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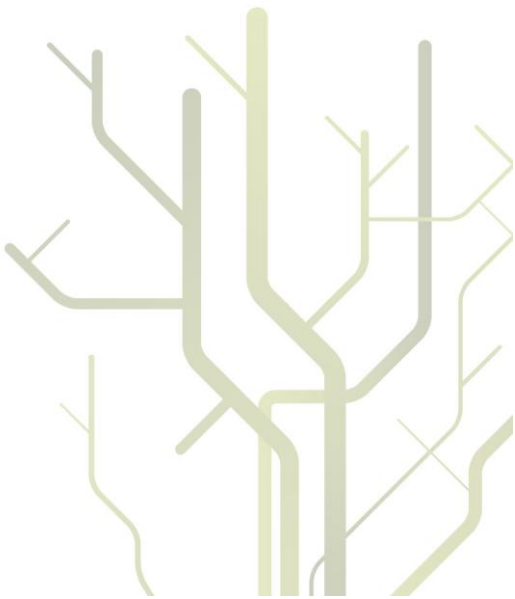
Staphylococcus aureus nasal carriage – Interplay between host, microbe and the environment.

-The Tromsø Staph and Skin Study

Karina Olsen

A dissertation for the degree of
Philosophiae Doctor

Tromsø 2013



Staphylococcus aureus nasal carriage – Interplay between host, microbe and the environment.

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PREFACE: FROM MICROBIOLOGY AND INFECTION CONTROL TO EPIDEMIOLOGICAL RESEARCH

During my more than 20 years as an MD in clinical medicine, infectious diseases, microbiology and infection control, I have met numerous patients with nosocomial- and community acquired infections with *Staphylococcus aureus*. For some patients, these infections caused severe diseases like deep surgical site infections, catheter related infections and septicemias. For others, however, colonization with methicillin-resistant *S. aureus* (MRSA) caused serious trouble for those in need of treatment from medical health services or for those working as a healthcare professional. This fact developed my interest for host susceptibility factors for *S. aureus* carriage and my main supervisor Anne-Sofie Furberg introduced me to this field.

Most of the patients with *S. aureus* infections or MRSA colonization were living in the community of Tromsø, and the Tromsø Study had for years explored the health of its inhabitants. The Tromsø 6 survey was in the planning phase when I prepared my PhD project. It is a short distance from the University Hospital in Tromsø to the epidemiological setting at the Department of Community Medicine where I met Anne-Sofie Furberg. She had a background both in microbiology, epidemiology and cancer research. During these last three years, I have had the privilege to more carefully investigate the interesting relationships between different host susceptibility factors like lifestyle, and metabolic and hormonal profile, and *S. aureus* nasal carriage.

ACKNOWLEDGEMENTS

This research was done at the Department of Community Medicine and Department of Medical Biology, Faculty of Health Sciences, University of Tromsø and at the Department of Microbiology and Infection Control, University Hospital of North Norway during October 2007- pt. The financial support by grants from the Research Council of Norway, Northern Norway Regional Health Authority (Helse Nord RHF) and the Odd Berg Group Medical Research Fund is highly acknowledged.

I am very grateful that I was given the opportunity to join the Tromsø Staph and Skin Study group and to perform the studies described in the thesis.

First and foremost, I would like to thank my main supervisor and mentor, Anne-Sofie Furberg. She has been an excellent teacher, always attentive and interested in my work, and always responding friendly and constructively to my sometimes less coherent thoughts and ideas. I appreciate her patience and for sharing her significant knowledge concerning aspects of microbiology and in particular *S. aureus* carriage, epidemiology and statistical methods. Her efficiency and sense of structure is impressing and inspiring, and has been essential along the way.

I will thank Gunnar Skov Simonsen, director at the Department of Microbiology and Infection Control, and one of my co-supervisors, for giving me the opportunity, for letting me in to this fascinating world of host-microbe interactions for *S. aureus* carriage, and for his significant knowledge concerning microbiology and *S. aureus* in particular.

Furthermore, I want to thank Inger Thune, my second co-supervisor, for her enthusiasm and critical guidance, and for her sharing of her significant experience and knowledge and for heaps of encouragements along the way.

I will thank Johanna Ericson Sollid for her critical guidance on the microbiological- and host-microbe interaction aspects and also, Mona Johannessen for her contribution on immunological aspects facilitating *S. aureus* carriage.

I want to thank Maria Sangvik, my fellow PhD candidate, for her contribution in *spa* typing the *S. aureus* isolates and for her discussions regarding bacterial factors facilitating *S. aureus* colonization. Tom Wilsgaard is thanked for both brief and more extensive discussions regarding statistical problems. I want to thank my other co-authors for good collaboration. My colleagues and staff at the Department of Microbiology and Infection Control are thanked for taking on a larger share of work during my period of absence.

The technical staff at the Department of Community Medicine and The Norwegian Reference Centre for Detection of Antimicrobial Resistance (K-Res) is thanked for their contribution in data collection and the analysis of swab cultures.

The warmest thanks to my sisters Sigrid, Anna and Elisabeth for their interest and commitment and my nearest friends for continuous support during the ups and downs throughout the project!

Karina

February, 2013

CONTENTS

ENGLISH SUMMARY

Staphylococcus aureus (*S. aureus*) can act both as a human commensal that persistently colonizes 20–30% of the adult population, and as an invasive pathogen. *S. aureus* nasal carriage often precedes infection. Emergence and spread of antimicrobial resistance combined with increasing numbers of immune-compromised patients make infections increasingly difficult to treat. Thus, new insight into the predisposing factors of *S. aureus* nasal carriage may give novel clues to host-microbe-environmental interactions of importance for the carrier state, and thus, contributing substantially in reducing the burden of *S. aureus* disease.

In this thesis, we investigated whether host factors (gender, serum vitamin D levels, body mass index [BMI], and waist circumference [WC]), environmental factors (smoking, work in healthcare services, and residing with children) and microbe (*spa* types) were associated with *S. aureus* nasal carriage among women and men aged 30–87 years who participated in the Tromsø Staph and Skin Study– part of the sixth Tromsø survey (Tromsø 6) carried out from October 2007 to December 2008.

S. aureus nasal carriage was more common in men than in women (34.1% and 21.3%, respectively) and more common among non-smokers than among smokers. There was an inverse dose-response association between serum 25(OH)D concentration and the odds of *S. aureus* nasal colonization and carriage in non-smoking men.

We observed that young and premenopausal women with higher BMI and WC had increased odds of *S. aureus* nasal colonization independent of pre-diabetes/diabetes, and use of hormonal contraceptives. There was no association among older women and men while the association with higher WC was observed among young men.

Work in healthcare services was associated with increased odds of *S. aureus* nasal carriage among women. Odds were even higher among women residing with children. Among men, work in healthcare services and residing with children were associated with increased odds of common *spa* types. Our study suggests that a synergism between environmental risk factors (work and household) is of importance for the overall *S. aureus* carrier state in HCWs.

In summary, our cross-sectional study supports the view that there is a complex interplay between host-, microbial-, and environmental factors during colonization and carriage. Prospective studies are needed to determine causal relationships and targets for prevention.

SAMMENDRAG

Staphylococcus aureus er en av de viktigste årsakene til alvorlige infeksjoner hos mennesker. Bakterien kan kolonisere oss uten å skape sykdom, men den kan også invadere ulike typer vev og blodbanen og gi alvorlig infeksjon. *S. aureus* trives best i nesen, og oftest er det vår egen nesestamme som er årsak til infeksjonen. Effektiv behandling av *S. aureus* infeksjon er en klinisk utfordring pga globalt økende antibiotikaresistens og flere immunsupprimerte pasienter med mer kompliserte behandlingsforløp. Økt kunnskap om faktorer som fremmer kolonisering med bakterien, kan gi kunnskap om nye metoder for å forebygge infeksjon med *S. aureus.*

Ca 20–30% av den voksne normalbefolkning er bærere av *S. aureus* og årsakene til at noen er bærere mens andre ikke er det, er i stor grad ukjent. Både vert- og miljøfaktorer samt forhold ved mikroben synes å spille en rolle.

I denne avhandlingen har vi testet om ulike faktorer hos vert (kjønn, vitamin D-nivå i serum, kroppsmasseindeks og livvidde), miljø (røyking, arbeid i helsevesenet, bo med barn) og mikrobe (*spa* type) har betydning for bærerskap av *S. aureus* hos kvinner og menn i alderen 30–87 år som deltok i den befolkningsbaserte undersøkelsen–Tromsø 6 i 2007–2008.

Resultatene viser at menn er hyppigere bærere av *S. aureus* i nesen enn kvinner (34.1% versus 21.3%). Røykere har lavere prevalens av *S. aureus* bærerskap enn ikke-røykere. Høyere serum vitamin D var forbundet med lavere risiko for bærerskap hos ikke-røykende menn; en halvert risiko ble observert hos de med høyest serum vitamin D ≥75 nmol/l versus de med lavest nivå <50 nmol/l.

Hos unge og premenopausale kvinner var høyere kroppsmasseindeks og livvidde forbundet med økt risiko for *S. aureus* nesebærerskap uavhengig av diabetes og bruk av hormonelle prevensjonsmidler. Sammenhengen med høy livvidde ble også funnet hos unge menn, mens det ikke ble funnet tilsvarende sammenhenger hos eldre kvinner og menn.

Kvinnelige helsearbeidere og især de som bodde sammen med barn, hadde økt risiko for nesebærerskap av *S. aureus*. Funnene var ikke signifikante hos mannlige helsearbeidere. *spa* type t012 og t015 var assosiert med jobb som helsearbeider. Resultatene tyder på at nesebæreskap av *S. aureus* bestemmes av både vert, miljø og mikrobielle faktorer. Prospektive studier er nødvendige for å avklare årsakssammenhenger og mål for forebygging.

LIST OF PAPERS

This thesis is based on the following three papers, which are referred to in the text by their Roman numerals.

Paper I

Olsen K, Falch BM, Danielsen K, Johannessen M, Sollid JUE, Thune I, Grimnes G, Jorde R, Simonsen GS, Furberg A-S.

Staphylococcus aureus nasal carriage is associated with serum 25-hydroxyvitamin D levels, gender and smoking status. The Tromsø Staph and Skin Study. *European Journal of Clinical Microbiology & Infectious Diseases.* 2012;31(4):465-473.

Paper II

Olsen K, Danielsen K, Wilsgaard T, Sangvik M, Sollid JUE, Thune I, Eggen AE, Simonsen GS, Furberg A-S.

Obesity and *Staphylococcus aureus* nasal colonization among women and men in a general population. Accepted in *PLoS ONE,* April 2013.

Paper III

Olsen K, Sangvik M, Simonsen GS, Sollid JUE, Sundsfjord A, Thune I, Furberg A-S.

Prevalence and population structure of *Staphylococcus aureus* nasal carriage in healthcare workers in a general population. The Tromsø Staph and Skin Study. *Epidemiology and Infection.* 2013;141(1):143-52.

1. INTRODUCTION

Staphylococcus aureus (*S. aureus*) can act both as a human commensal, that persistently colonizes 20–30% of the adult human population (*S. aureus* carriers), and as an invasive pathogen [1]. *S. aureus* is the major cause of skin and soft tissue infections, and the bacterium can invade any tissue in the body, causing other serious life-threatening diseases such as osteomyelitis, endocarditis, and pneumonia. *S. aureus* is a major cause of bloodstream infection and was the 2nd most common pathogen isolated in blood cultures in Norway in 2011 [2]. *S. aureus* nasal carriage often precedes infection. The bacterium colonizes the skin and mucosa of humans and several animal species [3, 4]. Although multiple body sites can be colonized in human beings, the anterior nares of the nose are the main body sites. Emergence and spread of antimicrobial resistance combined with increasing numbers of immunocompromised patients make infections increasingly difficult to treat [5]. Thus, new insight into the patophysiology as well as predisposing factors of *S. aureus* nasal carriage may give novel clues to host-microbe-environmental interactions of importance for the carrier state and provide new potential targets for prevention of infection.

1.1 Clinical significance

S. aureus is one of the most widespread human pathogens with the potential to cause serious and fatal diseases. The organism is well armed with potent virulence factors, survival fitness, and antimicrobial resistance determinants [6]. The spectrum of infections encompasses skin and soft tissue infections (SSTIs), muscle and visceral abscesses, septic arthritis, osteomyelitis, endocarditis, pneumonia, brain abscesses, meningitis and bacteremia, as well as toxinoses with toxic shock syndrome, scalded skin syndrome, and food poisoning [6]. Globally, *S. aureus* is the cause of a large proportion of bloodstream infections (22%), and skin and soft tissue infections (39%) [7]. In Norway, *S. aureus* is the second most common bacterial species in blood cultures, accounting for 14.2% of the isolates when skin contaminants are excluded [2].

The annual incidence of *S. aureus* bacteremia (SAB) varies between 19.7 and 50 per 100,000 populations in different countries such as Canada and the Scandinavian countries with the lowest incidence and USA with the highest incidence. These large geographical discrepancies may reflect differences in the prevalence of *methicillin-resistant S. aureus*

(MRSA), healthcare systems, infection control practices and the completeness of surveillance data [8]. There is substantial variation in the mortality rates (range 10–30%) [8] most likely attributable to differences in patient groups and complications due to bacteremiae, prevalence of MRSA and the mortality measurements used. Remarkably, in the Western part of the world, the 30-day all-cause mortality of SAB exceeds that of AIDS, tuberculosis and viral hepatitis, and is almost equal to that of breast and prostate cancers [8].

The Centers for Disease Control and Prevention (CDC) definition divides *S. aureus* infections into nosocomial (onset of infection >48 h after hospital admission), community-onset healthcare-associated (HA) [onset of infection in the community or <48 h after hospital admission and the presence of at least one of the following risk factors: a history of hospitalization, surgery, dialysis, or residence in a long-term healthcare facility within 1 year before the culture date; or the presence of a permanent indwelling catheter or percutaneous medical device at the time of culture; or previous isolation of methicillin-resistant *S. aureus* (MRSA)], and community-associated (CA) (onset of infection in the community or <48 h after hospital admission with none of the above risk factors) [5, 9]. About 20% of patients undergoing surgery acquire at least one nosocomial infection, leading to increased morbidity, mortality, hospital stay and costs [10-15]. Hospital treatment often requires that first line barriers for pathogens, of which skin is the most important one, are intentionally breached, resulting in an increased risk of infections. *S. aureus* is a predominant cause of endemic nosocomial infections, and is also responsible for large numbers of outbreaks of HA infections. Using hospital discharge data and infection surveillance (NNIS) system during 1999–2000, infections with *S. aureus* occur with an incidence of 9.13 per 1000 hospital discharges in the USA [16]. In a study from Calgary Health Region, approximately 29% of all nosocomial *S. aureus* infections were respiratory, 18% were associated with intravascular catheters, 18% arose from skin or soft tissue, and 13% represented bacteremiae without an identified source [17].

MRSA is associated with higher mortality, morbidity and financial costs compared to methicillin-sensitive *S. aureus* (MSSA) [14, 18-20]. MRSA is today accounting for 20–60% of all *S. aureus* infections in many countries and has thus become a great burden in most parts of the world [21]. In Europe, the prevalence varies considerably between geographic areas and countries from <1% to 50%, as shown in (Figure 1) [22].

Even though the percentage of MRSA among *S. aureus* isolates seems to stabilise, or even decrease in some European countries, MRSA remains a public health problem, since the proportion of MRSA is still above 25% in more than one fourth of the reporting countries

[23]. The Nordic countries and the Netherlands, are considered low-endemic countries regarding MRSA, as the frequency in bacteremia cases has remained <1 to 5%. However, since the late 1990s a substantial increase in the number of persons found MRSA positive has been observed in Norway as well as in other low endemic countries [2, 22, 24].

1.2 *S. aureus* carriage precedes infection

In about 80% of the cases, *S. aureus* infections are caused by the carrier strain already present on the skin or mucosa of the patient [25, 26]. *S. aureus* nasal carriage has been identified as a risk factor for the development of nosocomial infections among surgical patients [27, 28], patients on haemodialysis or continuous peritoneal dialysis [29-31], patients with liver cirrhosis and after liver transplantation [32-34], as well as HIV positive patients and patients admitted to intensive care units [35-38]. Previous studies have shown a three to six fold increase in risk of acquiring a nosocomial *S. aureus* infection in patients who are *S. aureus* nasal carriers with a large bacterial load versus non-carriers, or those with a low bacterial load

[5, 31, 39, 40]. A causal relation between *S aureus* nasal carriage and infection is supported by the fact that the nasal *S aureus* strain and the infecting strain share the same phage type or genotype [25, 26, 31] and that also eradication of *S. aureus* from the nares has proved to be effective in reducing the incidence of infection with the bacteria [27, 41-45]. Thus, prevention of the carrier state may provide new potential targets for prevention of infection.

1.3 *S. aureus* nasal carriage patterns

Staphylococcus aureus is part of the normal flora of humans and can also be found in other mammals as well as in birds [4]. In humans, the anterior nares are the most consistent sites of *S. aureus* colonization [3, 46]. Extra-nasal sites that typically harbour the organism include the skin, perineum, and throat [3, 47-49]. Other carriage sites including the gastrointestinal tract and vagina harbour *S. aureus* less frequently [1, 3]. Several studies have suggested that colonization of the throat is more prevalent than colonization of the anterior nares [50-53]. However, as decolonization of the nose usually has a decolonizing effect on skin and perineum, the nose is considered to be the major site of *S. aureus* colonization [42, 54, 55].

Most studies on *S. aureus* nasal carriage have used a cross-sectional study design with a single nasal swab culture to classify an individual as a carrier or not. However, based on longitudinal studies with repeated samples the population has been categorized into three *S. aureus* nasal carriage patterns: The persistent carriers, ~20% of individuals (range 12–32%), the intermittent carriers, ~30% of individuals (range 16–70%) and the non-carriers, ~50% (range 16–69%) [1, 46, 56-59]. The proportions of intermittent and non-carriers have a wide range, resulting from differences in culture methods, populations studied and interpretation guidelines [60]. The definition of persistent nasal carriage varies from study to study. There is an ongoing debate on how many cultures should be taken, at which interval, and the number or proportion of positive cultures to define persistence. One study has proposed a “culture rule” that combines qualitative and quantitative results of two nasal swabs taken with a 1-week interval to accurately classify *S. aureus* nasal carriage [57]. The mean number of colony forming units (CFU) has been reported to be higher in persistent carriers than in intermittent carriers [61], resulting in an increased risk of infections [40, 62] and of spreading staphylococci to the surroundings [63]. It has also been shown that the genotypes of *S. aureus* isolated from repeated cultures differ more often among intermittent carriers than among persistent carriers [56]. This indicates that there may be differences in the determinants of

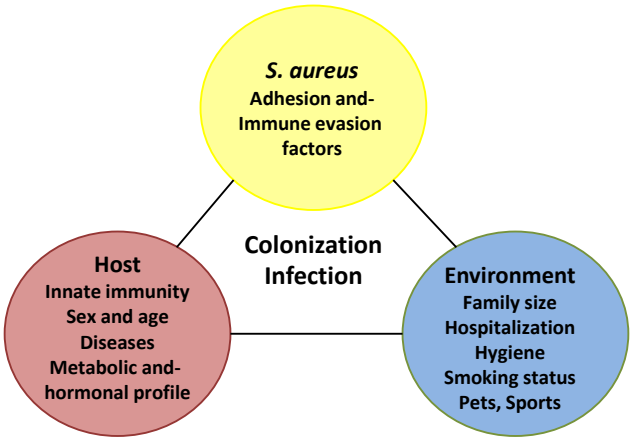
persistent and intermittent carriage. Recently, a reclassification of the *S. aureus* nasal carriage state has been proposed; the persistent carriers and the others (intermittent carriers) [64]. The proposed reclassification was based on results where intermittent carriers and non-carriers shared the same antistaphylococcal antibody profiles and responses to inoculation with a *S. aureus* mixture, as well as the previously described higher risk of infection among persistent carriers than in intermittent and non-carriers [25, 26, 62]. The study participants were first undergoing *S. aureus* eradication and then artificially inoculated with a mixture of different *S. aureus* strains. The originally persistent carriers were found to become carriers again with their original strain from the inoculation mixture, while the others (non-carriers and intermittent-carriers) quickly eliminated *S. aureus* cells from their nares [64, 65].

1.4 Determinants of *S. aureus* nasal carriage

Persistent nasal carriage of *S. aureus* has a high prevalence of 20–30% in healthy adults and is a major risk factor for infections with the bacterium. Nasal carriage of *S. aureus* is characterized by a subclinical inflammatory response that is insufficient to remove *S. aureus* from the nares [66, 67]. It seems as multiple mechanisms are involved in *S. aureus* nasal carriage, and that there is a fine-tuned interaction between the microbe and the host [68]. Host susceptibility factors (e.g. conditions influencing the immune response, or serious underlying diseases), environmental factors (e.g. crowding, hospitalization, and current smoking) and bacterial factors (e.g. cell-wall associated proteins, toxins and bacterial resistance mechanisms) may play important roles (Figure 2). The relative importance of these factors involved in *S. aureus* nasal carriage is largely unknown. Nevertheless, it has been suggested that host factors play a key role, as the overall picture is that in principle all *S. aureus* strains can be tolerated as a human commensal given the proper circumstances [68]. However, these primarily host-defined circumstances are still largely unknown. On the other hand, bacterial factors may decide which strain is carried rather than the carriage status as Peacock et al demonstrated that most mothers carry the same strain as their infants [69].

Mechanisms for establishment and maintenance of nasal carriage need further elucidation [1, 46]. There is a constant shedding of squamous epithelial cells and mucus from the nose that leads to a constant clearance of *S. aureus* cells. To compensate for the mechanical removal, the bacterium needs to be able to adhere to the nasal squamous

epithelium and to proliferate [70]. In addition, the host's immune defences must be evaded for *S. aureus* to become a persistent colonizer.



Staphylococcacea. *S. aureus* was discovered in 1880 by the surgeon Sir Alexander Ogston. He systematically viewed stained slide preparation of pus from patients with postoperative wound suppuration and abscesses under a microscope and observed grape-like clusters of bacteria, which he therefore named Staphylococcus from the Greek expression staphyle ("a bunch of grapes") [72]. In 1884, Rosenbach was able to isolate and grow these bacteria from abscesses and called them *Staphylococcus aureus* because of the yellow-orange or "gold" pigmented appearance of the colonies, "aureus" meaning golden in Latin [73] . *S. aureus* is part of the genus Staphylococcus, which currently contains 47 species and 24 subspecies species (http://www.bacterio.cict.fr/s/staphylococcus.html, accessed 21. Sept. 2012). *S. aureus* is by far the species most pathogenic to humans within the genus.

Traditional identification of *S. aureus* is based on morphological characteristics and biochemical tests. Staphylococci have a Gram positive cell wall with a diameter of 0.7-1.2 µm. *S. aureus* is a facultative anaerobe that grows most rapidly under aerobic conditions and

in the presence of CO_2. Colonies of *S. aureus* are β-hemolytic due to the production of several hemolysins: α-toxin, β-toxin, γ-toxin, and δ- toxin. The species is catalase positive, coagulase positive, and produces pigments (carotenoids) under aerobic conditions. *S. aureus* contains free coagulase enzyme (staphylocoagulase) and bound coagulase (clumping factor), a cell surface-associated fibrinogen-binding protein [74, 75]. Staphylocoagulase (free coagulase) is encoded by the coa gene and causes fibrinogen polymerization and clotting of plasma. Clumping factor encoded by the clfA gene, can directly convert fibrinogen to insoluble fibrin and cause the staphylococci to clump together. Staphylococci can grow in a wide pH range (4.8-9.4), resist desiccation for several weeks, and can survive at temperature extremes as high as 60°C for 30 min. In addition, *S. aureus* grows in high-salt medium due to the production of osmoprotectants [76], and can tolerate 7.5–10% NaCl.

Polymerase chain reaction (PCR) testing is not yet routine practice for daily characterization of *S. aureus* isolates, but its use is becoming more widely available in clinical settings as well as in research. One of the most reliable PCR tests for identification of *S. aureus* detects the presence of the thermonuclease gene, nuc [77]. PCR can also be used to determine the presence of the methicillin-resistance genes *mecA* and others.

Host specificity and host range

In addition to human colonization, *S. aureus* is also known to colonize and infect both pets and livestock, including dogs, cats, rabbits, horses, cattle and pigs [78]. A major concern is the presence of MRSA in pets and livestock, as these may serve as reservoirs for human colonization, exemplified by ST398 from pigs [4, 79]. Various genetic analyses have shown that lineages of *S. aureus* are not so commonly found in animals, and vica-versa. However, there is also an exchange of strains between the reservoirs. Furthermore, livestock-associated and human-associated strains share virulence factors, but have also distinct virulence factors that appear to be important in host adaptation, supporting that there is an exchange of genes encoding virulence factors between strains from livestock and humans. These factors may expand the host range and thereby threaten public health [4].

The genome

Genome sequencing of *S. aureus* has enabled investigators to explore questions of virulence, resistance, physiology, host interactions, and the microbe's success as a bacterial pathogen. The genome size of *S. aureus* typically varies from 2.5 to 3.1 megabase (Mb), and contains

~2,500 open reading frames. The first *S. aureus* genome sequences were published in 2001 by Hiramatsu's group comparing the genomes of two methicillin-resistant strains, N315, Mu50 [80]. Today, full genome sequencing has become commonly used in research, and the number of sequenced genome drafts has exploded in recent years, however only a subset of these are fully annotated and completed [81]. The *S. aureus* genome consists of 1) 80% core genes, conserved between different lineages, and 2) 20% accessory genes with mobile genetic elements (MGEs).

The core genome contains genes vital to cell survival, including genes for surface proteins involved in adhesion and surface architecture as well as genes encoding essential metabolic and regulatory functions. Within the core genome are core variable (CV) regions containing genes with a higher nucleotide substitution rate than the more stable core genes and often showing variation associated with lineage [82]. The core variable regions often encode regulators of virulence genes or surface proteins involved in host interactions during nasal carriage, such as global virulence regulations (accessory gene regulator [agr], the target of RNAIII-activating protein [trap] and staphylococcal accessory regulator T gene [sarT]) known to regulate expression of surface proteins including Staphylococcal protein A (s*pa*) [82].

The accessory genome is assembled from mobile genetic elements (MGEs) that are integrated throughout the genome and carry about 50% of known *S. aureus* virulence factors. These elements include plasmids, bacteriophages, pathogeniticy islands, transposons and insertion sequences, and they are capable of horizontal transfer between strains. There is an exchange of virulence factors between strains contributing to adaption of clones specialized for infection of selected hosts or environments [83, 84].

