.25
Heart disease	1.04	0.99-1.10	0.15	1.03	0.95-1.12	0.51
Cancer	0.99	0.93-1.05	0.70	0.91	0.84-0.99	0.04
Cancer (HUNT3 only)	0.98	0.91-1.06	0.64	0.92	0.83-1.01	0.09
SRH sensitivity analysis	1.01	0.98-1.04	0.68	-	-	-

Table 7: Odds ratios (OR) for all outcomes. In all analyses sex and age were corrected for

3.4.1 Results for the ever-smokers

For the ever-smokers rs16969968 had no significant effect on self-reported health. A sensitivity analysis was done on SRH, and the analyses redone with a stricter selection criteria for ever-smokers. For this analysis the results for the odds ratio and confidence interval were identical to at least two decimal places.

For the other outcomes, there was no significant effect on chronic illness, stroke or heart disease. I did find a significant effect on COPD and lung symptoms. As we see in Table 6, the number of participants with lung disease symptoms is much higher than for COPD, but the size of the effect of the allele on the outcomes is very similar.

3.4.2 Results for the control group

For the negative controls there were no significant results, with the exception of the result for cancer. For cancer there was a significant ($p<0.05$) effect for the negative control group. As there was a very large number of missing values for the question on cancer from HUNT2 the analysis was re-done with only the values from HUNT3, where the number of missing values is much lower. In this case there was no longer a significant result.

For the other outcomes there are no significant results for the never-smokers. In particular there are no significant results for COPD and lung symptoms, which are the two where there were significant results for the exposure group.

4 Discussion

4.1 Main results

4.1.1 Main results ever-smokers

For the main question, does smoking more negatively impact self-assessed health rs16969968 had no significant effect on the outcome. Having the smoking-increasing allele significantly impacted COPD or presence of self-reported coughing symptoms, and had a large impact on these outcomes. However, it did not have a significant impact on having a chronic disease. The number with COPD is very small compared to the total number of people with chronic disease, so the effect may not be large enough.

For stroke/cerebral haemorrhage and heart disease the results provide weak evidence of an effect of having the allele, but not a statistically significant one. Taken together they could show a trend that having the allele has an impact on the cardiovascular system, however this study finds nothing conclusive here. For cancer the allele seems to have no impact on the risk of developing cancer, and the risk estimate is even below 1.

4.1.2 Results never-smokers

There were no significant results among the never-smokers, apart from the results for "have you ever had cancer". Due to the large number of missing answers on that particular outcome from HUNT2 I redid the analysis using only the data from HUNT3. In this case the result was no longer statistically significant. For further discussion on this outcome see below.

4.2 Methodological considerations

4.2.1 Smoking status

The way smokers and never-smokers were measured and selected could not be completely precise, considering how the data was collected. In addition to adding the category "occasional smoker" in HUNT3, the main distinction made was based on the answer to "Have you ever smoked" for HUNT3 and "Have you ever smoked daily" for HUNT2. This might have led to some degree of misclassification as we used smoking status to define a negative control group, and some occasional smokers from HUNT2 will have ended up in the negative controls, which could introduce information bias. It is difficult to estimate how much of a difference the information bias made with accuracy. The fact that less than 500 who claimed to be occasional smokers in HUNT3 gave their status as "Never smokers" in HUNT2 suggests the number is not enough to greatly affect the analysis. Some of these may have started smoking between the two screenings, but as smoking is a habit most start in their teens, this seems unlikely to be true for all of them.

In the analysis care was taken to remove participants from the never-smokers group in the HUNT2 data if they were present in the ever-smoker group for HUNT3. This precaution would have no impact on those occasional smokers who gave their status as

"Never smoker" in HUNT2, but did not participate in HUNT3. As mentioned in 2.3, HUNT has used further answers (age at start of smoking, answers from HUNT1 etc) to remove contradictory positives from this category, which also helps make the data more robust. The fact that there was no effect for COPD with the control group suggests this was effective.

4.2.2 Missing data

On the whole relatively small amounts of participants are excluded from the analysis due to missing data. The way the information is collected means that there is no missing data for gender and age, the two confounding variables the analysis corrects for. The decision to divide simply into smokers and never-smokers meant no participants were lost here either, though as discussed, this may affect the precision of the data for the exposure group.

4.2.2.1 No genetic information

The exception is in the data that is not included because there is no genetic information. This accounts for 9000 participants, which is a significant section of the participants. However, as mentioned in the cohort profile, there is no particular reason to believe there is a strong bias here. And as mentioned in 2.2.2.2 the data excluded from the samples given are due to methodological concerns for MR studies.

4.2.2.2 Cancer

For cancer in particular there is a large amount of missing data, and a marked difference between the number of missing cases in HUNT2 and HUNT3. For HUNT2 the number of missing data for that question is higher than positive responses. There is also a much higher number of respondents answering "yes" in HUNT3 despite a smaller total. There are many factors that could be influencing both the high number of missing cases in HUNT2 and the increase of cases in HUNT3.

There was significant progress made in cancer treatments between 1995 and 2005(70). As such there may well have been more survivors of cancer in HUNT3 than in HUNT2. Cancer is also much more common among the oldest in the population, and the incidence of cancer has increased as the average age of the population has increased. These two things taken together suggest there might genuinely be more cancer survivors in HUNT3 than in HUNT2.

Another explanation may be that a relatively high proportion of the missing cases from HUNT2 would have been positive answers. It can be easy to forget these days, but cancer was a disease that was much more stigmatized a few decades ago. HUNT2 taking place in the mid-90s, the question about cancer may have been one more people weren't comfortable answering in 1995, and cancer survivors may have been less open about the fact. A lower participation rate in HUNT3 could also mean that the average level of motivation among those that showed up was higher, and those that did were more likely to answer every question. There could be more missing data from some questions from HUNT2 than HUNT3 because of study design, or the graphic layout of the questions. The high number of missing from HUNT2 would at any rate make results less reliable.

4.2.3 Chronic disease

One category where we see a slightly similar trend to the one for cancer is for chronic disease. This is less significant because there is a much higher number of people who have responded positively to the question of whether they have a chronic disease. There

were however more participants who had not answered in HUNT2 than in HUNT3. This may be a similar question of stigma, or simply that the layout of the questionnaire had improved by HUNT3.

Other studies and reviews examining chronic or long-term disease also comment on the ambiguity of the term, and sometimes use long-lasting illness or disability as categories that overlap with chronic disease(20). Does a chronic disease mean long-lasting or any disease that is incurable? If you are diagnosed with a chronic condition that is well-managed and has little or no impact on your daily life, do you think of yourself as someone who is chronically ill? In HUNT this question is phrased in a particular way;

> Do you suffer from any long-term illness or injury of a physical or psychological nature that impairs your functioning in your everyday life?

What constitutes "impairing function" may be subjective.

4.2.4 Potential survivor bias

The results for some of the outcomes may have been affected by survivor bias. As it is well known from medical literature that smokers have worse outcomes from a range of diseases(9), there may be more who succumbed to illness among the smokers, and more who became too ill to participate in the study. This question could be examined in the future by coupling the data with the death registry, or other health registries in Norway. There were no significant differences between those with and without the allele for stroke, heart disease and cancer. This could be survivor bias playing into the numbers. The question is obviously "have you had *and survived* a stroke". We know from Langhammar et al (2012) that non-participation is highest among the oldest and youngest(38). For the oldest the most common reason given for non-participation was that their health was too bad.

4.2.4.1

Cancer may also have been a poor choice for variable because survivor bias may have a high impact when looking at smokers and cancers. There is no access to the death registry or other medical information for this study, and as such we do not have the accurate incidence rate. The cancers that are most closely associated with smoking are cancers of the lungs and throat. These cancers have a very low 5-year survival rate. For lung cancer in Norway in 2009 the 5-year survival rate for lung cancer was 15% compared to the more common breast and prostate cancers that have survival rates around 85%, and where smoking plays a much smaller role in developing the disease. In addition, smoking significantly reduces the chances of 5-year survival in all cancers, because of an increased chance of complications after surgery and increased chances of the cancer metastasizing(70-72).

A literature review by Dieteren et al (2021) looking at time spent with low SRH, long term disease or a disability in smokers and never-smokers found mixed results from the studies they examined. Smokers consistently became disabled at a younger age than never-smokers, but in half of the studies they spent shorter time with the disability or long-term illness than never-smokers (20). The other half of the studies mostly found smokers were ill for the same amount of time, while a few showed smokers were disabled or ill for longer. If smokers spend less time with a chronic disease before they become too ill to participate in population studies, this could be the reason rs16969968 has no effect on chronic disease. The same study found no similar effects in duration for

SRH, and all studies found that smokers spent more years with low SRH than non-smokers, so this would not explain the lack of effect on that outcome.

4.3 Assumptions for the instrumental variable

We made three assumptions about the allele that need to be satisfied in order for the allele to be a valid instrument for increased smoking and nicotine dependency.

1. rs16969968 affects smoking
2. There is no horizontal pleiotropy
3. rs16969968 is randomly distributed

4.3.1 rs16969968 affects smoking

The relevance of rs16969968 for smoking intensity has been thoroughly assessed previously, and has also been verified within the HUNT Study. A previous study had found that rs16969968 added on average 0.66 daily extra cigarettes for participants with one allele as compared to those without it(48). The reason for not doing a full randomization was that there were several studies that found reasons to believe the real-life effect was larger than this, possibly due to taking longer puffs or under-reporting smoking in surveys(41). A further reason was the influence of the gene on the chances of successfully quitting smoking. This mechanism can be seen clearly in the numbers in Table 5; with the allele you have a lower chance of quitting smoking once you have started.

In the same table we see that there is a lower percentage of daily smokers, and higher rates of both occasional smokers and former smokers among those with no copies of the SNP. Among current daily smokers from the most recent data there is a significant difference in the SNP distribution compared to the general population. This indicated that you have a significantly lower chance of successfully quitting smoking if you have 1 or 2 of the gene. The effect is also stronger with two alleles compared to only one.

In addition the gene suggests a higher chance of going from casual to daily smoker. Another reason there are more people with 0 of the allele in the "occasional smoker" group may not just be that the allele influences moving from occasional to daily smoker, but also that those with the allele may be too strongly addicted to be able to smoke occasionally after quitting daily smoking.

4.3.2 Horizontal pleiotropy

Choosing well-described genetic instruments with known effects have been recommended to reduce the chance of bias from pleiotropy in Mendelian randomization studies{Burgess, 2019 #34}. With the exception of the outcome cancer for the whole study population, there were no significant results in the control group which suggests there is no horizontal pleiotropy that is immediately obvious. In other words, the SNP does not seem to affect any of the outcomes, except through the exposure (smoking). If the cancer result reflects a real effect of rs16969968 it is very hard to imagine a pathway based on what we know about the allele so far. I was unable to find any reasonable

explanation in the literature. The most likely explanation seems that the large amount of missing data from HUNT2 biased the results.

There is never a guarantee that the gene does not affect the outcomes we are interested in in other ways, especially in a gene that directly impacts a function in the human brain. A previous study did find that in never-smokers rs16969968 does seem to increase the chances of experiencing anxiety(45), which could particularly affect the more subjective outcomes. It is not outside the realm of possibility that if smoking is an effective self-medication for people with rs16969968 who experience anxiety, it could help them feel in better health. However, if that were the explanation, the anxiety did not have a strong enough effect to affect the outcome for never-smokers.

4.3.3 Allele is randomly distributed

The allele is as close to randomly distributed as we are likely to come, when compared to a hypothetical ideal population in Table 4. This is not a guarantee that the allele is randomly distributed in the entire population of Nord-Trøndelag. Among men there were more smokers among the non-participants than the participants for HUNT3(38). As mentioned in the introduction, there is an effect of marginalized people participating less in population surveys(36). In HUNT3 poor health was the most common cause of non-participation among those over 60(38). When taken into account that smokers with the allele have higher risk of COPD, there may be more people with one or two copies of the allele among the non-participants.

There is also still the possibility of confounding due to dynastical effects, where behaviour is "inherited" through social mechanisms{Brumpton, 2020 #51}. Since exposure to smoking in childhood can also affect health outcomes, and passive smoking can cause ill effects, this can introduce a bias. People with the allele may be more likely to grow up in a household with a smoking parent.

4.3.3.1 Does the allele influence smoking uptake?

One way to check for dynastical effects could be seeing if rs16969968 has the same distribution among never-smokers as it does in the general population. It would not prove there are no such effects, but it could be a useful indicator. In Table 5 it seems the distribution among never-smokers is very close to the distribution in the general study population. HUNT3 data is the most accurate to use for this as it distinguished between those that have never smoked, and those that never smoked daily. Comparing the general population and never-smokers from HUNT3 the two are not statistically different in a Chi-square test.

There is a significant difference if I include the never-smokers from HUNT2, but as mentioned, this is a less precise category. We see that 7% of the population fell into the category "occasional smokers" in HUNT3. If we compare to Figure 1 the rate of occasional smokers seems relatively stable between 1995 and 2005. Still, all these clearly did not end up in the "never-smoker" category for HUNT2, which was a concern in the study design. It seems a significant proportion of the occasional smokers in HUNT3 fell in the category "former daily smoker" in HUNT2. This could have created a bias if we had distinguished between current and former smokers in the analysis, as it seems clear there is a higher chance of quitting smoking if you do not have the allele.

A reasonable explanation could be a result of the allele influencing the move from occasional smoker to daily smoker. Occasional smokers who never developed a daily smoking habit would give their smoking status as "I have never smoked daily" in HUNT2.

As the numbers seem to show that having one or two copies of the allele increases the chance of transitioning from occasional to daily smoker, the number of never-smokers with no copies of the allele would be slightly higher, as observed.

In Table 5Table 3 we also see that there is a slightly higher percentage overall included in the ever-smoker group in HUNT2 vs HUNT3, despite the inclusion criteria being stricter for HUNT3 than HUNT2. This is likely due to the reduction in smoking rates, that as per Figure 1 have been steadily decreasing since the 1970s.

Performing the analyses within families, to account for the confounding social effects of inheriting behaviour along with genes from our families, would have strengthened the inference. However, this was not feasible, as I did not have available data on siblingships, and statistical power would likely have been insufficient, if the data had been available{Brumpton, 2020 #51}.

4.3.4 Main results never-smokers

For the control group the allele has no significant effect, except in the case of cancer. The results indicate is a slightly lower risk of cancer for participants with the SNP. I struggle to find an explanation for this. For the other results there are no trends of possible effects that are statistically significant. This is important as it would be easy to imagine people with the allele being more likely to grow up in a household where one or both parents smoke, and second hand smoke exposure in childhood has been found to have a measurable impact on some of the health outcomes studied in this thesis.

4.3.5 Conclusion MR assuptions and methodology

Taken together it seems reasonable to use rs16969968 as an instrument for heavier smoking. I have also demonstrated that the effect the allele has on smoking behaviour goes beyond the 1 cigarette extra per day that the former studies have estimated. Given that it influences both moving from occasional to daily smoking and successfully quitting it would also increase the number of years smoked.

In the negative control group rs16969968 had no significant impact on the OR for any outcome, except in the case of cancer, which is likely to be caused by a bias in the missing data.

4.4 In relation to other research and speculation

There is no correlation between rs16969968 and low self-reported health in these data. This is surprising given that the allele has a major impact on health and mortality, and the strong association SRH has to both objective health status(44) and mortality.

4.4.1 Are there expectations of ill health?

The lack of effect of smoking intensity on overall self-reported health is particularly striking considering the clear effect on reported airway symptoms. There may be a certain expectation of ill health among smokers. We do call it “røykhoste” (smokers cough) in everyday language, so the feeling may be that daily coughing is to be expected rather than being a sign of ill health. This seems to be contrary to studies that have found self-reported health has such a strong correlation to mortality and is a good predictor for health status{Dramé, 2023 #42}.

There was no statistically significant effect from the allele on having a chronic disease. This is surprising as smoking has been linked to a greater chance of developing a chronic

or long-term disease(73) and developing a chronic disease at an earlier age(20). It would also seem to be a more objective measure, less affected by expectations. While non-participation among the least healthy people in the oldest generations {Langhammer, 2012 #50}, smokers being at greater risk for multimorbidity{Stagg, 2023 #46} may mean more of them remain at home instead of making the trip. However, the way the question was phrased included both mental and physical conditions, and that is a group where we have seen the case for smoking as a causative agent is divided. The question the way it was phrased also asked if the disease impacted their functioning in everyday life. Many cardiovascular conditions tied to smoking can be managed well with surgeries or medication, and participants may not have felt that such conditions impacted their daily life to a great extent.

COPD has a significant impact on health and quality of life and impacts all parts of daily life(74). The group that reported having COPD was relatively small, and we know from the non-participation study that there is significantly higher levels of COPD among the older population in general than in the study, which coincides well with the most common reason given for non-participation in those over 80 being poor health. The number of participants with COPD is a small portion of the overall people with a chronic disease, so it might not be enough to show on the scale.

4.4.2 Shorter periods of ill health

As the population gets older, complex medical cases also become more common, and many of the oldest population have several chronic diseases. Other studies have found that smoking increases the chances of going from one to multiple long-term diseases, or from a long term disease to a disability (73). Since we have established that people with rs16969968 find it harder to quit smoking than people without the allele, it is very likely that they are over-represented in the group that does not quit smoking after a major health scare. It is easy to see that this could lead to increased mortality and therefore a shorter period spent living with a chronic condition or bad health. Since it also increases the risk of multimorbidity and disability, as mentioned above there may be more with rs16969968 who are in too bad health to show up to the HUNT screening, compared to those without.

4.4.3 Does denial play a part?

It was mentioned in the introduction that smokers often underestimate the effect of smoking on their health. For the examples of COPD and daily coughing, these seem like symptoms that would have an adverse effect on a subjective feeling of health. Heavy breathing impacts all parts of daily life and might be reasonably expected to have a substantial impact on an individual's quality of life. If 15% of the population have these lung symptoms, and 1 or 2 of the allele has a large impact on the chance of developing these symptoms, it seems unreasonable that this does not have an impact on the subjective health experience. This could be due to smokers having a reduced expectation of their own health.

The way the question regarding chronic health particularly was asked does leave some room for subjective thinking on the part of the participants. The phrasing was "Do you suffer from any long-term illness or injury of a physical or psychological nature that impairs your functioning in your everyday life?" COPD is a disease that gets worse very gradually, as does smokers cough and shortness of breath. For a patient with COPD over time their bodies adjust to having lower levels of oxygen to the extent that oxygen

therapy can even be harmful. The change to the daily functioning may come so slowly that there is no sudden noticeable shift(72). If there is a combination here of the idea that smokers have internalized the expectation of ill health and the slow approach of the worsening symptoms, that may have some part to play in their answers. It may make it easier to deny the impact smoking has on their daily lives.

One study did find a correlation between rs16969968 and anxiety in people who did not smoke(45). Studies have shown that it is those with most anxiety after a cancer diagnosis that are least likely to quit smoking, which seems counterintuitive(16). If one is very concerned about a cancer diagnosis, quitting smoking would be the best thing to reduce the chance of a bad outcome. The impulse to self-soothe can be very strong for people with anxiety(14), and if they feel the cigarettes help it may be very comforting to be in denial about the effect smoking has on overall health.

4.4.4 Health is not just physical

If smoking reduces anxiety for people with rs16969968, the subjective experience of health may very well be improved by smoking. When looking at the global disease burden and factors that contribute to a reduction in QALY's (Quality Adjusted Life Years), mental health issues contribute a great deal to that reduction. That is not to say that smoking is on the whole good for mental health. The same study that found smoking did not have a causative effect on anxiety did instead find that smoking probably has an effect on depression, which is also a major mental health issue(45).

Though several studies have found a strong correlation between smoking and low SRH, many of studies have found stronger correlations between low SES and low SRH(7, 26, 73, 76). Having a small support network can also be strongly correlated with negative outcomes(73). If smoking is part of someone's social life, smoking cessation may have a negative impact on self-reported health in a negative direction.

4.4.5 Conclusions

I have shown that rs16969968 seems to increase the chance of moving from occasional to daily smoker, and reduces the chance of successfully quitting smoking among, and that the effect is stronger with two alleles than with one. This is confirmation of previous research on the field, though the statistics on occasional vs daily smoking is not explicitly stated in the previous literature studied for this thesis. The result that the gene distribution among never-smokers is the same as among the general population is a useful one, and helps add to the validity of rs16969968 as an instrument for smoking.

Having the smoking-increasing allele of rs16969968 is not associated with lower SRH or a higher incidence of chronic disease among ever-smokers. This indicates that higher intensity of smoking does not lead to poorer SRH or more higher prevalence of chronic disease. This is surprising, as SRH is tied to higher mortality and morbidity, and smoking is similarly tied to mortality and morbidity in many studies, including studies which have used rs16969968. While positive health outcomes may be an important source of motivation for people to quit smoking, the subjective experience of health improvement from quitting smoking may not be the same. A focus on helping people trying to quit tackle anxiety and develop healthier coping mechanisms may be more fruitful in achieving higher levels of smoking cessation.

Referanser

Vedlegg 4: Referanser

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Appendix

Appendix 1: The questionnaire Q1 for HUNT2

Appendix 2: The questionnaire Q1 for HUNT2

Appendix 3: Information on the genetic cohort from HUNT Biobank

Appendix 4: Sette inn inndelingsskift

Appendix 5: REK application and application for extention

Appendix 6: REK approval and extension of approval

Appendix 7: Documentation from HUNT for the data

Spørreskjemaet er en viktig del av Helseundersøkelsen. Her finner du spørsmål om tidligere sykdom og om andre forhold som har betydning for helsa. Vennligst fyll ut skjemaet på forhånd og ta det med til Helseundersøkelsen. Dersom enkelte spørsmål er uklare, lar du dem bare stå ubesvarte til du møter fram, og drøfter dem med personalet som gjennomfører undersøkelsen. Alle svar vil bli behandlet strengt fortrolig.

Flere steder i skjemaet ber vi deg oppgi din alder da eventuell sykdom inntrådte. Hvis du ikke husker nøyaktig hvor gammel du var, skriver du et tall som er nærmest det du antar er korrekt.

Når resultatene fra undersøkelsen foreligger, vil det være enkelte som trenger ny undersøkelse hos egen lege. Dette vil du få beskjed om i det brevet som vi sender deg om dine resultater. Samtidig sender vi melding om resultatene dine til legen din. Det er derfor om å gjøre at du i rubrikken helt til slutt i skjemaet oppgir navnet på den allmennpraktiserende lege, kommunelege eller det helsesenter som du ønsker skal ta hånd om eventuell etterundersøkelse, og som vi skal sende resultatene til.

Med vennlig hilsen

Helsetjenesten i Nord-Trøndelag • Statens helseundersøkelser • Statens Institutt for Folkehelse

DET HANDLER OM HELSA DI

Hvordan er helsa di nå?

Bare ett kryss

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

LUFTVEGSPLAGER

	JA	NEI
Hoster du daglig i perioder av året?		
Hvis JA:		
Er hosten vanligvis ledsaget av oppspytt? .. 14		
Har du hatt hoste med oppspytt i minst 3 mnd. sammenhengende i hvert av de to siste åra?		
Har du hatt noe anfall med pipende eller tung pust de siste 12 måneder? 16		

	JA	NEI	Alder første gang
Har du eller har du hatt astma? 17			år

	JA	NEI
Har du brukt eller bruker du astmamedisiner? 20		

HJERTE-KARSYKDOMMER, DIABETES

Har du, eller har du hatt:	JA	NEI	Alder første gang
Hjerteinfarkt 21			år
Angina pectoris (hjertekrampe) 24			år
Hjerneslag/hjerneblødning 27			år
Diabetes (sukkersyke) 30			år

Hva ble resultatet siste gang du målte blodtrykket ditt?

Bare ett kryss

Begynne med/fortsette med blodtrykksmedisin	33	☐ 1
Komme til kontroll, men ikke ta blodtrykksmedisin		☐ 2
Ingen kontroll og ingen medisin nødvendig		☐ 3
Har aldri fått målt blodtrykket		☐ 4

Bruker du medisin mot høyt blodtrykk?

Bare ett kryss

Nå	34	☐ 1
Før, men ikke nå		☐ 2
Aldri brukt		☐ 3

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

STOFFSKIFTE

Har du noen gang fått påvist:	JA	NEI	Alder første gang
for høyt stoffskifte 36			år
for lavt stoffskifte 39			år
struma 42			år
annen sykdom i skjoldbruskkjertelen			år

Bruker du eller har du brukt noen av disse medisinene:			
Thyroxin 48			år
Neo-Mercazole 51			år
Er du operert i skjoldbruskkjertelen			år
Har du fått radiojodbehandling 57			år

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? 60		

Hvis NEI, gå videre til neste side øverst.

Hvis JA, svar på følgende:

Hvor har du hatt disse plagene?	JA	NEI
Nakke 61		
Skuldre (aksler)		
Albuer		
Håndledd, hender		
Bryst/mage 65		
Øvre del av ryggen		
Korsryggen		
Hofter		
Knær		
Ankler, føtter 70		

Hvis du har hatt plager i flere områder i minst 3 mnd. det siste året, setter du ring rundt det ja-krysset hvor plagene har vart lengst

Hvor lenge har plagene vart sammenhengende?

Svar for det området hvor plagene har vart lengst

Hvis under 1 år, oppgi antall mnd. . 71	Antall mnd.
Hvis 1 år eller mer, oppgi antall år.. 73	Antall år

Har plagene redusert din arbeidsevne det siste året?

Gjelder også hjemmearbeidende. Bare ett kryss

Nei/ubetydelig	I noen grad	I betydelig grad	Vet ikke
☐	☐	☐	☐

	JA	NEI	IKKE I ARBEID
Har du vært sykmeldt pga. disse plagene det siste året? 76			

	JA	NEI
Har plagene ført til redusert aktivitet i fritida?		

Har lege noen gang sagt at du har/har hatt noen av disse sykdommene:

	JA	NEI
Beinskjørhet (osteoporose) ... 78		
Fibromyalgi (fibrositt/kronisk smertesyndrom)		
Leddgikt (reumatoid artritt) ...		
Slitasjegikt (artrose) ...		
Bechterews sykdom ... 82		
Andre langvarige skjelett- eller muskelsykdommer		

Har du noen gang hatt:

	JA	NEI	Alder *siste* gang
Lårhalsbrudd ... 84			år
Brudd i håndledd/underarm ... 87			år
Nakkesleng (whiplash) ... 90			år
Skade som førte til sykehusinnleggelse			år

ANDRE PLAGER

I hvilken grad har du hatt disse plagene i de siste 12 månedene?

	Ikke plaget	Litt plaget	Mye plaget
Kvalme ... 96	☐	☐	☐
Brystbrann/sure oppstøt ...	☐	☐	☐
Diaré ...	☐	☐	☐
Treg mage ...	☐	☐	☐
Hjertebank ...	☐	☐	☐
Åndenød ... 101	☐	☐	☐

ANDRE SYKDOMMER

Har du eller har du noen gang hatt:

	JA	NEI	Alder første gang
Epilepsi ... 102			år
Psykiske plager hvor du har søkt hjelp			år
Kreftsykdom ... 108			år
Annen langvarig sykdom ... 111			

DAGLIGE FUNKSJONER

Har du noen langvarig sykdom, skade eller lidelse av fysisk eller psykisk art som nedsetter dine funksjoner i ditt daglige liv? ... 112

JA	NEI

Langvarig: minst ett år

Hvis JA:

Hvor mye vil du si at dine funksjoner er nedsatt?

	Litt nedsatt	Middels nedsatt	Mye nedsatt
Er bevegelseshemmet ... 113	☐	☐	☐
Har nedsatt syn ...	☐	☐	☐
Har nedsatt hørsel ...	☐	☐	☐
Hemmet pga. kroppslig sykdom.	☐	☐	☐
Hemmet pga. psykiske plager... 117	☐	☐	☐

MENN fortsetter øverst neste spalte

BESVARES BARE AV KVINNER

Hvor mange barn har du født? ... 118
Sett 0 hvis du ikke har født barn

Antall barn

Hvis du har født barn, besvar:

Hvor gammel var du da du fødte ditt første barn? ... 120

Alder ____ år

Hvor gammel var du da du fødte ditt siste barn? ... 122

____ år

Besvares ikke hvis du har født bare ett barn

Hvor gammel var du da du fikk menstruasjon? ... 124

____ år

Sett 0 hvis du ikke noen gang har hatt menstruasjon

Fortsett neste spalte øverst

RØYKING

Røykte noen av de voksne hjemme da du vokste opp? ... 126

JA	NEI

Bor du, eller har du bodd, sammen med noen dagligrøykere etter at du fylte 20 år? ... 127

JA	NEI

Hvor lenge er du vanligvis daglig til stede i røykfylt rom? ... 128

Antall timer

Sett 0 hvis du ikke oppholder deg i røykfylt rom

Røyker du selv?

	JA	NEI
Sigaretter daglig? ... 130		
Sigarer/sigarillos daglig? ...		
Pipe daglig? ... 132		

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

Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet? ... 134

Antall år

Hvis du røyker daglig nå eller har røykt tidligere:

Hvor mange sigaretter røyker eller røykte du vanligvis daglig? ... 136

Antall sigaretter

Hvor gammel var du da du begynte å røyke daglig? ... 140

Alder ____ år

Hvor mange år tilsammen har du røykt daglig? ... 142

Antall år

KAFFE/TE/ALKOHOL

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

	Antall kopper
Kokekaffe ... 144	
Annen kaffe ... 146	
Te ... 148	

Alkohol:
Er du total avholdsmann/-kvinne? ... 150

JA	NEI

Hvor mange ganger i måneden drikker du vanligvis alkohol? ... 151

Antall ganger

Regn ikke med lettøl. Sett 0 hvis mindre enn 1 gang i mnd.

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 153

Øl	Vin	Brennevin
glass	glass	glass

FYSISK AKTIVITET

I FRITIDA

Hvordan har din fysiske aktivitet i fritida vært det siste året? *Tenk deg et ukentlig gjennomsnitt for året.*

Arbeidsveg regnes som fritid

	Timer pr. uke: Ingen	Under 1	1-2	3 og mer
Lett aktivitet *(ikke svett/andpusten)* ... 159	☐	☐	☐	☐
Hard fysisk aktivitet *(svett/andpusten)* ... 160	☐ 1	☐ 2	☐ 3	☐ 4

UNDER ARBEID

Hvis du er i lønnet eller ulønnet arbeid:

Hvorledes vil du beskrive arbeidet ditt?
Bare ett kryss

For det meste stillesittende arbeid
(f.eks. skrivebordsarbeid, montering) ... 161 ☐ 1

Arbeid som krever at du går mye
(f.eks. ekspeditørarb., lett industriarb., undervisning) ... ☐ 2

Arbeid hvor du går og løfter mye
(f.eks. postbud, pleier, bygningsarbeid) ... ☐ 3

Tungt kroppsarbeid
(f.eks. skogsarbeid, tungt jordbruksarb.,tungt bygningsarb.) ☐ 4

Bla om!

HVORLEDES FØLER DU DEG?

Har du de siste to ukene følt deg:

	Nei	Litt	En god del	Svært mye
Trygg og rolig? 162	☐	☐	☐	☐
Glad og optimistisk?	☐	☐	☐	☐
Har du følt deg:				
Nervøs og urolig?	☐	☐	☐	☐
Plaget av angst? 165	☐	☐	☐	☐
Irritabel?	☐	☐	☐	☐
Nedfor/deprimert?	☐	☐	☐	☐
Ensom? 168	☐ 1	☐ 2	☐ 3	☐ 4

Her kommer noen flere spørsmål om hvorledes du føler deg. For hvert spørsmål setter du kryss for ett av de fire svarene som best beskriver dine følelser ***den siste uka.*** *Ikke tenk for lenge på svaret - de spontane svarene er best*

Jeg gleder meg fortsatt over ting slik jeg pleide før 169
Avgjort like mye ..... ☐ 1 Bare lite grann ..... ☐ 3
Ikke fullt så mye ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg har en uroføelse som om noe forferdelig vil skje 170
Ja, og noe svært ille .... ☐ 1 Litt, bekymrer meg lite . ☐ 3
Ja, ikke så veldig ille ... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg kan le og se det morsomme i situasjoner 171
Like mye nå som før .... ☐ 1 Avgjort ikke som før .... ☐ 3
Ikke like mye nå som før ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg har hodet fullt av bekymringer 172
Veldig ofte ..... ☐ 1 Av og til ..... ☐ 3
Ganske ofte ..... ☐ 2 En gang i blant ..... ☐ 4

Jeg er i godt humør 173
Aldri ..... ☐ 1 Ganske ofte ..... ☐ 3
Noen ganger ..... ☐ 2 For det meste ..... ☐ 4

Jeg kan sitte i fred og ro og kjenne meg avslappet 174
Ja, helt klart ..... ☐ 1 Ikke så ofte ..... ☐ 3
Vanligvis ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg føler meg som om alt går langsommere 175
Nesten hele tiden ..... ☐ 1 Fra tid til annen ..... ☐ 3
Svært ofte ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg føler meg urolig som om jeg har sommerfugler i magen 176
Ikke i det hele tatt ..... ☐ 1 Ganske ofte ..... ☐ 3
Fra tid til annen ..... ☐ 2 Svært ofte ..... ☐ 4

Jeg bryr meg ikke lenger om hvordan jeg ser ut 177
Ja, har sluttet å bry meg ☐ 1 Kan hende ikke nok .... ☐ 3
Ikke som jeg burde ..... ☐ 2 Bryr meg som før ..... ☐ 4

Jeg er rastløs som om jeg stadig må være aktiv 178
Uten tvil svært mye ..... ☐ 1 Ikke så veldig mye ..... ☐ 3
Ganske mye..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg ser med glede frem til hendelser og ting 179
Like mye som før ..... ☐ 1 Avgjort mindre enn før . ☐ 3
Heller mindre enn før ... ☐ 2 Nesten ikke i det hele tatt ☐ 4

Jeg kan plutselig få en følelse av panikk 180
Uten tvil svært ofte ..... ☐ 1 Ikke så veldig ofte ..... ☐ 3
Ganske ofte ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg kan glede meg over gode bøker, radio og TV 181
Ofte ..... ☐ 1 Ikke så ofte ..... ☐ 3
Fra tid til annen ..... ☐ 2 Svært sjelden ..... ☐ 4

UTDANNING

Hvilken utdanning er den høyeste du har fullført?

Grunnskole 7-10 år, framhaldsskole, folkehøgskole ..... 182 ☐ 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

ARBEID

Hva slags arbeidssituasjon har du nå?
Ett eller flere kryss

Lønnet arbeid ..... 183 ☐
Selvstendig næringsdrivende..... ☐
Heltids husarbeid ..... ☐
Utdanning, militærtjeneste ..... ☐
Arbeidsledig, permittert..... ☐
Pensjonist/trygdet..... 188 ☐

Hvor mange timer lønnet arbeid har du i uka? ..... 189 Antall timer

	JA	NEI
Har du skiftarbeid, nattarbeid eller går vakt?		

ALT I ALT

Når du tenker på hvordan du har det for tida, er du stort sett fornøyd med tilværelsen eller er du stort sett misfornøyd?
Bare ett kryss

Svært fornøyd ..... 192 ☐ 1
Meget fornøyd ..... ☐ 2
Ganske fornøyd..... ☐ 3
Både/og..... ☐ 4
Nokså misfornøyd ..... ☐ 5
Meget misfornøyd..... ☐ 6
Svært misfornøyd..... ☐ 7

DIN LEGE

Hvis denne helseundersøkelsen viser at du bør undersøkes nærmere, hvilken allmennpraktiserende lege/kommunelege ønsker du skal foreta undersøkelsen?

Skriv navnet på legen her: 193 *Ikke skriv her*

Takk for utfyllingen!

Nok en gang:

Velkommen til undersøkelsen!

IE 332 5201 - 50.000 - 09.96

Invitasjon til HUNT 3

Viktig
Enkelt
Gratis

Du inviteres herved til å delta i den tredje store Helseundersøkelsen i Nord-Trøndelag (HUNT 3). Ved å delta får du en enkel undersøkelse av din egen helse, og du gir samtidig et viktig bidrag til medisinsk forskning.

Hver deltaker er like viktig, enten du er ung eller gammel, frisk eller syk, er HUNT-veteran eller møter for første gang. Tilsvarende undersøkelse er tidligere gjennomført i 1984-86 (HUNT 1) og 1995-97 (HUNT 2 og Ung-HUNT). For å kunne studere årsaker til sykdom, er det viktig at også de som tidligere har deltatt møter fram.

Vennligst fyll ut spørreskjemaet, og ta det med når du møter til undersøkelse.

Undersøkelsen tar vanligvis ca 1/2 time. Du vil få brev med resultater fra dine prøver etter noen uker. Dersom noen av resultatene er utenom det normale, vil du bli anbefalt undersøkelse hos fastlegen din.

Du kan lese mer om HUNT 3 i den vedlagte brosjyren eller på www.hunt.ntnu.no. Har du spørsmål, kan du også ringe til HUNT forskningssenter, tlf 74075180.

Vel møtt til undersøkelsen!

Vennlig hilsen

Steinar Krokstad
Førsteamanuensis
Prosjektleder HUNT 3

Jostein Holmen
Professor, daglig leder
HUNT forskningssenter

Stig A. Slørdahl
Professor, dekanus
Det medisinske fakultet, NTNU

Tid og sted for oppmøte

Dersom det foreslåtte tidspunktet ikke passer for deg, behøver du ikke bestille ny time. Du kan møte når det passer deg innenfor åpningstiden, men det kan da bli noe ventetid. Du kan også møte i en annen kommune, hvis det skulle passe bedre. Takk for at du deltar!

Åpningstida:

hunt 3
Helseundersøkelsen i Nord-Trøndelag

NTNU
HUNT forskningssenter

En time for bedre folkehelse

Slik fyller du ut skjemaet

- Skjemaet vil bli lest maskinelt.
- Det er derfor viktig at du krysser av riktig: **Rett** ☒ **Galt** ☐ ☑
- Krysser du feil sted, retter du ved å fylle boksen slik: ■
- Skriv tydelige tall: 0 1 2 3 4 5 6 7 8 9
- Bruk bare svart eller blå penn. Ikke bruk blyant eller tusj.

HELSE OG DAGLIGLIV

1 Hvordan er helsa di nå?

☐ Dårlig ☐ Ikke helt god ☐ God ☐ Svært god

2 Har du noen langvarig (minst 1 år) sykdom, skade eller lidelse av fysisk eller psykisk art som nedsetter dine funksjoner i ditt daglige liv?

	Ja	Nei
	☐	☐

Hvis ja:
Hvor mye vil du si at dine funksjoner er nedsatt?

	Litt nedsatt	Middels nedsatt	Mye nedsatt
Er bevegelseshemmet	☐	☐	☐
Har nedsatt syn	☐	☐	☐
Har nedsatt hørsel	☐	☐	☐
Hemmet pga. kroppslig sykdom	☐	☐	☐
Hemmet pga. psykisk sykdom	☐	☐	☐

3 Har du kroppslige smerter nå som har vart mer enn 6 måneder?

Ja	Nei
☐	☐

4 Hvor sterke kroppslige smerter har du hatt i løpet av de siste 4 uker?

Ingen	Meget svake	Svake	Mode-rate	Sterke	Meget sterke
☐	☐	☐	☐	☐	☐

5 I hvilken grad har din fysiske helse eller følelses-messige problemer begrenset deg i din vanlige sosiale omgang med familie eller venner i løpet av de siste 4 uker?

Ikke i det hele tatt	En del	Litt	Mye	Kunne ikke ha sosial omgang
☐	☐	☐	☐	☐

HELSETJENESTER

6 Har du i løpet av de siste 12 måneder vært hos:

	Ja	Nei
Fastlege/allmennlege	☐	☐
Annen legespesialist utenfor sykehus	☐	☐
Konsultasjon uten innleggelse		
- ved psykiatrisk poliklinikk	☐	☐
- ved annen poliklinikk i sykehus	☐	☐
Kiropraktor	☐	☐
Homøopat, akupunktør, soneterapeut, hånds-pålegger eller annen alternativ behandler	☐	☐

7 Har du vært innlagt i sykehus i løpet av de siste 12 måneder?

Ja	Nei
☐	☐

SYKDOMMER OG PLAGER

8 Har du hatt noe anfall med pipende eller tung pust de siste 12 måneder?

Ja	Nei
☐	☐

9 Har du noen gang de siste 5 år brukt medisiner for astma, kronisk bronkitt, emfysem eller KOLS?

Ja	Nei
☐	☐

10 Bruker du, eller har du brukt, medisin mot høyt blodtrykk?

Ja	Nei
☐	☐

11 Har du, eller har du noen gang hatt, noen av disse sykdommene/plagene:
(Sett ett kryss pr. linje)

	Ja	Nei	Hvis ja, hvor gammel var du **første** gang?
Eksempel:			3 4 *år gammel*
Hjerteinfarkt	☐	☐	*år gammel*
Angina pectoris (hjertekrampe)	☐	☐	*år gammel*
Hjertesvikt	☐	☐	*år gammel*
Annen hjertesykdom	☐	☐	*år gammel*
Hjerneslag/hjerneblødning	☐	☐	*år gammel*
Nyresykdom	☐	☐	*år gammel*
Astma	☐	☐	*år gammel*
Kronisk bronkitt, emfysem, KOLS	☐	☐	*år gammel*
Diabetes (sukkersyke)	☐	☐	*år gammel*
Psoriasis	☐	☐	*år gammel*
Eksem på hendene	☐	☐	*år gammel*
Kreftsykdom	☐	☐	*år gammel*
Epilepsi	☐	☐	*år gammel*
Leddgikt (reumatoid artritt)	☐	☐	*år gammel*
Bechterews sykdom	☐	☐	*år gammel*
Sarkoidose	☐	☐	*år gammel*
Beinskjørhet (osteoporose)	☐	☐	*år gammel*
Fibromyalgi	☐	☐	*år gammel*
Slitasjegikt (artrose)	☐	☐	*år gammel*
Psykiske plager som du har søkt hjelp for	☐	☐	*år gammel*

12 Har du noen gang fått påvist for høyt blodsukker?

Ja	Nei
☐	☐

Hvis ja: I hvilken situasjon første gang?