Molecular typing

By use of molecular typing techniques, the spread of clones in hospitals and in the community can be identified and kept under surveillance. In outbreak situations, typing of bacteria is important for resolving transmission routes and thus for infection control. For epidemiologic surveillance, typing systems reveal the prevalence of different clones in the population in different geographical areas [85]. Today, a range of techniques are in use for typing of staphylococci, with different strengths and weaknesses. One of these methods uses the *spa* gene which encodes the *S. aureus* specific surface protein A in the core variable genome. Sequence-based typing of the *spa* gene has a relatively high discriminatory power and can be

used both for outbreak investigations as well as population studies due to slow accumulation of point mutations and relatively fast changes in repeat numbers [86]. The typing method uses the region X of the *spa* gene containing a variable number of mainly 24–27bp tandem repeats. Repeats are assigned a numerical code according to the actual sequence and the *spa* type is deduced from the repeat succession (Figure 3). The *spa* repeat and *spa* type annotations are mediated at a central localized internet server that ensures the maintenance of unique annotations by the RidomStaphType software [87]. The method has been demonstrated to be highly reproducible between laboratories. The recognized *spa* types may be grouped into clusters, *spa* CC groups, using the Based Upon Repeat BURP algorithm [88].

Other methods in use are the pulsed field gel electrophoresis (PFGE) that became the "gold standard" in typing of MRSA through the 1990s. PFGE has a high discriminatory power that makes it excellent for investigation of person-to-person transmission in a restricted time-frame; e.g. outbreaks [89]. However, PFGE has disadvantages regarding long-term analysis as genetic variations are expected. Furthermore, the comparison of inter-laboratory results are difficult and no common nomenclature exists [90].

Multilocus sequence typing (MLST) is another important typing method using the sequences of internal fragments of seven house-keeping genes in *S. aureus* (arcC, aroE, glpF, gmk, pta, tpi, and ygiL). Sequence variation within these genes, which occurs primarily as a result of point mutations [91], provides an allelic profile that defines the sequence type (ST) and a determination of long-term genetic variation and evolution. Related sequence types can be grouped into clonal complexes (CC) using the eBURST analysis (www.MLST:net) [92-94]. MLST is today one of the most frequently used molecular typing methods in evolutionary epidemiology, but MLST does not have the discriminatory power to be used in *S. aureus* outbreak situations [95]. Several other methods have been applied for typing of *S. aureus*, including variable number of tandem repeat (VNTR) methods and amplified fragment length polymorphism (AFLP). Microarrays can also be used for population analysis and smaller DNA microarrays have been developed focusing on detection of genes associated with virulence, antimicrobial resistance or adhesion [96-98]. Whole genome sequencing has an extremely large discriminatory power, and has been proven to be a valuable research tool [99]. The main challenge is the need for data interpretation. A recent method is the matrix-assisted laser desorption/ionisation time of flight mass spectrometry (MALDI-TOF-MS), which analyses surface-associated proteins by mass spectral analysis and can be used on intact bacterial cells [100]. However, it is so far not clear which role this method will have when it comes to bacterial typing.

The various typing methods differ with respect to discriminatory power, accuracy, reproducibility, costs and technical challenges. The choice of method will depend on the study design and hypothesis. For local studies of population structure and short-term outbreaks, it is advantageous to use a method with relatively high discriminatory power, such as *spa* typing, whereas for global population surveys and long-term studies, methods based on stable housekeeping genes (such as MLST) may be preferred [95].

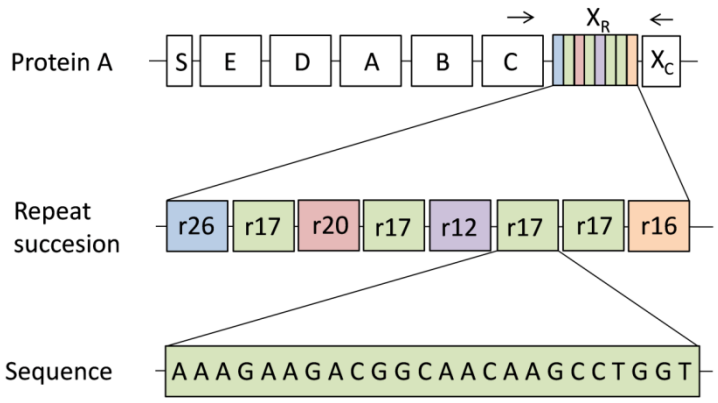


Figure 3. The principle of *spa* typing. The VNTR repeat region X_R of Protein A is the basis for *spa* typing. This region consists of a number of short repeats, and the number of repeats as well as their order determines the *spa* type. The particular repeat succession in the figure represents *spa* type t003. Arrows indicate the primers used in *spa* typing (PhD thesis, ISBN 978-82-7589-370-1, Jan 2013 of Sangvik M). Used with permission.

Population structure and invasiveness of S. aureus

Most *S. aureus* isolates (colonizing as well as invasive isolates of MSSA and MRSA) have been placed in five major, universally occurring clusters: clonal complex(CC) 8, CC30, CC5, CC22 and CC45 using the MLST typing method [91, 93, 101-103]. A similar analysis was performed using AFLP and this demonstrated that all strains fell into three major and two minor clusters, much like the MLST analysis [104]. Also, different studies have shown no distinction between colonizing and invasive isolates [82, 91, 104]. However, subclusters of strains with different degrees of pathogenicity have been observed, suggesting that the presence of accessory genes apart from the core genome of *S. aureus* may enhance or reduce the pathogenic potential of a given clone [104, 105]. Important examples of this phenomenon are genes giving rise to antimicrobial resistance, since the ability to overcome antimicrobial therapy gives a microorganism a selective advantage in hospitals or other settings where antibiotics are frequently used [68, 106]. Furthermore, MRSA has been found in all the major

clusters, suggesting that acquisition of the *mecA* gene has occurred across distinct phylogenetic subpopulations [68, 103, 107].

Geographic diversity

One may question whether the distribution of *S. aureus* genotypes from various geographical locales differs significantly or, alternatively, is rather similar. A study of Melles et al of non-clinical isolates showed that the same genotypes were identified both among individuals from USA (N = 391) and from The Netherlands (N = 829) [108]. The AFLP clusters II and III, which represent MLST CC30 and CC45, respectively, accounted for 46.6% of all carriage MSSA isolates, which underlines that these two clonal complexes have evolved to be very successful in colonizing humans. These findings are also supported by Grundmann et al [109]. They collected 2,890 clinical MSSA and MRSA isolates from blood cultures from 357 laboratories in 26 countries. The MSSA *spa* types showed a high degree of diversity with extensive geographic distribution compared with the MRSA *spa* types which displayed relatively more geographical clustering. Nevertheless, data from Indonesia have shown that one of the major AFLP classes, AFLP cluster II, as identified both in the USA and in Europe was non-existent in that East region [110]. Whether these findings are caused by a certain level of host resistance needs to be addressed in further studies [68].

Bacterial factors possibly influencing nasal carriage.

Many microbial features have been implicated in the host microbe interaction. *S. aureus* lineages have individual combinations of surface proteins involved in adhesion as well as secreted proteins involved in immune response evasion [111] (Figure 4). During *S. aureus* colonization, the individual combinations of adhesion and immune evasion factors as well as their expression levels may be of importance.

Adhesion factors

Wall teichoic acid (WTA) of *S. aureus* is suggested to play an important role in attachment, both in the early stages and for continued colonization [112, 113]. In addition, a class of cell wall-associated proteins termed microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) [114] may have critical roles at a later stage of colonization of the nose [115]. In vitro experiments show that *S. aureus* can directly adhere to the keratinized squamous epithelial cells in the anterior nares via cell wall anchored clumping factor B

(ClfB). *S. aureus* ClfB binds to cytokeratin 10 which is a component of the squamous cell [116]. Also, the iron-regulated surface determinant A (IsdA) protein of *S. aureus* can bind to cytokeratin 10, loricrin and involucrin, important proteins of the matrix surrounding the upper anucleated layers of the epithelium [117]. ClfB and IsdA have both been demonstrated to promote colonization of the nares of rodents in *in vivo* models [118, 119] and were expressed during nasal colonization in humans [120]. *S. aureus* surface protein G (SasG) and serine-aspartic acid repeat proteins SdrC and SdrD are other bacterial surface proteins probably contributing to adhesion to nasal epithelial cells [121, 122].

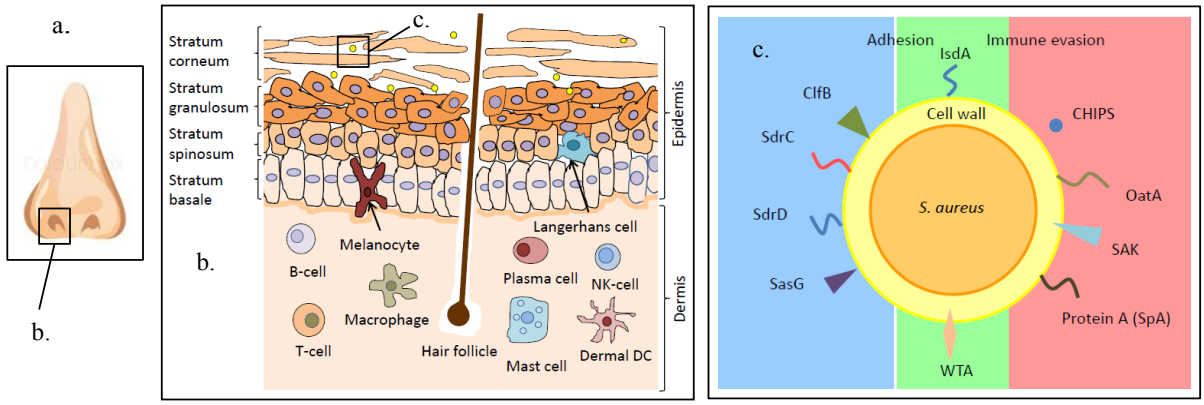


Figure 4. a. The nose with the vestibulum nasi **b.** The epidermis with the layers of keratinocytes: stratum corneum, stratum granulosum, stratum spinosum and stratum basale. During *S. aureus* colonization, *S. aureus* can be found in the epidermis. The immune cell type, Langerhans cell, is found in the epidermis. The dermis includes several immune cells such as natural killer (NK) cells, macrophages, T-cells, B-cells, mast cells, dermal dendritic cells (DC) and plasma cells. **c.** *S. aureus* exhibits adhesion factors (blue background), factors involved in immune evasion (pink background), and factors influencing both adhesion and immune evasion (green background) during nasal colonization.
Abbreviations: ClfB, clumping factor B; SdrC, serine-aspartic acid repeat protein C; SdrD, serine-aspartic acid repeat protein D; SasG, *S. aureus* surface protein G; CHIPS, chemotaxis inhibitory protein of *S. aureus*; OatA: O-acetyl transferase, SAK, staphylokinase; *spa*, protein A; WTA, wall teichoic acid, (Modified from PhD thesis, ISBN 978-82-7589-370-1, Jan 2013 of Sangvik M). Used with permission.

Immune evasion factors

S. aureus can produce a large variety of secreted proteins involved in immune evasion. Some of the proteins target immunoglobulins, complement or neutrophil recruitment, whereas others counteract the effects of antimicrobial molecules such as lysozyme and defensins. Nasal secretion is the first line of host defence against inhaled bacteria. The nasal secrete is a complex mixture of proteins, sugars and salts, containing e.g. lysozyme and immunoglobulins IgA and IgG [123], as well as defensins [124] and complement proteins [125]. *S. aureus* is

resistant to lysozyme due to the cell wall modifying enzyme O-acetyltransferase (OatA) in combination with WTA [126]. In a study of *S. aureus* isolated from persistent nasal carriers, several factors, including staphylococcal protein A (*spa*), staphylokinase (SAK) and chemotaxis inhibitory protein of *S. aureus* (CHIPS) were expressed [120]. *Spa* is able to limit opsonisation by binding to the Fc-region of IgG in a conformation that inhibit recognition by the neutophils [127]. Through this IgG-binding, *spa* also interferes with binding to the complement system [128]. SAK and CHIPS are suggested to inhibit immune response in different ways [129-131].

Nasal microflora

The availability of resources (e.g. nutrients and attachment sites), the presence of harmful substances, and the host's immune responses can be influenced by the presence of established bacterial communities in the nose [132] and determine the colonization success of different bacteria.

The microbial ecology of the vestibulum nasi is complex. The nares are colonized by a temporally stable microbiota that by culture-independent approaches in healthy adults consists primarily of the phylum Actinobacteria (e.g., *Propionebacterium* spp, and *Corynebacterium* spp), Firmicutes (*Lactobacillae spp* and *Staphylococcus* spp) and Proteobacteria (*Enterobater* spp) [133].

A persistent carrier seem to be protected from acquiring new strains of *S. aureus*, e.g. during hospitalization, also known as colonization resistance. This was exploited in the 1960s, to protect infants of hospital acquisition of virulent strains of *S. aureus* [134, 135]. The colonization resistance is reduced when carriers are treated with antibiotics [135, 136]. It has also been shown that MSSA nasal carriage interferes with and hence may protect against MRSA acquisition [137].

The prevalence of *S. aureus* carriage has previously been found to be lower among those colonized with corynebacteria, but the underlying mechanism is not known [138, 139].

Frank et al observed negative associations between *S. aureus* and *S. epidermidis* and suggested microbial competition as a cause [133]. Mechanisms of bacterial interference applied by *S. epidermidis* may also involve production of phenol-soluble modulins (PSMs) [140, 141] that induces antimicrobial effects against *S. aureus*, peptide pheromones [142, 143] and induction of human β-defensins [144]. Furthermore, a serine protease (Esp, 27kDa) secreted by a subset of *S. epidermidis* has been reported to inhibit *S. aureus* nasal colonization

through reduced biofilm formation [145]. As *S. aureus* does not form a typical biofilm in the nasal cavity this mechanism has been questioned [146]. However, the Esp protease may inhibit *S. aureus* nasal colonization by removing adhesion or immune evasion factors essential for colonization [70].

Bogaert et al noted a negative correlation for co-colonization of *S. aureus* and vaccine-type of pneumococci but not for *S. aureus* and non-vaccine type pneumococci in the nasopharynx of children [147]. However, a study in children did not reveal an increase in prevalence of *S. aureus* colonization after introduction of the 7-valent pneumococcal-conjugate vaccine (PCV7) [148]. It has been proposed that the displacement of *S. aureus* by *S. pneumonia* in nasopharynx may be explained by H_2O_2-mediated bacterial interference [149], but this has not been confirmed by others [150].

Another study has concluded that nasal microbiomes may be grouped into 12 supergroups, with *S. aureus* present in 2 but absent in the others [151]. In contrast, Frisoni ED et al [152] found in nasal metagenome analyses that the microbial diversity was similar in both *S. aureus* carriers and non-carriers which may imply that *S. aureus* seem to come in addition to the other normal flora, and that large-scale carriage eradication is discouraged [152].

1.4.2 Host factors

Although the role of host factors in nasal carriage of *S. aureus* has been extensively studied, the host-defined circumstances are still somewhat unclear.

The results from studies of host genetic factors on nasal colonization are not consistent, suggesting that the role of heritability is modest [153].

S. aureus nasal carriage rates vary by ethnic groups, with higher rates among Caucasians [66, 154]. Previous studies have consistently found increased carriage rates associated with male gender [154, 155], younger age [47, 68, 69, 154], and oral contraceptive use [156]. Children have higher persistent carriage rates than adults [47, 157]. The colonization rate declines from approximately 45% during the first 8 weeks to about 21 % by 6 months [69]. A transition zone from persistent carriage to intermittent carriage or non-carriage has been proposed, which implies development of the immune response during maturation from childhood to adolescence [3, 47]. Patients with chronic skin diseases [68, 158, 159], HIV/AIDS [36, 38], end stage renal disease [31, 160] and end stage liver disease

[32, 34] are at increased risk of *S. aureus* nasal carriage supporting the view that impaired immune responses may increase the risk of carriage. There are only a few reports on the association between measured biomarkers, as metabolic and hormonal factors, and *S. aureus* nasal carriage in the general population; diabetes mellitus (DM) [161, 162], obesity [154, 155], and vitamin D deficiency [163], have been positively associated with *S. aureus* nasal carriage. Also, polymorphisms in the glucocorticoid receptor gene increasing the sensitivity and endogenous levels of glucocorticoid hormones were positively associated with *S. aureus* nasal carriage [164]. However, long-term cortisol levels determined in hair segments of 72 healthy individuals were not associated with the carrier state [165].

Host immunity and S. aureus carriage

S. aureus predominantly colonizes the anterior human nares in an area covered with ordinary skin supplemented with nasal secretion. Nasal secretions are a part of the host defence against microbes, and it has been shown that nasal fluids from non-carriers were bacteriostatic or bactericidal, whereas the nasal fluids from carriers allowed growth of *S. aureus* [166], and it has been proposed that the presence of haemoglobin in nasal secretions promotes *S. aureus* carriage through inhibition of the *agr* system [167]. The epidermis contains several antimicrobial lipids, peptides and proteins provided by keratinocytes, sebocytes, mast cells, and eccrine sweat glands and also by circulating neutrophils or natural killer cells that are recruited to the skin [168]. The individual or combined expression patterns of the various antimicrobial molecules may influence the colonization status of *S. aureus* [169]. Lipids in epidermidis have antimicrobial activity against *S. aureus*, and a reduction of synthesized fatty acids has been found to be associated with *S. aureus* carriage in atopic dermatitis patients [170, 171].

Epidermal keratinocytes shape the physical barrier of the skin and contribute to innate immunity. Professional innate immune cells, such as dendritic cells (DCs) and macrophages reside in the skin ready to respond to bacterial invasion [172]. The keratinocytes and cells involved in the innate immune system sense pathogens by expressing pattern recognition receptors (PRRs) that recognize pathogen-associated molecular patterns (PAMPs) [173]. PAMPs are evolutionary conserved microbial components, including lipopolysaccharide (LPS), peptidoglycan, flaggelin and nucleic acids [172]. The bacterial cell wall of *S. aureus* is composed of multiple peptidoglycan layers in combination with WTAs, LTA, and various MSCRAMMs or other substances that can be recognized as PAMPs [174, 175]. The most

important PRR known to be involved in recognizing *S. aureus* is the Toll-like receptor (TLR) 2 [174, 176] as well as the intracellular nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs) NOD2 and NLRP3 [174, 176]. Activation of PRRs induce intracellular signalling resulting in altered gene expression with the final result of increased expression and secretion of various antimicrobial peptides (AMPs), cytokines and chemokines with initiation of innate and adaptive immune responses which promote killing of *S. aureus* [177, 178].

AMPs have the capability to kill various pathogens and modulate innate and adaptive immune functions and are secreted from keratinocytes, other resident cells in the skin (e.g cells in eccrine glands, mast cells, sebocytes) and invading immune cells (e.g. neutrophils, NK cells) [179-181]. Two important and well studied AMP gene families in the skin are the defensins and the cathelicidin [182, 183]. The human β-defensins expressed in mucosa and epithelial cells, have been compared in their antimicrobial activity against *S. aureus*, and the most potent is the β-defensin 3 (HBD3) followed by β-defensin 2 (HBD2) and 1 [184-186]. A higher induction of β-defensin 3 is associated with a better clinical course and outcome of *S. aureus* skin infection and the level of both constitutive and induced β-defensin 3 is lower in persistent *S. aureus* carriers than non-carriers [187, 188]. Also, the Cathelicidin and its active peptides LL-37 and others, have all antimicrobial activity against *S. aureus* [189].

Vitamin D

Vitamin D was discovered in 1922 and has, because of its effect on bone metabolism, for decades been used in prevention and treatment of rickets in children and osteoporosis in adults [190, 191]. Vitamin D is a fat soluble vitamin, which exists in two forms, ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) [190]. The two sources of vitamin D are diet and sun exposure [191]. Dietary sources include fatty fish, cod liver oil, egg yolk, mushrooms, fortified products and supplements [191]. Solar ultraviolet B (UVB) radiation at wavelength 290-320 nm induces conversion of 7-dehydrocholesterol to pre-vitamin D_3 in skin, which under normal temperature conditions isomerizes to vitamin D_3 [192]. The relative importance of vitamin D from UVB exposure and vitamin D from dietary sources varies between populations and is affected by ethnicity/skin pigmentation, climate conditions, dietary habits and cultural practices [193, 194].

Although vitamin D is a vitamin by name, the molecular structure is that of a secosteroid [195]. Physiologically it acts more like a pre-hormone as it is not biologically

active until it has been metabolized [195]. In the liver vitamin D is converted to $25(OH)D_2$ or $25(OH)D_3$ by 25-hydroxylase [190]. In the following these will be referred to as 25(OH)D. In the kidneys 25(OH)D is further converted to 1,25-dihydrovitamin D ($1,25(OH)_2D$) by 1α-hydroxylase [190]. This renal conversion is tightly regulated by calcium and phosphate levels. However, the 1α-hydroxylase is also present in many other tissues throughout the body [196]. This extra-renal conversion of 25(OH)D to $1,25(OH)_2D$, which is thought to be regulated by local growth factors and cytokines, is dependent on the amount of substrate available and works locally in an autocrine or paracrine fashion [190].

Ligand binding to the vitamin D receptor (VDR), a member of the superfamily of nuclear receptors for steroid hormones, is necessary for the biological activities of $1,25(OH)_2D$ and 25(OH)D [190]. The most potent metabolite 1,25 $(OH)_2D$ binds to the VDR with high affinity while 25(OH)D binds to the receptor nearly 100 times less avidly [190]. The VDR regulates the transcription of several target genes in a variety of vitamin D target cells.

Polymorphisms of the VDR have been associated with insulin resistance, decreased bone density, infections, *S. aureus* nasal colonization among type 1 diabetes patients, autoimmune diseases, cancer and resistance to vitamin D therapy [197-200]. Several functional VDR polymorphisms have been found [201], but the field is still under exploration [190].

Measurement of vitamin D

The preferred biomarker for an individual's vitamin D status is 25(OH)D, the major form in the circulation. This is due to its high stability in stored serum and plasma samples, a characteristic that makes accurate, long-term epidemiological studies possible [202]. Serum 25(OH)D reflects the amount of vitamin D ingested from food and produced in the skin during UVB exposure. $1,25(OH)_2D$ does not enter the circulation in large amounts, but as the local conversion is dependent on the 25(OH)D available, measuring serum 25(OH)D is a good alternative [190]. 25(OH)D is measured by use of immunoassays or chromatographic methods. High throughput automated immunoassay methods are the most commonly used in large population and clinical studies [203]. However, the immunoassay methods are prone to performance change over time and have varying ability to distinguish between $25(OH)D_2$ and $25(OH)D_3$ in contrast to the chromatographic methods [203, 204].

The variability of 25(OH)D levels between individuals is explained by both environmental factors and heritability [205], and several polymorphisms have been identified

as important determinants of serum 25(OH)D levels [201]. There is no consensus as to what is the optimal serum concentration of 25(OH)D, but a serum concentration <50 nmol/l is considered as deficient as this level is associated with an increase in Parathyroid hormone (PTH) level [206] and decrease in physical performance among elderly [207]. Concentrations between 50–75 nmol/l are considered as insufficient [191] and a recent consensus panel recommended that a serum concentration 75–100 nmol/l for different health outcomes should be targeted [208, 209]. Very high levels of serum 25(OH)D also seem to be disadvantageous. Data from the National Health and Nutrition Examination Survey (NHANES) III showed a lower risk of mortality at levels of 75–125 nmol/l, but a higher risk of mortality among women at levels higher than 125 nmol/l [210]. On the other hand, serum 25(OH)D levels >150 nmol/l have been found in healthy populations living in areas close to equator and spending much time outdoors [211, 212], and currently 250 nmol/l is considered the upper physiological limit [213]. In the Nordic countries the recommended intakes of vitamin D supplementation are 400 IU daily for infants, elderly, pregnant and lactating women, and 300 IU daily for all others 2–60 years [214].

Vitamin D and risk of infection and bacterial colonization

As the VDR and the 1α hydroxylase are found in many tissues and cells in the body [196], serum 25(OH)D levels have been proposed to influence risk of several common diseases including infections and *S. aureus* nasal colonization [163, 191, 196].

Several studies suggest that vitamin D has a protective role in respiratory tract infections where viruses represent the most common pathogens. Seasonality in the occurrence of influenza and respiratory tract infections has been attributed to low wintertime vitamin D levels [215-217]. Recently, inverse associations between 25(OH)D concentrations and incidence of respiratory tract infections with thresholds of 25(OH)D ≥75 nmol/l [218] and ≥40 nmol/l [219] has been observed.

The associations between vitamin D and bacterial infections have been addressed in different studies. Epidemiological data have established that vitamin D deficiency is associated with increased *Mycobacterium tuberculosis* (TB) prevalence and susceptibility to active TB disease [220-224]. *In vitro* studies have also proved that vitamin D_3 has inhibitory activity on strains of *S. aureus*, *Streptococcus pneumonia, Klebsiella pneumonia* and *Escherichia coli*. In the presence of 50,000–90,000 IU/mL of vitamin D_3, the organisms were killed or demonstrated marked growth inhibition [225]. Furthermore, pneumococcal

infections have been shown to increase each winter and extended periods of low UV radiation have been related to invasive pneumococcal disease [226, 227]. Supplementation with oral vitamin D_3 has been observed reducing the risk of a repeated episode of pneumonia among children in Kabul [228].

In the US National Health and Nutrition Examination Survey (NHANES) 2000–04 including 14,000 women and men, vitamin D deficiency was associated with an increased risk of nasal carriage of MRSA but not MSSA [163]. Furthermore, a study from a diabetic clinic of Heraklion, Crete, Greece, reported possible associations between VDR polymorphisms and nasal carriage of *S. aureus* among 93 type I diabetes patients aged 3–25 years [200], but a population-based cohort study from Rotterdam, Netherlands, including more than 2000 healthy elderly individuals did not observe any associations with VDR polymorphisms [229]. Moreover, vitamin D deficiency has been linked to adverse outcomes in veterans with *Clostridium difficile* and MSSA infections [230]. However, there is still limited knowledge of the possible relationships between serum vitamin D levels and *S. aureus* nasal carriage in an adult general population, also considering possible age and gender interactions.