☐ Ved helseundersøkelse... ☐ Under sykdom .....
☐ Under svangerskap ..... ☐ Annet .....

SKADER

13 Har du noen gang hatt:

	Ja	Nei	Hvis ja, hvor gammel var du **første** gang?
Eksempel:			3 4 *år gammel*
Lårhalsbrudd	☐	☐	___ *år gammel*
Brudd i handledd/underarm	☐	☐	___ *år gammel*
Brudd/sammenfall av ryggvirvler	☐	☐	___ *år gammel*
Nakkesleng (whiplash)	☐	☐	___ *år gammel*

14 Har du foreldre, søsken eller barn som har, eller har hatt, følgende sykdommer?
(Sett ett kryss pr. linje)

	Ja	Nei	Vet ikke
Hjerneslag eller hjerneblødning før 60 års alder	☐	☐	☐
Hjerteinfarkt før 60-års alder	☐	☐	☐
Astma	☐	☐	☐
Allergi/høysnue/neseallergi	☐	☐	☐
Kronisk bronkitt/emfysem/KOLS	☐	☐	☐
Kreftsykdom	☐	☐	☐
Psykiske plager	☐	☐	☐
Beinskjørhet (osteoporose)	☐	☐	☐
Nyresykdom (ikke nyresten, urinveisinfeksjon, urinlekkasje)	☐	☐	☐
Diabetes (sukkersyke)	☐	☐	☐

15 Har noen av dine besteforeldre, dine foreldres søsken eller dine søskenbarn fått diagnosen diabetes (type 1 eller type 2)?

Ja ☐ Nei ☐

HVORDAN FØLER DU DEG?

16 Har du de to siste uker følt deg:
(Sett ett kryss pr. linje)

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

17 Har du noen gang i livet opplevd at noen over lengre tid har forsøkt å kue, fornedre eller ydmyke deg?

Ja ☐ Nei ☐

TOBAKK

18 Røykte noen av de voksne innendørs da du vokste opp? Ja ☐ Nei ☐

19 Røykte mora di da du vokste opp? Ja ☐ Nei ☐

20 Røyker du selv?

- **Nei**, jeg har aldri røykt ☐
  Hvis du aldri har røykt, hopp til spørsmål 22.
- **Nei**, jeg har sluttet å røyke ☐
- **Ja**, sigaretter av og til (fest/ferie, ikke daglig) ☐
- **Ja**, sigarer/sigarillos/pipe av og til ☐
- **Ja**, sigaretter daglig ☐
- **Ja**, sigarer/sigarillos/pipe daglig ☐

21 A Svar på dette hvis du nå røyker **daglig** eller tidligere har røykt **daglig**:

Hvor mange sigaretter røyker eller røykte du vanligvis daglig? ___ *sigaretter pr. dag*

Hvor gammel var du da du begynte å røyke daglig? ___ *år gammel*

Hvis du tidligere har røykt daglig, hvor gammel var du da du sluttet? ___ *år gammel*

21 B Svar på dette hvis du røyker eller har røykt **av og til**, men ikke daglig:

Hvor mange sigaretter røyker eller røykte du vanligvis i måneden? ___ *sigaretter pr. mnd*

Hvor gammel var du da du begynte å røyke av og til? ___ *år gammel*

Hvis du tidligere har røykt av og til, hvor gammel var du da du sluttet? ___ *år gammel*

22 Bruker du, eller har du brukt, snus?

Nei, aldri ☐ Ja, av og til ☐
Ja, men jeg har sluttet ☐ Ja, daglig ☐

Hvis du aldri har brukt snus, hopp til spørsmål 23.

Hvis ja:

Hvor gammel var du da du begynte med snus? ___ *år gammel*

Hvor mange esker snus bruker/brukte du pr. måned? ___ *esker snus pr. måned*

Hvis du bruker eller har brukt både sigaretter og snus, hva begynte du med først?

- Snus ☐
- Sigaretter ☐
- Omtrent samtidig (innenfor 3 måneder) ☐
- Husker ikke ☐

Da du begynte å bruke snus, var det for å prøve å slutte å røyke eller for å redusere røykinga?

- Nei ☐
- Ja, for å slutte å røyke ☐
- Ja, for å redusere røykinga ☐

MATVARER

23 Hvor ofte spiser du vanligvis disse matvarene? *(Sett ett kryss pr. linje)*

	0-3 ganger pr. mnd	1-3 ganger pr. uke	4-6 ganger pr. uke	1 gang pr. dag	2 ggr el mer pr. dag
Frukt/bær	☐	☐	☐	☐	☐
Grønnsaker	☐	☐	☐	☐	☐
Sjokolade/smågodt	☐	☐	☐	☐	☐
Kokte poteter	☐	☐	☐	☐	☐
Pasta/ris	☐	☐	☐	☐	☐
Pølser/hamburgere	☐	☐	☐	☐	☐
Fet fisk (laks, ørret, sild, makrell, uer som pålegg/middag)	☐	☐	☐	☐	☐

24 Bruker du følgende kosttilskudd? *(Sett ett kryss for hvert kosttilskudd)*

	Ja, daglig	Av og til	Nei
Tran	☐	☐	☐
Omega-3-kapsler	☐	☐	☐
Vitamin- og/eller mineraltilskudd	☐	☐	☐

25 Hvor mange glass drikker du vanligvis av følgende?
½ liter = 3 glass *(Sett ett kryss pr. linje)*

	Sjelden eller aldri	1-6 gl. pr uke	1 gl. pr. dag	2-3 gl. pr. dag	4 gl. eller mer pr. dag
Vann, farris o.l	☐	☐	☐	☐	☐
Helmelk (søt/sur)	☐	☐	☐	☐	☐
Annen melk (søt/sur)	☐	☐	☐	☐	☐
Brus/saft med sukker	☐	☐	☐	☐	☐
Brus/saft uten sukker	☐	☐	☐	☐	☐
Juice eller nektar	☐	☐	☐	☐	☐

26 Hvor mange kopper kaffe/te drikker du pr. døgn? *(Sett 0 dersom du ikke drikker kaffe/te daglig)*

	Koke-kaffe	Annen kaffe	Te
Antall kopper			

27 Hvor mange kopper kaffe drikker du om kvelden (etter kl 18)? Antall kopper ☐

ALKOHOLBRUK

28 Omtrent hvor ofte har du i løpet av de siste 12 måneder drukket alkohol? *(Regn ikke med lettøl)*

- 4-7 ganger pr. uke ☐
- 2-3 ganger pr. uke ☐
- ca 1 gang pr. uke ☐
- 2-3 ganger pr. måned ☐
- Ca 1 gang pr. måned ☐
- Noen få ganger pr. år ☐
- Ingen ganger siste år ☐
- Aldri drukket alkohol ☐

29 Har du drukket alkohol i løpet av de siste 4 uker? Ja ☐ Nei ☐

Hvis ja:
Har du drukket så mye at du har kjent deg sterkt beruset (full)?

- Nei ☐
- Ja, 1-2 ganger ☐
- Ja, 3 ganger eller mer ☐

30 Hvor mange glass øl, vin eller brennevin drikker du vanligvis i løpet av 2 uker? *(Regn ikke med lettøl)*
(Sett 0 hvis du ikke drikker alkohol)

	Øl	Vin	Brenne-vin
Antall glass			

31 Hvor ofte drikker du 5 glass eller mer av øl, vin eller brennevin ved samme anledning?

- Aldri ☐
- Månedlig ☐
- Ukentlig ☐
- Daglig ☐

MOSJON/FYSISK AKTIVITET

Med mosjon mener vi at du f.eks går tur, går på ski, svømmer eller driver trening/idrett.

32 Hvor ofte driver du mosjon? *(Ta et gjennomsnitt)*

- Aldri ☐
- Sjeldnere enn en gang i uka ☐
- En gang i uka ☐
- 2-3 ganger i uka ☐
- Omtrent hver dag ☐

33 Dersom du driver slik mosjon, så ofte som en eller flere ganger i uka; hvor hardt mosjonerer du? *(Ta et gjennomsnitt)*

- Tar det rolig uten å bli andpusten eller svett ☐
- Tar det så hardt at jeg blir andpusten og svett ☐
- Tar meg nesten helt ut ☐

34 Hvor lenge holder du på hver gang? *(Ta et gjennomsnitt)*

- Mindre enn 15 minutter ☐
- 15-29 minutter ☐
- 30 minutter – 1 time ☐
- Mer enn 1 time ☐

35 Har du vanligvis minst 30 minutter fysisk aktivitet daglig på arbeid og/eller i fritida? Ja ☐ Nei ☐

36 Omtrent hvor mange timer sitter du i ro på en vanlig hverdag? *(Regn med både jobb og fritid)* Antall timer ☐

ARBEID

37 Hvis du er i lønnet eller ulønnet arbeid, hvordan vil du beskrive arbeidet ditt? *(Sett ett kryss)*

For det meste stillesittende arbeid *(f.eks skrivebordsarbeid, montering)* ☐

Arbeid som krever at du går mye *(f.eks ekspeditørarbeid, lett industriarb., undervisning)* ☐

Arbeid hvor du går og løfter mye *(f.eks postbud, pleier, bygningsarbeid)* ☐

Tungt kroppsarbeid *(f.eks skogsarbeid, tungt jordbruksarbeid, tungt bygningsarbeid)* ☐

HØYDE/VEKT

38 Omtrent hva var din høyde da du var 18 år? ☐ cm Husker ikke ☐

39 Omtrent hva var din kroppsvekt da du var 18 år? ☐ kg Husker ikke ☐

40 Er du fornøyd med vekta di nå?

Ja ☐ Nei, for lett ☐ Nei, for tung ☐

41 Har du forsøkt å slanke deg i løpet av de siste 10 år?

Nei ☐ Ja, noen ganger ☐ Ja, mange ganger ☐

42 Er din kroppsvekt minst 2 kg lavere nå enn for 1 år siden? Ja ☐ Nei ☐

Hvis ja:

Hva er grunnen til dette?

Slanking ☐ Sykdom/stress ☐ Vet ikke ☐

ALVORLIGE LIVSHENDELSER SISTE 12 MÅNEDER

43 Har det vært dødsfall i nær familie? *(barn, ektefelle/samboer, søsken eller foreldre)* Ja ☐ Nei ☐

44 Har du vært i overhengende livsfare pga. alvorlig ulykke, katastrofe, voldssituasjon eller krig? Ja ☐ Nei ☐

45 Har du hatt samlivsbrudd i ekteskap eller i lengre samboerforhold? Ja ☐ Nei ☐

46 Hvis du har svart ja på et eller flere av spm 43, 44 eller 45; i hvilken grad har du hatt reaksjoner på dette de siste 7 dager?

Ikke i det hele tatt ☐ I moderat grad ☐
Litt ☐ I høy grad ☐

OPPVEKST - DA DU VAR 0-18 ÅR

47 Hvem vokste du opp sammen med?

Mor ☐ Andre slektninger ☐
Far ☐ Adoptivforeldre ☐
Stemor/stefar ☐ Foster-/pleieforeldre ☐

48 Ble dine foreldre skilt, eller flyttet de fra hverandre, da du var barn?

Nei ☐
Ja, før jeg var 7 år ☐
Ja, da jeg var 7-18 år ☐

49 Døde noen av dine foreldre da du var barn?

Nei ☐
Ja, før jeg var 7 år ☐
Ja, da jeg var 7-18 år ☐

50 Vokste du opp med kjæledyr?

Nei ☐
Ja, katt ☐ Ja, hund ☐
Ja, hest ☐ Ja, annet levende dyr ☐

51 Hvor mye melk eller yoghurt drakk du vanligvis?

Sjelden/ aldri	1-6 gl. pr. uke	1 glass pr. dag	2-3 gl. pr. dag	Mer enn 3 glass pr. dag
☐	☐	☐	☐	☐

52 Vokste du opp på gård med husdyr? Ja ☐ Nei ☐

53 Når du tenker på barndommen/oppveksten din, vil du beskrive den som:

Svært god ☐ Vanskelig ☐
God ☐ Svært vanskelig ☐
Middels ☐

ALT I ALT

54 Når du tenker på hvordan du har det for tida, er du stort sett fornøyd med tilværelsen eller er du stort sett misfornøyd? *(Sett ett kryss)*

Svært fornøyd ☐ Nokså misfornøyd ☐
Meget fornøyd ☐ Meget misfornøyd ☐
Ganske fornøyd ☐ Svært misfornøyd ☐
Både/og ☐

NTNU
K.G. Jebsen Center for
Genetic Epidemiology

ALL-IN

HUNT cohort description and genotyped data

This document provides a description of the handling of the all-in genotyped data.

Document version 2021-07-07

Table of content

Change-log

2020-09-22 – updated document to have only one version and document for all SNP data, not separated for gwas and fast-track.
2021-03-25 – updated document with info regarding the content in the individual level file.
2021-06-16 – updated acknowledgement section or the genetics in hunt
2021-07-01 – minor adjustments and corrections to the text

Documentation for genotyped data

This document provides a brief description of the handling of the all-in genotyped data from genotyping through QC. The purpose of the document is to provide background information for research using single or multiple SNP's which have been extracted and made available from the total dataset or the entire set of genetic variants.

Background

From 2012-2015 the HUNT-Michigan (HUNT-MI) collaboration genotyped approximately 72.000 individuals from the HUNT biobank. The genotyping effort was a research collaboration between researchers at NTNU and the University of Michigan. Every individual with a DNA sample with a suitable DNA concentration was selected for genotyping. Samples were picked at random and genotyped in batches. All genotyping was performed at the Genomics-Core Facility (GCF) at the Norwegian University of Science and Technology, NTNU.

Cohort description

The Nord-Trøndelag Health Study (HUNT) is a large population-based cohort from the county Nord-Trøndelag in Norway. All residents in the county, aged 20 years and older, have been invited to participate. Data was collected through three cross-sectional surveys, HUNT1 (1984-1986), HUNT2 (1995-1997) and HUNT3 (2006- 2008), and has been described in detail previously (Krokstad *et al*., 2013), with the fourth survey recently completed (HUNT4, 2017-2019). DNA from whole blood was collected from HUNT2 and HUNT3, with genotypes available from 71,860 participants. All genotyped participants have signed a written informed consent regarding the use of data from questionnaires, biological samples and linkage to other registries for research purposes.

Contact list

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Acknowledgements

When using genotyped data from HUNT in publications, please acknowledge the following:
The Trøndelag Health Study (HUNT) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology NTNU), Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health.
The genetic investigations of the HUNT Study, is a collaboration between researchers from the K.G. Jebsen center for genetic epidemiology and University of Michigan Medical School and the University of Michigan School of Public Health. The K.G. Jebsen Center for Genetic Epidemiology is financed by Stiftelsen Kristian Gerhard Jebsen; Faculty of Medicine and Health Sciences, NTNU, Norway
The SNP genotyping was performed by the Genomics Core Facility (GCF), Norwegian University of Science and Technology (NTNU).

Funding

The genotyping was financed by the National Institute of health (NIH), University of Michigan, The Norwegian Research council, and Central Norway Regional Health Authority and the Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU). The genotype quality control and imputation has been conducted by the K. G. Jebsen center for genetic epidemiology, Department of public health and nursing, Faculty of medicine and health sciences, Norwegian University of Science and Technology (NTNU). GCF is funded by the Faculty of Medicine and Health Sciences at NTNU and Central Norway Regional Health Authority.

Quick overview

Genotyping platform: Illumina

Chip: HumanCoreExome arrays:

- HumanCoreExome 12 v.1.0
- HumanCoreExome 12 v.1.1
- UM HUNT Biobank v1.0 (HumanCoreExome 24 with custom content)

Imputation: Human reference consortium (HRC) and custom panel including 2200 HUNT individuals with low pass WGS

Below you will find the description of the handling of the original data-set.

Quality control

In total, DNA from 71,860 HUNT samples was genotyped using one of three different Illumina HumanCoreExome arrays (HumanCoreExome12 v1.0, HumanCoreExome12 v1.1 and UM HUNT Biobank v1.0). Samples that failed to reach a 99% call rate, had contamination > 2.5% as estimated with BAF Regress (Jun *et al*., 2012), large chromosomal copy number variants,

lower call rate of a technical duplicate pair and twins, gonosomal constellations other than XX and XY, or whose inferred sex contradicted the reported gender, were excluded. Samples that passed quality control were analysed in a second round of genotype calling following the Genome Studio quality control protocol described elsewhere (Guo *et al.*, 2014). Genomic position, strand orientation and the reference allele of genotyped variants were determined by aligning their probe sequences against the human genome (Genome Reference Consortium Human genome build 37 and revised Cambridge Reference Sequence of the human mitochondrial DNA; http://genome.ucsc.edu) using BLAT (Dunham et al., 2012). Variants were excluded if (1) their probe sequences could not be perfectly mapped to the reference genome, cluster separation was < 0.3, Gentrain score was < 0.15, showed deviations from Hardy Weinberg equilibrium in unrelated samples of European ancestry with p-value < 0.0001), their call rate was < 99%, or another assay with higher call rate genotyped the same variant.

Ancestry/Population structures

Ancestry of all samples was inferred by projecting all genotyped samples into the space of the principal components of the Human Genome Diversity Project (HGDP) reference panel (938 unrelated individuals; downloaded from http://csg.sph.umich.edu/chaolong/LASER/) (Li et al., 2008; Wang et al., 2014), using PLINK v1.90 (Chang *et al.*, 2015). Recent European ancestry was defined as samples that fell into an ellipsoid spanning exclusively European populations of the HGDP panel. The different arrays were harmonized by reducing to a set of overlapping variants and excluding variants that showed frequency differences > 15% between data sets, or that were monomorphic in one and had MAF > 1% in another data set. The resulting genotype data were phased using Eagle2 v2.3 (Loh *et al.*, 2016).

Imputation

Imputation was performed on the 69,716 samples of recent European ancestry using Minimac3 (v2.0.1, http://genome.sph.umich.edu/wiki/Minimac3) (Das *et al.*, 2016) with default settings (2.5 Mb reference-based chunking with 500kb windows) and a customized Haplotype Reference consortium release 1.1 (HRC v1.1) for autosomal variants and HRC v1.1 for chromosome X variants (McCarthy *et al.*, 2016). The customized reference panel represented the merged panel of two reciprocally imputed reference panels: (1) 2,201 low-coverage whole-genome sequences samples from the HUNT study and (2) HRC v1.1 with 1,023 HUNT WGS samples removed before merging. We excluded imputed variants with Rsq < 0.3 resulting in over 24.9 million well-imputed variants.

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SNP-info

<u>This information is for individuals receiving genetic data for a selection of specific SNPs ordered from HUNT.</u>

The file **snp-info.txt** contains the first columns from the VCF-file. Each row contains information for one variant.
This information can be found in the file: dose_PIDXXXXXX_varSubset_info.txt

COLUMN heading	**Explanation**
CHROM	Numbers 1-22, or X
POS	Chromosomal position, build 37
MARKERID	Chromosome:position_ref/alt
REF	Reference allele A/T/G/C
ALT	Alternative allele A/T/G/C
ALT_AF	Allele frequency of alternative allele
MAF	Minor allele frequency
R2	Estimated Imputation accuracy

The data file: **dose_PIDXXXXXX_varSubset.txt** contains the individual level data.
Format:

- One row per person
- One column pr. Variant

All SNPs in the file have been imputed (including the also genotyped SNPs). Genotypes are coded as dosage. The value given is the dosage of the alternate allele

	Explanation
Chr:position_ref/alt	Genotype given as dosage
Sex	1=Male, 0=Female. Sex is given for individuals where self-reported and gentic sex matched
BirthYear	From HUNT file
*Batch**	0-5
PC1-20	Principal component 1-20

*The genotyping was done in batches. This column indicates in which batch the individual was genotyped

NTNU
Fakultet for medisin og helsevitenskap
Institutt for samfunnsmedisin og sykepleie

Vår dato 25.11.2019
Deres dato 30.10.2019
Vår referanse 2019/36248/TRS
Deres referanse

Gunnhild Åberge Vie
Institutt for samfunnsmedisin og sykepleie
Boks 8905
7491 Trondheim

HUNT-avtale til signering

Vedlagt oversendes HUNT-avtale for prosjektet "Is higher smoking intensity associated with poorer self-reported health? A Mendelian Randomisation study in the HUNT Study" for signering.