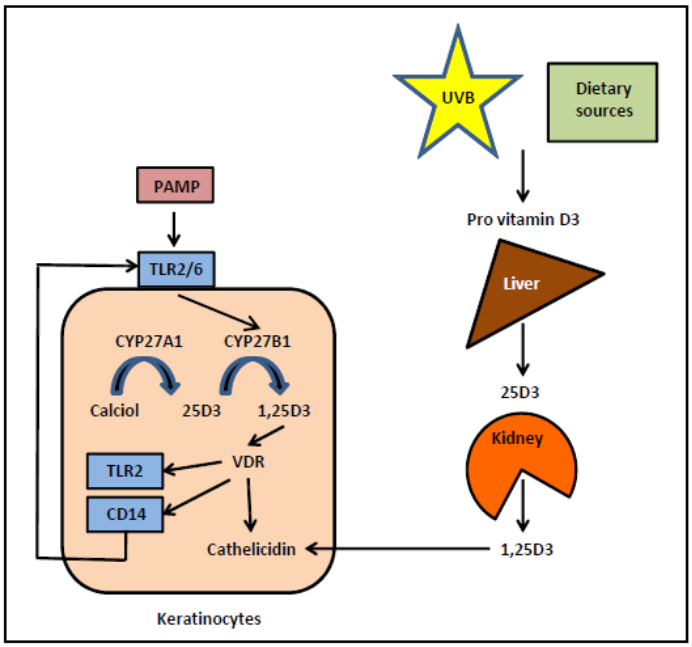


Figure 5. Keratinocyte. Mechanisms of vitamin D_3 activation and cathelicidin response. Extrarenal metabolism of vitamin D_3 by keratinocytes provides a system for rapid control of cathelicidin expression. Activation of calciol to $25D_3$ and $1,25D_3$ requires two hydroxylations steps that occur sequentially in liver and kidney as well as in keratinocytes who expresses CYP27A1 and CYP27B1.$1,25D_3$ binds to and activates the vitamin D receptor (VDR) which subsequently activates transcription of cathelicidin. Based on [231].

Vitamin D and immune response

Vitamin D has modulatory effects on both innate and adaptive immunity, which may influence susceptibility to infection and bacterial colonization [163, 232]. Nearly all immune cells display a specific vitamin D receptor (VDR) including B and T lymphocytes, monocytes and dendritic cells [233]. The capacity of $1,25(OH)_2D_3$ to modulate cytokine responses to a Th2 signalling pattern and induce AMP production are important biological effects possibly protecting individuals against microbial infections and colonization. In a distinct immune regulatory role, vitamin D_3 affects the innate antimicrobial defense at epithelial barriers, such as the airway epithelium or the skin.

Keratinocytes can also activate vitamin D_3 independent of renal and hepatic hydroxylation steps [233] with the final result of increased expression and secretion of various AMPs, cytokines and chemokines leading to initiation of innate and adaptive immune responses which promote killing of *S. aureus* and other microbial agents (Figure 5).

The Cathelicidin, often referred to by its peptide form hCAP18, is stored in keratinocytes and secreted into different layers in the epidermis prossessing the protein to active peptides LL-37 and others, which all have antimicrobial activity against *S. aureus* [189]. Furthermore, LL-37 influences TLR2 signalling and CD14 expression in keratinocytes [231], which may result in increased ability to detect pathogens. All these studies support that vitamin D protects against different infections and also against *S. aureus* nasal carriage (Figure 5).

Obesity

The incidence of obesity worldwide has increased dramatically during recent decades. Obesity and associated disorders now constitute a serious threat to the current and future health of all human populations on earth. The World Health Organization (WHO) estimates that more than 1 billion adults worldwide are overweight (body mass index [BMI] 25.0–<30.0 kg/m^2), 300 million of whom are clinically obese with a BMI ≥30.0 kg/m^2 [234, 235]. Obesity has been associated with numerous health problems and chronic diseases, including increased risk of insulin resistance, type 2 diabetes, fatty liver disease, atherosclerosis, degenerative disorders such as dementia, airway diseases and some cancers [235-237]. These co-morbidities have been attributed to hormonal and metabolic changes related to increased adipose tissue mass [235, 238].

Measurement of body fat

There are various anthropometric methods for estimating body fat. Underwater weighing based on Archimedes' principle has long been considered to be the gold standard for estimation of body fat percentage, but this is a labour-intensive method that is not feasible in larger studies [239].

Dual energy X-ray absorptiometry, or DXA (formerly DEXA), is a practical and newer method for estimating body fat percentage, and determining body composition and bone mineral density [240]. Percent visceral and subcutaneous body fat assessed by DXA has been associated with metabolic syndrome and through it DM as well as cardiovascular disease [241].

The most widely used methods for measuring adipose tissue depots are the estimation of BMI from an individual's height and weight, and the use of waist circumference (WC), hip circumference, and the waist/hip ratio. BMI is calculated as weight (kg) divided by height (m) squared (kg/m^2). There are different methods for measuring WC. WHO STEPS protocol for measuring WC instructs that the measurement be made at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest [242]. The United State (US) National Institutes of Health (NIH) protocol and the protocol used by the US National Health and Nutrition Examination Survey (NHANES) III indicate that the WC measurement should be made at the top of the iliac crest [243]. The NIH also provided a protocol for measurement of WC for the Multi-Ethnic Study Atherosclerosis (MESA) study. This protocol indicates that the WC measurement should be made at the level of the umbilicus [243]. Some studies have assessed the WC at the point of minimal waist [244]. A review of 120 studies concluded that different WC measurement protocols had no substantial influence on the association between WC, all-cause mortality and cardiovascular disease (CVD)-specific mortality, and risk of CVD and diabetes [244].

Regarding measurements of hip circumference, all the protocols mentioned indicate that the hip circumference measurement should be taken around the widest portion of the buttocks.

Obesity and immune response

Adipose tissue represents an endocrine organ from which a high number of proteins and hormones, so called adipokines, are synthesized and secreted [245, 246]. One of the adipokines, leptin, produced predominantly by subcutaneous adipose tissue [247], is probably

one of the best characterized links between the obesity-induced chronic low-grade inflammation and modulation of immune function [248]. In malnourished infants who have low plasma leptin, impairment of both the innate and adaptive immune response has been observed [249]. Obesity may promote a chronic low-grade inflammation that attenuates leptin signalling [248]. Along this line, it has been observed an underreactivity of the innate immune response to clear *S. aureus* invasive infection and survive sepsis in diet-induced obese mice and genetically obese Ob/Ob mice on low fat diet [250]. These findings are further supported by the observation of chronically increased leptin levels in obese mice associated with a state of leptin resistance in the central nervous system, a hallmark of the obesity-induced impaired immune response [248]. Also, leptin seems to modulate the expression of antimicrobial peptides observed for Human β-defensin-2 (HBD2) in keratinocytes [251]. Taken together, these results suggests that leptin may play a key role in antimicrobial defense, and allows us to hypothesize that leptin has a role in *S. aureus* nasal carriage as well as infections [248, 251, 252].

Obesity is often linked to elevated serum glucose concentration and type 2 diabetes [253]. Both insulin dependent- and independent DM have been associated with *S. aureus* nasal carriage and infections including also other types of microbial pathogens [68, 161, 254]. The pathophysiological basis for this association remains to be discovered. Increased blood and mucosal glucose levels may influence bacterial adherence, promote staphylococcal growth, reduce neutrophil chemotaxis, and phagocyte activation in neutrophils and macrophages, as well as impair killing of intracellular micro-organisms (including *S. aureus*) [162, 254, 255].

Obesity and insulin resistance have also been linked to changes in circulating levels of reproductive hormones [256-258]. Estrogens generally exert immune enhancing activities while androgens exert suppressive effects on both innate and adaptive immune responses [259, 260]. One may thus hypothesize that in premenopausal women, obesity may be linked to anovulatory cycles and a lower estrogen/androgen ratio with increased susceptibility to colonization [257, 261] whereas in postmenopausal women and men obesity may be linked to higher estrogen/androgen ratio and lower susceptibility to colonization [256, 258].

Obesity and S. aureus infection and carriage

Recent clinical findings indicate that obesity may be linked to increased susceptibility to infections. The various infections include community- acquired pneumonia and wound

infections, as well as nosocomial infections such as sepsis, pneumonia, surgical site infections, catheter-related infections and respiratory related hospitalizations during influenza seasons [252, 262-266]. These associations may partly reflect a mechanical dysfunction in the respiratory tract due to obesity, as well as prolonged surgery and hospitalization with increased risk of nosocomial infections.

Interestingly, former studies have observed obesity as a risk factor for *S. aureus* nasal colonization [154, 155]. However, epidemiological studies in a general population investigating the role of obesity on *S. aureus* colonization are limited, and the role of obesity per se, independent of DM, is of particular interest.

1.4.3 Environmental factors

An important determinant of *S. aureus* nasal carriage is exposure to the bacterium. *S. aureus* is acquired from sources in the environment, with human carriers as the most important source. Hands are the main vector for transmitting *S aureus* from other humans or surfaces to the nasal niche; e.g. nose picking [267]. A typical transmission route of *S. aureus* is from the nose to the hand of a person, then to a surface (e.g. a door knob), and/or via the hand to the nose of a second person. *S. aureus* may also reach the nose directly through the air, but this probably occurs less frequently [268]. However, airborne transmission is important for the dispersal of staphylococci to many different reservoirs, from where, via the hands, the microbe can reach the nose [268]. *S. aureus* nasal carriers with rhinitis can disperse high loads of *S aureus* into the environment, and may be the source of outbreaks of *S. aureus* infections [269].

Environmental factors such as crowding, transmission between household members and family size seem to be risk factors for carriage [69, 147, 270-272]. Cross-sectional surveys of healthy adults have reported a decline in *S. aureus* nasal carriage rates from 35% in 1934 to 27% in the year 2000 [1]. Explanations for this decline include improved personal hygiene, changes in socioeconomic class and smaller families [147, 273].

Activities involving close physical contact and the risk of minor injuries, such as sports, are positively correlated with *S. aureus* spread and acquisition [147, 274]. In contrast, current smoking seems to reduce the risk of *S. aureus* carriage probably due to the bactericidal activity of cigarette smoke [162, 275], and the increased immune and

inflammatory responses in smokers [162]. As pets also may be colonized with *S. aureus*, they may serve as vehicles for transmission to humans [276].

Healthcare - associated environmental exposure determinants for S. aureus nasal carriage.

Healthcare-associated environmental exposure is defined as an environmental exposure that occurs in any healthcare facility as a result of medical care.

The levels of crowding and hygiene in both hospital and household settings are important for the rate of transmission [3]. Hospitalization implying breaching of skin and/or mucosal barriers in patients has been observed to increase the risk of *S. aureus* carriage [1]. Despite various infection control strategies receiving increased attention, about 20% of patients undergoing surgery still acquire at least one nosocomial infection [1].

HCWs have been reported to have rates of *S. aureus* nasal carriage comparable to the general population in different cross-sectional studies [46, 277] but the range of carriage rates is large possibly due to differences in the quality of sampling and culture techniques as summarized by Kluytmans et al [46]. Recent reports have revealed higher *S. aureus* nasal carriage rates among surgeons than among high-risk patients groups [278], among physicians compared with other professionals in the society [279], and among nurses compared to other HCWs [280, 281]. This supports the view that working in healthcare services with substantial patient contact may be a risk factor for carriage.

Nearly 20% of *S. aureus* nosocomial infections have an exogenous origin [25, 26, 43], where HCWs may serve as an important vector. Colonized HCWs are capable of transmitting *S. aureus* to patients [1, 282, 283], and of introducing *S. aureus* into their families [270-272]. The bacterium can also be reintroduced into the hospital by intrafamilial spread from and to healthcare workers [270, 272]. The typical transmission route of *S. aureus* from HCWs to patients appears to be transiently contaminated hands of HCWs, who have acquired the microorganism from their nose, by direct patient contact, by direct contact with their family members or by handling contaminated materials [272, 282, 283].

In general, many of the studies in healthcare settings may have been biased by a lack of information on background prevalence in the relevant general population as well as in households. Thus, the role of working in healthcare settings as well as exposures in households as independent risk factors for *S. aureus* colonization in a general population may need further research.

2. AIMS OF THE THESIS

The main objectives of this thesis were to investigate whether sex, metabolic and hormonal profiles such as serum 25(OH)D levels and obesity, and environmental factors such as current daily smoking, being a healthcare worker and residing with children are associated with *S. aureus* nasal colonization and carriage in an adult general population. Also, host susceptibility and- environmental factors and their associations with *S. aureus spa* types were explored to contribute to the knowledge on possible interactions between *S. aureus* strains, the host and the environment for nasal carriage.

The aims of this thesis were:

- to examine the relationship between serum 25(OH)D concentration and *S. aureus* nasal colonization and carriage among men and women in a unselected general population.

- to investigate whether excess body weight and abdominal adiposity are associated with *S. aureus* nasal colonization independent of pre-diabetes and diabetes among women and men in an unselected general population.

- to study whether being a healthcare worker is associated with *S. aureus n*asal carriage overall and certain *S. aureus spa* types compared with non-healthcare workers and if residing with children influences the odds of *S. aureus* nasal carriage and *spa* types among women and men in an unselected general population.

3. MATERIAL AND METHODS

3.1 The Study population-The Tromsø Staph and Skin Study (TSSS)

The Tromsø Study is a longitudinal population-based multipurpose study with five previous surveys undertaken between 1974–2001. These were all focused on lifestyle-related diseases [284, 285]. The sixth survey (Tromsø 6) was carried out from October 2007 to December 2008 in the municipality of Tromsø. Based on the official population registry, residents of the municipality of Tromsø were invited to take part in the survey. The subjects who were invited included all residents in Tromsø aged 40–42 and 60–87 years (N=12,578), a 10% random sample of individuals aged 30–39 years (N = 1,056), a 40% random sample of individuals aged 43–59 years (N = 5,787), and all subjects who had attended the second visit in Tromsø 4, if not already included in the three groups mentioned above (N = 341; in **Paper III**, the number N = 295 is incorrect). Of the total of 19,762 invited, 12,984 men and women aged 30–87 years attended Tromsø 6 (65.7%). Women constituted 51.3% of the invited and 53.4% of the participants [284, 285].

The Tromsø Staph and Skin Study (TSSS) was part of the Tromsø 6. For the study of *S. aureus* nasal colonization in the TSSS, a more evenly distributed sampling across age groups was considered to be suitable and the inclusion of 4,000 observations to be sufficient for subgroup analysis of host-microbe relationships. Thus, TSSS collected nasal swab cultures during October 2007 to June 2008. The eligible group was all participants in Tromsø 6 aged 30–49 years (N = 1,730) and random samples of older participants aged 50–87 years (N = 2,629, relative distribution of birth cohorts as in the municipality). A total of 4,026 men and women aged 30–87 years **(**30–49 years, N = 1,597; 50–87 years, N = 2,429) had a nasal swab culture taken and were included in the TSSS at the first visit. Of these, 2,997 subjects (30–49 years, N = 1,118; 50-87 years, N = 1,879) had a repeated culture taken (Figure 6). The median interval between cultures was 28 days and for 90% of the observations the interval was ≥12 days.

Ethics

The study was approved by the Regional Committee of Medical and Health Research Ethics, North Norway, and all attendees signed an informed consent form. Interviews, clinical examinations, nasal swab cultures, and blood samples were performed according to standardized procedures by trained healthcare personnel at the screening centre. Two self-

administered structured questionnaires covered a broad range of issues related to socioeconomic status, lifestyle, health and disease. Further information about the Tromsø Study, including invitation letter, consent form and questionnaires is available at the study web pages www.tromsoundersokelsen.no, for questionnaires, please, also see Appendices A – D.

3.1.1 Study population - Paper I-III

The study population in **Paper I** consisted of participants with either a single nasal swab culture (taken at the first visit) or double nasal swab cultures (taken at first and second visit). Participants with missing data on serum 25(OH)D (N = 60) or smoking status (N = 48) and those without valid swab cultures at the first and the second visit (first swab N = 129, second swab N = 49), were excluded. Thus, we included 3,789 participants with a minimum of one nasal swab culture for analysis of *S. aureus* nasal colonization, and 2,780 participants with two nasal swab cultures for the analysis of *S. aureus* nasal carriage (Figure 6).

The study population in **Paper II** consisted of participants who attended the first visit. Thus, the *S. aureus* colonization state was determined by a single nasal swab culture taken at the first visit. This decision was based on the evaluation of the agreement between culturing results in a sub-cohort of the TSSS including 2,868 participants with two valid swab cultures. These participants had made a second visit to the screening centre and had a second nasal swab culture taken after a median time of 28 days. In 90% of these participants the interval was ≥12 days, and only 113 of the 2,868 participants (3.9%) were misclassified as colonized from the culturing results of the first nasal swab (i.e. first swab culture positive and second swab culture negative). Among those with two positive swab cultures (N = 727), 669 participants (92%) had the same *spa* type in both samples. Among the 4,026 participants aged 30–87 years who attended the first visit, 129 nasal swab cultures were considered invalid due to the use of antibiotics within the last 24 hours (N = 27) or no bacterial growth in cultures (N = 102). Pregnant women (N = 15) and participants with missing height and/or weight data (N = 4) were excluded, leaving 3,878 participants for analysis of BMI. In addition, 103 participants with missing WC data were excluded, leaving 3,775 participants for analysis of WC (Figure 6).

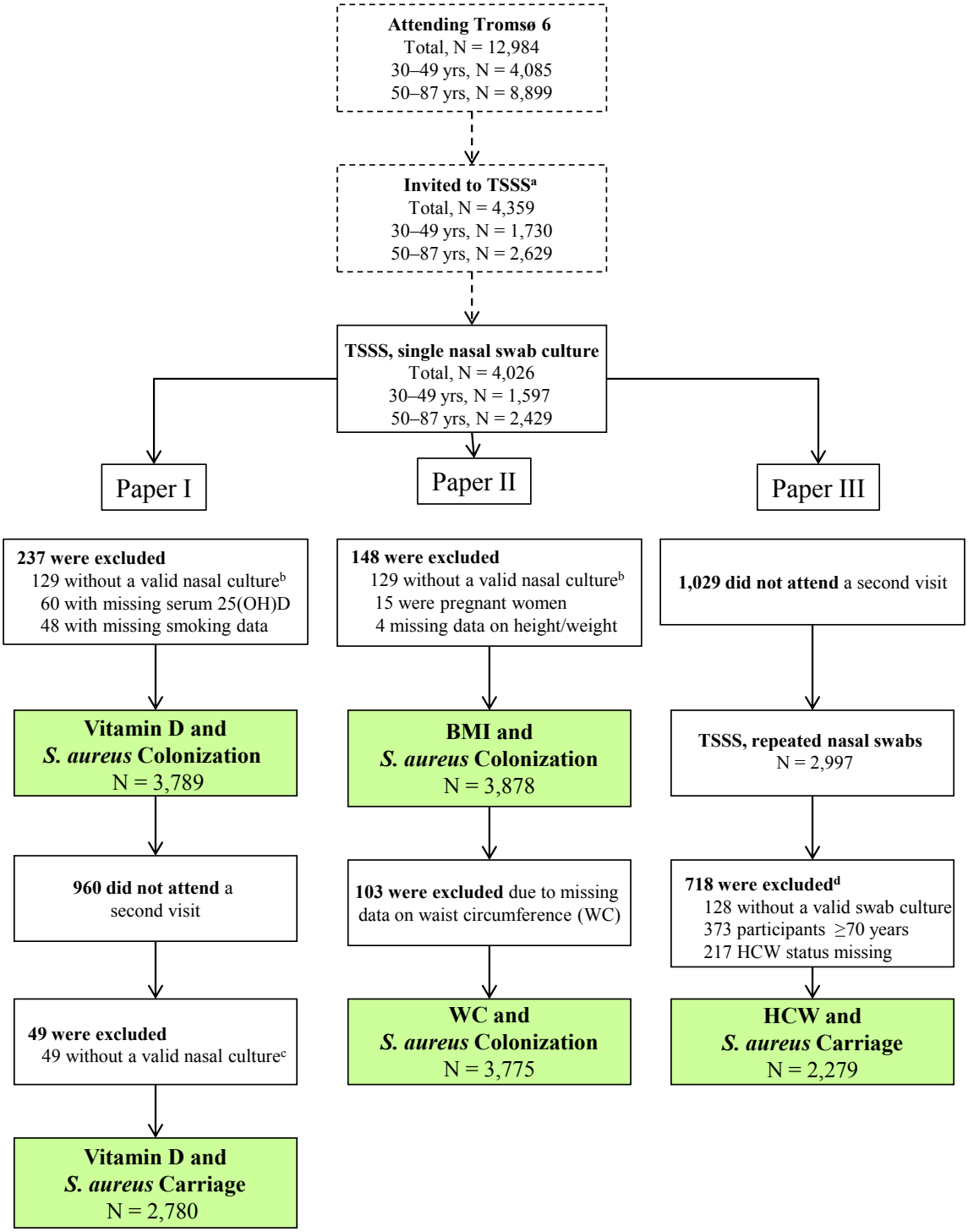


Figure 6. The study populations of The Tromsø 6 and The Tromsø Staph and Skin Study, Papers I-III. [a] Invited to The Tromsø Staph and Skin Study. Age group <50 years: all subjects. Age group 50–87 years: random samples of subjects. [b] Not valid swab culture at the first visit: 102 had no growth in swab culture and 27 had taken antibiotics last 24 hours before visit (systemic or eye drops/ointments). [c] Not valid swab culture at the second visit: 35 had not growth in swab culture and 14 had taken antibiotics last 24 hours before visit (systemic or eye drops/ointments). [d] Of the 2,997 participants with a repeated nasal swab culture, 718 participants were excluded. Abbrevations: TSSS, The Tromsø Staph and Skin Study; BMI, body mass index; WC, waist circumference; HCW, Healthcare worker.

The study population in **Paper III** consisted of participants with a double set of nasal swab cultures taken (first and second visit). Of the 2,997 participants 30–87 years who had repeated nasal swab cultures taken, a total of 373 subjects aged 70 years or more were excluded due to normal age of retirement in Norway, 217 subjects had missing data on HCW status, and 128 had no valid swab cultures. Thus, for the present analysis 2,279 participants aged 30–69 were included (Figure 6).

3.2 Measurements

3.2.1 Assessment of S. aureus nasal colonization/carriage

Both vestibuli nasi were sampled by the same NaCl-moistened sterile rayon-tipped swab and placed in Amies charcoal transport medium (Copan, Brescia, Italy). Within three days, all specimens were cultured on blood agar (Oxoid, Cambridge, UK), chromId™ *S. aureus* and chromId™ MRSA agars (bioMérieux, Marcy I'Etoile, France) and incubated for 42–48 hours at 37°C. If positive (green) colonies were found on the chromId plates, the most dominating colony was selected and confirmed as *S. aureus* by the Staphaurex Plus (Remel, Lenexa, KS, USA) agglutination test. All *S. aureus* isolates were frozen at –70°C in glycerol-containing liquid media. No MRSA was detected. In **Paper I** and **II** the *S. aureus* nasal colonization state was defined as positive or negative for *S. aureus* in the first nasal sample. In **Paper I** and **III**, the carrier state was based on the culturing results of two consecutive samples; carrier = two positive samples and non-carrier (intermittent carrier) = one or none positive sample [64].

3.2.2 spa *typing*

S. aureus isolates from frozen cultures (–70°C) in glycerol-containing medium were inoculated on blood agar (Oxoid) and incubated overnight at 37°C. 2–3 colonies were transferred to 200 µl dH_2O and vortexed. The isolates were *spa* typed using the primers *spa*-1113f and *spa*-1514r with the following cycling conditions: 95°C for 10 min; 35 cycles of 95°C for 30 s, 60°C for 15 s, and 72°C for 1 min; and 72°C for 10 min and then kept at 4°C as described previously [286, 287]. PCR products were sequenced on both strands by Macrogen Korea or Macrogen Europe, and *spa* types were assigned using Ridom StaphType software (Ridom GmbH, Würzburg, Germany) [87]. *spa*

types were obtained from 99% of the isolates, and 364 unique *spa* types were assigned according to the Ridom StaphType software in the first visit. Six isolates were not typed due to repeated negative *spa* PCR amplification or deviating repeat length.

3.2.3 Questionnaires

Healthcare workers

Self-reported information on work in the healthcare services was obtained by the interview question 'Do you work in healthcare services (hospitals, nursing home, senior care service, general practitioner (GP)´s office, and public health centre) ?' (Yes/No) (Appendices C and D).

Two self-administered questionnaires were filled out and checked for any errors at the screening center by the interviewers (Appendices A and B).

Smoking

Smoking status was determined from the question 'Do you/Did you smoke daily?' (Yes, now/Yes, previously/Never) and recoded into 'Current daily smoking' (Yes/No). If you currently smoke, how many cigarettes do you usually smoke per day? and if you currently smoke, how many years in all have you smoked daily?

Other variables

Alcohol intake was determined from the question 'How often do you usually drink alcohol?' (Never/Monthly or more infrequently/2–4 times a month/2–3 times a week/4 or more times a week) and dichotomized into two categories (< or ≥2–3 times/week). Physical activity was obtained through the following: 'Exercise and physical exertion in leisure time the last twelve months was divided in four levels' (Reading, watching TV, or other sedentary activity?/Walking, cycling, or other forms of exercise at least 4 hours a week including walking or cycling to place of work, Sunday-walking, etc.?/ Participation in recreational sports, heavy gardening etc. duration of activity at least 4 hours a week?/Participation in hard training or sports competitions, regularly several times a week?). The response categories were recoded to three levels with the two upper categories merged.

Residing with children was determined from the question 'Do you live with people younger than 18 years of age?'(Yes/No). Education level was determined from the question

'What is the highest level of education you have completed?' (Primary, Secondary/Secondary, O-level (GCSE)/A-level/college, university) recoded into two levels (< or ≥ college, university). Total household income was determined from 'What is the household's total taxable income last year? Include income from work, social benefits and similar', and dichotomized into < or ≥ level of the lowest income quintile (37,000 Euro/years).

Use of hormonal contraceptives was determined from the question 'Do you currently use any prescription drug that influences the menstruation? Including oral or dermal contraceptives, intra uterine device with hormones or similar' (Yes/No). Diabetes status was determined from the question 'Do you have or have you had diabetes?' (Yes/No). The information available did not permit subclassification of type 1 or type 2 diabetes mellitus (DM). Atopic eczema was determined from the question' Have you ever been diagnosed with atopic eczema by a physician?' (Yes/No). Psoriasis was determined from the question 'Have you ever been diagnosed with psoriasis by a physician?'(Yes/No). Recent hospitalization was determined from the question 'Have you during the past year been admitted to a hospital?' (Yes/No).

3.2.4 Clinical examiniation

Body height in centimetres (cm) and weight in kilograms (kg) were electronically measured to the nearest 0.1 unit wearing light clothing and no shoes (Jenix DS 102 stadiometer, Dong Sahn Jenix, Seoul, Korea). BMI was calculated as weight divided by height squared (kg/m^2) [284]. WC was measured without outerwear by using a measuring tape. WC was measured at the umbilical line to the nearest cm [284]. The World Health Organization (WHO) defines BMI ≥30.0 kg/m^2 as obesity and WC values >88 cm and >102 cm in women and men, respectively, as high risk abdominal obesity [234, 243].