Med hilsen

Steinar Krokstad
professor dr. med./daglig leder

Inger D. Holmen
for Turid Rygg Stene
rådgiver

Vedlegg: Avtale

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NTNU
Fakultet for medisin og helsevitenskap
Institutt for samfunnsmedisin og sykepleie

Vår dato 25.11.2019 | Vår referanse 2019/36248/TRS
Deres dato 30.10.2019 | Deres referanse

Avtale

HUNT forskningssenter, Institutt for samfunnsmedisin og sykepleie, Fakultet for medisin og helsevitenskap, NTNU

og

Institutt for samfunnsmedisin og sykepleie, Fakultet for medisin og helsevitenskap, NTNU

inngår med dette en avtale om bruk av forskningsmateriale fra Helseundersøkelsen i Nord-Trøndelag (HUNT) til studentprosjekt for masterstudent Inger Ådnøy Ellingsen og veileder Gunnhild Åberge Vie

Prosjekttittel: "Is higher smoking intensity associated with poorer self-reported health? A Mendelian Randomization study in the HUNT study"

Partene blir enige om følgende:

GRUNNLAGET FOR AVTALEN

Grunnlaget for bruk av data fra Helseundersøkelsen i Nord-Trøndelag (HUNT) er deltakernes samtykke ihh til Helseforskningsloven kapittel 4 og Forskrift om befolkningsbaserte helseundersøker.

Avtalen bygger på prosjektbeskrivelse med protokoll og publikasjonsplan datert 30.10.19. Avtalen bygger også på godkjenning i Regional komite for medisinsk og helsefaglig forskningsetikk, REK midt 34035, datert 14.10.19.

Avtalen gjelder for masteroppgave med samme tittel som prosjektet.

Rammene for forvaltning av HUNT-data er beskrevet i *Retningslinjer for forvaltning og bruk av data og biologisk materiale fra Helseundersøkelsen i Nord-Trøndelag.*

Prosjektleder er ansvarlig for at forskningsarbeidet skjer i henhold til Helseforskningslovens krav og REK- godkjenningen, og for at forskningsmaterialet blir brukt kun til de oppgitte formål som beskrevet i søknad, protokoll og publikasjonsplan tilhørende prosjektet.

FORSKNINGSMATERIALET

HUNT forskningssenter skal levere en avidentifisert datafil som beskrevet i variabelbestillingen og godkjent av HUNT DAC til prosjektleder. Estimert dato for utlevering av datafilen er innen 3 uker etter at signert avtale er mottatt.

HUNT forskningssenter skal levere ut forskningsmateriale som spesifisert i vedlegg 1HUNT forskningssenter kan ikke holdes ansvarlig for forsinket levering når forsinkelser skyldes uklarheter rundt materialets art, forsendelsesmetode, eller andre forhold som må avklares før utlevering kan skje. HUNT forskningssenter vil gi beskjed ved slike forsinkelser.

DATASIKKERHET

Prosjektleder er ansvarlig for sikkerheten for mottatte data, dette innebærer håndtering og lagring i henhold til lover og forskrifter. Vedlegg 2 spesifiserer HUNTs krav til sikker datalagring.

Kun personer nevnt i REK- godkjenning og i søknaden til HUNT forskningssenter kan ha tilgang til det utleverte eller koblede forskningsmaterialet. Forskningsmaterialet kan ikke overføres til land utenfor EU/EØS/land uten «adequacy decision» fra EU. Listen over godkjente land finnes her: https://ec.europa.eu/info/law/law-topic/data-protection/data-transfers-outside-eu/adequacy-protection-personal-data-non-eu-countries_en

Når de planlagte analyser av data er fullført og prosjektet avsluttes skal datasettet slettes og bekreftelse på dette sendes til HUNT forskningssenter.

GYLDIG AVTALE UNDER PROSJEKTPERIODE

Så lenge prosjektet pågår har prosjektleder ansvar for gyldig REK- godkjenning og gyldig avtale med HUNT forskningssenter. Uten gyldig REK godkjenning anses avtalen ikke å være gyldig. Uten gyldig avtale har prosjektet ikke anledning til å bruke data, biologisk materiale eller analysesvar fra biologisk materiale, eller til å publisere resultater fra prosjektet.

ENDRINGER I PROSJEKTET

Prosjektleder skal søke godkjenning fra HUNT forskningssenter ved ønsker om endringer i prosjektet. Eksempler er: Endringer i publikasjonsplan, forlengelse av avtale, nye medarbeidere og ønsker om flere variabler.

PARTENES ANSVAR VED FEIL

Når prosjektleder har mistanke om feil i mottatt forskningsmateriale skal prosjektleder melde dette til HUNT forskningssenter.
Om HUNT forskningssenter oppdager feil i utlevert forskningsmateriale, skal HUNT forskningssenter gi beskjed til prosjektleder.
Uavhengig av hvordan feil blir oppdaget, vil HUNT forskningssenter bistå i å rette opp feilene og begrense følgene for prosjektet.
HUNT forskningssenter er ikke ansvarlig for eventuelle feil, skader eller økonomisk tap som følge av feil i forskningsmateriale, men vil bistå i tiltak for å unngå disse.
Prosjektleder skal kontakte HUNT forskningssenter umiddelbart hvis det oppdages forhold som truer personvernet for HUNT- deltakere.

BETALING

Prosjektleder har ansvar for betaling av kostnader fakturert fra HUNT forskningssenter som bestemt av Fakultet for medisin og helse ved dekanus og som oppgitt på HUNTs nettsider ved tidspunkt for avtaleinngåelse..

Kostnaden for tilgang til data for bruk i masteroppgave i dette prosjektet er kr 2000,-. Mva kommer i tillegg hvis betalingen skjer fra en ikke-NTNU konto. Faktura sendes separat.

MANUSINNSENDING

Prosjektleder skal sende manus til HUNT publikasjonsutvalg før det tilbys tidsskrift for publisering, og sende inn publiserte artikler til HUNT forskningssenter etter at de er publisert. For PhD-prosjekt skal prosjektleder sende 2 eksemplarer av sammenskrivning når den foreligger og det er ønskelig for HUNT å få melding om disputasdato. *For studentoppgaver skal en kopi av godkjent oppgave sendes til HUNT med godkjenningsdato.*

KOMMERSIELLE INTERESSER

Materiale, data eller resultater fra HUNT kan ikke selges eller patenteres uten at det foreligger en tilleggsavtale med HUNT forskningssenter / NTNU. NTNUs gjeldende regelverk skal følges.

VIDERE FORPLIKTELSER FOR HUNT FORSKNINGSSENTER

HUNT forskningssenter skal være tilgjengelig for spørsmål og henvendelser om bruk av forskningsmaterialet.

HUNT forskningssenter vil levere ut tilleggsvariabler uten tilleggskostnad etter godkjenning av Data Access Committee.

HUNT forskningssenter håndterer en svarfrist på henvendelser av maksimalt én måned.

UENIGHET MELLOM PARTENE

I tilfelle uenighet om innholdet i avtalen vil partene først forsøke å komme til enighet. Om dette ikke skulle føre fram, kan ledelsen ved Fakultet for medisin og helsevitenskap ha en meglende rolle. Det er Rektor ved NTNU som har høyest beslutningsmyndighet.

AVTALENS GYLDIGHET

Avtalen gjelder fra dato for underskrift av alle parter og fram til **31.12.22**. Før denne dato skal analysearbeidet være fullført og datafilen slettet. Det er mulig å søke om forlengelse av avtalens gyldighet ved å sende en søknad til HUNT forskningssenter før avtalen går ut. Denne søknaden må inneholde en begrunnelse for ønsket om forlengelse og eventuelle endringer i prosjektets protokoll og publikasjonsplan.

AVTALEN UNDERSKRIVES AV PROSJEKTLEDER OG FORSKNINGSANSVARLIG FOR PROSJEKTLEDERS INSTITUTT OG ØVERSTE LEDER FOR HUNT FORSKNINGSSENTER

for Institutt for samfunnsmedisin og sykepleie, MH, NTNU

Dato

student Inger Ådnøy Ellingsen

for HUNT forskningssenter, MH, NTNU

Levanger, 26.11.19

Steinar Krokstad
professor dr. med. /daglig leder

Dato 27.11.2019

Gunnhild Åberge Vie

prosjektleder Gunnhild Åberge Vie

VEDLEGG 1: FORSKNINGSMATERIALE

Det er avtalt å levere ut følgende:

- Datafil i henhold til godkjent variabelbestilling med tillegg av 2 stk SNP's i bestillingsliste

VEDLEGG 2: IT SIKKERHET RETNINGSLINJER

Tilgangsbeskyttelse:

Data relatert til deltakere i HUNT må alltid lagres på en server med passordbeskyttelse, og skal kun unntaksvis lagres på mobile enheter for filoverføring.

Når datamaskiner og mobile lagringsenheter ikke er bevoktet, må utstyret være passordbeskyttet mot uautorisert bruk eller endringer og tyveri. Alternativt skal alt datamateriale være kryptert.

Autorisering:

Hvis datamaskinen brukes av mer enn én person må tilgangen til datamaterialet skje med autorisering slik at kun personer som trenger opplysningene fra datamaterialet i deres arbeid har tilgang. Brukernavn og passord er personlig og kan ikke brukes av flere. Det skal være prosedyrer for hvem som skal få brukernavn og passord og hvordan disse utdeles.

Dataoverføring:

Dataoverføring til eksterne servere skal skje med en autoriseringssjekk. Dataoverføring til datamaskiner som er plassert utenfor organisasjonens kontroll må skje kryptert.

Sletting av datafiler:

Når stasjonære eller mobile lagringsenheter med Data fra deltakere i HUNT ikke lenger skal brukes til å lagre datamaterialet skal lagringsenhetene bli destruert. Alternativt skal all Data bli slettet på en måte som gjør det umulig å gjenopprette materialet.

Reparasjon og sørvis:

Når datautstyr skal repareres eller få sørvis av en tredjepart skal bedriften som utfører reparasjonen eller sørvis skrive under en sikkerhetsavtale, som i det minste skal inneholde taushetsplikt og forbud mot overføring eller spredning av datamaterialet, eller dets innhold.

Når sørvis utføres skal all data være fjernet fra lagringsenheter, eller lagringsenheter være fjernet fra datamaskiner. Hvis dette ikke er mulig må sørvis utføres under tilsyn av organisasjonen som har fått utlevert datamaterialet.

Sørvis utført via en datalenke kan kun skje etter at personen som utfører sørvis har vært identifisert på en sikker måte. Sørvispersonale skal ha tilgang til datasystemet kun mens sørvisarbeidet varer. Om en separat kommunikasjonskanal åpnes i forbindelse med sørvis, skal den være lukket når sørvis ikke utføres.

#34035 Gir mer røyking dårligere selvopplevd helse? Mendelsk randomisering i HUNT

Application Info

Søknadsid:	34035
Utlysning:	Prosjektsøknad
Søker:	Gunnhild Åberge Vie
Prosjektleder:	Gunnhild Åberge Vie

1 GENERELLE OPPLYSNINGER

1.1 Utsatt offentlighet

1.1 Søkes det om utsatt offentliggjøring?	Nei

1.2 Tidsramme for prosjektet

1.2.1 Prosjektstart dato?	20.08.2019
1.2.2 Prosjektslutt dato?	31.12.2022

1.3 Prosjekttittel

1.3.1 Norsk tittel	Gir mer røyking dårligere selvopplevd helse? Mendelsk randomisering i HUNT

1.3.2 Vitenskapelig tittel

Is higher smoking intensity associated with poorer self-reported health? A Mendelian Randomisation study in the HUNT Study

1.4 Prosjektleder

1.5 Forskningsansvarlig institusjon

1.5.1 Hvilken norsk forskningsinstitusjon er prosjektleder knyttet til i prosjektet (Koordinerende institusjon)?	Norges teknisk-naturvitenskapelige universitet

Kontaktperson

Kontaktperson

1.6 Prosjektmedarbeidere

Navn	Johan Håkon Bjørngaard
Stilling	Professor
Institusjon	Norges teknisk-naturvitenskapelige universitet
Akademisk grad	PhD / Doktorgrad
Prosjektrolle	Co-supervisor
Navn	Inger Ådnøy Ellingsen
Stilling	Masterstudent
Institusjon	Norges teknisk-naturvitenskapelige universitet
Akademisk grad	Bachelorgrad

Prosjektrolle	Masterstudent - will perform the research

1.7 Initiativtaker

1.7.1 Hvem er initiativtaker til prosjektet?	Prosjektleder og/eller forskningsansvarlig institusjon (bidragsforskning)

1.8 Utdanningsprosjekt

1.8.1 Er prosjektet del av en ph.d. eller annen utdanning?	Ja
1.8.1.1 Studium/fag?	Master i folkehelse
1.8.1.2 Nivå?	Master

1.9 Utprøving av medisinsk utstyr

1.9.1 Utprøving av medisinsk utstyr?	Nei

1.10 Samarbeid med utlandet

1.10.1 Har prosjektet noen form for samarbeid med utlandet?	Nei

1.11 Andre prosjekter med betydning for vurderingen

1.11.1 Har REK behandlet noe annet prosjekt etter mai 2009, generell biobank, framleggingsvurdering eller annet, som er relevant for vurderingen av dette prosjektet?	Nei
1.11.2 Er det annen informasjon som REK bør vite om i forbindelse med vurdering av søknaden?	Nei

2 PROSJEKTOPPLYSNINGER OG METODE

Oppsummering av forskningsprosjektet

2.1 Prosjektbeskrivelse?

Målet med studien er å brukt genetisk variasjon i røykeintensitet for å se om vi finner indikasjon på en kausal sammenheng med selvopplevd helse. Fordi røyking er assosiert med økt sykelighet, skulle man forvente en sammenheng, og dårligere helse kan motivere for røykeslutt. Dersom røykere selv ikke opplever helsen som dårligere, vil dette gi mindre motivasjon for å slutte å røyke. Vi vil bruke data om selvopplevd helse fra HUNT2 og HUNT3, og informasjon om genetisk variant rs16969968/rs1051730.

Studiemetode/-design

2.2.1 Metode for analysering av data?	Kvantitative analysemetoder
2.2.2 Prosjekttype?	Epidemiologisk studie

3 FORSKNINGSDATA

Innsamling av data

3.1 Skal det samles inn nye data i prosjektet Nei

Tidligere registrerte opplysninger

3.2 Skal det forskes på tidligere registrerte opplysninger? Ja

3.2.1 Skal det hentes opplysninger fra tidligere godkjent(e) forskningsprosjekt(er)? Nei

3.2.2 Skal det hentes opplysninger fra Sentrale helseregistre? Nei

3.2.3 Skal det hentes opplysninger fra nasjonale kvalitetsregistre? Nei

3.2.4 Skal det hentes opplysninger fra befolkningsbasert(e) helseundersøkelse(r)? Ja

3.2.4.1 Opplysninger fra befolkningsbaserte helseundersøkelser?

Helseundersøkelse	Hvilke opplysninger skal hentes, oppgi kategorier av variabler og anslag på antall
HUNT, Helseundersøkelsen i Nord-Trøndelag	genetisk variant: rs1051730/rs16969968 Bakgrunnsvariabler (ca 5): kjønn, alder, utdanning, Røykeinformasjon: ca 10 variabler fra hver HUNT-studie Helse/symptomer selvrapportert: ca 15 variabler fra hver HUNT-studie (selvrapportert helse, hjerte- og lungesymptomer og medisiner for dette, kjent hjerte-/lungesykdom)

3.2.5 Skal det hentes opplysninger fra regionalt eller lokalt helseregister? Nei

3.2.6 Skal det hentes opplysninger fra pasientjournal? Nei

3.2.7 Skal det hentes opplysninger fra annet behandlingsrettet register? Nei

3.2.8 Skal det hentes opplysninger fra registre om annet enn helse? Nei

Nye helseopplysninger

3.3 Skal det forskes på nye helseopplysninger? Nei

Humant biologisk materiale

3.4 Skal det forskes på humant biologisk materiale? Nei

Begrunnelsen for data og metode

3.5 Redegjør for den faglige og vitenskapelige begrunnelsen for valg av data og metode?

Det er velkjent at røyking er sykdomsfremkallende, men hvordan (om) røykere selv opplever at helsen deres blir påvirket - eventuelt før de får diagnostisert alvorlig sykdom, er mindre kjent. Mendelsk randomisering er en metode hvor man bruker genetiske varianter som en instrumentvariabel. Dermed kan man unngå problemer med confounding og omvendt årsakssammenheng, som ellers kan påvirke sammenhengene mellom hvor mye noen røyker og hvordan de beskriver helsen sin. Helseundersøkelsen i Nord-Trøndelag inneholder både informasjon om genetiske varianter, selvopplevd helse og røyking. I studiepopulasjonen er det også mange som er eller har vært røykere, som er de gruppene hvor genetisk tilbøyelighet til å røyke mer kan ha effekt. Aldri-røykere kan brukes som negativ kontrollgruppe, hvor man ikke forventer å se noen sammenheng.

4 AVVEINING AV NYTTE OG RISIKO

4.1 Angi forutsigbar nytte eller fordeler

4.1.1 Nå eller i fremtiden for den enkelte deltaker/pasient?

No direct advantage for the participants.

4.1.2 Nå eller i fremtiden for gruppen?

Information about the how smokers evaluate their own health, and any discrepancy between self-rated health and objectively measured health consequences of smoking, might help health professionals to better target smoking cessation advice.

4.1.3 Nå eller i fremtiden for samfunnet eller vitenskapen?

Information about the how smokers evaluate their own health, and any discrepancy between self-rated health and objectively measured health consequences of smoking, might help health professionals to better target smoking cessation advice.

4.2 Angi mulig risiko/ulempe nå eller i fremtiden

4.2.1 For den enkelte deltaker/pasient?

No direct risk associated with the present study. There is a risk of information about participant's health being identified by others. The number of variables in this project are limited, with limited possibilities to identify participants based on the dataset.

4.2.2 For gruppe?

The dangers of smoking are well-known, and we do not believe that this study will increase the stigma associated with being a smoker.

4.2.3 For samfunnet eller vitenskapen?

Improper reporting of results will potentially mislead the public's beliefs about smoking and self-rated health. However, we neither consider the risk of falsely reported results, nor the risk of severely impacting peoples' perception of smoking as dangerous, to be likely.

4.3 Stråling

4.3.1 Ioniserende stråling? Nei

4.4 Tiltak

4.4.1 Redegjør for tiltak for å redusere eller begrense risiko og ulempe?

We plan to keep the data on NTNU's server in files with restricted access. The researchers will not have access to the identity of the participants, this information will be stored at HUNT. We plan to perform appropriate analyses and report them in appropriate manner. Methods and results will be made available as a master thesis.

4.5 Forsvarlighet

Gi en samlet vurdering av prosjektets forsvarlighet for å begrunne at nytten står i et rimelig forhold til den risiko/ulempe som pasienter/deltakere utsettes for?

We consider the risks for the individual participants to be negligible, and that, given appropriate management of data files, analyses, and presentation of the results, this study is unlikely to cause any relevant disadvantages.

5 STUDIEPOPULASJON OG SAMTYKKE

Studiepopulasjon (forskningsdeltakere/utvalg)

5.1 Beskriv hvilke grupper av forskningsdeltakere/utvalg som inngår?

We will include participants in the HUNT2 and HUNT3 Study (adults). Participants with available genetic data will be included in the main analyses.

5.2 Hvor mange forskningsdeltakere er planlagt inkluderte totalt? 100 000

5.2.1 Planlagt antall forskningsdeltakere i Norge? 100 000

5.2.2 Begrunn antallet – dersom det er relevant, redegjør også for styrkeberegning med statistiske analysemetoder?

Mendelian randomisation requires fairly large number of participants for statistical power. The SNP explains 0.33% of variance in number of cigarettes smoked, with 70 000 participants, the power to detect 0.2 sd change in outcome per sd change in smoking is 82%

5.3 Hvem skal inkluderes i studiet? Andre personer enn pasienter

5.4 Hvordan skal deltakere identifiseres?

The HUNT Databank will generate the appropriate population and extract the data.

5.5 Er prosjektet del av samisk helseforskning og/eller forskning på samisk humant biologisk materiale? Nei

Samtykke

5.6.2 Samtykke for Voksne? Nei

5.6.2.1.1 Begrunn hvorfor ikke

Consent was obtained for participation in the HUNT Study. Giving consent for each specific subproject using HUNT data would be expensive, and hardly wanted by the participants.