3.2.5 Blood samples

Non-fasting blood samples were collected from an antecubal vein and were taken throughout the survey opening hours. Serum was prepared by centrifugation after 30 minutes respite at room temperature and analysed at the Department of Medical Biochemistry at the University Hospital of North Norway.

Vitamin D

The sera were consecutively analysed for 25(OH)D by immunometry (electrochemiluminescence immunoassay), using an automated clinical chemistry analyser (Modular E170; Roche Diagnostics) [288, 289]. The total analytical coefficient of variation (CV) was 7.3%. This was in accordance with the total analytic precision reported from the producer, where the CV was ≤7.8% as judged in any of the three different concentrations (48.6–73.8–177.0 nmol/l). The cross-reactivity with 25(OH)D_2 was <10% and the detection limit was 10 nmol/l. This analysis has been approved by the Norwegian Accreditation Authority. It has recently been found that smokers have 15–20% higher serum 25(OH)D levels than non-smokers when this method was used. The same effect of smoking was not detected when measuring serum 25(OH)D with other immunological methods or the liquid chromatography mass spectrometry (LC-MS) method [290]. We presently do not have an explanation for this discrepancy. Thus, in **Paper I** non-smokers and smokers are analysed separately.

HbA1c

HbA1c was measured from EDTA-blood samples and determined by high performance liquid chromatography (HPLC) using an automated analyzer (Variant II, Bio-Rad Laboratories INC., Hercules, CA, USA) the day after blood sampling. The reference interval was 4.3–6.1% and the total analytical coefficient of variation (CV) was <3.0%. This analysis has been certified by the National Glycohemoglobin Standardization Program (NGSP) as having documented traceability to the Diabetes Control and Complication Trial (DCCT) reference method [291]. The laboratory analysis was approved by the Norwegian Accreditation Authority. HbA1c has recently been recommended by the World Health Organization (WHO) and the American Diabetes Association (ADA) as an alternative to measurements of glucose levels in diagnosing pre-diabetes and diabetes, and an international expert committee has proposed cut-off values for pre-diabetes (HbA1c 6.0–6.4%) and diabetes (HbA1c ≥6.5%) [292].

3.2.6 Statistical analysis

Logistic regression models were used to test whether metabolic and hormonal profiles and environmental factors were associated with *S. aureus* nasal colonization and carriage with estimation of Odds Ratios (ORs) and 95% confidence intervals (CIs). Multiple logistic

regression models to evaluate the joint statistical significance of several independent variables in relation to the outcome variables were used. As studies have identified higher *S. aureus* nasal carriage rates among men as compared to women [68, 154, 155, 162] and previous reports have shown that predictors of *S. aureus* nasal carriage may vary by sex [154], the regression models were stratified by sex. Tests for interaction were performed by inclusion of multiplicative terms in the models. Tests of reliability of the final analyses were done by the Hosmer-Lemeshow goodness of fit test.

In **Paper I**, logistic regression models were used to study the association between serum 25(OH)D and *S. aureus* colonization and carriage (single and double set of nasal swab cultures). The models were stratified by sex and smoking status [290]. As established thresholds for the associations between serum 25(OH)D and *S. aureus* nasal colonization and carriage are lacking, serum 25(OH)D tertiles were selected as suitable for the samples; non-smokers: <44.9 nmol/l, 44.9–58.6 nmol/l, >58.6 nmol/l; and smokers: <59.6 nmol/l, 59.6–75.3 nmol/l, >75.3 nmol/l. Also, proposed cut-points for vitamin D deficiency/insufficiency were examined (i.e. <50.0, 50.0– <75.0, ≥75.0 nmol/l) among non-smokers [208]. Selected characteristics of men and women in the different serum 25(OH)D tertiles were compared by oneway ANOVA and Kruskal-Wallis test for continuous variables and two-sided Pearson chi-squared test for categorical variables. We evaluated model fit and biological plausibility of several covariates and the final multivariable models included age, BMI, DM (yes/no), and calendar month (2 months categories), and in smokers also number of cigarettes smoked per day and total years smoked [154, 161, 162, 290, 293-295].

In **Paper II**, as established thresholds for the associations between BMI, WC and *S. aureus* nasal colonization are lacking, BMI categories (<22.5, 22.5 –<25.0, 25.0 –<27.5, 27.5 –<30.0, 30.0 –<32.5, ≥32.5 kg/m^2), WC quintiles among women (< 80, 80–86, 87–92, 93–100, ≥101 cm) and WC quintiles among men (<91, 91–95, 96–101, 102–107, ≥108 cm) were defined. Selected characteristics of women and men were compared using age adjusted regression analysis with linear *Ptrend* across all BMI categories. On the basis of biological plausibility and model fit, the variables age (continuous), DM, current daily smoking, education level, and total household income were included as covariates in the multivariable model [154, 155, 161, 162, 296]. Possible interactions with age in logistic regression models stratified by age tertiles (30–43, 44–59, and 60–87 years) for both sexes and by proposed pre-/postmenopausal age ranges (<55 and ≥55 years) among women were explored by inclusion of multiplicative terms in the models. To control for possible confounding by pre-diabetes and undiagnosed diabetes, sensitivity analysis restricted to those with HbA1c < 6.0% (N = 3,207)

was performed. To control for possible confounding by exogenous reproductive hormones, additional restriction analysis, including only non-users of hormonal contraceptives, was performed among young and premenopausal women [156].

Tests for linear trend in **Paper I** and **II** were performed by assigning consecutive integers to each serum 25(OH)D tertiles- and categories, BMI categories and WC quintiles, and testing whether the slope coefficient differed from zero by using the Wald chi-square test. Tests of statistical significance of the interaction terms were done by the likelihood ratio test comparing models with and without the multiplicative interaction terms.

In **Paper III**, selected characteristics of HCW and non-HCW were compared by two-sided Student's t-test for continuous variables and two-sided Pearson chi-squared/Fisher's exact test for categorical variables. Multivariable logistic regression models were used with adjustments of possible confounders. We tested whether residing with children modified the association between HCW status and *S. aureus nasal* carriage in stratified logistic regression analysis. Test for interaction was done by inclusion of the multiplicative terms of the two predictor variables in the model.

The analysis of *spa* types was restricted to the first visit's nasal swab culture as persistent *S. aureus* nasal carriage is not defined as concordance of *spa* types in repeated samples but as overall growth of *S. aureus* in repeated samples. The six predominant *spa* types were chosen and the logistic regression models where age- and sex adjusted [287]. In general, all tests were done two sided, and significance level was set at 0.05. Normal distribution of the continuous variables was assessed by visual inspection of histograms and where non-normality were found, ANOVA with the non-parametric Kruskal Wallis test were used for the continuous variables.

In all the three papers, subjects with missing data were excluded from the analyses.

Power calculations were performed for some of the predictors before the data collection and 4000 participants were considered to be sufficient for subgroup analysis of host-microbe relationships. Further power calculations for the same predictors were also carried out to test whether the number of participants achieved with a double set of nasal swab cultures were sufficient for subgroup analysis (See Table 1 and 2).

Table 1. Power calculations for continuous predictor variables. Tromsø Staph and Skin Study N = 2,986. Persistent *S. aureus* nasal carriers: N = 747 (25%). Non-persistent *S. aureus* nasal carriers: N = 2,239.

Predictor variable	Mean*	SD*	**Statistical Power %** Difference in mean between the two carrier groups			
			2.5%	5%	10%	15%
Serum Vit 25-OH-D3 (mmol/l)	60.9	19.2	**48**	**96**	**100**	**100**
Serum Glucose (mmol/l)	5.2	1.2	**73**	**99**	**100**	
Serum HbA1c (%)	5.6	0.7	**99**	**100**		
Waist Circumference (cm)	94.9	12.2	**99**	**100**		

* Total study population in the Sixth Tromsø Study. SD = standard deviation

Table 2. Power calculations for categorical predictor variables. Tromsø Staph and Skin Study N = 2,986. Persistent *S. aureus* nasal carriers: N = 747 (25%). Non-persistent *S. aureus* nasal carriers: N = 2,239.

Predictor variable	Prevalence in carriers*	**Statistical Power %** Absolute increase in prevalence in non-persistent carriers			
		2%	4%	6%	8%
Ex. Current Smoking Low level of leisure physical activity	20%	**22**	**64**	**93**	**99**

* Estimate based on the total study population in the Sixth Tromsø Study.

4. SUMMARY OF MAIN RESULTS

4.1 Paper I

Staphylococcus aureus *nasal carriage is associated with serum 25-hydroxyvitamin D levels, gender and smoking status.The Tromsø Staph and Skin Study*.

- The prevalence of *S. aureus* nasal colonization and carriage was 37.5% (506/1,351) and 34.1% (338/992) among non-smoking men, and 24.4% (403/1,655) and 21.3% (264/1,239) among non-smoking women, respectively.
- In non-smoking men, we observed a 6.6% and 6.7% decrease in the probability of *S. aureus* colonization and carriage, respectively, for each 5 nmol/l increase in serum 25(OH)D concentration (*P<0.001 and P=0.001; unadjusted*).
- There was a 35% and 33% reduction in odds of colonization and carriage in upper *versus* bottom tertile of serum 25(OH)D among non-smoking men, (OR, 0.65; 95% CI, 0.49–0.87; *Ptrend* = 0.004, and OR, 0.67; 95% CI, 0.48–0.95; *Ptrend* = 0.03, respectively) and those with serum 25(OH)D concentration ≥75 nmol/l versus <50 nmol/l had almost half the odds of *S. aureus* colonization and carriage (OR, 0.54; 95% CI, 0.35–0.84; *Ptrend* = 0.004, and OR, 0.52; 95% CI, 0.31–0.90; *Ptrend* = 0.02, respectively).
- In non-smoking men aged 44–60 years, the odds ratio for *S. aureus* colonization and carriage was 0.44 and 0.51, (95% confidence interval, 0.28−0.69; *Ptrend* <0.001 and 95% CI, 0.30-0.88; *P* for trend, 0.02, respectively) in the top tertile versus the bottom tertile of serum 25(OH)D, while in younger and older adult men no association was observed (*P* for interaction = 0.10 and 0.45, respectively).
- In the smoking population, average vitamin D concentration was higher than in non-smokers; mean serum 25(OH)D concentration was 66.8 nmol/l among men and 71.3 nmol/l among women.
- The prevalence of *S. aureus* nasal colonization and carriage was 29.1% (94/323) and 24.5% (57/233) among smoking men, and 18.3% (84/460) and 15.2% (48/316) among smoking women, respectively. All the prevalence rates were significantly lower than in non-smokers (all *P*-values < 0.05).

- We did not observe any associations between serum 25(OH)D concentration and *S. aureus* nasal colonization or carriage rates either among non-smoking and smoking women or among smoking men.

4.2 Paper II

Obesity and* Staphylococcus aureus *nasal colonization among women and men in a general population.

- There was a positive relationship between BMI and *S. aureus* nasal colonization among women. For each 2.5 kg/m^2 increase in BMI a 7% increase in the odds of *S. aureus* nasal colonization was observed (multivariable model; OR 1.07, 95% CI 1.01–1.14).
- Among women, the odds of *S. aureus* nasal colonization was 67% higher in those with BMI ≥32.5 versus <22.5 kg/m^2 (OR, 1.67; 95% CI 1.11–2.52).
- When comparing obese and lean women aged 30–43 years, we observed that BMI ≥ 32.5 versus <22.5 kg/m^2 and WC ≥101 versus <80 cm were associated with a 2.60 and 2.12 times higher odds of *S. aureus* colonization, respectively (95% confidence intervals [CI] 1.35–4.98 and 95% CI 1.17–3.85).
- When comparing obese and lean women aged 30–54 years, we observed that BMI ≥ 32.5 versus <22.5 kg/m^2 and WC ≥101 versus <80 cm were essentially unchanged compared with women aged 30–43 years.
- When restricting the analysis to those with HbA_{1c} <6.0%, the estimated ORs for the relationships between BMI and S. *aureus* nasal colonization for women 30–43 years (*P* for interaction = 0.03), and 30–54 years (*P* for interaction = 0.67), remained essentially unchanged. Also, regarding the analysis of WC restricted to those with HbA_{1c} <6.0%, the estimated ORs among women and men remained essentially unchanged.
- Among women aged 30–43 and 30–54 years, further sensitivity analyses to non-users of hormonal contraceptives did not change the results significantly.
- BMI was not associated with *S. aureus* nasal colonization among men, but for men aged 30–43 years, being in the 5th and 1st WC quintiles (≥108 and <91cm) were both

associated with a 1.88 times higher odds of *S. aureus* nasal colonization, compared to being in the 4th WC quintile (95% CI 1.01–3.49 and 95% CI 1.08–3.28).

4.3 Paper III

Prevalence and population structure of Staphylococcus aureus nasal carriage among healthcare workers in a general population. The Tromsø Staph and Skin Study.

- HCWs comprised 25.7% (334/1,302) women and 7.3% 71/977 men. HCWs were younger than non-HCWs among both women and men (both *P*-values < 0.05).
  The overall prevalence of *S. aureus* nasal carriage was 26.2 % in HCWs and 26.0 % in non-HCWs. The corresponding sex-specific rates were 22.5% and 18.4 % in women (*P* = 0.11), and 43.7% and 34.1% in men (*P* = 0.10), respectively.
- Although HCW status in the total population was not associated with *S. aureus* nasal carriage in multivariable analysis, among women, HCWs had 54% higher odds of *S. aureus* nasal carriage versus non-HCWs (OR 1.54, 95% CI 1.09–2.19). In men, no such differences were observed.
- Among women residing with children, HCWs had an 86% higher odds of *S. aureus* nasal carriage compared with non-HCWs (multivariable analysis: OR 1.86, 95% CI 1.14– 3.04), whereas among women not residing with children there was no difference in odds by HCW status (*P* for interaction = 0.42), and for men, there was no pattern of effect modification by family status.
- The majority of *spa* types were observed in both HCWs and non-HCW.
- Among *S. aureus* nasal carriers, HCWs had 2.17 and 3.16 times higher odds of *spa* types t012 and t015 in the first sample, respectively, compared with non-HCWs (multivariable analysis: OR 2.17, 95% CI 1.16–4.08 and OR 3.16, 95% CI 1.13–8.87).
- For nasal carriers residing with children, HCWs had a 2.42 times higher odds of *spa* type t012 compared with non-HCWs (age- and sex-adjusted analysis: OR 2.42, 95% CI 1.03–5.70), and this association was particularly strong in male nasal carriers (age-adjusted analysis: OR 4.61, 95% CI 1.36–15.61).

5. DISCUSSION

5.1 Discussion–methodology

5.1.1 Considerations of internal validity

Epidemiological observational studies are prone to limitations regarding the validity of the findings. Internal validity refers to whether the findings are true for the population studied, while external validity refers to whether the findings also apply to populations not studied. The cross-sectional study design of this study is prone to the important limitation regarding temporality. The temporal relationship between the exposure and outcome is not clear, thus, the study design is useful for finding associations and creating hypotheses, but will not give clear answers with regard to causal relationship between exposure and outcome.

5.1.1.1 Study design

The Tromsø Staph and Skin Study is the first attempt in Norway to address the prevalence as well as the bacterial, host and environmental determinants of *S. aureus* nasal carriage in a large population-based study. Our results were in concordance with a recent study of 348 individuals who visited two shopping centers in Southern Norway during the period 2001–2005, regarding overall *S. aureus* nasal carriage rates, sex differences and predominating *S. aureus* clones [287, 297]. Furthermore, two other previous smaller Norwegian studies regarding *S. aureus* carriage in hospital settings have been performed [298, 299].

However, we aimed to describe a large unselected population of 4,026 participants of community-living adult women and men as distinct from hospital in-patients in order to better understand the interaction between microbial, host and environmental determinants for *S.aureus* carriage. The chosen population-based study design was important for the generalizability of the results in relation to the aims of our study.

5.1.1.2 Study population–Selection bias

The random population selection, high attendance rate (65.7%) and the age range 30–87 years in the sixth Tromsø Study, may reduce the risk of selection bias and increase both the internal and external validity, thus, the findings may be true for the population studied and the study

population may represent the general population of the Tromsø area [284]. However, the attendance rate varied substantially between the age groups, being 47% in the age group 30–39 years, 60% in the age group 40–49 years, 71% in the age group 50–59 years, 74% in the age group 60–79 years, and 40% in the age group 80–87 years [284]. Thus, in summary, the younger and very old subjects were underrepresented in the survey due to low attendance rates. Furthermore, the population in age group <30 years was not invited at all [284, 285].

For the study of *S. aureus* nasal colonization in the TSSS, a more evenly distributed sampling across age groups was considered to be suitable and the inclusion of 4,000 observations to be sufficient for subgroup analysis of host-microbe relationships. Of the eligible group included (N = 4,359), the attendance rate for the TSSS was 92.4% (Figure 6). The lack of participants in the age group <30 years, implies that the findings in the study are only generalizable to the age group 30–87 years, and in Paper III, in particular, the lack of participant <30 years may represent a limitation of the study as the prevalence of *S. aureus* carriage is higher in younger compared with older adults. Thus, the role of work in healthcare services for carriage among the working population below 30 years should be addressed in further studies.

Differences in motivation (little interest in health screening, which could give lower participation rates among younger adults-a trend in the Tromsø Study as well as in other population studies both in Norway and internationally) [284, 285] or other obstacles (e.g. nursing home residence, chronically ill or bedridden patients and homeless people) to participate can produce a non-response bias among certain subgroups. Thus, participants in this study may represent a healthier population compared to non-participants and thus have lower rates of *S. aureus* nasal carriage [1, 284, 285]. Also, women had an overall higher attendance rate than men (68.4 vs. 62.9%) increasing the generalizability for the female part of the population [285].

5.1.1.3 Misclassification bias

Misclassification bias results from a systematic tendency for individuals selected for inclusion in the study to be erroneously placed in different exposure/outcome categories, thus leading to misclassification [300]. This misclassification can be differential or non-differential, depending on whether the degree of misclassification of exposure is dependent on the outcome or not, respectively. Whereas non-differential misclassification tends to weaken true

associations, the direction of the bias when differential misclassification occurs is difficult to predict [300].

The outcome variable–S. aureus nasal colonization and carriage

The sampling procedure and frequency as well as the culturing methods gives possibilities for misclassification of the *S. aureus* nasal colonization and carriage state in the current study. The nasal swabs were collected with well established methods [57] by a team of technicians, mostly nurses. Before the screening, technicians were trained in the sampling techniques and the standard procedures were specified in a protocol. In spite of this, we recognized that growth of any bacteria on the control blood agar plates in some of the nasal cultures was poor or even totally lacking, possibly caused by inadequately performed sampling. Repeated quality control activities were performed including training and observation of the technicians who did the sampling, and the swab cultures with no growth of any bacteria on both the control blood agar- and the chromId^{TM} *S. aureus* plates were excluded from the analyses. Also, a validation study among 108 participants of the TSSS after the quality control activity, revealed that the inter-rater reliability for nasal swab cultures taken by different technicians, was excellent (simple kappa = 0.94; 95% CI = 0.87–1.00) [301].

The number of samplings required to identify persistent carriers has been debated over time, and the more samplings that are performed and the longer time interval the carrier carries the same strain, the more accurate the classification [57, 64, 302]. We used two nasal swab cultures with a time period between the first and the second swab of 0–124 days (median 28 days and in 90% of the observations the interval was ≥12 days). According to the "culture rule" proposed by Nouwen et al [57], in the validation study among 108 participants in the TSSS, we also assessed the concordance between *S. aureus* culturing results comparing samplings a 1-week apart with a flexible interval of 2–6 weeks. The inter-method reliability or validity was excellent for nasal carriage (weighted kappa = 0.85; 95 % CI= 0.77–0.92) [301]. However, a recent work showed that the transiently colonized subjects carried the organism for a median of 14 days [64]. The large scale screening setting in the TSSS did not allow us to strictly follow the most optimal interval of 14 days or more. Consequently the inclusion of a second sample after a shorter interval than 14 days, may have increased the risk of misclassifying some of the participants (N = 104 with two positive cultures) into the persistent carrier group.

The rationale for using the result of a single nasal swab culture to assess *S. aureus* nasal colonization state as "a proxy" for *S. aureus* nasal carriage in **Paper II** was developed from the analysis of the same sub-cohort of 2,868 participants in the TSSS who had a valid nasal swab culture taken at two different time points. We observed that only 113 of the 2,868 participants (3.9%) were misclassified as colonized from the culturing results from the first nasal swab (i.e. first swab culture positive and second swab culture negative). Furthermore, when using results of both swab cultures, 2,141 of 2,868 participants were classified as non- or transiently colonized, whereas 2,028 participants were classified as non-colonized when only the results from the first sampling were used. The concordance was thus very high with a specificity of 94.7% (2,028/2,141). Moreover, among those with two positive nasal swab cultures, 92% had the same *spa* type in both samples supporting some degree of persistency. Taken together, the high concordance of the culture results in first and second samples taken with a median time interval of 28 days implies that the use of a single nasal swab culture to assess *S. aureus* nasal colonization state as "a proxy" for *S. aureus* nasal carriage in our study may be justified.

Another important issue that could have affected the data quality of the outcome variable is the laboratory method without use of enrichment broths for analysing the swab cultures. In a recent survey of about 990 high-school students (FitFutures) which is part of the Tromsø Study, we found the sensitivity of direct plating of nasal swab cultures to be 77.2% compared with using enrichment broths (unpublished data). A number of studies have estimated the prevalence of *S. aureus* nasal colonization in the general population to be approximately 20–32% [1, 59, 154, 157]. In the present study, we observed a prevalence of *S. aureus* nasal colonization (first culture positive) and carriage (both cultures positive) of 28.7% and 25.4%, respectively) which shows good concordance with previous reports. Thus, based on a cost-effectiveness analysis, we chose to omit the enrichment step. The culturing method may have led to reduced sensitivity resulting in false-negatives by misclassifying some of the study participants as non-persistent nasal carriers when their true status should have been persistent carriers. On the other hand, the chosen culture method may have increased the specificity of the *S. aureus* nasal carriage state reducing the amount of intermittent carriers and those persistent carriers with low numbers of colony forming units (CFUs).

The nares were the only body site sampled, whereas colonization may occur also in other sites such as the throat, skin, perineum and gastrointestinal tract [1, 3, 46-49]. However, as decolonization of the nose usually has a decolonizing effect on skin, the nose is assumed to be the major site of *S. aureus* colonization [42, 54, 55]. Also, nasal carriage of the microbe

has been identified as an important risk factor for the development of *S. aureus* nosocomial infections [25, 26]. When considering the main aims of this study, nasal carriage therefore seems to play a key role.

Overall, we would expect the possible misclassifications of the outcome to be independent of the exposures, i.e. non-differential, as the study design was cross-sectional implying that neither the participants nor screening personnel would know the culturing results during the data collection. The possible misclassifications would thus attenuate the associations between the predictors and outcome.

The exposure variable–Serum 25(OH)D

In a validation study, based on data and material in the Tromsø Study, it was recently observed that smokers had 15–20% higher serum 25(OH)D levels than non-smokers when using the ECLIA (Roche) method but not when using other immunological and liquid-chromatography mass spectrometry methods [290]. Also, there was a clear dose-response relationship between the serum 25(OH)D levels and the amount of smoking and the number of years of smoking as well as overall current smoking status [290]. We do not at present have any explanation for this discrepancy, but the measurement error has led to a differential misclassification of the serum 25(OH)D levels; i.e. relatively more smokers have been classified in the higher serum 25(OH)D tertiles and categories as compared to non-smokers (**Paper I**). Furthermore, as current smoking is a known determinant reducing the risk of *S. aureus* nasal colonization and carriage, these relationships may have led to an overestimation of the association between serum 25(OH)D and *S. aureus* nasal colonization and carriage if we had analysed non-smokers and smokers together. These factors were important reasons for stratifying by smoking status in **Paper I**. Also, non-respondent participants regarding smoking status were excluded from the analysis.

The exposure variable–Healthcare worker status

In **Paper III**, self-reported information on current healthcare-associated environmental exposure was obtained by interviews (Appendices C and D). There was no information about the actual healthcare professions or in which part of the healthcare services the participants' worked in. This has probably resulted in a less precise exposure variable. Previous studies may support that the risk of *S. aureus* carriage could differ depending on the type of healthcare profession and in which part of the healthcare services the study participants work

[280, 281]. Thus, more precise information about actual jobs and working tasks would have improved the validity of this exposure variable. The imperfect definition of this exposure variable may have obscured/diluted the associations between being a "high risk healthcare worker" in hospitals and the outcome variable. Taking into account the cross-sectional study design, this misclassification would be expected to be non-differential, possibly attenuating our findings.

Furthermore, changes in the data collection regarding this variable led to missing information on healthcare worker status (N = 217) until the fifth week of the survey. However, the 217 subjects with missing data on the healthcare-associated environmental exposure were unselected as invitation letters were sent randomly, avoiding selection bias during the sampling period.

The exposure variables BMI and WC

Cardiovascular diseases and their risk factors, including overweight, obesity and diabetes, are the main focus of the Tromsø Study cohort [284, 285]. This has ensured high quality of clinical and anthropometric measurements. However, high BMI may represent muscle mass [234]. Therefore, BMI as an estimate of total body fat may be biased. As shown in **Paper II**, this may partly be supported by abdominal adiposity found to be a risk factor for *S. aureus* nasal colonization among men in contrast to high BMI.

There are measurement errors regarding **WC**. Previous studies have observed that both the intra-observer and inter-observer variability for WC were higher than for BMI [303]. Nevertheless, the differences in repeated measurements of WC were relatively small and thus, the reliability of WC should be considered in clinical practice. Also, WC has been evaluated on the prediction or estimation of specific adipose tissue depot (by DXA-derived abdominal fat mass) and found satisfactorily [304]. Taken together, this supports using WC as a predictor for abdominal fat mass in **Paper II.**

5.1.1.4 Confounding and interaction

The term confounding refers to situations when a non-causal association between a given exposure and an outcome is observed as a result of a third variable associated with both the exposure and the outcome [300]. There are no formal tests for confounding but in

observational studies, multivariable- and restriction analyses or stratification are the analytic tools that are used to control for confounding effects [300].

Paper I

Serum 25(OH)D levels have a seasonal variation in the Tromsø survey population [289] and *S. aureus* carriage has also in other studies been found to vary by season [305]. Thus, adjustment for season seems to be required in the multivariable model. This could have been solved in different ways, from dichotomizing into summer and winter, to splitting the years into three, four, six parts or by each month. In **Paper I**, we chose to adjust for season by dividing into two month periods as the two consecutive months had relatively similar serum 25(OH)D levels. However, a simulated model has shown that simple adjustments for season in observational studies, might result in a bias away from nil [306]. The authors suggested stratification of serum 25(OH)D within each month, with subsequent pooling of strata. When applying this method to our data, the associations between serum 25(OH)D levels and *S. aureus* nasal colonization still reached statistical significance levels (results not shown).

Other possible confounders that were adjusted for in **Paper I** included age, diabetes and BMI as these covariates were associated with serum 25(OH)D and *S. aureus* nasal colonization and carriage or changed the effect estimates of serum 25(OH)D on the outcome by 10% or more.

Paper II

On the basis of model fit, biological plausibility, and literature review the multivariable model included age, current daily smoking, self-reported diabetes, education level and household income as risk factors for *S. aureus* nasal colonization when evaluating the associations with BMI and WC [154, 155, 161, 162, 296, 307]. Age was included as a continuous variable.

As age is inversely related to *S. aureus* nasal carriage rates [154, 155, 162], and may also modulate lean and fat body mass and reproductive hormonal profiles in women, we explored possible interactions with age in logistic regression models stratified by age tertiles (30–43, 44–59, and 60–87 years) for both sexes and by proposed pre-/postmenopausal age ranges (30–54 and 55–87 years) among women. We were able to find an interaction between young (30–43 years) and middle aged (44–59 years) women with increasing BMI and a pattern of significant interaction between young (30–43 years) and older (60–87 years) women with increasing WC. This supports possible differences between younger (30–43) and older (44–59 years and 60–87 years) women in the effects of general and abdominal obesity

on *S. aureus* nasal colonization (**Paper II**, Table 1S and 2S). The reason for the differences is not clear but may include biological and/or environmental factors, please, see 5.2 Discussion of main results.

Serum HbA1c was used in sensitivity analyses to control for possible influences of pre-diabetes and undiagnosed diabetes by restriction of the logistic regression analysis to those with HbA1c <6.0% (N=3,207). Use of hormonal contraceptives has been found to increase the risk of *S. aureus* nasal carriage among young women [156]. To eliminate possible residual confounding by use of certain types of these exogenous hormones, restriction analysis including only non-users of hormonal contraceptives was performed among young and premenopausal women. We observed that BMI and WC as significant predictors of *S. aureus* nasal colonization among younger and premenopausal women remained or became even stronger among non-users of hormonal contraceptives.

Paper III

We adjusted for age, smoking status, BMI, education level, household income and residing with children <18 years as these factors seemed to be associated with *S. aureus* carriage and HCW status or changed the effect estimate with 10% or more. It is more disputable whether it was appropriate to adjust for recreational physical activity and alcohol intake, as these two variables did not seem to be important covariates in the model. The stratification analysis of residing with children, showed that female HCWs residing with children had an even higher odds of *S. aureus* nasal carriage than female HCWs in general, and that the female HCWs not residing with children had no increased odds of *S. aureus* nasal carriage compared with female non-HCWs.

5.1.1.5 Bias in analysis

Finding associations by chance

A statistical type 1 error denotes reporting a difference which is not real. To avoid such errors, strict statistical criteria are predefined to assess when a finding should be regarded significant. We have in the papers included in this thesis, set the significance level at 0.05, which means that $p<0.05$ leads to rejection of the null hypothesis. According to the normal distribution, one in 20 non-significant findings will by chance turn out significant. Hence, the more statistical comparisons performed, the greater the chance will be for reporting a false significant finding.

Since multiple testing was performed in **Paper II**, one may question if chance is an alternative explanation for the presented associations. However, the primary hypothesis was tested in all the statistical models, thus reducing the risk of chance findings. Furthermore, subgroup analysis was done as a result of formal tests for interaction. Importantly, we performed sensitivity analyses to minimize the effect of confounding by diabetes and use of hormonal contraceptives, though increasing the numbers of tests, but possibly also increasing the validity of the results.

The sample size of the study

A type 2 error denotes a situation with failure to detect a difference which is real. This might happen if the number of participants included in the study is too small or the drop-out rate is higher than expected. Adequately sized study samples will prevent this type of error.

All the papers were based on data from the TSSS which included a relatively large number of participants attending the first (N = 4,026) and second (N = 2,997) visit, minimizing the risk for type 2 error. However, the relatively extensive stratifications with subgroup analyses performed in **Paper II** and also in **Paper I**, required large sample sizes. When the initial analysis showed high concordance between two repeated nasal swab cultures with a median interval of 28 days, and that about 92% had the same *spa* type in both samples [287], the decision to use the data from the first visit in **Paper I** and **II** was made. In **Paper I**, the power was further restricted due to the need of stratifying by current daily smoking [290].

In **Paper III** we used a study population based on participants from first and second visit, as the information on current healthcare-associated environmental exposure was collected during the second visit. This study population included only 71 male HCWs which in the analyses may have caused a type 2 error, as the difference in prevalence of *S. aureus* nasal carriage among male HCWs compared with non-HCWs was relatively large, 43.7% and 34.1%, respectively. Stratifying the analysis on 'residing with children' enhanced the risk of type 2 errors in the analysis among men. Thus, all together, the interpretation of the results among men has to be done with caution.

In **Paper III,** we analyzed the associations between HCW status and the distribution of different *spa* types. We used the six predominant *spa* types to minimize the risk of type 2 errors as about 65% of the *spa* types were only observed in single individuals, implying a large genetic diversity.

5.1.2 Considerations of external validity

In spite of the limitations discussed above, the overall internal validity may be satisfactory, which is a requirement of external validity. The major threat to external validity is the representativeness of the study population. The large scale study with high numbers of participants in the age range 30–87 years, random population selection and high attendance rate (65.7%) of the sixth Tromsø Study, may secure external validity. Thus, the study population represents an ethnically homogenous, healthy general population in a society with high living standards and relatively small differences in socio-economic status. On this basis our results should be held true and allow for generalization to other populations.

5.2 Discussion of main results

Epidemiological research seeks to provide a broad perceptive on causes of disease. With the many complex known and unknown mechanisms and risk factors behind the development of *S. aureus* nasal colonization and carriage, in addition to the cross-sectional study design of the current study, we are investigating associations, not causality [308]. However, there might exist causal relationships between the variables presented here as defined by the criteria for causality published by Hill [308]. Hill's criteria of causation such as strength of the association, dose-response, consistency with other studies, specificity, biological plausibility and adjustments for important confounders will be discussed where they are relevant to evaluate our findings [308].

Persistent nasal carriage of *S. aureus*, a major risk factor for invasive *S. aureus* serious infections with high mortality [25, 26], is a complex condition determined by host, bacterial and environmental factors. The relative importance of these factors is largely unknown, but it has been suggested that host factors are the most significant [68]. It is still unclear what these host-defined circumstances are. However, in a recent Danish study of 617 middle-aged and elderly twin pairs it was concluded that the host genetic contribution to nasal carriage with *S. aureus*, is at most, very limited [153]. Nevertheless, candidate gene case-control studies have observed associations with polymorphisms in genes encoding the glucocorticoid receptor [164], interleukin 4, complement factor H, C-reactive protein [309], and HLA [310], as well as polymorphisms in vitamin D responsive genes among type 1 diabetes patients but not among healthy elderly [200, 229]. None of the studies pointing to these candidate genes have

so far been confirmed in other populations. Furthermore, bacterial factors may determine which strain is carried rather than the overall carriage status [69]. As host genetic- and bacterial factors seems to be modest determinants for overall carriage, gene-environment interactions have been proposed as alternative determinants for the *S. aureus* carriage status [153]. The microbial community consisting of *S. epidemidis*, other *S. aureus* strains, *S. pneumonia* and C*orynebacterium* spp. may also be of relevance [133, 134, 137, 139, 145, 147] as well as repeated antibiotic exposure [68]. These factors reflect the complexity of the determinants of *S. aureus* nasal carriage

5.2.1 The host-microbe-environment interplay

Sex and S. aureus nasal colonization and carriage

We observed that *S. aureus* nasal colonization and carriage rates varied by the non-modifiable host attribute sex, being highest among men (**Paper I**). Variation in *S. aureus* nasal carriage rates by sex, age and hormonal contraceptive use, with lower carriage rates among women, elderly and non-users of hormonal contraceptives, is well-known [154-156, 162]. The sex-difference may suggest a biological mechanism between reproductive hormones and carriage. Differences in behavioral and environmental factors between genders may also play a role [260, 311]. It has been proposed that women are inherently better protected to infections due to estrogens, which enhance immune functions [259, 260, 312]. In general, females may generate more robust and potentially protective innate and adaptive immune responses than their male counterparts, thereby reducing females' susceptibility to infections but increasing their risk of developing autoimmune diseases as estrogens generally exert immune enhancing activities while androgens exert suppressive effects on both innate and adaptive immune responses [259, 260]. Interestingly, the expression of antimicrobial peptides (AMPs), some of which are associated with *S. aureus* skin infections and nasal colonization [187, 188, 313], are modified by reproductive hormones in other body sites, e.g. the genital tract [314, 315]. Furthermore, sex steroid hormones may regulate behaviours possibly resulting in differential exposure and contact with pathogens between sexes [311]. Thus, we hypothesize that the stable, low prevalence of *S. aureus* carriage in women may be explained by endogenous estrogens.

The interrelationships of serum 25(OH)D, obesity and S. aureus nasal colonization and carriage

Since about 20% of healthy adults are persistent nasal carriers [1], and persistent nasal carriage of *S. aureus* is a major risk factor for infection with the microbe [25, 26], prevention or elimination of the carrier state may contribute substantially in reducing the *S. aureus* disease burden. However, there is still limited evidence in relation to modifiable risk factors for the carrier state [68].

In our study, we identified various modifiable host factors as determinants for *S. aureus* nasal colonization and carriage. Low serum 25(OH)D and obesity were associated with increased odds of *S. aureus* nasal colonization and carriage among men and women, respectively (**Paper I and II**). The inverse dose-response association between serum 25(OH)D and *S. aureus* nasal colonization and carriage in adjusted models were observed among non-smoking men with no such clear association among smoking men and non-smoking and smoking women.

Various findings in the research literature render a causal relationship between serum 25(OH)D levels and *S. aureus* carriage biologically plausible. Vitamin D appears to promote both innate and adaptive immune responses [233]. $1,25(OH)_2D_3$ has been found to enhance the antimicrobial peptide function against *S. aureus* in vivo [231, 316]. The promoter of the antimicrobial protein cathelicidin and human β-defensin 2 have vitamin D responsive elements (VDRs) [317], and $1,25(OH)_2 D_3$ can induce cathelicidin and/or β-defensin 2 in isolated keratinocytes, monocytes, neutrophils, and myeloid cells as well as in human skin biopsies [317-319]. In addition to induce AMP expression, $1,25(OH)_2D_3$ has been found to induce CD14 and TLR2 in keratinocytes [231], which may result in increased ability to detect pathogens. All these studies are suggestive of biological mechanisms that may partly explain how serum concentrations of vitamin D may protect against carriage of *S. aureus*.

The observed findings in **Paper I** are partly in line with others [163]. However, the data in **Paper I**, are to our knowledge, the first to report an association between serum vitamin D levels and MSSA carriage in a general population. In a recent study including single nasal swab cultures from 14,000 children and adults across USA, an inverse- and dose-response association between vitamin D levels and odds of MRSA but not MSSA was observed [163]. Matheson et al [163] suggested that the microbe-dependent association could be due to the increased resistance of MRSA to natural antimicrobial peptides (i.e. cathelicidin) induced by vitamin D in host defence against *S. aureus* [320]. The apparent discrepancy with

our MSSA results may be explained by several factors such as lack of more detailed subgroup analysis as well as geographical and ethnical heterogeneity which may have influenced the findings by Matheson et al [163].

Studies have also suggested that polymorphisms in the vitamin D responsive genes, might be associated with *S. aureus* carriage among type 1 diabetes patients, but not among healthy elderly [200, 229]. A recent retrospective study including 52 subjects with *Clostridium difficile* and *S. aureus* infections showed a link between low vitamin D status and adverse outcome [230]. This may support vitamin D's immune enhancing activities.

Previous studies of other infectious disease outcomes than *S. aureus* suggest that higher vitamin D status is protective against respiratory tract infections [218, 219] and that seasonal influenza may be linked to the wintertime deficiency of vitamin D [215]. Furthermore, vitamin D deficiency has been associated with increased risk of tuberculosis (TB) [221], and immunomodulatory effects of vitamin D and sunlight in TB therapy have been observed [321].

We observed that *S. aureus* nasal colonization and carriage was significantly less frequent among smokers than among non-smokers (**Paper I**). This is in line with previous reports observing current smoking as an important determinant reducing *S. aureus* nasal carriage [68, 275]. Furthermore, serum 25(OH)D levels did not vary by *S. aureus* colonization or carriage states among smokers. The reason for the lack of association among smokers is unclear. However, we hypothesize that these findings may be caused by smoking masking the inverse association between vitamin D and *S. aureus* colonization and carriage, a possible example of gene-environment interactions [153].

Although we adjusted our analysis for important risk factors for nasal colonization, we cannot exclude that residual confounding may account for the presented associations. High serum 25(OH)D concentrations may be a proxy for a healthier lifestyle in general. More outdoor physical activity may lead to lower BMI as well as increased sun exposure. Higher socioeconomic status may be linked to a healthier lifestyle and fewer hospital admissions, all factors that may be associated with higher serum 25(OH)D and reduced risk of *S. aureus* nasal carriage. There are also several other possible confounders that may have influenced the current results such as microbial interference (*S. epidemidis*, *S. pneumonia*, C*orynebacterium* spp) [133, 139, 145, 147], repeated antibiotic use [68], and host genetic factors such as polymorphisms in the VDR gene [200, 229] but information of these variables were not included in our data.

Paper II, is to our knowledge, the first report which shows that women with higher BMI and WC have increased odds of *S. aureus* nasal colonization independent of pre-diabetes and diabetes, suggesting that excess body weight may be a marker of increased susceptibility to colonization. The association seemed to be restricted to young and premenopausal women and the associations remained stable or became even stronger among non-users of hormonal contraceptives. There was no association among older and postmenopausal women. The current study indicates that a threshold effect of fat mass may be more important than a dose-response effect on *S. aureus* nasal colonization.

Previous studies have observed that obese patients are more likely to develop community acquired pneumonia and wound infections, as well as nosocomial sepsis, bacteremia, surgical site infections, and catheter-related infections [252, 262-265]. *S. aureus* is a frequent causative agent in several of these infections.

Our results are partly in consistency with others, i.e. obesity was associated with *S. aureus* nasal colonization among both women and men in the US National Health and Nutrition Examination Survey (NHANES) 2000–04 [154]. The associations in NHANES were not adjusted for DM as this covariate was not significantly associated with the outcome. Furthermore, obesity has also been identified as an independent risk factor for preoperative *S. aureus* nasal colonization among 4,039 surgical patients when adjusting for age, sex, current smoking, and previous antimicrobial therapy [155]. As elevated serum glucose concentration has been associated with *S. aureus* nasal colonization and carriage [161, 162], and obesity is linked to elevated serum glucose levels [253], one may assume that altered glucose metabolism may mediate obesity-related effects on immune responses [162, 252, 254, 255]. Importantly, **Paper II** shows associations between BMI and WC and *S. aureus* nasal colonization independent of pre-diabetes or diabetes, and thus, extends previous findings. The reasons for these associations are unclear, but may include physical, biochemical, hormonal, or environmental factors. Studies in humans and animals have suggested that adiposity in itself may cause impaired immune responses through immunomodulatory effects of changes in reproductive hormones [256-259, 312] and that obesity may cause a chronic low-grade inflammation which may attenuate leptin signalling and thus, reducing the immune responses [248, 322].

The reason for the restriction of the associations to young and premenopausal women in the current study is not clear, but we hypothesize that the possible effects of adiposity increasing *S. aureus* nasal colonization in young and premenopausal women is caused by

impaired immune responses through immunomodulatory effects of changes in reproductive hormones in this group [257, 259-261] as opposed to older and postmenopausal women [256].

In the current study, we observed that the association between BMI and *S. aureus* nasal colonization was modified by sex, which is in contrast to others who have observed increased odds of colonization among both obese women and men [154]. Nevertheless, the current study also suggests a U-shaped relationship between WC and *S. aureus* nasal colonization among young men. This may reflect non-causal relationships or sex-associated differences in lean and fat body mass. A possible lack of association between obesity and *S. aureus* nasal colonization among men may be caused by the immunomodulatory effects of changes in reproductive hormones due to obesity [258]. Also, we hypothesize that obese women may be more susceptible to leptin resistance with reduced immune responses and increased *S. aureus* colonization compared to obese men, as extra fat mass is generally accumulated subcutaneously in women and as intraabdominal visceral fat in men [323]. Lower estrogen levels may also increase the risk of leptin resistance [324].

Important risk factors of nasal colonization were included as covariates in the models, but there may still be residual confounding factors, which may account for the presented associations. Residing with children may be one of these. Environmental factors such as transmission between household members and residing with children have been shown to be risk factors for colonization [69, 147]. However, adjustments for residing with children in our analysis did not change the effect of the associations. Genetic–environment interactions as determinants of obesity and risk of carriage and infection may also be considered. Altered methylations and histone modifications of gene transcripts of cells in the immune system and leptin production, adapted in response to intrinsic and environmental stimuli, may be of importance [248]. Further studies are needed addressing the effects of diet-induced obesity on epigenetic modification of cells in the immune system and leptin production.

In contrast to the positive associations between BMI, WC and *S. aureus* nasal colonization among women, low serum 25(OH)D concentrations were associated with *S. aureus* nasal colonization and carriage among non-smoking men. The reason for the variation in determinants for *S. aureus* nasal colonization and carriage by sex in our study is unclear, but previous reports have shown that predictors of *S. aureus* nasal colonization may vary by sex [154]. However, spurious associations in our study cannot be excluded. Nevertheless, we hypothesize that the low prevalence of *S. aureus* carriage in women is mainly explained by endogenous estrogens that may overwhelm the protective effect of vitamin D. The observed

sex difference is in accordance with studies of other outcomes; type 2 diabetes and insulin resistance have been associated with low vitamin D status in men only [325, 326].

Given that causality can be established, the inverse dose-response relationship between vitamin D status and *S. aureus* nasal colonization and carriage observed among non-smoking men in our study may point to targets for reducing the reservoir of *S. aureus* in the population. Although there is no agreement on the optimal serum concentration of 25(OH)D, a recent consensus panel recommended that a serum concentration 75–100 nmol/l for different health outcomes should be targeted [208, 209]. In our study, mean serum 25(OH)D concentration was 53.3 nmol/l and 52.4 nmol/l in non-smoking men and women, respectively, and among the 3,006 non-smoking participants, only 286 (9.5%) had serum levels of ≥75 nmol/l. The Tromsø area is situated at 69˚N and the UVB radiation at this latitude is below the threshold for dermal vitamin D production five months of the year. The arctic climate with its low temperatures may limit the degree of skin exposure in the remaining months of the year. The relatively low rates of participants having vitamin D levels ≥75.0 nmol/l, underlines that vitamin D insufficiency may be of significance in the Tromsø area as well as globally. Given the high risk of *S. aureus* infection in combination with malnutrition in specific patient populations (i.e. surgical, dialysis, ICU, HIV) [27-29, 35, 36, 38, 327], and the fact that most of the infections are caused by the patient's nasal strain [25, 26], it would be of interest in further studies to evaluate if vitamin D repletion ≥75 nmol/l might reduce the prevalence of *S. aureus* nasal carriage and thus reduce the risk of nosocomial infections. However, there have been divergent results of vitamin D supplementation to subjects for preventing different health outcomes [219, 228, 328, 329]. One of the reasons for a possible lack of effect of vitamin D supplementation might be too high baseline serum 25(OH)D concentrations [328]. Another reason may be unrecognized confounding. Large randomized control trials (RCT) are needed to determine a possible role of vitamin D supplementation and repletion in relation to *S. aureus* colonization, carriage and infection. Importantly, a U-shaped association between serum 25(OH)D concentration and risk of active TB was recently observed [330], indicating that vitamin D supplementation may have detrimental effects on the immune function among individuals with normal or high serum vitamin D levels. The low proportion of participants with higher serum 25(OH)D concentrations ≥100 nmol/l (N = 33) in our study gave us less statistical power to evaluate the odds of *S. aureus* nasal colonization and carriage in those with high compared with low serum 25(OH)D levels.

As obesity has become endemic worldwide, even small increases in risk may have major impact on the overall *S. aureus* disease burden in a population. Thus, given that

causality can be established, the positive relationship between adiposity and *S. aureus* nasal colonization observed in the current study may points to important targets for intervention. For example, adipose young women in child bearing age undergoing caesarean delivery and men in need of surgery may be at particular risk for surgical site infections [252, 265]. However, future prospective studies of long term effects of obesity and weight change on the risk of *S. aureus* colonization and subsequent infections are needed.

Healthcare worker status and S. aureus nasal carriage and spa *types*

In **Paper III**, we observed that work in healthcare services was associated with a 54% increased odds of *S. aureus* nasal carriage among women. The odds were even higher among female HCWs residing with children, whereas in female HCWs not residing with children there was no difference in odds by HCW status. Working in the healthcare services was associated with increased odds of *spa* type t012 and t015. For men, work in healthcare services and residing with children was associated with increased prevalence of the common *spa* type t012.

To our knowledge, this is the first study which reports that female HCWs have higher odds of *S. aureus* nasal carriage than female non-HCWs in a general working-age population. Several studies have investigated whether working in healthcare services may be an environmental risk factor for MSSA colonization, but the results are not consistent [46, 277, 278, 280]. In general, many of the studies in healthcare settings may have been biased by a lack of information on background prevalence in the relevant general population as well as in households. However, in consistency with our findings, other studies confined to HCWs observed higher nasal carriage rates of MRSA among nurses than among other healthcare professionals, and cited increased patient contact as a cause [280, 281]. Our screening study did not include information about the HCWs' profession. However, the majority of the Norwegian healthcare workforce is nurses and auxiliary nurses, and about 90% of these are women [331, 332].

Our findings are in agreement with current literature supporting the view that contact transmission within HCWs' families may affect the burden of MRSA infections in hospitals [270, 272]. Households have been suggested to serve as a reservoir for *S. aureus* in the community [333] and children have been found to have a higher prevalence of *S. aureus* colonization than adults [154, 334, 335]. *S. aureus* nasal carriers may impose their carrier status upon other family members [69, 271, 272] and family size of more than 5 persons has

been found to be correlated with a higher risk of *S. aureus* colonization in children [147]. Importantly, residing with children *per se* was not associated with *S. aureus* nasal carriage in our study, and the number of children <18 years did not differ between HCWs and non-HCWs (results not shown). Thus, we hypothesize that the environmental pressure caused by high rates of contact transmission of *S. aureus* from both patients and children may exceed female HCWs' ability (i.e through hand hygiene, immune responses) to defend themselves against colonization.

The increased odds of *spa* type t012 and t015 among healthcare workers in our study are in agreement with the findings of others [109]. Grundmann et al observed that *spa* types t012 and t015 were among the top 5 predominant *spa* types that causes invasive infections in Europe [109]. Also, different studies have shown no distinction between colonizing and invasive isolates [82, 104, 287]. Thus, we may expect *spa* types t012 and t015 to be frequent causes of auto-infections among patients in the community and in hospitals, with an increased potential for transmission, which partly may explain our findings.

Among men, HCWs status and residing with children predicted *S. aureus* carriage by common *spa* types but not overall carriage rates. Men are generally at increased risk of *S. aureus* nasal carriage [154, 155, 162]. Thus, we hypothesize that the sex-associated susceptibility to *S. aureus* among men may overwhelm the effect of environmental risk factors (i.e. work and family status) for nasal carriage in our study, particularly considering the imperfect definition of the exposure variable "Do you work in healthcare services" that may have obscured/diluted the association between being a "high-risk" healthcare worker in hospitals and the outcome. However, the actual strain acquired may be determined by the surroundings [69]. Interestingly, among women who are generally at low risk of *S. aureus* nasal carriage, the opposite picture was observed; HCW status predicted nasal carriage rates overall and not by *spa* types. However, the uncertainty of this interpretation is considerable due to small numbers of male HCWs and lack of statistically significant interactions between the environmental risk factors (HCW status and residing with children). The external validity may therefore be limited. The female preference of *spa* type t012 in our study population may also possibly confound our results in women [287]. Another important limitation of this study is the lack of information of *S. aureus* nasal carriage and *spa* types among patients and household members, and the degree of direct contact between HCWs, their patients and household members. Future studies containing more detailed information on work and home environmental risk factors are therefore needed to increase our knowledge about the link

between HCWs and *S. aureus* nasal carriage, and to suggest novel targets for improved infection control strategies against exogenous MSSA and MRSA infections in patients.

Nearly 20% of nosocomial *S. aureus* infections have an exogenous origin [26], where HCWs may serve as an important vector. Furthermore, as colonized HCWs are capable of introducing *S. aureus* into their families [270-272], a possible clinical implication of our findings is the need for good adherence to infection control guidelines of HCWs at work [336]. Adherence to standard and- isolation precautions wherever needed at work as well as adequate routines for hand hygiene at home are of importance. Also, during outbreak investigation of MRSA in the healthcare setting, screening of patients, healthcare workers as well as their family members in question has to be considered to successfully eradicate MRSA and to reduce the risk of reintroducing MRSA into the healthcare services [272].

6. MAIN CONCLUSIONS

In summary, our cross-sectional study may support the view that there is a complex interplay between host-, microbial-, and environmental factors during *S. aureus* colonization and carriage.

- Our study suggests higher *S. aureus* nasal colonization and carriage rates among men compared with women and that predictors of colonization and carriage may vary by sex.
- The current study indicates an inverse dose-response association between serum 25(OH)D concentration and the odds of *S. aureus* nasal colonization and carriage in non-smoking men. Furthermore, we hypothesize that the relative importance of vitamin D in this context is particularly high in the male population, and that the inverse association between vitamin D and *S. aureus* colonization and carriage may be masked by smoking. Current smoking also reduced the odds of nasal colonization and carriage among both women and men.
- We observed that young and premenopausal women with higher BMI and WC have increased odds of *S. aureus* nasal colonization independent of pre-diabetes and diabetes and that the association remained significant among non-users of hormonal contraceptives. The results indicate that a threshold effect of fat mass may be more important than a dose-response effect on *S. aureus* nasal colonization. There was no association among postmenopausal women. High WC may also be a determinant for *S. aureus* nasal colonization among young men. The present findings imply support for additional biological mechanisms other than the glucose-insulin pathway.
- Work in healthcare services was associated with increased odds of *S. aureus* nasal carriage among women. Odds were even higher among women residing with children. Among men, work in healthcare services and residing with children were associated with increased odds of common *spa* types. Our study suggests that a synergism between environmental risk factors (work and household) is of importance for the overall *S. aureus* carrier state in HCWs. The *spa* types carried may be dictated by the surroundings.