5.7 Samtykke er allerede innhentet? Ja

5.7.1 For hvilke deltakere er det allerede innhentet samtykke og til hva?

All participants gave consent to participate. Separate information was sent to HUNT2 participants before genetic analyses were performed, as this was not included in the original consent.

5.7.2 Er det opprinnelige samtykket dekkende for dette prosjektet?

Yes.

5.7.3 Blir de som allerede har samtykket informert om prosjektet? Eventuelt på hvilken måte?

We will not inform the participants. HUNT nonetheless provides a searchable overview of ongoing projects online, participants who are interested will thus be able to identify the project.

5.8 Søkes det om fritak fra kravet om å innhente samtykke? Nei

6 PERSONVERN OG RETTIGHETER

Behandling av personopplysninger

6.1 Hvilke generelle og særlige kategorier av personopplysninger skal samles inn i prosjektet? Helseforhold, Genetiske opplysninger

6.2 Skal opplysningene kobles mot andre datasett? Nei

Behandling av personopplysningene i databehandlingsperioden

6.3 Indirekte identifiserbare ved bruk av koblingsnøkkel? Ja

6.3.1 Beskriv hvordan koblingsnøkkel vil bli oppbevart og hvem som vil ha tilgang?

The connection key will be stored at HUNT Datacenter.

6.4 Personidentifiserende opplysninger direkte identifiserbare med 11-sifret personnummer eller navn, adresse og/eller fødselsdato i hele prosjektperioden? Nei

6.5 Personlig identifiserbare opplysninger sytematisk reidentifiserbare ved kombinasjon av variabler? Ja

6.5.1 Utdyp om sammenstillingen av variabler?

Re-identification is not likely based on the variables available, however, the combination of age, sex, education, smoking habits and health information could potentially make it possible to identify someone, given that one already has extensive information about the person. Re-identification based solely on commonly known information like sex, birth year and level of education is unlikely.

6.6 Personlig identifiserbare opplysninger er avidentifisert? Nei

Vurdering av personvernrisiko

6.17 Behandling av helseopplysninger uten samtykke? Ja

6.17.1 Beskriv?

It will be possible to process HUNT data beyond the ethical clearance, but the risk of going beyond the broad consent is still low. Despite access restriction, unwarranted access is possible.

6.18 Behandling av særlige kategorier av personopplysninger? Ja

6.18.1 Beskriv?

The project contains health information and limited genetic data.

6.19 Sammenstilling av data? Nei

6.20 Størrelse (antall, detaljering, varighet, omfang)? Ja

6.20.1 Beskriv?

The number of study participants is large, but the amount of data collected on each of them is limited. The project will be limited to the master thesis, possibly with publication as a paper if the work is of sufficient quality.

6.21 Personer med særlige behov? Nei

6.22 Bruk av ny datateknologi? Nei

6.23 Dataminimering. Gi en detaljert vurdering av om enkelte variabler kan medføre bakveisidentifisering.

Age, sex and educational level is unlikely to be sufficient to re-identify participants. Combinations of smoking and health information will make it possible to identify someone already known fairly well.

6.24 Sammenfattet vurdering av risiko ved bruk av personopplysninger?

We believe the risks are small.

Ivaretakelse av deltakernes rettigheter

6.14 Hvordan ivaretas deltakernes rettigheter i form av krav til innsyn, retting, sletting og destruksjon av biologisk materiale?

The consent is handled by the HUNT Datacenter. If participants withdraw their consent, HUNT Datacenter will notify the researchers, and the given identification number will be deleted from the files.

6.15 Vil deltakerne få løpende informasjon i prosjektperioden? Nei

6.15.1 Utdyp?

They will not receive information about this specific project.

6.16 Hvem skal deltakerne kontakte for å fremme krav om innsyn, retting, sletting og destruksjon av biologisk materiale?

The HUNT Datacenter.

Håndtering av data/materiale ved prosjektslutt

6.25 Når et forskningsprosjekt er avsluttet (senest ved godkjent sluttdato) kan en eventuell koblingsnøkkel oppbevares i fem år (15 år ved legemiddelstudier) for kontrollhensyn. Deretter skal en eventuell kodenøkkel slettes og materialet destrueres eller anonymiseres. Planlegges det å fravike denne regelen? Nei

Datadeling

6.28 Planlegges det noen form for datadeling etter prosjekt slutt? Nei

7 FORSIKRING, FINANSIERING OG PUBLISERING

7.1 Forsikring for forskningsdeltakere

7.1.1 Forsikring for forskningsdeltakere? Særskilt forsikring

7.2 Interesser

7.2.1 Finansieringskilder?

We will seek support from NTNU for the data fee to HUNT. The main supervisor receives funding from the Norwegian Research Council.

7.2.2 Godtgjøring til institusjon?

None

7.2.3 Honorar prosjektleder/-medarbeidere?

None

7.2.4 Eventuelle interessekonflikter for prosjektleder/-medarbeidere?

No

7.3 Publisering

7.3.1 Er det restriksjoner med hensyn til offentliggjøring og publisering av resultatene fra prosjektet?	Nei

7.3.2 Redegjør for hvordan resultatene skal gjøres offentlig tilgjengelig?

The results will be published as a master thesis. If the work is of appropriate quality, publication in a peer-reviewed journal will be considered.

7.4 Kompensasjon til deltakere

7.4 Blir det gitt kompensasjon til pasienter/deltakere?	Nei

8 VEDLEGG

8.1 CV for prosjektleder	1 vedlegg (cv_aug19.pdf)
8.2 Forskningsprotokoll	1 vedlegg (masterprotokoll 20aug.pdf)
XX NB! 8.3 Opprinnelig godkjenning, søknad og informasjonsskriv/samtykkeskriv for Biobank før 2009	0 vedlegg
8.6 Spørreskjema	0 vedlegg
8.7 Intervjuguide	0 vedlegg
8.10 Tidligere godkjent informasjons-/samtykkeskriv	1 vedlegg (samtykke_hunt2_3.pdf)
8.11 Andre nødvendige vedlegg	1 vedlegg (information and consent forms.pdf)

9 ANSVARSERKLÆRING

Jeg er kjent med	Ja
Jeg erklærer at prosjektet vil bli gjennomført i henhold til gjeldende lover, forskrifter og retningslinjer	Ja
Jeg erklærer at prosjektet vil bli gjennomført i samsvar med opplysninger gitt i denne søknaden	Ja
Jeg erklærer at prosjektet vil bli gjennomført i samsvar med eventuelle vilkår for godkjenning, gitt av REK	Ja

Søknadsinformasjon

Utlysning	Prosjektsøknad
Søknad	Gir mer røyking dårligere selvopplevd helse? Mendelsk randomisering i HUNT
SøknadsId	34 035
Søkerorganisasjon	Norges teknisk-naturvitenskapelige universitet

Oppgave: Endring og/eller henvendelse

Oppgaveid	566917
Utført	06.12.2022
Sist oppdatert	06.12.2022

Hva gjelder endringen/henvendelsen?

- Endring i prosjektperiode

Ny startdato	20.08.2019
Ny sluttdato	31.12.2024
Legg ved revidert forskningsprotokoll med markerte endringer	1 vedlegg (masterprotokoll 20aug.pdf)
Andre nødvendige vedlegg	0 vedlegg

Beskrivelse av og begrunnelse for endringen

Studenten som skulle skrive oppgåva har blitt betydeleg forseinka på grunn av kombinasjon av sjukdom og oppstart i anna arbeid. Det er fortsatt håp om at ho kan få fullført master.

a) Title: Is higher smoking intensity associated with poorer self-reported health? A Mendelian Randomisation study in the HUNT Study

b) Introduction/background

This research project aims to use mendelian randomisation to assess the relationship between smoking intensity and self-reported health using data from HUNT3 and HUNT2.

The WHO lists tobacco related diseases as the second leading cause of death worldwide. Smoking has an established causal relationship with cancer, CVD and pulmonary diseases (1, 2). In Norway in 2017 cancer, CVD and pulmonary diseases were the three biggest causes of death according to FHI(3). There are previous studies that have shown a correlation between higher intake of cigarettes and higher levels of anxiety and depression (4), although this association may not represent a causal effect of smoking on mental symptoms (5).

Smoking prevalence has decreased significantly in the last decades thanks in part to awareness of ill effects (4). Previous studies have found that, along with social pressures and public policy, health benefits are one of the strongest motivations for people attempting to give up smoking(6), but also that some smokers seem to be in denial about the health impact of smoking (7). For example, 60-70% of smokers admitted to hospital with an acute coronary event give up smoking over the next 6 months (8). Still, the majority of patients with mild COPD smoke, and 38-51% of COPD patients continue to smoke despite severe disease (9). Finding what impact smoking intensity has for the self-observed health status of smokers might shed light on their own perception of the health impacts as they apply to themselves.

Self-reported health is not an objective measure. However, it is possibly the most relevant question in terms of motivation for attempting to give up smoking. Self-reported health is a consistent predictor of early mortality, both related to coronary deaths and death in general (10, 11) . In previous studies using data from HUNT self-reported health is also shown to have predictive values for early death in all age groups (12, 13). Severe smoking-related conditions would presumably have a major influence on self-reported health. Although most studies have considered associations between morbidity and mortality from specific disease groups, some studies have confirmed the expected association between smoking and health related quality of life. There are also studies linking lower scores of self-reported health to smoking behaviour.

In Norway, as in most western countries, there is a strong correlation between smoking behaviours and socioeconomic factors (14-16) Socioeconomic gradients in health are well described, and although differences in smoking patterns can contribute to these differences, there are also alternative pathways for the association between socioeconomic factors and morbidity (14). Socioeconomic factors could thus confound observational studies on the association between smoking and health. Using a single nucleotide polymorphism (SNP), which is associated with degree of smoking, as the exposure we can find a relationship between degree of smoking and self-reported health regardless of socioeconomic factors (17). Having one or two risk alleles of the relevant SNP will increase smoking intensity, but does not seem to affect taking up smoking in the first place, leaving a control group of never-smokers to ensure that any association between the SNP and the outcome is mediated through smoking intensity. If the SNP is associated with outcomes also among never-smokers, this would indicate that the association between health outcomes and smoking is confounded by genetic factors.

All health outcomes listed will be confounded by socioeconomic factor or reverse causation. One study found a connection between passive smoking and worse self-reported health, which may suggest social factors are strong (18).

c) Purpose, questions and hypothesis

The main question posited is “Does smoking intensity affect the level of self-reported health?”

A secondary question is whether self-reported health is reflected in other smoking-affected health issues, such as COPD, coughing and shortness of breath.

d) Methods

We will use Mendelian randomisation to find the causal effect of higher smoking intensity on self-reported health. SNP rs1051730/rs16969968 can be present as 0,1 or 2 alleles and is associated with a higher rate of nicotine intake among smokers (19). We will use the SNP as an instrumental variable when assessing the association between smoking intensity and self-reported health. In our model, the SNP is thus used as the exposure and self-reported health is the response variable.

Participants in HUNT3 and HUNT2 were asked to rate their own health. Options are very good, good, not entirely good and poor. We will estimate the association between smoking intensity-increasing alleles and reporting good or very good health among smokers. An association between the risk alleles and health will indicate that smoking intensity is causally associated with how individuals perceive their own health. As a sensitivity analysis, we will compare the results of those with and without the SNP using respondents who have never smoked as a negative control group. The purpose of this is to check that the gene does not affect other aspects of health that could influence the results to ensure that the results for the smokers are not confounded or an effect of reverse causation.

There are question concerning health in the HUNT questionnaire that are more objective than the open question “how do you rate your own heath”, which is, of course, entirely subjective. We plan to examine other co-efficients such as COPD, coughing and previous heart attacks to determine to what degree self-reported health is reflected in less subjective categories. There are no questions that specifically ask whether the smoker attributes any ill health to smoking.

We will use a logistic model and adjust for age and sex. Number of SNP alleles will be treated as a continuous variable. The number of cigarettes smoked per day does not capture the effect of the SNP on smoking intensity perfectly. We will therefore restrain to evaluate the association between the SNP and the outcomes, rather than to perform a full instrumental variable estimation of the effect size per cigarette smoked.

e) Ethical issues

HUNT is approved by REK. We are applying to REK for approval for our research and to HUNT for use of data. A Data Protection Impact Assessment (DPIA) will be performed.

f) Plan/feasibility

We will apply to REK and HUNT for use of data in early autumn 2019 and the analysis of the SNP will take place in autumn 2019. Statistical analyses will take place in the autumn and spring term (2019/2020) and the thesis will be completed and submitted in the autumn of 2020.

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DOKUMENTER

APP_COMMUNICATION (content identifier)

Svarbrev

Dato
14.10.2019 10:22

Fra
REK

Til
Gunnhild Åberge Vie

Alle skriftlige henvendelser om saken må sendes via REK-portalen
Du finner informasjon om REK på våre hjemmesider rekportalen.no

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK midt	Magnus Alm	73559949	14.10.2019	34035
			Deres referanse:	

Gunnhild Åberge Vie

34035 Gir mer røyking dårligere selvopplevd helse? Mendelsk randomisering i HUNT

Forskningsansvarlig: Norges teknisk-naturvitenskapelige universitet

Søker: Gunnhild Åberge Vie

Søkers beskrivelse av formål:

Målet med studien er å brukt genetisk variasjon i røykeintensitet for å se om vi finner indikasjon på en kausal sammenheng med selvopplevd helse. Fordi røyking er assosiert med økt sykelighet, skulle man forvente en sammenheng, og dårligere helse kan motivere for røykeslutt. Dersom røykere selv ikke opplever helsen som dårligere, vil dette gi mindre motivasjon for å slutte å røyke. Vi vil bruke data om selvopplevd helse fra HUNT2 og HUNT3, og informasjon om genetisk variant rs16969968/rs1051730.

REKs vurdering

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK midt) i møtet 25.09.2019. Vurderingen er gjort med hjemmel i helseforskningsloven § 10.

Komiteens prosjektsammendrag: Formålet med studien er å undersøke sammenhengen mellom røykeintensitet og selvopplevd helse. Man vil benytte mendelsk randomisering, som er en metode for å bruke genetiske varianter som instrumentvariabler. Mål på røykeintensitet vil utledes fra den genetiske varianten rs16969968/rs1051730. Data for den genetiske varianten og opplysninger om selvopplevd helse skal hentes fra den andre og tredje Helseundersøkelsen i Nord-Trøndelag (HUNT2 og HUNT3).

Forsvarlighet

Komiteen har vurdert søknad, forskningsprotokoll, målsetting og plan for gjennomføring. Prosjektet ligger innenfor de rammer som er lagt for Helseundersøkelsen i Nord-Trøndelag (HUNT), og innenfor de samtykkene som deltakerne har gitt til bruk av dette materialet. Under forutsetning av at du tar vilkårene nedenfor til følge vurderer vi at prosjektet er forsvarlig, og at hensynet til deltakernes velferd og integritet er ivaretatt.

Vilkår for godkjenning

- Komiteen forutsetter at du og alle prosjektmedarbeiderne følger institusjonens bestemmelser for å ivareta informasjonssikkerhet og personvern ved innsamling, bruk, oppbevaring, deling og utlevering av personopplysninger.
- Av dokumentasjonshensyn skal opplysningene oppbevares i 5 år etter prosjektslutt. Du og forskningsansvarlig institusjon er ansvarlig for at opplysningene oppbevares avidentifisert, dvs. atskilt i en nøkkel- og en datafil. Opplysningene skal deretter slettes eller anonymiseres.
- Komiteen forutsetter at ingen personidentifiserbare opplysninger kan framkomme ved publisering eller annen offentliggjøring.

Vedtak

Godkjent

Med vennlig hilsen

Vibeke Videm
Professor dr.med. / Overlege
Leder, REK Midt

Magnus Alm
Rådgiver, REK Midt

Vedlegg-1571041334676.pdf

@ Søknad Gunnhild Åberge Vie Ad Mini Strator 20.08.2019

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK midt	Magnus Alm	73559949	12.12.2022	34035

Gunnhild Åberge Vie

Prosjektsøknad: Gir mer røyking dårligere selvopplevd helse? Mendelsk randomisering i HUNT
Søknadsnummer: 34035
Forskningsansvarlig institusjon: Norges teknisk-naturvitenskapelige universitet

Prosjektsøknad: Endring godkjennes

Søkers beskrivelse

Målet med studien er å brukt genetisk variasjon i røykeintensitet for å se om vi finner indikasjon på en kausal sammenheng med selvopplevd helse. Fordi røyking er assosiert med økt sykelighet, skulle man forvente en sammenheng, og dårligere helse kan motivere for røykeslutt. Dersom røykere selv ikke opplever helsen som dårligere, vil dette gi mindre motivasjon for å slutte å røyke. Vi vil bruke data om selvopplevd helse fra HUNT2 og HUNT3, og informasjon om genetisk variant rs16969968/rs1051730.

Innledning

Vi viser til søknad om prosjektendring mottatt 06.12.2022 for ovennevnte forskningsprosjekt. Søknaden er behandlet av sekretariatet i REK midt på delegert fullmakt fra komiteen, med hjemmel i forskningsetikkforskriften § 7, første ledd, tredje punktum. Søknaden er vurdert med hjemmel i helseforskningsloven § 11.

REKs vurdering

Du søker om å utvide prosjektperioden til 31.12.2024.

Vi har ingen forskningsetiske innvendinger til dette. Hensynet til deltakernes velferd og integritet er fremdeles godt ivaretatt.

Vedtak

Godkjent

Sluttmelding

Prosjektleder skal sende sluttmelding til REK på eget skjema via REK-portalen senest 6

måneder etter sluttdato 31.12.2024, jf. helseforskningsloven § 12. Dersom prosjektet ikke starter opp eller gjennomføres meldes dette også via skjemaet for sluttmelding.

Søknad om endring
Dersom man ønsker å foreta vesentlige endringer i formål, metode, tidsløp eller organisering må prosjektleder sende søknad om endring via portalen på eget skjema til REK, jf. helseforskningsloven § 11.

Klageadgang
Du kan klage på REKs vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes på eget skjema via REK portalen. Klagefristen er tre uker fra du mottar dette brevet. Dersom REK opprettholder vedtaket, sender REK klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering, jf. forskningsetikkloven § 10 og helseforskningsloven § 10.

Med vennlig hilsen

Hilde Eikemo
Sekretariatsleder, REK midt

Magnus Alm
rådgiver, REK midt

Kopi til:

Norges teknisk-naturvitenskapelige universitet

NTNU
Fakultet for medisin og helsevitenskap
Institutt for samfunnsmedisin og sykepleie

Datautlevering

Vi viser til avtale og sender datafil iht. bestilling.

Vi har i årene etter HUNT3 gjennomført en omfattende kvalitetssikring av HUNT databank og denne prosessen pågår fortsatt. Vi har endret variabelnavn slik det er beskrevet i dette brevet. I tillegg har vi gjennomgått variabler, sjekket ekstremverdier opp mot originale skjema og tilsvarende mål fra andre studiedeler. Opplagt gale svar er slettet, men hvis annen datakilde har muliggjort det, har svarene blitt korrigert.

Vi jobber fortsatt med utvikling av metadata. I metadata inngår informasjon om ulike instrumenter som er benyttet, sentrale referanser, hvordan variablene er konstruert etc. Dette følger leveransen som en HTML-fil, men oversikt over alle variabler i databanken med søkefunksjon finner du også på https://hunt-db.medisin.ntnu.no/hunt-db/

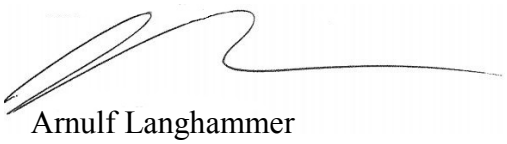
Datasettet utleveres med prosjektspesifikk personidentifikasjon (PID) og kan ikke kobles til andre datafiler fra HUNT. Sendingen er kryptert og passordbeskyttet, og kan pakkes ut ved hjelp av et zip-program (for eksempel 7-zip eller WinZip).

Kvalitetssikring av databasen er et omfattende arbeid og vil pågå i lang tid framover. Vi er derfor takknemlige over å få tilbakemelding dersom du finner feil, uklarheter eller har forbedringsforslag.

Hvis data skal kobles til ett eller flere register, må forskere i prosjektet være helt sikre på at alle bestilte HUNT-data er inkludert, og at utvalget som er satt er riktig. Vennligst gi tilbakemelding om hvorvidt datafilen er i overensstemmelse med bestillingen.

Lykke til med forskningen!

Med hilsen



Arnulf Langhammer
professor/dr. med.
leder HUNT databank

HUNT Variable Names

Each HUNT variable has a unique name, consisting of two parts separated by an @. The first part is called the *Topic Name*, and indicates what the variable measures or asks about. The second part is called the *Study Part Name*, and indicates the source of the variable. Both parts are constructed by concatenation of suitable abbreviations selected from a list developed and maintained by HUNT Research Centre.

The Topic Name aims to paraphrase the question text or describe the measurement of the variable in a succinct way. Examples:

Topic Name	Expansion	Question Text / Variable Label
DiaEv	Diabetes Ever	Have you ever had diabetes?
FeelNervLM	Feel Nervous Last month	During the last month, have you suffered from nervousness (felt irritable, anxious, tense or restless)?
BPDias1	Blood Pressure Diastolic 1	Diastolic blood pressure, measurement 1

The Study Part Name identifies the *Study Part* the variable belongs to. A Study Part is a collection of questions, measurements or analyses managed as a unit, e.g. in the form of a questionnaire or interview. The first abbreviation of a Study Part Name indicates which main survey it belongs to: NT1, NT2, NT3 (for HUNT1—3), YH1, YH2, YH3 (for the Young-HUNT studies) or others. Other important, frequently occurring abbreviations are Q (Questionnaire), I (Interview), M (Measurements) and BL (Baseline, indicating the common survey packages that the Nord-Trøndelag inhabitants were invited to). Examples:

Study Part Name	Expansion	Study Part Description
NT3BLQ1	HUNT3 Baseline Questionnaire 1	HUNT3 survey main questionnaire
NT2DiaQ	HUNT2 Diabetes Questionnaire	HUNT2 supplementary questionnaire for diabetics
YH1LuI	Young-HUNT1 Lung Interview	Young-HUNT1 Lung study interview

Identical or very similar questions/measurements frequently occur in multiple Study Parts, and in such cases the Topic Name is the same. Thus, AstEv@NT2BLQ1 and AstEv@NT3Lu1I both ask if the participant has or has ever had asthma, but the former in the baseline questionnaire of HUNT2, and the latter in the interview of phase 1 of the HUNT3 Lung Study.

Variables for Project 109536

Is higher smoking intensity associated with poorer self-reported health? A Mendelian Randomisation study in the HUNT Study

The Nord-Trøndelag Health Study (HUNT)

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Organisation and quality assurance of the HUNT data is managed by Arnulf Langhammer and the Databank staff.

HUNT Databank database software development by Jon Heggland.

Variables

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YH1LuI	Young-HUNT1 Lung Interview	Young-HUNT1 Lung study interview

Identical or very similar questions/measurements frequently occur in multiple Study Parts, and in such cases the Topic Name is the same. Thus, AstEv@NT2BLQ1 and AstEv@NT3Lu1I both ask if the participant has or has ever had asthma, but the former in the baseline questionnaire of HUNT2, and the latter in the interview of phase 1 of the HUNT3 Lung Study.

Variables sometimes change names due to quality assurance in the HUNT database, but the names used for each project is remembered. If this name is not the same as the current official variable name in the HUNT database, the official name (at the time of data file generation) is given in parentheses.

PartDat@NT2BLQ1

Question Text:
Dato og tid deltagelse HUNT2 screening (Q1/M)
English Question Text:
Date and time participation HUNT2 screening (Q1/M)
Study Part:
NT2BLQ1
Instrument:
Not applicable
Also Used In:
CAPBL4Daw, CAPBL4DawPar#1, CAPBL4DawPar#2, CAPBL4DawTeac, CAPFU1SelfQ, NT1Dia2Q, NT1Dia2QoLQ, NT2Dia2M2, NT2Dia2Q, NT3CogFail2, NT3DenM, NT3Dia2Q1, NT3Dia2Q2, NT3Dia2Q3, NT3Dia2Q4, NT3PaChr2MI, NT3PaChr2Q1, NT3PaNecQ1, NT3PaNecQ2, NT3PaNecQ3, NT3PaNecQ4, NT3PaNecQ5, NT4OneHealtQDog, YH1BLQ, YH2BLQ, YH2LuM3
Quality Assurance:
All participants have this variable, but some people have this variable without being participants.

PartAg@NT2BLQ1

Question Text:
Alder ved oppmøte screening
English Question Text:
Age at participation at screening
Study Part:
NT2BLQ1
Unit of Measurement:
year
Construction:
Base Variables: PartDat@NT2BLQ1
Instrument:
HUNTAg
Also Used In:
NT1Dia2MI1, NT3CogFail2, YH2LuM3

Healt@NT2BLQ1

Question Text:
Hvordan er helsa di nå?
English Question Text:
How is your health at the moment?
Study Part:
NT2BLQ1

Question Choices:

Nº	Text	English Text
1	Dårlig	Poor
2	Ikke helt god	Not so good
3	God	Good
4	Svært god	Very good

Instrument:
SWB
References:
bowling05just
Also Used In:
CAPBL1SelfQ, CAPFU1SelfQ, NT1BLQ1, NT1Dia2QoLQ, NT2Lu5Q, NT3BLQ1, NT3BLQNP, NT3DenQ, NT3Lu2Q, NT4BLQ1, NT4BmdQ, NT4Coe1Q, NT4EmigQ1, ST1BLQ, ST1EldQ1, YH1BLQ, YH2BLQ, YH3BLQ, YH4BLI, YH4BLQ
Comment:
The HUNT Study and other Norwegian epidemiological studies have used 4 answer choices in order to get answers either in positive or negative direction. The question also has been widely used internationally, see reference.

In the late 1970's, to increase the questions's discriminative ability, and because of the operation of "social desirability" or "optimism"bias (leading to most respondents to rate their health at the positive end of the scale), the developers of the SF-36 and others added a "very good"category in between the "excellent" and the "good" response choices. SF8 also includes a "very poor" category at the other end of the scale http://www.sf-36-org/demos/SF-8)

CougDy@NT2BLQ1

Question Text:
Hoster du daglig i perioder av året?
English Question Text:
Do you cough daily during periods of the year?
Study Part:
NT2BLQ1
Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:
HUNTBL
Also Used In:
NT2Lu5Q, NT3BLQ2, NT4BLQ2, NT4EmigQ2, ST1EldQ2
Quality Assurance:
MISSING and NO (value 0) were corrected to YES (value 1) if the participant had answered YES (Value 1) to one of the followup questions

CougPhle@NT2BLQ1

Cluster Text:
Hvis hoster daglig
English Cluster Text:
If daily coughing
Question Text:
Er hosten ledsaget av oppspytt?
English Question Text:

Do you usually bring up phlegm when coughing?

Study Part:
NT2BLQ1

Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:
HUNTBL

Also Used In:
NT1BLQ2, NT2Lu5Q, NT3BLQ2, NT4BLQ2, NT4EmigQ2, ST1EldQ2

Comment:
Missing recoded to No if answered No on CougDy

CougPhle3MoL2Y@NT2BLQ1

Cluster Text:
Hvis hoster daglig

English Cluster Text:
If daily coughing

Question Text:
Har du hatt hoste med oppspytt i minst 3 mnd sammenhengende i hvert av de to siste åra?

English Question Text:
Have you had a cough with phlegm for periods of at least 3 months during each of the last two years?

Study Part:
NT2BLQ1

Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:
HUNTBL

Also Used In:
NT2Lu5Q, NT3BLQ2, NT4BLQ2, NT4EmigQ2, ST1EldQ2

Comment:
Missing recoded to No if answered No on CougDy

WheeDysLYEd@NT2BLQ1

Question Text:
Har du hatt noe anfall med pipende eller tung pust siste 12 måneder?

English Question Text:
Have you had any kind of attack of wheezing or breathlessness during the last 12 months?

Study Part:
NT2BLQ1

Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Construction:
Base Variables:

Instrument:
HUNTBL

Comment:

Constructed; based on the original question WheeDysLY from the main questionnaire in HUNT2.

Contructed a new variable because of large variation in reported answerd between the main questionnaire and the lung interview regarding this variable. MISSING and NO (value 0) were correccted to YES (value 1) if the participant had answered YES (value 1) in one of the questions WheeLY and WheeDysLY from the lung questionnaire..

AstEv@NT2BLQ1

Question Text:

Har du eller har du hatt astma?

English Question Text:

Do you have or have you had asthma?

Study Part:

NT2BLQ1

Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:

NLQ

Also Used In:

CAPBL1SelfQ, NT2Lu1I, NT2Lu5Q, NT3BLQ1, NT3BLQNP, NT3LuI, NT4BLQ1, NT4EmigQ1, NT4LuIX, NT4LuQ, ST1BLQ, ST1EldQ1, YH1BLQ, YH1LuI, YH2BLQ, YH2LuI, YH3BLQ, YH3LuI

Quality Assurance:

MISSING or NO (value 0) were recoded to YES (value 1) if the participant had 1) answered the question age of onset of asthma from the same studypart and/or 2) answered YES (value 1) to the same question AstEv in the Lung Interview.

MISSING was set to NO (value 0) if the participant had answered NO to the same question AstEv in the Lung Interview and/or HUNT3 Q1.

AstMedEv@NT2BLQ1

Question Text:

Har du brukt eller bruker du astmamedisiner

English Question Text:

Do you use or have you used asthma medication?

Study Part:

NT2BLQ1

Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:

HUNTBL

Also Used In:

NT2Lu5Q, YH1LuI, YH2LuI, YH2LuM3, YH3LuI

Quality Assurance:

MISSING or NO (value 0) were corrected to YES (value 1) if the participant had answered YES (value 1) to one of the questions AstMedLY and AstMedPre from the Lung Interview.

MISSING was set to NO (value 0) if the participant had answered NO (value 0) to both of the questions AstMedLY and AstMedPre from the Lung Interview.

CarInfEv@NT2BLQ1

Cluster Text:
Har du, eller har du hatt?
English Cluster Text:
Do you have, or have you ever had?
Question Text:
Hjerteinfarkt
English Question Text:
Have you had or do you have myocardial infarction (heart attack)?
Study Part:
NT2BLQ1
Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:
HUNTBL
Also Used In:
NT1BLQ1, NT3BLQ1, NT3BLQNP, NT3CvdQ, NT3Dia2Q1, NT3Dia2Q2, NT3Dia2Q3, NT3Dia2Q4, NT3Lu2Q, NT4BLQ1, NT4EmigQ1, ST1BLQ, ST1EldQ1
Comment:
Chech of questionnaires if cardiac infarction before age 39.
Quality Assurance:
Answers were compared between the same questions in the baseline questionnaire (Q1) at HUNT1, HUNT2 and HUNT3 and corrected if possible.

Missing was set as No if the participant also had answered No to having the same disease in HUNT3.
Missing was corrected to Yes if the participant had answered Yes to the same disease in HUNT1.
No was corrected to Yes if the participant had answered Yes to the same disease in HUNT1 and HUNT3 or only in HUNT3 and reported age at first time having the disease before partAge in HUNT2.
A few Yes was corrected to No (value 0) if the participants had answered No to the same disease in both HUNT1 and HUNT3 and not reported the AGE first time having the disease in HUNT3.

CarAngEv@NT2BLQ1

Cluster Text:
Har du, eller har du hatt?
English Cluster Text:
Do you have, or have you ever had?
Question Text:
Angina pectoris (hjertekrampe)?
English Question Text:
Have you had or do you have angina pectoris (chest pain)
Study Part:
NT2BLQ1
Question Choices:

Nº	Text	English Text

0	Nei	No
1	Ja	Yes

Instrument:
HUNTBL
Also Used In:
NT1BLQ1, NT3BLQ1, NT3BLQNP, NT3CvdQ, NT3Dia2Q1, NT3Dia2Q2, NT3Dia2Q3, NT3Dia2Q4, NT4BLQ1, NT4EmigQ1, ST1BLQ, ST1EldQ1
Comment:
Chech of questionnaires if angina before age 39.
Quality Assurance:
Answers were compared between the same questions in the baseline questionnaire (Q1) at HUNT1, HUNT2 and HUNT3 and corrected if possible.

Missing was set as No if the participant also had answered No to having the same disease in HUNT3.
Missing was corrected to Yes if the participant had answered Yes to the same disease in HUNT1.
No was corrected to Yes if the participant had answered Yes to the same disease in HUNT1 and HUNT3 or only in HUNT3 and reported age at first time having the disease before partAge in HUNT2.
A few Yes was corrected to No (value 0) if the participants had answered No to the same disease in both HUNT1 and HUNT3 and not reported the AGE first time having the disease in HUNT3.

ApoplEv@NT2BLQ1

Cluster Text:
Har du, eller har du hatt?
English Cluster Text:
Do you have, or have you ever had?
Question Text:
Hjerneslag/hjerneblødning
English Question Text:
Have you had or do you have stroke/brain haemorrhage
Study Part:
NT2BLQ1
Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:
HUNTBL
Also Used In:
NT1BLQ1, NT3BLQ1, NT3BLQNP, NT3CvdQ, NT3Dia2Q1, NT3Dia2Q2, NT3Dia2Q3, NT3Dia2Q4, NT3Lu2Q, NT4BLQ1, NT4EmigQ1, NTDemDiag, ST1BLQ, ST1EldQ1
Comment:
Chech of questionnaires if apoplexia before age 39.
Quality Assurance:
Answers were compared between the same questions in the baseline questionnaire (Q1) at HUNT1, HUNT2 and HUNT3 and corrected if possible.

Missing was set as No if the participant also had answered No to having the same disease in HUNT3.
Missing was corrected to Yes if the participant had answered Yes to the same disease in HUNT1.
No was corrected to Yes if the participant had answered Yes to the same disease in HUNT1

and HUNT3 or only in HUNT3 and reported age at first time having the disease before partAge in HUNT2.
A few Yes was corrected to No (value 0) if the participants had answered No to the same disease in both HUNT1 and HUNT3 and not reported the AGE first time having the disease in HUNT3.

SmoCigDy@NT2BLQ1

Cluster Text:
Røyker du selv?
English Cluster Text:
Do you smoke?
Question Text:
Sigaretter daglig
English Question Text:
Cigarettes daily
Study Part:
NT2BLQ1
Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:
HUNTBL
Also Used In:
NT1BLQ2, NT3BLQ1, NT3BLQNP, YH1LuI, YH2LuI, YH2LuM3
Comment:
There are many inconsistencies regarding self-reported smoking status (never-smoker, ex-smoker or current smokers) between HUNT 1, 2 and 3. These are now by comparing answers from HUNT1-3, corrected if possible in the HUNT databank.
Quality Assurance:
Missing recoded to Yes if answered age of start, number of cigarettes but No to smoking cessation

Missing set as No (value 0) if
1) reported start age of daily smoking AND time since cessation.
2) reported previously smoking (SmoStat2=1) in HUNT3 AND cessation age was before participation in HUNT2.

Yes recoded to No if reported time since cessation.

SmoCigarDy@NT2BLQ1

Cluster Text:
Røyker du selv?
English Cluster Text:
Do you smoke?
Question Text:
Sigarer/sigarillos daglig
English Question Text:
Cigar/cigarillos daily
Study Part:
NT2BLQ1
Question Choices:

Nº	Text	English Text
0	Nei	No

1	Ja	Yes

Instrument:
HUNTBL
Also Used In:
NT1BLQ2
Quality Assurance:
Missing set as No (value 0) if
1) reported start age of daily smoking AND time since cessation.
2) reported previously smoking (SmoStat2=1) in HUNT3 AND cessation age was before participation in HUNT2.

SmoPipeDy@NT2BLQ1

Cluster Text:
Røyker du selv?
English Cluster Text:
Do you smoke?
Question Text:
Pipe daglig
English Question Text:
Pipe daily
Study Part:
NT2BLQ1
Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:
HUNTBL
Also Used In:
NT1BLQ2
Quality Assurance:
Missing set as No (value 0) if
1) reported start age of daily smoking AND time since cessation.
2) reported previously smoking (SmoStat2=1) in HUNT3 AND cessation age was before participation in HUNT2.

SmoDyNev@NT2BLQ1

Cluster Text:
Røyker du selv?
English Cluster Text:
Do you smoke?
Question Text:
Aldri røykt daglig
English Question Text:
Never smoked daily
Study Part:
NT2BLQ1
Question Choices:

Nº	Text	English Text
1	Aldri røykt daglig	Never smoked daily

Instrument:

HUNTBL

Quality Assurance:

Yes recoded to missing if
1) reported current daily tobacco smoking
2) reported daily or previous smoking in HUNT1
3) reported number of cigarettes daily and/or age of start or cessation of tobacco smoking.

SmoDyCesDu@NT2BLQ1

Cluster Text:

Hvis røykt daglig tidligere

English Cluster Text:

If ever smoked daily previously

Question Text:

Hvor lenge er det siden du sluttet?

English Question Text:

How long has it been since you stopped? (Number of years)

Study Part:

NT2BLQ1

Instrument:

HUNTBL

Also Used In:

NT3Lu2Q

Quality Assurance:

0 recoded to missing if a)missing on all other smoke variables, b)age at participation minus years since smoking cessation < 7

If missing and consistency between reported answers on cessation in HUNT1 and HUNT3; a value was calculated by using age of cessation from HUNT3 and age starting daily smoking from HUNT2.

SmoCigDyNEd@NT2BLQ1

Cluster Text:

Hvis røyker daglig nå eller har røykt daglig

English Cluster Text:

If currently daily or previously daily smoker

Question Text:

Hvor mange sigaretter røyker eller røykte du vanligvis daglig? Korrigert

English Question Text:

How many cigarettes do you or did you usually smoke daily? Edited

Study Part:

NT2BLQ1

Construction:

Base Variables:

Instrument:

HUNTBL

Comment:

A corrected variable from the original variable SmoCigDyN from HUNT2.

IF SmoStat@NT1BLQ2 =1 (exsmoker) AND SmoStat@NT2BLQ1 =1 (exsmoker) AND (Diff: SmoCigDyN@NT2BLQ1 - SmoCigDyN@NT1BLQ2 < 0)
Then SmoCigDyNEd@NT2BLQ1 = SmoCigDyN@NT1BLQ2

SmoDyAg@NT2BLQ1

Cluster Text:
Hvis røyker daglig nå eller har røykt daglig
English Cluster Text:
If currently daily or previously daily smoker
Question Text:
Hvor gammel var du da du begynte å røyke daglig?
English Question Text:
How old were you when you started smoking?
Study Part:
NT2BLQ1
Instrument:
HUNTBL
Also Used In:
NT1BLQ2, NT2Lu5Q, NT3BLQ1, NT3Lu2Q, NT4BLQ1, NT4EmigQ1, ST1BLQ, ST1EldQ1
Quality Assurance:
Some misunderstandings, instead of age some have reported Year or number of years since event.
Inconsistencies are checked, and if possible corrected based on probability and reported age in HUNT 1 and HUNT3.

Age < 6 yrs recoded to missing

MISSING was set equal to age of starting smoking from HUNT1 IF age of starting smoking from HUNT1 was approximatly equal to age of starting smoking from HUNT3.

SmoStat@NT2BLQ1

Question Text:
Røykestatus
English Question Text:
Smoking status
Study Part:
NT2BLQ1
Question Choices:

Nº	Text	English Text
0	Aldri røykt daglig	Never smoked daily
1	Tidligere daglig røyker	Ex smoker daily
2	Daglig røyker	Current smoker daily

Construction:
Base Variables:
Instrument:
HUNTBL
Also Used In:
HNTDem
Comment:
This variable is constructed from reported answers about current smoking status (SmoDyNev, SmoCigDy etc.) in HUNT2 and corrected regarding answers reported in HUNT1 and HUNT3.