7. FUTURE RESEARCH

- The cross-sectional study design of this work implies that further studies trying to establish a causal relationship between the main predictors and *S. aureus* nasal carriage are essential.
- The observed inverse dose-response association between serum 25(OH)D concentration and odds of *S. aureus* nasal colonization and carriage in non-smoking men needs further investigations. Prospective randomized controlled trials are needed to assess whether increase in circulating vitamin D concentration can effectively decrease the risk of *S. aureus* carriage and subsequent infection.
- The positive association between obesity and *S. aureus* nasal carriage among premenopausal women needs to be explored further. Thus, future prospective studies of long term effects of obesity, and weight loss on the risk of *S. aureus* colonization and subsequent infections are needed. Addressing serum levels of sex hormones as well as leptin among women and men in different age-strata as determinants of *S. aureus* nasal carriage may also be relevant.
- Previous studies on the relationships between the intestinal microbial flora and obesity have uncovered profound changes in the composition and metabolic function of the gut microbiota in obese individuals, which appear to enable an "obese microbiota" to extract more energy from the diet. There is increasing evidence that obese mice and humans exhibit a major reduction in the abundance of *Bacteroidetes (e.g. Enterobacter spp.)* and a proportional increase in *Firmicutes (e.g. Lactobacilli and Staphylococcus spp)* of the intestinal microbiota. Future studies addressing these questions are warranted.
- A seventh Tromsø Study is in the planning phase, where the 4,026 participants in the Tromsø 6 may be invited for a follow-up of nasal- and throat samples for culturing of *S. aureus*. This will give us the opportunity to further address the important question of persistent carriage, concordance of *spa* types between samples taken at Tromsø 6 and 7, and the relationships between different determinants and *S. aureus* carriage.
- Thus, as for the future, we will continue our search for determinants among hosts, microbes, and environmental factors that may be involved in *S. aureus* carriage of healthy individuals.

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Paper I

Paper II

Paper III

Appendix A

Questionnaire from the 6th Tromsø Study

English translation

The Tromsø Study

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

2007 - 2008 Confidential

HEALTH AND DISEASES

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

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

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

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

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

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

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

☐ Yes ☐ No

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

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

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

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

USE OF HEALTH SERVICES

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

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

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

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

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

☐ Yes ☐ No

USE OF MEDICINES

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

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

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

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

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

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

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

FAMILY AND FRIENDS

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

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

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

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

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

☐ Yes ☐ No

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

☐ Yes ☐ No

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

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

WORK, SOCIAL SECURITY AND INCOME

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

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

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

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

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

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

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

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

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

- ☐ Yes
- ☐ No

PHYSICAL ACTIVITY

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

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

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

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

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

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

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

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

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

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

ALCOHOL AND TOBACCO

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

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

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

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

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

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

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

- ☐ Yes
- ☐ No

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

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

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

Number of years ☐

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

Number of cigarettes ☐

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

Age in years ☐

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

Number of years ☐

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

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

DIET

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

☐ Yes ☐ No

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

Number of units ☐

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

Number ☐

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

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

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

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

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

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

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

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

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

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

QUESTIONS FOR WOMEN

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

☐ Yes ☐ No ☐ Uncertain

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

Number ☐

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

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

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

☐ Yes ☐ No

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

☐ The first ☐ Second or later

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

☐ Yes ☐ No

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

☐ The first ☐ Second or later

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

☐ Yes ☐ No

54 **If yes, which child?**

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

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

Age ☐

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

Oral contraceptives, hormonal intrautrine or similar ☐ Yes ☐ No

Hormone treatment for menopausal problems ☐ Yes ☐ No

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

Tromsø 6

- part of The Tromsø Study

FILL OUT THE FORM IN THIS WAY:

The form would be read by machine, it is therefore important that you tick appropriately:

☒ Correct

☑ Wrong

☒ Wrong

■ If you tick the wrong box, correct by filling the box like this

Write the numbers clearly 1 2 3 4 5 6 7 8 9 0

7 4 Correct

7 4 Wrong

Use only black or blue pen, do not use pencil or felt tip pen

1. DESCRIPTION OF YOUR HEALTH STATUS

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today:

1.01 **Mobility**

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

1.02 **Self-care**

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

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

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

1.04 **Pain and discomfort**

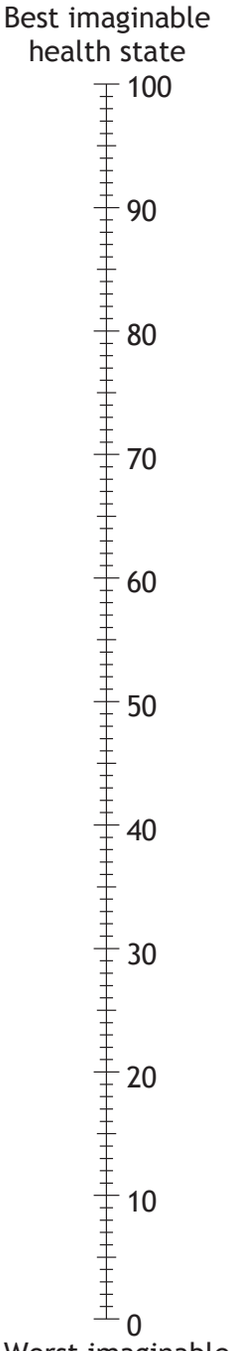
- ☐ I have no pain or discomfort
- ☐ I have moderate pain or discomfort
- ☐ I have extreme pain or discomfort

1.05 **Anxiety and depression**

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

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

Your own health state today



2. CHILDHOOD/YOUTH AND AFFILIATION

2.01 **Where did you live at the age of 1 year?**

- ☐ In Tromsø *(with present municipal borders)*
- ☐ In Troms, but not Tromsø
- ☐ In Finnmark
- ☐ In Nordland
- ☐ Another place in Norway
- ☐ Abroad

2.02 **How was your family's financial situation during your childhood?**

- ☐ Very good
- ☐ Good
- ☐ Difficult
- ☐ Very difficult

2.03 **What is the importance of religion in your life?**

- ☐ Very important
- ☐ Somewhat important
- ☐ Not important

2.04 **What do you consider yourself as?** (Tick for one or more alternatives)

- ☐ Norwegian
- ☐ Sami
- ☐ Kven/Finnish
- ☐ Another

2.05 **How many siblings and children do you have/have you had?**

Number of siblings ..... ☐☐

Number of children ..... ☐☐

2.06 **Is your mother alive?**

☐ Yes ☐ No

If NO: her age when she died ..... ☐☐

Is your father alive?

☐ Yes ☐ No

If NO: his age when he died ..... ☐☐

2.07 **What was/is the highest completed education for your parents and your spouse/partner?** (Tick once for each column)

	Mother	Father	Spouse/ partner
7-10 years primary/secondary school, modern secondary school	☐	☐	☐
Technical school, vocational school, 1-2 years senior high school	☐	☐	☐
High school diploma	☐	☐	☐
College or university (less than 4 years)	☐	☐	☐
College or university (4 years or more)	☐	☐	☐

3. WELL BEING AND LIVING CONDITIONS

3.01 **Below are three statements about satisfaction with life as a whole. Then there are two statements about views on your own health. Show how you agree or disagree with each of the statements by ticking in the box for the number you think fits best for you.** (tick once for each statement)

	Completely disagree 1	2	3	4	5	6	7 Completely agree
In most ways my life is close to my ideal	☐	☐	☐	☐	☐	☐	☐
My life conditions are excellent	☐	☐	☐	☐	☐	☐	☐
I am satisfied with my life	☐	☐	☐	☐	☐	☐	☐
I have a positive view of my future health	☐	☐	☐	☐	☐	☐	☐
By living healthy, I can prevent serious diseases	☐	☐	☐	☐	☐	☐	☐

3.02 **Below are four statements concerning your current job conditions, or if you are not working now, the last job you had.** (Tick once for each statement)

	Completely disagree 1	2	3	4	5	6	7 Completely agree
My work is tiring, physically or mentally	☐	☐	☐	☐	☐	☐	☐
I have sufficient influence on when and how my work should be done	☐	☐	☐	☐	☐	☐	☐
I am being bullied or harassed at work	☐	☐	☐	☐	☐	☐	☐
I am being treated fairly at work	☐	☐	☐	☐	☐	☐	☐

3.03 **I consider my occupation to have the following social status in the society** (if you are not currently employed, think about your latest occupation)

- ☐ Very high status
- ☐ Fairly high status
- ☐ Medium status
- ☐ Fairly low status
- ☐ Very low status

3.04 **Have you over a long period experienced any of the following?** (Tick one or more for each line)

	No	Yes, as a child	Yes, as adult	Yes, last year
Been tormented, or threatened with violence	☐	☐	☐	☐
Been beaten, kicked at or victim of other types of violence	☐	☐	☐	☐
Someone in your close family have used alcohol or drugs in such a way that it has caused you worry	☐	☐	☐	☐

If you have experienced anything of the above, how much are you affected by that now?

☐ Not affected ☐ Affected to some extent ☐ Affected to a large extent

4. ILLNESS AND WORRIES

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

☐ Yes ☐ No

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

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

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

☐ Yes ☐ No

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

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

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

☐ Yes ☐ No

If YES: Is the cough usually productive?

☐ Yes ☐ No

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

☐ Yes ☐ No

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

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

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

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

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

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

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

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

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

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

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

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

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

☐ Yes ☐ No

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

	No complaint	Little complaint	Severe complaint
Neck, shoulders	☐	☐	☐
Arms, hands	☐	☐	☐
Upper part of the back	☐	☐	☐
The lumbar region	☐	☐	☐
Hips, leg, feet	☐	☐	☐
Other places	☐	☐	☐

4.11 **Have you suffered from pain and/or stiffness in muscles or joints during the <u>last 4 weeks</u>?** (tick once for each line)

	No complaint	Little complaint	Severe complaint
Neck, shoulders	☐	☐	☐
Arms, hands	☐	☐	☐
Upper part of the back	☐	☐	☐
The lumbar region	☐	☐	☐
Hips, leg, feet	☐	☐	☐
Other places	☐	☐	☐

4.12 **Have you ever had:**

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

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

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

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

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

If Yes: was it due to:

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

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

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

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

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

4.18 **Have you ever had:**

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

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

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

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

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

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

☐ Yes ☐ No ☐ Do not know

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

☐ Yes ☐ No

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

☐ 0 ☐ 1-5 ☐ 6-10 ☐ 10+

4.26 **Have you been suffering from headache <u>the last year</u>?**

☐ Yes ☐ No

If No: go to section 5, food habits

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

☐ Migraine ☐ Other headache

4.28 **How many days <u>per month</u> do you suffer from headache?**

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

4.29 **Is the headache attacks <u>usually</u>:** (tick once for each line)

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

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

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

4.31 **What is the normal duration of the headache attacks?**

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

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

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

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

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

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

Number of days ☐☐

5. FOOD HABITS

5.01 **How often do you usually eat the following?** (tick once for each line)

	0-1 times per month	2-3 times per month	1-3 times per week	More than 3 times per week
Fresh water fish *(not farmed)*	☐	☐	☐	☐
Salt water fish *(not farmed)*	☐	☐	☐	☐
Farmed fish *(salmon, trout, char)*	☐	☐	☐	☐
Tuna fish *(fresh or canned)*	☐	☐	☐	☐
Fish bread spread	☐	☐	☐	☐
Mussels, shells	☐	☐	☐	☐
The brown content in crabs	☐	☐	☐	☐
Whale or seal meat	☐	☐	☐	☐
Pluck (liver/kidney/heart) from reindeer or elk/moose	☐	☐	☐	☐
Pluck (liver/kidney/heart) from ptarmigan/grouse	☐	☐	☐	☐

5.02 **How many times during the year do/did you usually eat the following?** (number of times)

	In adulthood	In childhood
Mølje (cod or pollack meat, liver, and roe) *(Number of times per year)*	☐☐	☐☐
Sea gull's egg *(Number of eggs per year)*	☐☐	☐☐
Reindeer meat *(Number of times per year)*	☐☐	☐☐
Local mushroom and wild berries *(blueberries/lingonberries/cloudberries) (Number of times per year)*	☐☐☐	☐☐☐

5.03 **How many times per month do you eat canned (tinned) foods (from metal boxes)?**

Number ☐☐

5.04 **Do you take vitamins and/or mineral supplements?**

☐ Yes, daily ☐ Sometimes ☐ Never

5.05 **How often do you eat?**

	Never	1-3 times per month	1-3 times per week	4-6 times per week	1-2 times per day	3 times per day or more
Dark chocolate	☐	☐	☐	☐	☐	☐
Light chocolate/milk chocolate	☐	☐	☐	☐	☐	☐
Chocolate cake	☐	☐	☐	☐	☐	☐
Other sweets	☐	☐	☐	☐	☐	☐

5.06 **If you eat chocolate, how much do you usually eat each time?**

Compared with the size of a Kvikk-Lunsj sjokolade *(a chocolate brand in the market)* and describe how much do you eat in relation to it.

¼	½	1	1 ½	2	More than 2
☐	☐	☐	☐	☐	☐

5.07 **How often do you drink cocoa/hot chocolate?**

Never	1-3 times per month	1-3 times per week	4-6 times per week	1-2 times per day	3 times per day or more
☐	☐	☐	☐	☐	☐

6. ALCOHOL

6.01 **How often have you in the last year:**	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
Not been able to stop drinking alcohol when you have started?	☐	☐	☐	☐	☐
Failed to do what was normally expected of you because of drinking?	☐	☐	☐	☐	☐
Needed a drink in the morning to get yourself going after a heavy drinking session?	☐	☐	☐	☐	☐
Had feeling of guilt or remorse after drinking?	☐	☐	☐	☐	☐
Not been unable to remember what happened the night before because of your drinking?	☐	☐	☐	☐	☐

	Never	Yes, but not in the last year	Yes, during the last year
6.02 **Have you or someone else been injured because of your drinking?**	☐	☐	☐
Has a relative, friend, physician, or other health care workers been concerned about your drinking or suggested you to cut down?	☐	☐	☐

7. WEIGHT

7.01 **Have you involuntary lost weight during the last 6 months?**

☐ Yes ☐ No

If Yes: how many kilograms? ..... ☐☐

7.02 **Estimate your body weight when you were 25 years old:**

Number of kilograms ..... ☐☐☐

7.03 **Are you satisfied with your present body weight?**

☐ Yes ☐ No

7.04 **What weight would you be satisfied with (your "ideal" weight)?**

Number of kilograms ..... ☐☐☐

8. SOLVENTS

8.01 **How many hours per week, do you do the following leisure- or professional activities:**

Automobile repair/paint, ceramic work, painting/varnishing/solvents, hair dressing, glazier, electrician. (Put 0 if you do not engage in such leisure or professional activities)

Number of hours per week on average ☐☐

8.02 **Do you use hair color preparations**

☐ Yes ☐ No

If Yes: How many times per year? .. ☐☐

9. USE OF HEALTH SERVICES

9.01 **Have you ever experienced that diseases have been insufficiently examined or treated, and this had a serious consequence?**

- ☐ Yes, this has happened to me
- ☐ Yes, this has happened to a close relative *(child, parents, spouse)*
- ☐ No

If Yes, was it caused by? (tick once or more):

- ☐ general practitioner
- ☐ emergency medical doctor
- ☐ private practising specialist
- ☐ hospital doctor
- ☐ other health personnel
- ☐ alternative practitioner
- ☐ more than one person due to deficient routines and interaction

9.02 **Have you ever felt persuaded to accept an examination or treatment that you did not want?**

☐ Yes ☐ No

If Yes, do you think this has had unfortunate consequences for your health?

☐ Yes ☐ No

9.03 **Have you ever complained about a treatment you have received?**

- ☐ Have never had a reason for complaining
- ☐ Have considered complaining, but did not do
- ☐ Have complained verbally
- ☐ Have complained in writing

9.04 **How long have you had your current general practitioner/other physician?**

- ☐ Less than 6 months
- ☐ 6 to 12 months
- ☐ 12 to 24 months
- ☐ More than 2 years

9.05 **At the last visit to your GP, did you have a hard time to understand what the doctor(s) told you?** Answer on a scale from 0 to 10, where 0 = they were difficult to understand and 10 = they were always easy to understand

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

9.06 **How would you rate the treatment or counselling, you got at your last visit to your GP?** Answer on a scale from 0 to 10, where 0 = worst treatment or counselling, and 10 = best treatment or counselling

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

9.07 **During the last 12 months, how much of a problem, if any, was it to get a referral to special examinations (as x-ray, etc.) or to a specialist health care (private practising specialist or at hospital)?**

- ☐ Not relevant
- ☐ No problem
- ☐ Some problem
- ☐ Major problem

9.08 **During the last 12 months, how much of a problem, if any, was it to get a referral to physiotherapist, chiropractor, etc.?**

- ☐ Not relevant
- ☐ No problem
- ☐ Some problem
- ☐ Major problem

9.09 **Altogether, how much of a problem, if any, was it to get a referral to specialist health care?**

- ☐ Not relevant
- ☐ Very difficult
- ☐ Some difficulties
- ☐ Easy
- ☐ Very easy

9.10 **During the last 12 months, have you been examined or treated by the specialist health care?**

☐ Yes ☐ No

If Yes, did you have a difficult time to understand what the doctor(s) told you? Answer on a scale from 0 to 10, where 0 = they were difficult to understand and 10 = they were always easy to understand

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

9.11 **How would you rate the treatment or counselling you got at your last visit to a specialist?** Answer on a scale from 0 to 10, where 0 = worst treatment or counselling, and 10 = best treatment or counselling

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

9.12 **Have you ever, <u>previous to the year 2002</u>, had an operation at a hospital or a specialist clinic?**

☐ Yes ☐ No

9.13 **Have you, during the <u>last 12 months</u>, used herbal or natural medicine?**

☐ Yes ☐ No

9.14 **Have you, during the <u>last 12 months</u>, used meditation, yoga, qi gong or thai chi as self-treatment?**

☐ Yes ☐ No

10. USE OF ANTIBIOTICS

10.01 **Have you used antibiotics during <u>the last 12 months</u>?** (all penicillin-like medicine in the form of tablets, syrups or injections)

☐ Yes ☐ No ☐ Do not remember

If YES: What did you get the treatment for? Have you taken many antibiotic treatments, tick for each treatment.

	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	Treatment 6
• Urinary tract infection *(bladder infection, cystitis)*	☐	☐	☐	☐	☐	☐
• Respiratory tract infection *(ear, sinus, throat or lung infection, bronchitis)*	☐	☐	☐	☐	☐	☐
• Other	☐	☐	☐	☐	☐	☐
Treatment duration: number of days	|	|	|	|	|	|

How did you acquire the antibiotics for treatment? Have you acquired many treatments, tick for each one.

	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	Treatment 6
With prescription from a physician/dentist	☐	☐	☐	☐	☐	☐
Without contacting a physician/without prescription:						
· Purchase from a pharmacy abroad	☐	☐	☐	☐	☐	☐
· Purchase over the internet	☐	☐	☐	☐	☐	☐
· Remnants from earlier treatment at home	☐	☐	☐	☐	☐	☐
· From family/friends	☐	☐	☐	☐	☐	☐
· Other ways	☐	☐	☐	☐	☐	☐

10.02 **Do you presently have antibiotics at home?**

☐ Yes ☐ No

If YES:is this after an agreement with your physician for treatment of chronic or frequently recurring disease?

☐ Yes ☐ No

If No: how did you acquire this antibiotic? (Multiple ticks are possible)

Purchased from a pharmacy abroad ☐
Purchased over the internet ☐
Remnants from earlier treatment ☐
From family/friends ☐
Other ways ☐

10.03 **Would you consider using antibiotics without consulting your physician?**

☐ Yes ☐ No

If YES: which conditions would you treat in such situation? (multiple ticks are possible)

Common cold ☐
Cough ☐
Bronchitis ☐
Sore throat ☐
Sinusitis ☐
Fever ☐
Influenza ☐
Ear infection ☐
Diarrhoea ☐
Urinary tract infection ☐
Other infections ☐

11. YOUR CIRCADIAN RHYTHM

We will ask you some questions about your sleeping habits

11.01 **Have you worked in a shift work schedule during the last 3 months?**

☐ Yes ☐ No

11.02 **Number of days per week which you <u>cannot</u> freely choose when you sleep (e.g. work days)?**

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐

Then I go to bed at ..... ☐☐:☐☐

I get ready to fall asleep at ..... ☐☐:☐☐

Number of minutes I need to fall asleep ..... ☐☐

I wake up at ..... ☐☐:☐☐

With help of: ☐ Alarm clock ☐ External stimulus *(noise, family members etc.)* ☐ By myself

Number of minutes I need to get up ..... ☐☐

11.03 **Number of days per week which you <u>can</u> freely choose when you sleep** (e.g. free days or holidays)

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐

Then I go to bed at ..... ☐☐:☐☐

I get ready to fall asleep at ..... ☐☐:☐☐

Number of minutes I need to fall asleep ..... ☐☐

I wake up at ..... ☐☐:☐☐

With help of: ☐ Alarm clock ☐ External stimulus *(noise, family members etc.)* ☐ By myself

Number of minutes I need to get up ..... ☐☐

12. SKIN AND DERMATOLOGY

12.01 **How often do you usually take a shower or a bath?** (tick once)

- ☐ 2 or more times daily
- ☐ 1 time daily
- ☐ 4-6 times per week
- ☐ 2-3 times per week
- ☐ Once a week
- ☐ Less than once a week

12.02 **How often do you usually wash your hands with soap daily?** (tick once)

- ☐ 0 times
- ☐ 1-5 times
- ☐ 6-10 times
- ☐ 11-20 times
- ☐ More than 20 times

12.03 **Have you ever taken any antibiotics (penicillin and penicillin-like medicines) because of a skin disease, for example infected eczema, acne, non-healing leg ulcers, recurrent abscess?**

☐ Yes ☐ No

If Yes: How many times in average per year did you take antibiotics during the period you were most affected (tick once)

☐ 1-2 ☐ 3-4 ☐ More than 4 times

12.04 **Have you or have you ever had the following skin disorders?** (tick once for each line)

	Yes	No
Psoriasis	☐	☐
Atopic eczema (children's eczema)	☐	☐
Recurrent hand eczema	☐	☐
Recurrent pimples/spots for several months	☐	☐
Leg or foot ulcer that did not heal for 3-4 weeks	☐	☐

If YES on the question concerning leg and/or foot ulcer, do you have any leg ulcer today?

☐ Yes ☐ No

12.05 **Have you often or always any of the following complaints?** (tick once for each line)

	Yes	No
Swelling in the ankles or legs, particularly in the evenings	☐	☐
Varicose veins	☐	☐
Eczema (red, itchy rash) on your legs	☐	☐
Leg pain that is getting worse when you are walking and is relieved when you are standing still	☐	☐

12.06 **Have you ever had the following diagnoses by a physician?** (tick once for each line)

	Yes	No
Psoriasis	☐	☐
Atopic eczema	☐	☐
Rosacea	☐	☐

12.07 **Have you recurring large acne/abscesses that are tender/painful and often form scars in the following places?** (tick once for each line)

	Yes	No
Armpits	☐	☐
Under the breasts	☐	☐
Stomach groove/the navel	☐	☐
Around the genitalia	☐	☐
Around the anus	☐	☐
The groin	☐	☐

If Yes: Have you ever visited a physician because of abscesses?

☐ Yes ☐ No

If Yes, did you get any of the following treatments? (tick once for each line)

	Yes	No
Antibiotic ointment	☐	☐
Antibiotic tablets	☐	☐
Surgical drainage	☐	☐
A larger surgical intervention including skin removal	☐	☐
Surgical laser treatment	☐	☐

Follow-up questions

INFORMATION TO FOLLOW-UP QUESTIONS

The following pages with questions should not be answered by everybody. If you have answered yes to one or more of questions below, we ask you to move on to the follow-up questions on the topic or topics you have answered yes to. The first four topics are from the first questionnaire and the last question is from this form.

We have for the sake of simplicity highlighted topics with different colours so that you will find the questions that applies to you.

If you answered YES to that you have: long-term or recurrent pain that has lasted for 3 months or more, please answer the questions on page 19 and 20. The margin is marked with green.

If you answered YES to that you have undergone any surgery during the last 3 years, please answer the questions on page 21 and 22. The margin is marked with purple.

If you answered YES to that you're working outdoors at least 25% of the time, or in facilities with low temperature, such as warehouse/industrial halls, please answer the questions on page 23. The margin is marked with red.

If you answered YES to that you have used non-prescription pain relievers, please answer questions on page 24. The margin is marked with orange.

If you answered YES to that you have or have ever had skin problems (such as psoriasis, atopic eczema, non-healing leg or foot ulcers, recurrent hand eczema, acne or abscesses), please answer the questions on page 25. The margin is marked with yellow.

If you have answered **NO** to these five questions, you are finished with your answers. The questionnaire is to be returned in the reply envelope you were given at the survey site. The postage is already paid.

Should you wish to give us written feedback on either the questionnaire or The Tromsø Study in general, you are welcome to that on page 26.

Do you have any questions, please contact us by phone or by e-mail. You can find the contact information on the back of the form. **THANK YOU** for taking the time to the survey and to answer our questions.

13. FOLLOW-UP QUESTIONS ON PAIN

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

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

Number of years ☐☐ months ☐☐

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

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

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

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

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

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

Describe the other cause:

.....

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

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

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

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

14. FOLLOW-UP QUESTIONS ON SURGERY

In the first questionnaire you answered that you have undergone an operation during the last 3 years.

14.01 **How many times have you undergone surgery during the last 3 years?**

Number ..... ☐☐

Below, please describe the operation. If you have undergone several operations during the last 3 years, these questions concern the last surgery you underwent.