HCOtMdLY@NT2BLQ2

Cluster Text:
Har du i løpet av de siste 12 månedene vært hos:
English Cluster Text:
During the last 12 months, have you visited:

Question Text:
Annen lege
English Question Text:
Another doctor
Study Part:
NT2BLQ2 (M1, M2, W1, W1, W2)
Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:
HUNTBL
Also Used In:
NT1BLQ1

HCHospMdLY@NT2BLQ2

Cluster Text:
Har du i løpet av de siste 12 månedene vært hos:
English Cluster Text:
During the last 12 months, have you visited:
Question Text:
Sykehuslege
English Question Text:
Doctor at hospital (without being hospitalized)
Study Part:
NT2BLQ2 (M1, M2, W1, W1, W2)
Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:
HUNTBL
Also Used In:
NT1BLQ1

HCGPConLY@NT2BLQ2

Cluster Text:
Har du i løpet av de siste 12 månedene vært hos:
English Cluster Text:
During the last 12 months, have you visited:
Question Text:
Allmennprakt.lege (kommunelege, privatpraktiserende lege, turnuskandidat)
English Question Text:
General practitioner (community doctor, private doctor, intern)
Study Part:
NT2BLQ2 (M1, M2, W1, W1, W2)
Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:
HUNTBL

Also Used In:
NT3BLQ1, NT3BLQNP, NT3PaChr2Q1, NT3PaChrQ1, NT3PaChrQ5, NT3PaChrQ6, NT3PaChrQ7, NT3PaChrQ8, NT4BLQ1, NT4EmigQ1, ST1BLQ, ST1EldQ1, YH1BLQ, YH2BLQ, YH3BLQ, YH4BLQ

HCCompaMdLY@NT2BLQ2

Cluster Text:
Har du i løpet av de siste 12 månedene vært hos:
English Cluster Text:
During the last 12 months, have you visited:
Question Text:
Bedriftslege
English Question Text:
Company physician
Study Part:
NT2BLQ2 (M1, W1, W1)
Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:
HUNTBL
Also Used In:
NT1BLQ1
Comment:
Only asked women and men age 20-69 years old

MedAstMo@NT2BLQ2

Cluster Text:
[Hvis daglig bruk av medisiner siste 12 måneder:] Angi hvor mange måneder du brukte følgende medisiner:
English Cluster Text:
If daily use of medication last 12 months; how many months have you used:
Question Text:
Astmamedisin
English Question Text:
Asthma medicine.
Study Part:
NT2BLQ2 (M1, M2, W1, W1, W2)
Instrument:
HUNTBL
Quality Assurance:
Answers given as zero (value 0) months were set as missing if the participant had answered No to daily medication use. They were not going to answere this question.

MedCarMo@NT2BLQ2

Cluster Text:
[Hvis daglig bruk av medisiner siste 12 måneder:] Angi hvor mange måneder du brukte følgende medisiner:
English Cluster Text:
If daily use of medication last 12 months; how many months have you used:
Question Text:
Hjertemedisin

English Question Text:
Heart medicine
Study Part:
NT2BLQ2 (M1, M2, W1, W1, W2)
Instrument:
HUNTBL
Comment:
(Not blood pressure medicine).
Quality Assurance:
Answers given as zero (value 0) months were set as missing if the participant had answered No to daily medication use. They were not going to answere this question.

PartDat@NT3BLQ1

Question Text:
Dato og tid deltagelse HUNT3 (Q1/M/I)
English Question Text:
Date and time participation HUNT3 Baseline (Q1/M/I)
Study Part:
NT3BLQ1
Instrument:
Not applicable
Also Used In:
CAPBL4Daw, CAPBL4DawPar#1, CAPBL4DawPar#2, CAPBL4DawTeac, CAPFU1SelfQ, NT1Dia2Q, NT1Dia2QoLQ, NT2Dia2M2, NT2Dia2Q, NT3CogFail2, NT3DenM, NT3Dia2Q1, NT3Dia2Q2, NT3Dia2Q3, NT3Dia2Q4, NT3PaChr2MI, NT3PaChr2Q1, NT3PaNecQ1, NT3PaNecQ2, NT3PaNecQ3, NT3PaNecQ4, NT3PaNecQ5, NT4OneHealtQDog, YH1BLQ, YH2BLQ, YH2LuM3
Comment:
The time component is 00:00:00 if unknown. For participants who didn't attend the screening station, their appointment dates and times are used.
Quality Assurance:
All participants have this variable, but some people have this variable without being participants.

PartAg@NT3BLQ1

Question Text:
Alder ved oppmøte screening
English Question Text:
Age at participation at screening
Study Part:
NT3BLQ1
Unit of Measurement:
year
Construction:
Base Variables: PartDat@NT3BLQ1
Instrument:
HUNTAg
Also Used In:
NT1Dia2MI1, NT3CogFail2, YH2LuM3

Healt@NT3BLQ1

Question Text:
Hvordan er helsa di nå?
English Question Text:

How is your health at the moment?

Study Part:
NT3BLQ1

Question Choices:

Nº	Text	English Text
1	Dårlig	Poor
2	Ikke helt god	Not so good
3	God	Good
4	Svært god	Very good

Instrument:
SWB

References:
bowling05just

Also Used In:
CAPBL1SelfQ, CAPFU1SelfQ, NT1BLQ1, NT1Dia2QoLQ, NT2BLQ1, NT2Lu5Q, NT3BLQNP, NT3DenQ, NT3Lu2Q, NT4BLQ1, NT4BmdQ, NT4Coe1Q, NT4EmigQ1, ST1BLQ, ST1EldQ1, YH1BLQ, YH2BLQ, YH3BLQ, YH4BLI, YH4BLQ

Comment:
The HUNT Study and other Norwegian epidemiological studies have used 4 answer choices in order to get answers either in positive or negative direction. The question also has been widely used internationally, see reference.

In the late 1970's, to increase the questions's discriminative ability, and because of the operation of "social desirability" or "optimism"bias (leading to most respondents to rate their health at the positive end of the scale), the developers of the SF-36 and others added a "very good"category in between the "excellent" and the "good" response choices. SF8 also includes a "very poor" category at the other end of the scale http://www.sf-36-org/demos/SF-8)

DisSomImp@NT3BLQ1

Cluster Text:
Hvis ja [langvarig lidelse som nedsetter funksjonevnen] Hvor mye vil du si at dine funksjoner er nedsatt?

English Cluster Text:
If Yes [longstanding illness that impairs your functioning] Would you describe your impairment as slight, moderate or severe?

Question Text:
Hemmet pga. kroppslig sykdom

English Question Text:
Impairment due to physical illness

Study Part:
NT3BLQ1

Question Choices:

Nº	Text	English Text
1	Litt nedsatt	Slight
2	Middels nedsatt	Moderate
3	Mye nedsatt	Severe

Instrument:
HUNTBL

Also Used In:
NT1BLQ1, NT2BLQ1, NT4BLQ1, NT4EmigQ1, ST1BLQ, ST1EldQ1, YH1BLQ, YH2BLQ, YH3BLQ

Quality Assurance:
Checked

DisChr@NT3BLQ1

Question Text:
Har du noen langvarig sykdom (minst 1 år), skade eller lidelse av fysisk eller psykisk art som nedsetter dine funksjoner i ditt daglige liv?
English Question Text:
Do you suffer from longstanding (at least 1 year) illness or injury of a physical or psychological nature that impairs your functioning in your daily life?
Study Part:
NT3BLQ1
Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:
HUNTBL
References:
bowling05just
Also Used In:
NT2BLQ1, NT3BLQNP, NT4BLQ1, NT4EmigQ1, ST1BLQ, ST1EldQ1
Comment:
This question is widely used as a single item measure of disability, see ref. It has, however, been shown to be sensitive to question wording and question order effects, to the mode of data collection, to the survey process and the sponsorship or contextual effects of the survey.
Quality Assurance:
If any value in any of the subsequent variables (MotImp, VisImp, HearImp, DisSomImp or DisPsycImp); value set to 1 (Yes) if missing or value 0 (No).

CarInfEv@NT3BLQ1

Cluster Text:
Har du, eller har du noen gang hatt, noen av disse sykdommene/plagene:
English Cluster Text:
Have you had or do you have any of the following diseases:
Question Text:
Hjerteinfarkt
English Question Text:
Myocardial infarction (heart attack)
Study Part:
NT3BLQ1
Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:
HUNTBL
Also Used In:
NT1BLQ1, NT2BLQ1, NT3BLQNP, NT3CvdQ, NT3Dia2Q1, NT3Dia2Q2, NT3Dia2Q3, NT3Dia2Q4, NT3Lu2Q, NT4BLQ1, NT4EmigQ1, ST1BLQ, ST1EldQ1
Quality Assurance:
Answers were compared between the same questions in the baseline questionnaire (Q1) at HUNT1, HUNT2 and HUNT3 and follow-up CVD-questionnaire after HUNT3. Answers were corrected if possible.

No was corrected to Yes if the participant had

1) reported Yes to the same disease in HUNT2 and reported age first time having the the disease in HUNT2 and/or HUNT3,
2) reported Yes at both HUNT2 and at CVD follow-up in HUNT3 or
3) reported Yes at the CVD follow-up in HUNT3 and reported age at first time having the disease.

A few Yes was corrected to No (value 0) if the participants had answered No to the same disease at the CVD follow-up and in HUNT1 and/or HUNT2 and not reported the age at first time having the disease in HUNT3.

CarAngEv@NT3BLQ1

Cluster Text:
Har du, eller har du noen gang hatt, noen av disse sykdommene/plagene:
English Cluster Text:
Have you had or do you have any of the following diseases:
Question Text:
Angina pectoris (hjertekrampe)
English Question Text:
Angina pectoris (chest pain)
Study Part:
NT3BLQ1
Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:
HUNTBL
Also Used In:
NT1BLQ1, NT2BLQ1, NT3BLQNP, NT3CvdQ, NT3Dia2Q1, NT3Dia2Q2, NT3Dia2Q3, NT3Dia2Q4, NT4BLQ1, NT4EmigQ1, ST1BLQ, ST1EldQ1
Quality Assurance:
Answers were compared between the same questions in the baseline questionnaire (Q1) at HUNT1, HUNT2 and HUNT3 and follow-up CVD-questionnaire after HUNT3. Answers were corrected if possible.

No was corrected to Yes if the participant had
1) reported Yes to the same disease in HUNT2 and reported age first time having the the disease in HUNT2 and/or HUNT3,
2) reported Yes at both HUNT2 and at CVD follow-up in HUNT3 or
3) reported Yes at the CVD follow-up in HUNT3 and reported age at first time having the disease.

A few Yes was corrected to No (value 0) if the participants had answered No to the same disease at the CVD follow-up and in HUNT1 and/or HUNT2 and not reported the age at first time having the disease in HUNT3.

CarFaiEv@NT3BLQ1

Cluster Text:
Har du, eller har du noen gang hatt, noen av disse sykdommene/plagene:
English Cluster Text:
Have you had or do you have any of the following diseases:
Question Text:
Hjertesvikt
English Question Text:

Heart failure

Study Part:

NT3BLQ1

Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:

HUNTBL

Also Used In:

NT3Dia2Q1, NT3Dia2Q2, NT3Dia2Q3, NT3Dia2Q4, NT4BLQ1, NT4EmigQ1, ST1BLQ, ST1EldQ1

Quality Assurance:

IF missing set equal to answers given to the question "doctor said that you have heart failure" from the follow-up CVD-questionnire in HUNT3.

CarDisOtEv@NT3BLQ1

Cluster Text:

Har du, eller har du noen gang hatt, noen av disse sykdommene/plagene:

English Cluster Text:

Have you had or do you have any of the following diseases:

Question Text:

Annen hjertesykdom

English Question Text:

Other heart disease

Study Part:

NT3BLQ1

Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:

HUNTBL

ApoplEv@NT3BLQ1

Cluster Text:

Har du, eller har du noen gang hatt, noen av disse sykdommene/plagene:

English Cluster Text:

Have you had or do you have any of the following diseases:

Question Text:

Hjerneslag/hjerneblødning

English Question Text:

Stroke/brain haemorrhage

Study Part:

NT3BLQ1

Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:

HUNTBL

Also Used In:

NT1BLQ1, NT2BLQ1, NT3BLQNP, NT3CvdQ, NT3Dia2Q1, NT3Dia2Q2, NT3Dia2Q3, NT3Dia2Q4, NT3Lu2Q, NT4BLQ1, NT4EmigQ1, NTDemDiag, ST1BLQ, ST1EldQ1

Quality Assurance:

Answers were compared between the same questions in the baseline questionnaire (Q1) at HUNT1, HUNT2 and HUNT3 and follow-up CVD-questionnaire after HUNT3. Answers were corrected if possible.

No was corrected to Yes if the participant had
1) reported Yes to the same disease in HUNT2 and reported age first time having the the disease in HUNT2 and/or HUNT3,
2) reported Yes at both HUNT2 and at CVD follow-up in HUNT3 or
3) reported Yes at the CVD follow-up in HUNT3 and reported age at first time having the disease.

A few Yes was corrected to No (value 0) if the participants had answered No to the same disease at the CVD follow-up and in HUNT1 and/or HUNT2 and not reported the age at first time having the disease in HUNT3.

AstEv@NT3BLQ1

Cluster Text:

Har du, eller har du noen gang hatt, noen av disse sykdommene/plagene:

English Cluster Text:

Have you had or do you have any of the following diseases:

Question Text:

Astma

English Question Text:

Asthma

Study Part:

NT3BLQ1

Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:

NLQ

Also Used In:

CAPBL1SelfQ, NT2BLQ1, NT2Lu1I, NT2Lu5Q, NT3BLQNP, NT3LuI, NT4BLQ1, NT4EmigQ1, NT4LuIX, NT4LuQ, ST1BLQ, ST1EldQ1, YH1BLQ, YH1LuI, YH2BLQ, YH2LuI, YH3BLQ, YH3LuI

Quality Assurance:

NO (value 0) was corrected to YES if the participant had answered; 1) on the question AstOnAge from the same questionnaire or 2) YES to the question AstEv from the HUNT3 lung interview or 3) YES to the AstEv togheter with AstOnAg from HUNT2.

MISSING was set to NO (value 0) if the participant had answered NO (value 0) to the same question AstEv in the HUNT3 lung interview.

CopdEv@NT3BLQ1

Cluster Text:

Har du, eller har du noen gang hatt, noen av disse sykdommene/plagene:

English Cluster Text:

Have you had or do you have any of the following diseases:

Question Text:

Kronisk bronkitt, emfysem, KOLS

English Question Text:
Chronic bronchitis, emphysema or COPD
Study Part:
NT3BLQ1
Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:
HUNTBL
Also Used In:
NT3BLQNP, NT4BLQ1, NT4EmigQ1, ST1BLQ, ST1EldQ1
Quality Assurance:
MISSING or NO (value 0) were corrected to YES (value 1) if the participant had answered YES (value 1) to diagnosed as having chronic bronchitis, emphysema or COPD by a doctor from the HUNT3 lung interview

SmoNev@NT3BLQ1

Cluster Text:
Røyker du selv?
English Cluster Text:
Do you smoke?
Question Text:
Nei, jeg har aldri røykt
English Question Text:
No, I have never smoked
Study Part:
NT3BLQ1
Question Choices:

Nº	Text	English Text
1	Nei, jeg har aldri røykt	No, I have never smoked

Instrument:
HUNTBL
Also Used In:
NT3BLQNP, NT4BLQ1, NT4EmigQ1, ST1BLQ, ST1EldQ1, YH3BLQ
Comment:
There are many inconsistencies regarding self-reported smoking status (never-smoker, ex-smoker or current smokers) between HUNT 1, 2 and 3.
Quality Assurance:
Yes recoded to missing if
1) reported current or previous daily and occasionally tobacco smoking in both HUNT1, HUNT2 and HUNT3
2) reported number of cigarettes daily/monthly and/or age of start or cessation of tobacco smoking.

SmoPre@NT3BLQ1

Cluster Text:
Røyker du selv?
English Cluster Text:
Do you smoke?
Question Text:
Nei, jeg har sluttet å røyke

English Question Text:
No, I have quit smoking
Study Part:
NT3BLQ1
Question Choices:

Nº	Text	English Text
1	Nei, jeg har sluttet å røyke	No, I quit smoking

Instrument:
HUNTBL
Also Used In:
NT2BLQ1, NT3BLQNP, NT3DiaVisQ, NT4BLQ1, NT4EmigQ1, ST1BLQ, ST1EldQ1
Quality Assurance:
Missing set to Yes if
1) reported smoke cessation age
2) reported previously smoking in HUNT1 and/or HUNT2

Yes was recoded to missing if reported current daily or occasionally smoking and not answered on cessation age.

SmoCigOc@NT3BLQ1

Cluster Text:
Røyker du selv?
English Cluster Text:
Do you smoke?
Question Text:
Ja, sigaretter av og til
English Question Text:
Yes, cigarettes occasionally (parties/vacation, not daily)
Study Part:
NT3BLQ1
Question Choices:

Nº	Text	English Text
1	Ja, sigaretter av og til	Yes, cigarettes occasionally (parties/vacation, not daily)

Instrument:
HUNTBL
Also Used In:
NT3BLQNP
Quality Assurance:
Yes recoded to missing if answered Yes to previous smoking ans reported cessation age.

SmoCigarPipeOc@NT3BLQ1

Cluster Text:
Røyker du selv?
English Cluster Text:
Do you smoke?
Question Text:
Ja, sigar/sigarillos/pipe av og til
English Question Text:
Yes, cigars/cigarillos/pipe occasionally
Study Part:
NT3BLQ1
Question Choices:

Nº	Text	English Text

1	Ja, sigarer/sigarillos/pipe av og til	Yes, cigars/cigarillos/pipe occasionally

Instrument:
HUNTBL
Quality Assurance:
Yes recoded to missing if answered Yes to previous smoking ans reported cessation age.

SmoCigDy@NT3BLQ1

Cluster Text:
Røyker du selv?
English Cluster Text:
Do you smoke?
Question Text:
Ja, sigaretter daglig
English Question Text:
Yes, cigarettes daily
Study Part:
NT3BLQ1
Question Choices:

Nº	Text	English Text
1	Ja, sigaretter daglig	Yes, cigarettes daily

Instrument:
HUNTBL
Also Used In:
NT1BLQ2, NT2BLQ1, NT3BLQNP, YH1LuI, YH2LuI, YH2LuM3
Quality Assurance:
Yes recoded to missing if answered Yes to previous smoking ans reported cessation age.

SmoCigarPipeDy@NT3BLQ1

Cluster Text:
Røyker du selv?
English Cluster Text:
Do you smoke?
Question Text:
Ja, sigarer/sigarillos/pipe daglig?
English Question Text:
Yes, cigars/cigarillos/pipe daily
Study Part:
NT3BLQ1
Question Choices:

Nº	Text	English Text
1	Ja, sigarer/sigarillos/pipe daglig	Yes, cigars/cigarillos/pipe daily

Instrument:
HUNTBL
Quality Assurance:
Yes recoded to missing if answered Yes to previous smoking and reported cessation age.

SmoStat@NT3BLQ1

Question Text:
Røykestatus
English Question Text:
Smoking status
Study Part:

NT3BLQ1

Question Choices:

Nº	Text	English Text
0	Aldri røykt	Never smoked
1	Tidligere røyker	Ex smoker
2	Daglig røyker	Current smoker
3	Røyker av og til	Occasionally smoker

Construction:

Base Variables:

Instrument:

HUNTBL

Also Used In:

HNTDem

Comment:

This variable is constructed from reported answers about current smoking status (SmoStat1-5) in HUNT3 and corrected regarding answers reported in HUNT1 and HUNT2.

SmoCigDyN@NT3BLQ1

Cluster Text:

Hvis nå eller tidligere daglig røyking

English Cluster Text:

If now or earlier daily smoking

Question Text:

Hvor mange sigaretter røyker eller røykte du vanligvis daglig?

English Question Text:

How many cigarettes do/did you usually smoke daily?

Study Part:

NT3BLQ1

Instrument:

HUNTBL

Also Used In:

CAPBL1SelfQ, CAPBL4Daw, CAPFU1SelfQ, NT1BLQ2, NT2BLQ1, NT2Lu4M, NT2Lu5Q, NT3Dia2Q1, NT3Dia2Q2, NT3Dia2Q3, NT3Dia2Q4, NT3DiaVisQ, NT3Lu2Q, NT4BLQ1, NT4EmigQ1, ST1BLQ, ST1EldQ1, YH3BLQ, YH4BLQ

Quality Assurance:

Checked for outliers. Reported 0 sigarettes were set as missing.

SmoDyAg@NT3BLQ1

Cluster Text:

Hvis nå eller tidligere daglig røyking

English Cluster Text:

If now or earlier daily smoking

Question Text:

Hvor gammel var du da du begynte å røyke daglig?

English Question Text:

How old were you when you started smoking daily?

Study Part:

NT3BLQ1

Instrument:

HUNTBL

Also Used In:

NT1BLQ2, NT2BLQ1, NT2Lu5Q, NT3Lu2Q, NT4BLQ1, NT4EmigQ1, ST1BLQ, ST1EldQ1

Quality Assurance:

Some misunderstandings, instead of age some have reported Year or number of years since event.
Inconsistencies are checked, and if possible corrected based on probability and reported age in HUNT1 and HUNT2.

MISSING was set equal to age of starting smoking from HUNT1 IF age of starting smoking from HUNT1 was approximatly equal to age of starting smoking from HUNT2.

SmoDyCesAg@NT3BLQ1

Cluster Text:
Hvis nå eller tidligere daglig røyking
English Cluster Text:
If now or earlier daily smoking
Question Text:
Hvis du tidligere har røykt daglig, hvor gammel var du da du sluttet?
English Question Text:
If you previously smoked daily; how old were you when you quit smoking?
Study Part:
NT3BLQ1
Instrument:
HUNTBL
Also Used In:
NT2Lu5Q, NT4BLQ1, NT4EmigQ1, ST1BLQ, ST1EldQ1
Quality Assurance:
Checked for outliers. There are some erros regarding reported age. Some have reported the correct age, some the year, and some number of year since event. Inconsistencies are checked and if possible corrected.