14.02 **Where in your body did you have surgery?** (If you were operated simultaneously in several places in the body, tick more than once)

Surgery in the head/neck/back
- Head/face ..... ☐
- Neck/throat ..... ☐
- Back ..... ☐

Surgery in the chest
- Heart ..... ☐
- Lungs ..... ☐
- Breasts ..... ☐
- Another surgery in the chest region ..... ☐

Surgery in the stomach/pelvis
- Stomach/intestines ..... ☐
- Inguinal hernia ..... ☐
- Urinary tract/reproductive organs ☐
- Gall bladder/biliary tract ..... ☐
- Another surgery in the stomach/pelvis ..... ☐

Surgery in the hip/legs
- Hip/thigh ..... ☐
- Knee/leg ..... ☐
- Ankle/foot ..... ☐
- Amputation ..... ☐

Surgery in the shoulder and arm
- Shoulder/overarm ..... ☐
- Elbow/underarm ..... ☐
- Hand ..... ☐
- Amputation ..... ☐

14.03 **Reason for the surgery:**
- Acute illness/trauma ..... ☐
- Planned non-cosmetic operation ..... ☐
- Planned cosmetic operation ..... ☐

14.04 **Where did you have the surgery?**
- The hospital in Tromsø ..... ☐
- The hospital in Harstad ..... ☐
- Other public hospital ..... ☐
- Private clinic ..... ☐

14.05 **How long time is it since you had surgery?**

Number of years ..... ☐☐ Months ..... ☐☐

14.06 **Do you have reduced sensitivity in an area near the surgical scar?**

☐ Yes ☐ No

14.07 **Are you hypersensitive to touch, heat or cold in an area near the surgical scar?**

☐ Yes ☐ No

14.08 **Does slight touch from clothes, showering or similar cause discomfort/pain?**

☐ Yes ☐ No

14.09 **If you had pain at the site of surgery before you had surgery, do you have the same type of pain now?**

☐ Yes ☐ No

14.10 **The pain at the site of surgery:** Answer on a scale from 0 to 10, where 0=no pain and 10=worst pain you can imagine

How strong pain did you have at the site of surgery <u>before</u> you had surgery	No pain	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	Worst imaginable pain
How strong pain do you normally have at the site of surgery now	No pain	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	Worst imaginable pain
How strong pain do you normally have at the site of surgery when it is most intense	No pain	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	Worst imaginable pain

15. FOLLOW-UP QUESTIONS ABOUT WORK IN COLD ENVIRONMENT

In the first questionnaire you answered yes to that you work in cold environments. Here are some follow-up questions that we hope you will answer.

15.01 **Do you feel cold at work?**

- ☐ Yes, often
- ☐ Yes, sometimes
- ☐ No, never

15.02 **For how long have you been exposed to cold air below 0°C during the last winter?**

Leisure/hobbies *(hours/week)* ..... ☐☐

Work *(hours/week)* ..... ☐☐

Outdoors, with suitable clothing *(hours/week)* ..... ☐☐

Outdoors, without suitable clothing *(hours/week)* ..... ☐☐

Indoors, with no heating *(hours/week)* ☐☐

In cold, with wet clothing *(hours/week)* ..... ☐☐

Contact with cold objects/tools *(hours/week)* ..... ☐☐

15.03 **What ambient temperature prevents you from:**

	Under °C
Working outdoors	☐☐
Training outdoors	☐☐
Performing other activities outdoors	☐☐

15.04 **Have you during the <u>last 12 months</u> had a frostbite with blisters, sores or skin injury?**

☐ Yes ☐ No

If Yes, how many times? ..... ☐☐

15.05 **Have you had itching and/or rash in relation to cold exposure?**

☐ Yes ☐ No

15.06 **Have you during the <u>last 12 months</u> had an accident where cold has been involved, and which required medical treatment?**

	Yes	No
At work	☐	☐
In leisure time	☐	☐

15.07 **Do you experience any of the following symptoms while you are in a cold environment? If so, at what temperature do the symptoms occur?**

	Yes	No	Under °C
Breathing problems	☐	☐	☐☐
Wheezy breathing	☐	☐	☐☐
Mucus secretion from lungs	☐	☐	☐☐
Chest pain	☐	☐	☐☐
Disturbance in heart rhythm	☐	☐	☐☐
Impaired blood circulation in hands/feet	☐	☐	☐☐
Visual disturbance *(short term/transient)*	☐	☐	☐☐
Migraine *(short term/transient)*	☐	☐	☐☐
Fingers turning white *(short term/transient)*	☐	☐	☐☐
Fingers turning blue-red *(short term/transient)*	☐	☐	☐☐

15.08 **How does cold environments and cold-related symptoms influence your performance?**

	Decrease	No effect	Improve
Concentration	☐	☐	☐
Memory	☐	☐	☐
Finger sensitivity *(feeling)*	☐	☐	☐
Finger dexterity *(motor)*	☐	☐	☐
Control of movement *(for example tremor)*	☐	☐	☐
Heavy physical work	☐	☐	☐
Long-lasting physical work	☐	☐	☐

16. USE OF NON-PRESCRIPTION PAINKILLERS

In the first questionnaire you answered that you had used non-prescription painkillers (analgesics) in the last 4 weeks. Here are some follow-up questions we hope you will answer.

16.01 **What types of non-prescription painkillers have you used?**

Paracetamol: *(Pamol, Panodil, Paracet, Paracetamol, Pinex)*

- ☐ Not used
- ☐ Less than every week
- ☐ Every week, but not daily
- ☐ daily

How much do you usually take daily when you use these medicines?
(number of tablets, suppositories) ..... ☐☐

Acetylsalicylates: *(Aspirin,Dispril, Globoid)*

- ☐ Not used
- ☐ Less than every week
- ☐ Every week, but not daily
- ☐ Daily

How much do you usually take daily when you use these medicines?
(number of tablets) ..... ☐☐

Ibuprofen: *(Ibumetin, Ibuprofen, Ibuprox, Ibux)*

- ☐ Not used
- ☐ Less than every week
- ☐ Every week, but not daily
- ☐ Daily

How much do you usually take daily when you use these medicines?
(number of tablets, suppositories) ..... ☐☐

Naproxen: *(Ledox, Naproxen)*

- ☐ Not used
- ☐ Less than every week
- ☐ Every week, but not daily
- ☐ Daily

How much do you usually take daily when you use these medicines?
(number of tablets) ..... ☐☐

Phenazone with caffeine: *(Antineuralgica, Fanalgin, Fenazon-koffein, Fenazon-koffein sterke)*

- ☐ Not used
- ☐ Less than every week
- ☐ Every week, but not daily
- ☐ daily

How much do you usually take daily when you use these medicines?
(number of tablets) ..... ☐☐

16.02 **For which complaints do you use non-prescription painkillers?** (multiple ticks are possible)

- ☐ Headache
- ☐ Menstrual discomfort
- ☐ Migraine
- ☐ Back pain
- ☐ Muscle/joint pain
- ☐ Tooth pain
- ☐ Other

16.03 **Do you think you have experienced side effects of some of the medicines?** (tick once for each line)

	Yes	No
Paracetamol	☐	☐
Acetylsalicylates	☐	☐
Ibuprofen	☐	☐
Naproxen	☐	☐
Phenazone with caffeine	☐	☐

16.04 **Where do you usually purchase painkillers?**

- ☐ Pharmacy
- ☐ Grocery
- ☐ Petrol stations
- ☐ Abroad
- ☐ Internet

16.05 **Do you combine the treatment with the use of painkillers on prescription?**

☐ Yes ☐ No

17. FOLLOW-UP QUESTIONS ABOUT SKIN DISEASES

On page 15 in this questionnaire you answered that you have or have had a skin disease. Here are some follow-up questions we hope you will answer.

Answer on a scale from 0 to 10, where 0 corresponds to no symptoms and 10 correspond to worst imaginable complaints. If you answered YES to that you have or have had:

No complaint — 0 1 2 3 4 5 6 7 8 9 10 — Worst imaginable complaints

17.01 **Psoriasis**
- How much are you affected by your psoriasis today? ☐☐☐☐☐☐☐☐☐☐☐
- How much are you affected by your psoriasis when it is most severe? ☐☐☐☐☐☐☐☐☐☐☐

17.02 **Atopic eczema**
- How much are you affected by your atopic eczema today? ☐☐☐☐☐☐☐☐☐☐☐
- How much are you affected by your atopic eczema when it is most severe? ☐☐☐☐☐☐☐☐☐☐☐

17.03 **Hand eczema**
- How much are you affected by your hand eczema today? ☐☐☐☐☐☐☐☐☐☐☐
- How much are you affected by your hand eczema when it is most severe? ☐☐☐☐☐☐☐☐☐☐☐

17.04 **Acne**
- How much are you affected by your acne today? ☐☐☐☐☐☐☐☐☐☐☐
- How much are you affected by your acne when it is most severe? ☐☐☐☐☐☐☐☐☐☐☐

17.05 **Abscesses**
- How much are you affected by your abscesses today? ☐☐☐☐☐☐☐☐☐☐☐
- How much are you affected by your abscesses when it is most severe? ☐☐☐☐☐☐☐☐☐☐☐

17.06 **Here is a list of factors that might trigger or exacerbate abscesses, tick for what you think apply to you:**

	Yes	No
Stress/psychological strain	☐	☐
Narrow/tight clothing	☐	☐
Menstrual periods	☐	☐
Pregnancy	☐	☐
Other	☐	☐

17.07 **How many episodes of abscesses do you usually have per year?** (tick once)

☐ 0-1 ☐ 4-6
☐ 2-3 ☐ More than 6

17.08 **How old were you when you got abscesses for the first time?**

☐ 0-12 years ☐ 26-35 years
☐ 13-19 years ☐ 36-50 years
☐ 20-25 years ☐ Older than 50 years

17.09 **If you no longer have abscesses, how old were you when it disappeared?**

☐ 0-12 years ☐ 26-35 years
☐ 13-19 years ☐ 36-50 years
☐ 20-25 years ☐ Older than 50 years

FEEDBACK

Should you wish to give us a written feedback on either the questionnaire or The Tromsø Study in general, you are welcome to do it here:

Thank you for your help

Tromsø-undersøkelsen

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Appendix B

Questionnaire from the 6th Tromsø Study

Original questionnaire

Tromsø-undersøkelsen

Skjemaet skal leses optisk. Vennligst bruk blå eller sort penn. Du kan ikke bruke komma, bruk blokkbokstaver.

2007 – 2008 KONFIDENSIELT

HELSE OG SYKDOMMER

1 **Hvordan vurderer du din egen helse sånn i alminnelighet?**

- ☐ Meget god
- ☐ God
- ☐ Verken god eller dårlig
- ☐ Dårlig
- ☐ Meget dårlig

2 **Hvordan synes du at helsen din er sammenlignet med andre på din alder?**

- ☐ Mye bedre
- ☐ Litt bedre
- ☐ Omtrent lik
- ☐ Litt dårligere
- ☐ Mye dårligere

3 **Har du eller har du hatt?**

	Ja	Nei	Alder første gang
Hjerteinfarkt	☐	☐	
Angina pectoris *(hjertekrampe)*	☐	☐	
Hjerneslag/hjerneblødning	☐	☐	
Hjerteflimmer *(atrieflimmer)*	☐	☐	
Høyt blodtrykk	☐	☐	
Beinskjørhet *(osteoporose)*	☐	☐	
Astma	☐	☐	
Kronisk bronkitt/emfysem/KOLS	☐	☐	
Diabetes	☐	☐	
Psykiske plager *(som du har søkt hjelp for)*	☐	☐	
Lavt stoffskifte	☐	☐	
Nyresykdom, unntatt urinveisinfeksjon	☐	☐	
Migrene	☐	☐	

4 **Har du langvarige eller stadig tilbakevendende smerter som har vart i 3 måneder eller mer?**

☐ Ja ☐ Nei

5 **Hvor ofte har du vært plaget av søvnløshet de siste 12 måneder?**

- ☐ Aldri, eller noen få ganger
- ☐ 1-3 ganger i måneden
- ☐ Omtrent 1 gang i uken
- ☐ Mer enn 1 gang i uken

6 **Under finner du en liste over ulike problemer. Har du opplevd noe av dette den siste uken (til og med i dag)?** (Sett ett kryss for hver plage)

	Ikke plaget	Litt plaget	Ganske mye	Veldig mye
Plutselig frykt uten grunn	☐	☐	☐	☐
Føler deg redd eller engstelig	☐	☐	☐	☐
Matthet eller svimmelhet	☐	☐	☐	☐
Føler deg anspent eller oppjaget	☐	☐	☐	☐
Lett for å klandre deg selv	☐	☐	☐	☐
Søvnproblemer	☐	☐	☐	☐
Nedtrykt, tungsindig	☐	☐	☐	☐
Følelse av å være unyttig, lite verd	☐	☐	☐	☐
Følelse av at alt er et slit	☐	☐	☐	☐
Følelse av håpløshet mht. framtida	☐	☐	☐	☐

BRUK AV HELSETJENESTER

7 **Har du i løpet av de siste 12 måneder vært hos:** Hvis JA; Hvor mange ganger?

	Ja	Nei	Ant ggr
Fastlege/allmennlege	☐	☐	
Psykiater/psykolog	☐	☐	
Legespesialist utenfor sykehus *(utenom fastlege/allmennlege/psykiater)*	☐	☐	
Fysioterapeut	☐	☐	
Kiropraktor	☐	☐	
Annen behandler *(homøopat, akupunktør, fotsoneterapeut, naturmedisiner, håndspålegger, healer, synsk el.l)*	☐	☐	
Tannlege/tannpleier	☐	☐	

8 **Har du i løpet av de siste 12 måneder vært på sykehus?**

	Ja	Nei	Ant ggr
Innlagt på sykehus	☐	☐	
Konsultasjon ved sykehus uten innleggelse;			
Ved psykiatrisk poliklinikk	☐	☐	
Ved annen sykehuspoliklinikk	☐	☐	

9 **Har du gjennomgått noen form for operasjon i løpet av de siste 3 årene?**

☐ Ja ☐ Nei

BRUK AV MEDISINER

10 **Bruker du, eller har du brukt, noen av følgende medisiner?** (Sett ett kryss for hver linje)

	Aldri brukt	Nå	Før	Alder første gang
Medisin mot høyt blodtrykk	☐	☐	☐	
Kolesterolsenkende medisin	☐	☐	☐	
Medisin mot hjertesykdom	☐	☐	☐	
Vanndrivende medisin	☐	☐	☐	
Medisin mot beinskjørhet *(osteoporose)*	☐	☐	☐	
Insulin	☐	☐	☐	
Diabetesmedisin *(tabletter)*	☐	☐	☐	
Stoffskiftemedisinene Thyroxin/levaxin	☐	☐	☐	

11 **Hvor ofte har du i løpet av de siste 4 ukene brukt følgende medisiner?** (Sett ett kryss pr linje)

	Ikke brukt siste 4 uker	Sjeldnere enn hver uke	Hver uke, men ikke daglig	Daglig
Smertestillende på resept	☐	☐	☐	☐
Smertestillende reseptfrie	☐	☐	☐	☐
Sovemidler	☐	☐	☐	☐
Beroligende medisiner	☐	☐	☐	☐
Medisin mot depresjon	☐	☐	☐	☐

12 **Skriv ned alle medisiner – både de med og uten resept – som du har brukt regelmessig i siste 4 ukers periode.** (Ikke regn med vitaminer, mineraler, urter, naturmedisin, andre kosttilskudd etc.)

Får du ikke plass til alle medisiner, bruk eget ark.

VED FRAMMØTE vil du bli spurt om du har brukt antibiotika eller smertestillende medisiner de siste 24 timene. Om du har det, vil vi be om at du oppgir preparat, styrke, dose og tidspunkt

FAMILIE OG VENNER

13 **Hvem bor du sammen med?** (Sett kryss for hvert spørsmål og angi antall)

	Ja	Nei	Antall
Ektefelle/samboer	☐	☐	
Andre personer over 18 år	☐	☐	
Personer under 18 år	☐	☐	

14 **Kryss av for de slektninger som har eller har hatt**

	Foreldre	Barn	Søsken
Hjerteinfarkt	☐	☐	☐
Hjerteinfarkt før fylte 60 år	☐	☐	☐
Angina pectoris *(hjertekrampe)*	☐	☐	☐
Hjerneslag/hjerneblødning	☐	☐	☐
Beinskjørhet *(osteoporose)*	☐	☐	☐
Magesår/tolvfingertarmsår	☐	☐	☐
Astma	☐	☐	☐
Diabetes	☐	☐	☐
Demens	☐	☐	☐
Psykiske plager	☐	☐	☐
Rusproblemer	☐	☐	☐

15 **Har du nok venner som kan gi deg hjelp når du trenger det?**

☐ Ja ☐ Nei

16 **Har du nok venner som du kan snakke fortrolig med?**

☐ Ja ☐ Nei

17 **Hvor ofte tar du vanligvis del i foreningsvirksomhet som for eksempel syklubb, idrettslag, politiske lag, religiøse eller andre foreninger?**

☐ Aldri, eller noen få ganger i året
☐ 1-2 ganger i måneden
☐ Omtrent 1 gang i uken
☐ Mer enn en gang i uken

ARBEID, TRYGD OG INNTEKT

18 **Hva er din høyeste fullførte utdanning?** (Sett ett kryss)

☐ Grunnskole, framhaldsskole eller folkehøyskole
☐ Yrkesfaglig videregående, yrkesskole eller realskole
☐ Allmennfaglig videregående skole eller gymnas
☐ Høyskole eller universitet, mindre enn 4 år
☐ Høyskole eller universitet, 4 år eller mer

19 **Hva er din hovedaktivitet?** (Sett ett kryss)

☐ Yrkesaktiv heltid
☐ Yrkesaktiv deltid
☐ Arbeidsledig
☐ Hjemmeværende
☐ Pensjonist/trygdet
☐ Student/militærtjeneste

20 **Mottar du noen av følgende ytelser?**

- ☐ Alderstrygd, førtidspensjon (AFP) eller etterlattepensjon
- ☐ Sykepenger (er sykemeldt)
- ☐ Rehabiliterings-/attføringspenger
- ☐ Uføreytelse/pensjon, hel
- ☐ Uføreytelse/pensjon, delvis
- ☐ Dagpenger under arbeidsledighet
- ☐ Overgangstønad
- ☐ Sosialhjelp/-stønad

21 **Hvor høy var husholdningens samlede bruttoinntekt siste år?** Ta med alle inntekter fra arbeid, trygder, sosialhjelp og lignende.

- ☐ Under 125 000 kr
- ☐ 125 000-200 000 kr
- ☐ 201 000-300 000 kr
- ☐ 301 000-400 000 kr
- ☐ 401 000-550 000 kr
- ☐ 551 000-700 000 kr
- ☐ 701 000 -850 000 kr
- ☐ Over 850 000 kr

22 **Arbeider du utendørs minst 25 % av tiden, eller i lokaler med lav temperatur, som for eksempel lager-/industrihaller?**

- ☐ Ja
- ☐ Nei

FYSISK AKTIVITET

23 **Hvis du er i lønnet eller ulønnet arbeid, hvordan vil du beskrive arbeidet ditt?**

- ☐ For det meste stillesittende arbeid *(f.eks. skrivebordsarbeid, montering)*
- ☐ Arbeid som krever at du går mye *(f.eks ekspeditørarbeid, lett industriarbeid, undervisning)*
- ☐ Arbeid der du går og løfter mye *(f.eks postbud, pleier, bygningsarbeider)*
- ☐ Tungt kroppsarbeid

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

- ☐ Leser, ser på fjernsyn eller annen stillesittende beskjeftigelse
- ☐ Spaserer, sykler eller beveger deg på annen måte minst 4 timer i uken *(her skal du også regne med gang eller sykling til arbeidsstedet, søndagsturer med mer)*
- ☐ Driver mosjonsidrett, tyngre hagearbeid, snømåking e.l. *(merk at aktiviteten skal vare minst 4 timer i uka)*
- ☐ Trener hardt eller driver konkurranseidrett regelmessig og flere ganger i uka

25 **Hvor ofte driver du mosjon?** (Med mosjon mener vi at du f.eks går en tur, går på ski, svømmer eller driver trening/idrett)

- ☐ Aldri
- ☐ Sjeldnere enn en gang i uken
- ☐ En gang i uken
- ☐ 2-3 ganger i uken
- ☐ omtrent hver dag

26 **Hvor hardt mosjonerer du da i 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

27 **Hvor lenge holder du på hver gang i gjennomsnitt ?**

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

ALKOHOL OG TOBAKK

28 **Hvor ofte drikker du alkohol?**

- ☐ Aldri
- ☐ Månedlig eller sjeldnere
- ☐ 2-4 ganger hver måned
- ☐ 2-3 ganger pr. uke
- ☐ 4 eller flere ganger pr.uke

29 **Hvor mange enheter alkohol** (en øl, et glass vin, eller en drink) **tar du vanligvis når du drikker?**

- ☐ 1-2
- ☐ 3-4
- ☐ 5-6
- ☐ 7-9
- ☐ 10 eller flere

30 **Hvor ofte drikker du 6 eller flere enheter alkohol ved en anledning?**

- ☐ aldri
- ☐ sjeldnere enn månedlig
- ☐ månedlig
- ☐ ukentlig
- ☐ daglig eller nesten daglig

31 **Røyker du av og til, men ikke daglig?**

- ☐ Ja
- ☐ Nei

32 **Har du røykt/røyker du daglig?**

- ☐ Ja, nå
- ☐ Ja, tidligere
- ☐ Aldri

33 **Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet?**

Antall år ☐☐

34 **Hvis du røyker daglig nå eller har røykt tidligere: Hvor mange sigaretter røyker eller røykte du vanligvis daglig?**

Antall sigaretter ☐☐

35 **Hvor gammel var du da du begynte å røyke daglig?**

Antall år ☐☐

36 **Hvor mange år til sammen har du røykt daglig?**

Antall år ☐☐

37 **Bruker du, eller har du brukt, snus eller skrå?**

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

KOSTHOLD

38 **Spiser du vanligvis frokost hver dag?**

☐ Ja ☐ Nei

39 **Hvor mange enheter frukt og grønnsaker spiser du i gjennomsnitt per dag?** (Med enhet menes f.eks. en frukt, glass juice, potet, porsjon grønnsaker)

Antall enheter ☐☐

40 **Hvor mange ganger i uken spiser du varm middag?**

Antall ☐☐

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

	0-1 g pr. mnd	2-3 g pr.mnd	1-3 g pr.uke	4-6 g pr.uke	1-2 g pr. dag
Poteter	☐	☐	☐	☐	☐
Pasta/ris	☐	☐	☐	☐	☐
Kjøtt *(ikke kvernet)*	☐	☐	☐	☐	☐
Kvernet kjøtt *(pølser, hamburger o.l)*	☐	☐	☐	☐	☐
Grønnsaker, frukt, bær	☐	☐	☐	☐	☐
Mager fisk	☐	☐	☐	☐	☐
Feit fisk *(f.eks.laks, ørret, makrell, sild, kveite,uer)*	☐	☐	☐	☐	☐

42 **Hvor mye drikker du vanligvis av følgende?**
(Sett ett kryss pr. linje)

	Sjelden/ aldri	1-6 glass pr. uke	1 glass pr. dag	2-3 glass pr. dag	4 glass el. mer pr. dag
Melk, kefir, yoghurt	☐	☐	☐	☐	☐
Fruktjuice	☐	☐	☐	☐	☐
Brus/leskedrikker med sukker	☐	☐	☐	☐	☐

43 **Hvor mange kopper kaffe og te drikker du daglig?**
(sett 0 for de typene du ikke drikker daglig)

	Antall kopper
Filterkaffe	☐☐
Kokekaffe/presskanne	☐☐
Annen kaffe	☐☐
Te	☐☐

44 **Hvor ofte spiser du vanligvis fiskelever?**
(For eksempel i mølje)

☐ Sjelden/aldri ☐ 1-3 g i året ☐ 4-6 g i året
☐ 7-12 g i året ☐ Oftere

45 **Bruker du følgende kosttilskudd?**

	Daglig	Iblant	Nei
Tran, trankapsler	☐	☐	☐
Omega 3 kapsler *(fiskeolje,selolje)*	☐	☐	☐
Kalktabletter	☐	☐	☐

SPØRSMÅL TIL KVINNER

46 **Er du gravid nå?**

☐ Ja ☐ Nei ☐ Usikker

47 **Hvor mange barn har du født?**

Antall ☐☐

48 **Hvis du har født, fyll ut for hvert barn: fødselsår og vekt samt hvor mange måneder du ammet.**
(Angi så godt som du kan)

Barn	Fødselsår	Fødselsvekt i gram	Ammet ant.mnd
1	☐☐☐☐	☐☐☐☐	☐☐
2	☐☐☐☐	☐☐☐☐	☐☐
3	☐☐☐☐	☐☐☐☐	☐☐
4	☐☐☐☐	☐☐☐☐	☐☐
5	☐☐☐☐	☐☐☐☐	☐☐
6	☐☐☐☐	☐☐☐☐	☐☐

49 **Har du i forbindelse med svangerskap hatt for høyt blodtrykk?**

☐ Ja ☐ Nei

50 **Hvis Ja, i hvilket svangerskap?**

☐ Første ☐ Senere

51 **Har du i forbindelse med svangerskap hatt protein (eggehvite) i urinen?**

☐ Ja ☐ Nei

52 **Hvis Ja, i hvilket svangerskap?**

☐ Første ☐ Senere

53 **Ble noen av disse barna født mer enn en måned for tidlig (før termin) pga. svangerskapsforgiftning?**

☐ Ja ☐ Nei

54 **Hvis Ja, hvilke(t) barn**

Barn 1	Barn 2	Barn 3	Barn 4	Barn 5	Barn 6
☐	☐	☐	☐	☐	☐

55 **Hvor gammel var du da du fikk menstruasjon første gang?**

Antall år ☐☐

56 **Bruker du for tiden reseptpliktige legemidler som påvirker menstruasjonen?**

P-pille, hormonspiral eller lignende ☐ Ja ☐ Nei
Hormonpreparat for overgangs-alderen ☐ Ja ☐ Nei

VED FRAMMØTE vil du få utfyllende spørsmål om menstruasjon og eventuell bruk av hormoner. Skriv gjerne ned på et papir navn på hormonpreparater du har brukt, og ta det med deg. Du vil også bli spurt om din menstruasjon har opphørt og eventuelt når og hvorfor.