SmoCigDyNEd@NT3BLQ1

Question Text:
Hvor mange sigaretter røyker eller røykte du vanligvis daglig? Korrigert
English Question Text:
How many cigarettes do/did you usually smoke daily? Edited
Study Part:
NT3BLQ1
Construction:
Base Variables:
Instrument:
HUNTBL
Comment:
A corrected variable from the original variable SmoCigDyN from HUNT3.

IF SmoStat@NT2BLQ1 =1 (exsmoker) AND SmoStat@NT3BLQ1 =1 (exsmoker) AND (Diff: SmoCigDyN@NT3BLQ1 - SmoCigDyNEd@NT2BLQ1 < 0)
Then SmoCigDyNEd@NT3BLQ1 = SmoCigDyNEd@NT2BLQ1

Missing=SmoCigMyN/30 IF SmoCigMyN>15 AND Smostat=3 (daily smoker) OR SmoStat=1 (Exsmoker) AND answered on the variablesSmoDyAg ang SmoDyCesAg

Quality Assurance:
Checked for outliers

SmoDyCesDu@NT3BLQ1

Question Text:
Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet?
English Question Text:
If you previously smoked, how long has it been since you stopped?
Study Part:
NT3BLQ1
Construction:
Constructed in order to compare with original variable from NT2BLQ1 'If you previously smoked, how long has it been since you stopped?'
Base Variables: PartAg@NT3BLQ1, SmoDyCesAg@NT3BLQ1
Instrument:
HUNTBL
Also Used In:
NT2BLQ1, NT3Lu2Q
Comment:
Constructed in order to compare with original variable from NT2BLQ1 'If you previously smoked, how long has it been since you stopped?'

Educ@NT2BLQ1

Question Text:
Hvilken utdanning er den høyeste du har fullført?
English Question Text:
What is your highest level of education?
Study Part:
NT2BLQ1
Question Choices:

Nº	Text	English Text
1	Grunnskole 7-10 år, framhaldsskole, folkehøgskole	Primary school 7-10 years, continuation school, folk high school
2	Realskole, middelskole, yrkesskole 1-2 årig vgs	High school, intermediate school, vocational school, 1-2 years high school
3	Artium, øk.gymnas, allmennfaglig retning i vgs	University qualifying examination, junior college, A levels
4	Høgskole/universitet, mindre enn 4 år	University or other post-secondary education, less than 4 years
5	Høgskole/universitet, 4 år eller mer	University/college, 4 years or more

Instrument:
HUNTBL
Also Used In:
CAPFU1SelfQ, HNTDem, NT1BLQ2, NT3DenQ, NT3Dia2Q1, NT3Dia2Q2, NT3Dia2Q3, NT3Dia2Q4, NT3Lu2Q, NT3PaChr2Q1, NT4BLQ1, NT4EmigQ1, ST1BLQ, ST1EldQ1, YH1BLQ, YH2BLQ, YH3BLQ, YH4BLQ
Comment:
For details on differences in Education systems, see file Education system in England, Norway and USA.

SatLif@NT3BLQ1

Question Text:
Når du tenker på hvordan du har det for tida, er du stort sett fornøyd med tilværelsen eller er du stort sett misfornøyd?
English Question Text:
Thinking about your life at the moment, would you say that you by and large are satisfied with life, or are you mostly dissatisfied?

Study Part:
NT3BLQ1
Question Choices:

Nº	Text	English Text
1	Svært fornøyd	Very satisfied
2	Meget fornøyd	Satisfied
3	Ganske fornøyd	Somewhat satisfied
4	Både/og	Neither satisfied nor dissatisfied
5	Nokså misfornøyd	Somewhat dissatisfied
6	Meget misfornøyd	Dissatisfied
7	Svært misfornøyd	Very dissatisfied

Instrument:
SWB
References:
bowling05just, moum90hypertension, salek99compendium
Also Used In:
CAPBL1SelfQ, CAPFU1SelfQ, NT1BLQ1, NT1BLQ2, NT1Dia2QoLQ, NT2BLQ1, NT4BLQ1, NT4EmigQ1, ST1BLQ, ST1EldQ1, YH1BLQ, YH2BLQ, YH3BLQ
Comment:
General measure of life quality, used in many national and international studies

SatLif@NT2BLQ1

Question Text:
Når du tenker på hvordan du har det for tida, er du stort sett fornøyd med tilværelsen eller er du stort sett misfornøyd?
English Question Text:
Thinking about your life at the moment, would you say that you by and large are satisfied with life, or are you mostly dissatisfied?
Study Part:
NT2BLQ1
Question Choices:

Nº	Text	English Text
1	Svært fornøyd	Very satisfied
2	Meget fornøyd	Satisfied
3	Ganske fornøyd	Somewhat satisfied
4	Både og	Neither satisfied nor dissatisfied
5	Nokså misfornøyd	Somewhat dissatisfied
6	Meget misfornøyd	Dissatisfied
7	Svært misfornøyd	Very dissatisfied

Instrument:
SWB
Also Used In:
CAPBL1SelfQ, CAPFU1SelfQ, NT1BLQ1, NT1BLQ2, NT1Dia2QoLQ, NT3BLQ1, NT4BLQ1, NT4EmigQ1, ST1BLQ, ST1EldQ1, YH1BLQ, YH2BLQ, YH3BLQ
Comment:
General measure of life quality, used in many national and international studies

WorRetir@NT2BLQ1

Cluster Text:
Hva slags arbeidssituasjon har du nå?
English Cluster Text:

What is your current employment status?

Question Text:

Pensjonist/trygdet

English Question Text:

Retired / on Social Security

Study Part:

NT2BLQ1

Question Choices:

Nº	Text	English Text
1	Ja	Yes

Instrument:

HUNTBL

Also Used In:

NT3Dia2Q1, NT3Dia2Q2, NT3Dia2Q3, NT3Dia2Q4, NT3PaNecQ1, NT3PaNecQ2, NT3PaNecQ3, NT3PaNecQ4, NT3PaNecQ5

Quality Assurance:

Deleted answers if reported beeing paid employee or self-emploed, working >=37 hours a week and partAge<67 years old.

Missing was set equal to 1 (Yes) if partAge>= 67 years old (Age of retirement in Norway)

WorEducMil@NT2BLQ1

Cluster Text:

Hva slags arbeidssituasjon har du nå?

English Cluster Text:

What is your current employment status?

Question Text:

Utdanning, militærtjeneste

English Question Text:

Student, military service

Study Part:

NT2BLQ1

Question Choices:

Nº	Text	English Text
1	Ja	Yes

Instrument:

HUNTBL

Translation Comment:

Norway has a mandatory military service of one year for males.

WorUnemp@NT2BLQ1

Cluster Text:

Hva slags arbeidssituasjon har du nå?

English Cluster Text:

What is your current employment status?

Question Text:

Arbeidsledig, permittert

English Question Text:

Unemployed, laid off

Study Part:

NT2BLQ1

Question Choices:

Nº	Text	English Text

1	Ja	Yes

Instrument:
HUNTBL
Also Used In:
NT3PaNecQ1, NT3PaNecQ2, NT3PaNecQ3, NT3PaNecQ4, NT3PaNecQ5
Quality Assurance:
Deleted answers if:
1) reported working (paid employee or self-emploed) and working >=37 hours a week (paid).
2) reported beeing retired and PartAg>=67 (Age of retirement in Norway).

WorHome@NT2BLQ1

Cluster Text:
Hva slags arbeidssituasjon har du nå?
English Cluster Text:
What is your current employment status?
Question Text:
Heltids husarbeid
English Question Text:
Full-time housework
Study Part:
NT2BLQ1
Question Choices:

Nº	Text	English Text
1	Ja	Yes

Instrument:
HUNTBL
Also Used In:
NT2HearQ1, NT3BLI, NT4BLI

WorTrad@NT2BLQ1

Cluster Text:
Hva slags arbeidssituasjon har du nå?
English Cluster Text:
What is your current employment status?
Question Text:
Selvstendig næringsdrivende
English Question Text:
Self-employed
Study Part:
NT2BLQ1
Question Choices:

Nº	Text	English Text
1	Ja	Yes

Instrument:
HUNTBL
Also Used In:
NT2BLQ2

WorPaid@NT2BLQ1

Cluster Text:
Hva slags arbeidssituasjon har du nå?
English Cluster Text:

What is your current employment status?

Question Text:

Lønnet arbeid

English Question Text:

Paid work

Study Part:

NT2BLQ1

Question Choices:

Nº	Text	English Text
1	Ja	Yes

Instrument:

HUNTBL

Also Used In:

NT1BLQ2, NT3PaChr2Q1, NT3PaChrQ1, NT3PaChrQ5, NT3PaChrQ6, NT3PaChrQ7, NT3PaChrQ8, YH4BLQ

Quality Assurance:

Missing was set as 1 (Yes) if reportet working >=37 hours a week (paid) and partAge<67 years old.

Deleted answers if reported working zero hours a week AND reported beeing retired, student/military service and/or having full-time housework.

SickAbsLY@NT3BLI

Question Text:

Har du i løpet av de siste 12 måneder hatt sykefravær?

English Question Text:

Have you been on sick leave in the past 12 months?

Study Part:

NT3BLI

Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Also Used In:

NT3Lu2Q

Quality Assurance:

Missing and No answeres corrected to Yes IF the participants had answered Yes to one of the following questions about self-certified or medical certificate sick leave. Missing was set to No IF the participants had answered No to both of the following questions.

No (value 0) answers were set as missing IF the participants had answered No (value 0) to the question WorCu (currently working). These participants were not going to answer this question.

SickAbsMdLY@NT3BLI

Question Text:

Hvis sykefravær siste 12 måneder; Sykmelding fra lege?

English Question Text:

Sick leave medical certificate from doctor

Study Part:

NT3BLI

Question Choices:

Nº	Text	English Text

0	Nei	No
1	Ja	Yes

Also Used In:
NT2BLQ2
Quality Assurance:
No (value 0) answeres was set as missing IF the participants had also answered No to self-certified sick leave AND Yes to have taken sick leave the last year.

No (value 0) answers were set as missing IF the participants had answered No (value 0) to the question WorCu (currently working). These participants were not going to answer this question

SickAbsScLY@NT3BLI

Question Text:
Hvis sykefravær siste 12 måneder; Egenmelding?
English Question Text:
Sick leave without medical certificate from doctor
Study Part:
NT3BLI
Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Also Used In:
NT2BLQ2
Quality Assurance:
No (value 0) answeres was set as missing IF the participants had answered also No to medical certificate sick leave AND Yes to have taken sick leave the last year.

No (value 0) answers were set as missing IF the participants had answered No (value 0) to the question WorCu (currently working). These participants were not going to answer this question

SickAbsDu@NT2BLQ2

Cluster Text:
Hvis har inntektsgivende arbeid eller heltids husarbeid
English Cluster Text:
If having gainful employment or fulltime housework
Question Text:
Hvor lenge sykefravær tilsammen
English Question Text:
How long have you been on sick leave altogether?
Study Part:
NT2BLQ2 (M1, W1, W1)
Question Choices:

Nº	Text	English Text
1	2 uker eller mindre	2 weeks or less
2	2-8 uker	2-8 weeks
3	Mer enn 8 uker	More than 8 weeks

Instrument:
HUNTBL
Quality Assurance:

Deleted answers if reported having not been gainfully employed

SickAbsScLY@NT2BLQ2

Cluster Text:
Hvis har inntektsgivende arbeid eller heltids husarbeid
English Cluster Text:
If having gainful employment or fulltime housework
Question Text:
Har du i løpet av de siste 12 månedene hatt sykefravær med egenmelding?
English Question Text:
During the last 12 months, have you been on sick leave without a medical certificate?
Study Part:
NT2BLQ2 (M1, W1, W1)
Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:
HUNTBL
Also Used In:
NT3BLI
Quality Assurance:
Deleted answers if reported having not been gainfully employed

SickAbsMdLY@NT2BLQ2

Cluster Text:
Hvis har inntektsgivende arbeid eller heltids husarbeid
English Cluster Text:
If having gainful employment or fulltime housework
Question Text:
Har du i løpet av de siste 12 månedene hatt sykefravær med sykmelding fra lege?
English Question Text:
During the last 12 months, have you been on sick leave with a medical certificate?
Study Part:
NT2BLQ2 (M1, W1, W1)
Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:
HUNTBL
Also Used In:
NT3BLI
Quality Assurance:
Deleted answers if reported having not been gainfully employed

WorCu@NT3BLI

Question Text:
Er du yrkesaktiv?
English Question Text:
Do you have a job?
Study Part:

NT3BLI

Question Choices:

Nº	Text	English Text
0	Nei	No
1	Ja	Yes

Instrument:

HUNTBL

Also Used In:

NT1BLQ1, NT1BLQ2, NT3Lu2Q, NT4BLI, NT4EmigQ1, ST1BLQ

Quality Assurance:

Missing set as No (Value 0) IF answered Yes or No (Value 0 or 1) to the question WorPre (Previously working).
Missing or No (value 0) corrected to Yes (value 1) IF answered working part-time to the question WorTmFull AND Missing or answered No to beeing a student (WorStudCur).

Study Parts

The *Responded* number counts the people who participated in the study part. The *Invited* number (if present) counts the people who were invited to participate, including those who participated despite not fulfilling any selection criteria — probably due to some error.

NT2BLQ1

Name:

HUNT2 Questionnaire 1

Participation:

Invited: 93898, Responded: 65228 (69 %)

Selection:

- HUNT 2 invitees. Basically, this is all Nord-Trøndelag residents aged 20 or more at the time.

References:

holmen03nord

NT2BLQ2

Name:

HUNT2 Questionnaire 2

Variants:

Variant	Description
M1	Men 20--69
M2	Men 70+
W1	Women 20--69
W2	Women 70+

Participation:

Invited: 65451, Responded: 55452 (85 %)

Selection:

- HUNT2 Measurements participants

NT3BLI

Name:

HUNT3 Interview

Participation:

Invited: 93860, Responded: 50558 (54 %)

Selection:

- HUNT 3 invitees. Basically, this is all Nord-Trøndelag residents aged 20 or more at the time.

References:

hunt

NT3BLQ1

Name:

HUNT3 Questionnaire 1

Participation:

Invited: 93860, Responded: 50800 (54 %)

Selection:

- HUNT 3 invitees. Basically, this is all Nord-Trøndelag residents aged 20 or more at the time.

References:

krokstad13Cohort

Instruments

-

Name:

Manual processing

HUNTAg

Name:

HUNT Age

Description:

Age is computed as the number of days between birth (as registered by the Norwegian National Registry) and the date in question, divided by 365.2425 (the average number of days per year in the Gregorian calendar), rounded to one decimal. Note that this means that people are considered (say) 40.0 years old as early as 18 days before their 40th birthday.

HUNTBL

Name:

Inhouse made question for Q1/Q2 questionnaire in HUNT

Description:

This is an inhouse question made for the baseline questionnaires, Q1 and Q2 used in the HUNT surveys. For questions used in more than one survey, the question text may have been modified for improvement from the first survey to the next.

Some questions my also have been used in other health surveys in Norway, like:
-The Tromsø Study (managed by the University of Tromsø)
- Oslo Health Study (HUBRO, 2000-2001, managed by Norwegian Institute of Public Health)
- The Cardiovascular diesase prevention program (first started in 1972) organized by earlier National Mass Radiography Service (1943-1985) then the Norwegian Health investigation

(1985-2001) and now the Norwegian Institute of Public Health. One of the two questionnaires was used in the cardiovascular disease study performed in three Norwegian counties, Finnmark, Sogn og Fjordane and Oppland (1974-1676) and the second questionnaire was used in the so-called "Age-40 programme" (started in 1983 in Oslo and was nation-wide in 1993).

NLQ

Name:

Norwegian Lung Questionnaire

Description:

The questions were developed for the Lung Study in Bergen 1992-93. Some of the questions were included also in ECRHS, and for these the latter is reported as instrument.

SWB

Name:

Subjective/psychological well-being

Description:

Six items are included in the HUNT1 and HUNT2 surveys designed to tap overall subjective/psychological/emotional well-being. The subjective well-being scale includes questions regarding subjective health and life satisfaction, vigor and cheerfulness, and use of tranquilizers. The items were selected from questionnaires used in previous Norwegian studies (Moum 1983; Sørensen 1987) and have been shown valid in analyses of data from the HUNT1 survey (Moum et.al 1990a, b). Issues of psychometric qualities, reliability and validity for the six-item measure of SWB are addressed in Moum, Næss, Sørensen, Tambs and Holmen (1990a) and Moum (1988). A three item version of the subjective well-being scale is also used in a prospective study of a group of adolescents based on data from the Young-HUNT1 and Young-HUNT2 surveys (Størksen et.al 2005).

A thorough literature review on subjective well-being considering the three areas measurement, causal factors and theory are presented in Diener (2009).

References:

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hunt

HUNT 3 Interview Procedure..

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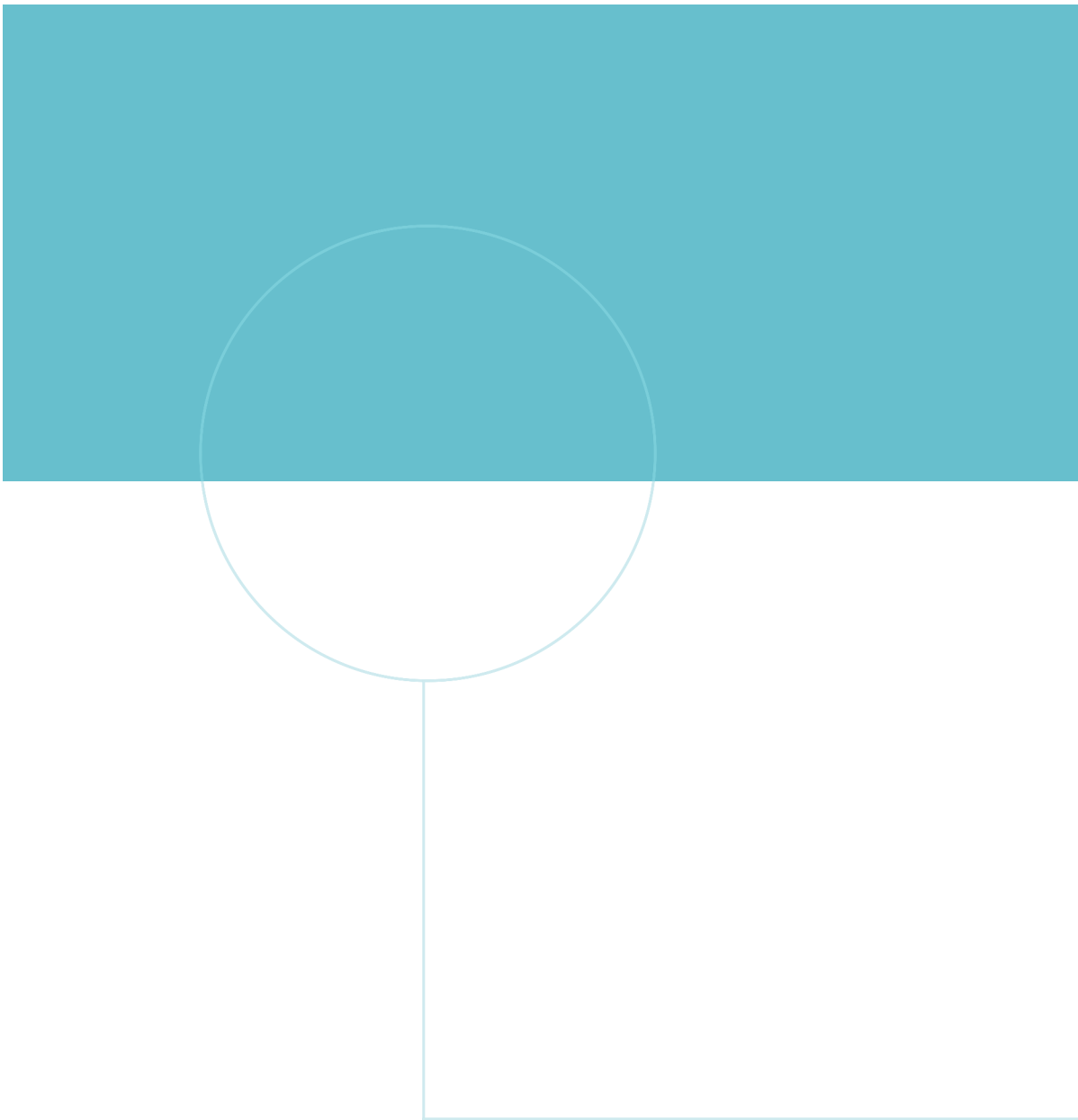

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