LUNDBLAD MEDIA AS, TROMSØ, 77 75 32 50 - ONR 082222

Tromsø 6

- en del av Tromsøundersøkelsen

SLIK FYLLER DU UT SKJEMAET:

Skjemaet vil bli lest maskinelt, det er derfor viktig at du krysser av riktig:

☒ Riktig

☑ Galt

☒ Galt

■ Om du krysser feil, retter du ved å fylle boksen slik

Skriv tydelige tall 1 2 3 4 5 6 7 8 9 0

7 | 4 Riktig

7 | 4 Galt

Bruk kun sort eller blå penn, bruk ikke blyant eller tusj

1. BESKRIVELSE AV DIN HELSETILSTAND

Vis hvilke utsagn som passer best på din helsetilstand i dag ved å sette ett kryss i en av rutene utenfor hver av de fem gruppene nedenfor:

1.01 **Gange**

- ☐ Jeg har ingen problemer med å gå omkring
- ☐ Jeg har litt problemer med å gå omkring
- ☐ Jeg er sengeliggende

1.02 **Personlig stell**

- ☐ Jeg har ingen problemer med personlig stell
- ☐ Jeg har litt problemer med å vaske meg eller kle meg
- ☐ Jeg er ute av stand til å vaske meg eller kle meg

1.03 **Vanlige gjøremål** (f.eks. arbeid, studier, husarbeid, familie- eller fritidsaktiviteter)

- ☐ Jeg har ingen problemer med å utføre mine vanlige gjøremål
- ☐ Jeg har litt problemer med å utføre mine vanlige gjøremål
- ☐ Jeg er ute av stand til å utføre mine vanlige gjøremål

1.04 **Smerte og ubehag**

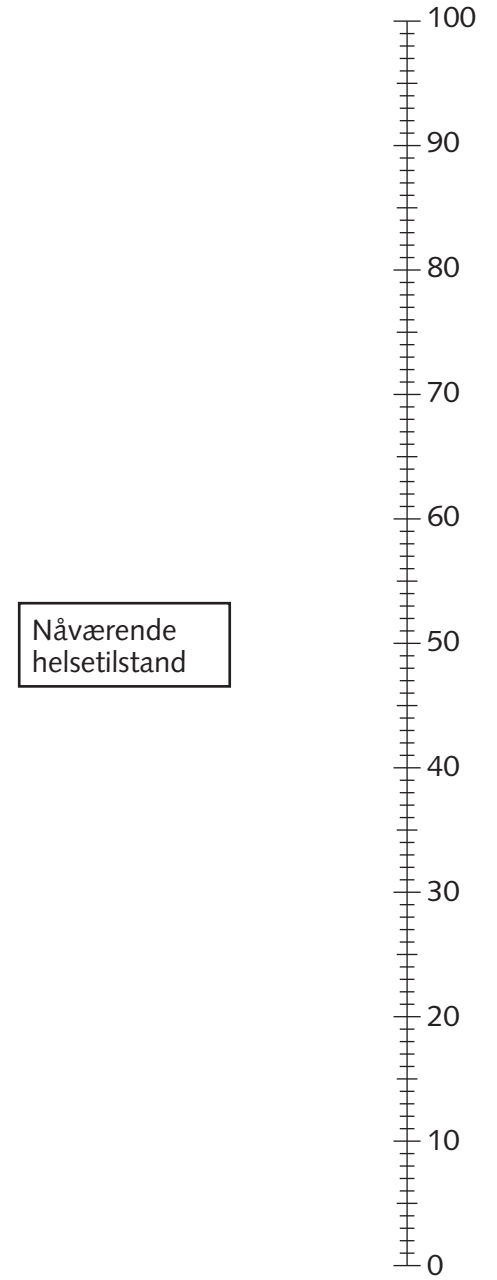
- ☐ Jeg har verken smerte eller ubehag
- ☐ Jeg har moderat smerte eller ubehag
- ☐ Jeg har sterk smerte eller ubehag

1.05 **Angst og depresjon**

- ☐ Jeg er verken engstelig eller deprimert
- ☐ Jeg er noe engstelig eller deprimert
- ☐ Jeg er svært engstelig eller deprimert

1.6 For at du skal kunne vise oss hvor god eller dårlig din helsetilstand er, har vi laget en skala (nesten som et termometer), hvor den beste helsetilstanden du kan tenke deg er markert med 100 og den dårligste med 0. Vi ber om at du viser din helsetilstand ved å trekke ei linje fra boksen nedenfor til det punkt på skalaen som passer best med din helsetilstand.

Best tenkelige helsetilstand



Verst tenkelige helsetilstand

2. OPPVEKST OG TILHØRIGHET

2.01 **Hvor bodde du da du fylte 1 år?**

- ☐ I Tromsø *(med dagens kommunegrenser)*
- ☐ I Troms, men ikke i Tromsø
- ☐ I Finnmark fylke
- ☐ I Nordland fylke
- ☐ Annet sted i Norge
- ☐ I utlandet

2.02 **Hvordan var de økonomiske forhold i familien under din oppvekst?**

- ☐ Meget gode
- ☐ Gode
- ☐ Vanskelige
- ☐ Meget vanskelige

2.03 **Hvilken betydning har religion i ditt liv?**

- ☐ Stor betydning
- ☐ En viss betydning
- ☐ Ingen betydning

2.04 **Hva regner du deg selv som?** (Kryss av for ett eller flere alternativ)

- ☐ Norsk
- ☐ Samisk
- ☐ Kvensk/Finsk
- ☐ Annet

2.05 **Hvor mange søsken og barn har du/har du hatt?**

Antall søsken ..... ☐☐

Antall barn ..... ☐☐

2.06 **Lever din mor?**

☐ Ja ☐ Nei

Hvis NEI: hennes alder ved død ..... ☐☐

Lever din far?

☐ Ja ☐ Nei

Hvis NEI: hans alder ved død ..... ☐☐

2.07 **Hva var/er den høyeste fullførte utdanning til dine foreldre og din ektefelle/samboer?**
(sett ett kryss i hver kolonne)

	Mor	Far	Ektefelle/ samboer
Grunnskole 7-10 år, framhaldsskole eller folkehøyskole	☐	☐	☐
Yrkesfaglig videregående, yrkesskole eller realskole	☐	☐	☐
Allmennfaglig videregående skole eller gymnas	☐	☐	☐
Høyskole eller universitet (mindre enn 4 år)	☐	☐	☐
Høyskole eller universitet (4 år eller mer)	☐	☐	☐

3. TRIVSEL OG LIVSFORHOLD

3.01 **Nedenfor står tre utsagn om tilfredshet med livet som et hele. Deretter står to utsagn om syn på din egen helse. Vis hvor enig eller uenig du er i hver av påstandene ved å sette et kryss i rubrikken for det tallet du synes stemmer best for deg.** (sett ett kryss for hvert utsagn)

	Helt uenig	1	2	3	4	5	6	7	Helt enig
På de fleste måter er livet mitt nær idealet mitt		☐	☐	☐	☐	☐	☐	☐	
Mine livsforhold er utmerkede		☐	☐	☐	☐	☐	☐	☐	
Jeg er tilfreds med livet mitt		☐	☐	☐	☐	☐	☐	☐	
Jeg ser lyst på min framtidige helse		☐	☐	☐	☐	☐	☐	☐	
Ved å leve sunt kan jeg forhindre alvorlige sykdommer		☐	☐	☐	☐	☐	☐	☐	

3.02 **Nedenfor står fire utsagn om syn på forhold ved din nåværende jobb, eller hvis du ikke er i arbeid nå, den jobben du hadde sist** (sett ett kryss for hvert utsagn)

	Helt uenig	1	2	3	4	5	6	7	Helt enig
Arbeidet mitt er for belastende, fysisk eller følelsesmessig		☐	☐	☐	☐	☐	☐	☐	
Jeg har tilstrekkelig innflytelse på når og hvordan arbeidet mitt skal utføres		☐	☐	☐	☐	☐	☐	☐	
Jeg blir mobbet eller trakassert på arbeidsplassen min		☐	☐	☐	☐	☐	☐	☐	
Jeg blir rettferdig behandlet på arbeidsplassen min		☐	☐	☐	☐	☐	☐	☐	

3.03 **Jeg opplever at yrket mitt har følgende sosiale status i samfunnet:** (dersom du ikke er i arbeid nå, tenk på det yrket du hadde sist)

- ☐ Meget høy status
- ☐ Ganske høy status
- ☐ Middels status
- ☐ Ganske lav status
- ☐ Meget lav status

3.04 **Har du over lengre tid opplevd noe av det følgende?** (sett ett eller flere kryss for hver linje)

	Nei	Ja, som barn	Ja, som voksen	Ja, siste år
Blitt plaget psykisk, eller truet med vold	☐	☐	☐	☐
Blitt slått, sparket eller utsatt for annen type vold	☐	☐	☐	☐
Noen i nær familie har brukt rusmidler på en slik måte at dette har vært til *bekymring* for deg	☐	☐	☐	☐

Dersom du har opplevd noen av disse forholdene, hvor mye plages du av dette nå?

☐ Ingen plager ☐ Noen plager ☐ Store plager

4. SYKDOMMER OG PLAGER

4.01 **Har du i løpet av den siste måneden følt deg syk eller hatt en skade?**

☐ Ja ☐ Nei

Hvis JA: har du i den samme perioden?
(sett ett kryss for hver linje)

	Ja	Nei
Vært hos allmennlege/fastlege	☐	☐
Vært hos spesialist	☐	☐
Vært på legevakt	☐	☐
Vært innlagt i sykehus	☐	☐
Vært hos alternativ behandler *(kiropraktor, homøopat eller lignende)*	☐	☐

4.02 **Har du merket anfall med plutselig endring i pulsen eller hjerterytmen siste året?**

☐ Ja ☐ Nei

4.03 **Blir du tungpustet i følgende situasjoner?**
(sett ett kryss for hvert spørsmål)

	Ja	Nei
Når du går hurtig på flatmark eller svak oppoverbakke	☐	☐
Når du spaserer i rolig tempo på flatmark	☐	☐
Når du vasker deg eller kler på deg	☐	☐
Når du er i hvile	☐	☐

4.04 **Hoster du omtrent daglig i perioder av året?**

☐ Ja ☐ Nei

Hvis JA: Er hosten vanligvis ledsaget av oppspytt?

☐ Ja ☐ Nei

Har du hatt slik hoste så lenge som i en 3 måneders periode i begge de to siste årene?

☐ Ja ☐ Nei

4.05 **Hvor ofte er du plaget av søvnløshet?**
(sett ett kryss)

☐ Aldri, eller noen få ganger i året
☐ 1-3 ganger i måneden
☐ Omtrent 1 gang i uka
☐ Mer enn 1 gang i uka

Hvis du er plaget av søvnløshet månedlig eller oftere, når på året er du mest plaget?
(sett ett eller flere kryss)

☐ Ingen spesiell tid
☐ Mørketida
☐ Midnattsoltida
☐ Vår og høst

4.06 **Har du i de siste par ukene hatt vansker med å sove?**

☐ Ikke i det hele tatt
☐ Ikke mer enn vanlig
☐ Heller mer enn vanlig
☐ Mye mer enn vanlig

4.07 **Har du de siste par ukene følt deg ulykkelig og nedtrykt (deprimert)?**

☐ Ikke i det hele tatt
☐ Ikke mer enn vanlig
☐ Heller mer enn vanlig
☐ Mye mer enn vanlig

4.08 **Har du i de siste par ukene følt deg ute av stand til å mestre dine vanskeligheter?**

☐ Ikke i det hele tatt
☐ Ikke mer enn vanlig
☐ Heller mer enn vanlig
☐ Mye mer enn vanlig

4.09 **Nedenfor ber vi deg besvare noen spørsmål om din hukommelse:** (sett ett kryss for hvert spørsmål)

	Ja	Nei
Synes du at din hukommelse har blitt dårligere?	☐	☐
Glemmer du ofte hvor du har lagt tingene dine?	☐	☐
Har du problemer med å finne vanlige ord i en samtale?	☐	☐
Har du fått problemer med daglige gjøremål som du mestret tidligere?	☐	☐
Har du vært undersøkt for sviktende hukommelse?	☐	☐

Hvis JA på minst ett av de fire første spørsmålene ovenfor: Er det et problem i hverdagen?

☐ Ja ☐ Nei

4.10 **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?** (sett ett kryss i hver linje)

	Ikke plaget	En del plaget	Sterkt plaget
Nakke, skuldre	☐	☐	☐
Armer, hender	☐	☐	☐
Øvre del av ryggen	☐	☐	☐
Korsryggen	☐	☐	☐
Hofter, ben, føtter	☐	☐	☐
Andre steder	☐	☐	☐

4.11 **Har du vært plaget med smerter og/eller stivhet i muskler og ledd i løpet av de siste 4 ukene?** (sett ett kryss i hver linje)

	Ikke plaget	En del plaget	Sterkt plaget
Nakke, skuldre	☐	☐	☐
Armer, hender	☐	☐	☐
Øvre del av ryggen	☐	☐	☐
Korsryggen	☐	☐	☐
Hofter, ben, føtter	☐	☐	☐
Andre steder	☐	☐	☐

4.12 **Har du noen gang hatt:**

	Ja	Nei	Alder siste gang
Brudd i håndledd/ underarm?	☐	☐	
Lårhalsbrudd?	☐	☐	

4.13 **Har du fått stilt diagnosen slitasjegikt av lege?**

☐ Ja ☐ Nei

4.14 **Har eller har du hatt noen av følgende:**

	Aldri	Litt	Mye
Nikkelallergi	☐	☐	☐
Pollenallergi	☐	☐	☐
Andre allergier	☐	☐	☐

4.15 **Har du opplevd ufrivillig barnløshet i mer enn 1 år?**

☐ Ja ☐ Nei

Hvis JA, skyldtes dette:

	Ja	Nei	Vet ikke
Forhold hos deg selv?	☐	☐	☐
Forhold hos partneren?	☐	☐	☐

4.16 **I hvilken grad har du hatt følgende plager i de siste 12 måneder?**

	Aldri	Litt	Mye
Kvalme	☐	☐	☐
Halsbrann/sure oppstøt	☐	☐	☐
Diare	☐	☐	☐
Treg mage	☐	☐	☐
Vekslende treg mage og diare	☐	☐	☐
Oppblåsthet	☐	☐	☐
Smerter i magen	☐	☐	☐

4.17 **Hvis du har hatt smerter i eller ubehag fra magen siste året:**

	Ja	Nei
Er disse lokalisert øverst i magen?	☐	☐
Har du hatt plagene så ofte som 1 dag i uka eller mer de siste 3 måneder?	☐	☐
Blir plagene bedre etter avføring?	☐	☐
Har plagene sammenheng med hyppigere eller sjeldnere avføring enn vanlig?	☐	☐
Har plagene noen sammenheng med løsere eller fastere avføring enn vanlig?	☐	☐
Kommer plagene etter måltid?	☐	☐

4.18 **Har du noen gang hatt:**

	Ja	Nei	Alder siste gang
Sår på magesekken	☐	☐	
Sår på tolvfingertarmen	☐	☐	
Magesår-operasjon	☐	☐	

4.19 **Til kvinnen: Har du spontanabortert?**

☐ Ja ☐ Nei ☐ Vet ikke

Hvis JA, antall ganger

4.20 **Til mannen: Har din partner noen gang spontanabortert?**

☐ Ja ☐ Nei ☐ Vet ikke

Hvis JA, antall ganger

4.21 **Bruker du glutenfri diett?**

☐ Ja ☐ Nei ☐ Vet ikke

4.22 **Har du fått stilt diagnosen Dermatitis Herpetiformis (DH)?**

☐ Ja ☐ Nei ☐ Vet ikke

4.23 **Har du fått stilt diagnosen cøliaki på bakgrunn av en vevsprøve fra tynntarmen tatt under en undersøkelse der du svelget en slange (gastroskopi)?**

☐ Ja ☐ Nei ☐ Vet ikke

4.24 **Har du egne tenner?**

☐ Ja ☐ Nei

4.25 **Hvor mange amalgamfyllinger har du/har du hatt?**

☐ 0 ☐ 1-5 ☐ 6-10 ☐ 10+

4.26 **Har du vært plaget av hodepine det siste året?**

☐ Ja ☐ Nei

Hvis NEI, gå til del 5, kosthold

4.27 **Hva slags hodepine er du plaget av?**

☐ Migrene ☐ Annen hodepine

4.28 **Omtrent hvor mange dager per måned har du hodepine?**

☐ Mindre enn 1 dag
☐ 1-6 dager
☐ 7-14 dager
☐ Mer enn 14 dager

4.29 **Er hodepinen vanligvis:**
(sett et kryss for hver linje)

	Ja	Nei
Bankende/dunkende smerte	☐	☐
Pressende smerte	☐	☐
Ensidig smerte *(høyre eller venstre)*	☐	☐

4.30 **Hvor sterk er hodepinen vanligvis?**

☐ Mild *(hemmer ikke aktivitet)*
☐ Moderat *(hemmer aktivitet)*
☐ Sterk *(forhindrer aktivitet)*

4.31 **Hvor lenge varer hodepinen vanligvis?**

☐ Mindre enn 4 timer
☐ 4 timer – 1 døgn
☐ 1-3 døgn
☐ Mer enn 3 døgn

4.32 **Dersom du er plaget av hodepine, når på året er du plaget mest?** (sett ett eller flere kryss)

☐ Ingen spesiell tid
☐ Mørketida
☐ Midnattsoltida
☐ Vår og/eller høst

4.33 **Før eller under hodepinen, kan du da ha forbigående:**

	Ja	Nei
Synsforstyrrelse? *(takkede linjer, flimring, tåkesyn, lysglimt)*	☐	☐
Nummenhet i halve ansiktet eller i hånden?	☐	☐
Forverring ved moderat fysisk aktivitet	☐	☐
Kvalme og /eller oppkast	☐	☐

4.34 **Angi hvor mange dager du har vært borte fra arbeid eller skole siste måned på grunn av hodepine:**

Antall dager ☐☐

5. KOSTHOLD

5.01 **Hvor ofte spiser du vanligvis følgende?** (sett ett kryss i hver linje)

	0-1 g per mnd	2-3 g per mnd	1-3 g per uke	Mer enn 3 g per uke
Ferskvannsfisk *(ikke oppdrett)*	☐	☐	☐	☐
Saltvannsfisk *(ikke oppdrett)*	☐	☐	☐	☐
Oppdrettsfisk *(laks, røye, ørret)*	☐	☐	☐	☐
Tunfisk *(fersk eller hermetisert)*	☐	☐	☐	☐
Fiskepålegg	☐	☐	☐	☐
Skjell	☐	☐	☐	☐
Den brune innmaten i krabbe	☐	☐	☐	☐
Hvalkjøtt/sel/kobbekjøtt	☐	☐	☐	☐
Innmat fra rein eller elg	☐	☐	☐	☐
Innmat fra rype	☐	☐	☐	☐

5.02 **Hvor mange ganger i året spiser du/spiste du vanligvis følgende?** (antall ganger)

	Som voksen	I din barndom
Mølje *(Antall ganger i året)*	☐☐	☐☐
Måsegg *(Antall egg i året)*	☐☐	☐☐
Reinsdyrkjøtt *(Antall ganger i året)*	☐☐	☐☐
Selvplukket sopp og bær *(blåbær/tyttebær/multe) (Antall ganger i året)*	☐☐☐	☐☐☐

5.03 **Hvor mange ganger i måneden spiser du hermetiske matvarer (fra metallbokser)?**

Antall ☐☐

5.04 **Bruker du vitaminer og/eller mineraltilskudd?**

☐ Ja, daglig ☐ Iblant ☐ Aldri

5.05 **Hvor ofte spiser du?**

	Aldri	1-3 g per mnd	1-3 g per uke	4-6 g. per uke	1-2 g. per dag	3 g. per dag eller mer
Mørk sjokolade	☐	☐	☐	☐	☐	☐
Lys sjokolade/melkesjokolade	☐	☐	☐	☐	☐	☐
Sjokoladekake	☐	☐	☐	☐	☐	☐
Andre søtsaker	☐	☐	☐	☐	☐	☐

5.06 **Hvis du spiser sjokolade, hvor mye pleier du vanligvis å spise hver gang?**
Tenk deg størrelsen på en Kvikk- Lunsj sjokolade, og oppgi hvor mye du spiser i forhold til den.

¼	½	1	1 ½	2	Mer enn 2
☐	☐	☐	☐	☐	☐

5.07 **Hvor ofte drikker du kakao/varm sjokolade**

Aldri	1-3 g per mnd	1-3 g per uke	4-6 g. per uke	1-2 g. per dag	3 g. per dag eller mer
☐	☐	☐	☐	☐	☐

6. ALKOHOL

6.01 **Hvor ofte har du <u>det siste året</u>:**

	Aldri	Sjeldnere enn månedlig	Månedlig	Ukentlig	Daglig, eller nesten daglig
Ikke klart å stoppe og drikke alkohol når du først har begynt?	☐	☐	☐	☐	☐
Ikke klart å gjøre det som normalt forventes av deg fordi du har drukket?	☐	☐	☐	☐	☐
Trengt en drink om morgenen for å få komme i gang etter en rangel?	☐	☐	☐	☐	☐
Følt skyld eller anger etter at du har drukket?	☐	☐	☐	☐	☐
Ikke klart å huske hva som skjedde kvelden før på grunn av at du hadde drukket?	☐	☐	☐	☐	☐

	Aldri	Ja, men ikke det siste året	Ja, det siste året
6.02 **Har du eller andre noen gang blitt skadet på grunn av at du har drukket?**	☐	☐	☐
Har en slektning, venn, lege, eller annet helsepersonell vært bekymret for din drikking, eller foreslått at du reduserer inntaket?	☐	☐	☐

7. VEKT

7.01 **Har du ufrivillig gått ned i vekt <u>siste 6 måneder</u>?**

☐ Ja ☐ Nei

Hvis JA: Hvor mange kilo? ☐☐

7.02 **Anslå din vekt da du var 25 år gammel:**

Antall hele kg ☐☐☐

7.03 **Er du fornøyd med vekta di nå?**

☐ Ja ☐ Nei

7.04 **Hvilken vekt ville du være tilfreds med (din trivselsvekt):**

Antall kg ☐☐☐

8. LØSEMIDLER

8.01 **Hvor mange timer i uka driver du med følgende <u>fritids- eller yrkesaktiviteter:</u>**
Bilreparasjoner/lakkering, keramikkarbeid, maling/lakkering/løsemidler, frisør, glassmester, elektriker (Sett 0 om du ikke driver med slike fritids eller yrkesaktiviteter)

Antall timer per uke i gjennomsnitt ☐☐

8.02 **Bruker du hårfargemidler?**

☐ Ja ☐ Nei

Hvis JA, hvor mange ganger per år? ☐☐

9. BRUK AV HELSETJENESTER

9.01 **Har du noen gang opplevd at sykdom er blitt mangelfullt undersøkt eller behandlet, og at dette har gitt alvorlige følger?**

- ☐ Ja, det har rammet meg selv
- ☐ Ja, det har rammet en nær pårørende *(barn, foreldre, ektefelle/samboer)*
- ☐ Nei

Hvis JA, hvor mener du årsaken ligger? (sett ett eller flere kryss):

- ☐ hos fastlege/allmennlege
- ☐ hos legevaktslege
- ☐ hos privatpraktiserende spesialist
- ☐ hos sykehuslege
- ☐ hos annet helsepersonell
- ☐ hos alternativ behandler
- ☐ hos flere på grunn av svikt i rutiner og samarbeid

9.02 **Har du noen gang følt deg overtalt til å godta undersøkelse eller behandling som du selv ikke ønsket?**

☐ Ja ☐ Nei

Hvis JA, mener du dette har hatt uheldige helsemessige følger?

☐ Ja ☐ Nei

9.03 **Har du noen gang klaget på behandling du har fått?**

- ☐ Har aldri vært aktuelt
- ☐ Har vurdert å klage, men ikke gjort det
- ☐ Har klaget muntlig
- ☐ Har klaget skriftlig

9.04 **Hvor lenge har du hatt din nåværende fastlege/annen lege?**

- ☐ Mindre enn 6 måneder
- ☐ 6 til 12 måneder
- ☐ 12 til 24 måneder
- ☐ Mer enn 2 år

9.05 **Ved siste legebesøk hos fastlegen, snakket legen(e) til deg slik at du forsto dem?** Svar på en skala fra 0 til 10, hvor 0=de var vanskelige å forstå og 10=de var alltid enkle å forstå

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

9.06 **Hvordan vil du karakterisere behandlingen eller rådgivingen du fikk siste gang du var hos lege?** Svar på en skala fra 0 til 10, hvor 0= meget dårlig behandling og 10 = meget god behandling

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

9.07 **Har du i løpet av de siste 12 måneder opplevd at det har vært vanskelig å bli henvist til spesielle undersøkelser (som røntgen eller liknende) eller til spesialist-helsetjenesten (privatpraktiserende spesialist eller ved sykehus)?**

- ☐ Ikke aktuelt
- ☐ Intet problem
- ☐ Noe problem
- ☐ Stort problem

9.08 **Har du i løpet av de siste 12 måneder opplevd at det er vanskelig å bli henvist til fysioterapeut, kiropraktor eller liknende?**

- ☐ Ikke aktuelt
- ☐ Intet problem
- ☐ Noe problem
- ☐ Stort problem

9.09 **Alt i alt, har du opplevd at det er vanskelig eller enkelt å bli henvist til spesialisthelse-tjenesten?**

- ☐ Ikke aktuelt
- ☐ Meget vanskelig
- ☐ Noe vanskelig
- ☐ Rimelig enkelt
- ☐ Meget enkelt

9.10 **Har du i løpet av de siste 12 måneder vært til undersøkelse eller behandling i spesialist-helsetjenesten?**

☐ Ja ☐ Nei

Hvis JA, snakket legen(e) til deg slik at du forstod dem? Svar på en skala fra 0 til 10, hvor 0=de var vanskelige å forstå og 10=de var alltid enkle å forstå

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

9.11 **Hvordan vil du karakterisere behandlingen eller rådgivningen du fikk siste gang du var hos spesialist?** Svar på en skala fra 0 til 10, hvor 0=meget dårlig og 10=meget god

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

9.12 **Har du noen gang før 2002 gjennomgått en operasjon på sykehus eller spesialist-klinikk?**

☐ Ja ☐ Nei

9.13 **Har du i løpet av de siste 12 måneder brukt urtemedisin , naturmidler eller naturlegemidler?**

☐ Ja ☐ Nei

9.14 **Har du i løpet av de siste 12 måneder brukt meditasjon, yoga, qi gong eller thai chi som egenbehandling?**

☐ Ja ☐ Nei

10. BRUK AV ANTIBIOTIKA

10.01 **Har du brukt antibiotika i løpet av de siste 12 måneder?** (all penicillinliknende medisin i form av tabletter, mikstur eller sprøyter)

☐ Ja ☐ Nei ☐ Husker ikke

Hvis JA, hva fikk du behandling mot? Har du tatt flere antibiotikakurer, sett ett kryss for hver kur.

	Kur 1	Kur 2	Kur 3	Kur 4	Kur 5	Kur 6
· Urinveisinfeksjon *(blærebetennelse, blærekatarr)*	☐	☐	☐	☐	☐	☐
· Luftveisinfeksjon *(øre-, bihule- hals- eller lungebetennelse, bronkitt)*	☐	☐	☐	☐	☐	☐
· Annet	☐	☐	☐	☐	☐	☐
Antall dagers antibiotika kur						

Hvordan skaffet du deg antibiotikakuren? Har du tatt flere kurer, sett ett kryss for hver kur.

Etter resept fra lege/tannlege	☐	☐	☐	☐	☐	☐
Uten kontakt med lege/uten resept:						
· Kjøp direkte fra apotek i utlandet	☐	☐	☐	☐	☐	☐
· Kjøp gjennom Internett	☐	☐	☐	☐	☐	☐
· Rest fra tidligere kur tilgjengelig hjemme	☐	☐	☐	☐	☐	☐
· Fått av familie/venner	☐	☐	☐	☐	☐	☐
· Andre måter	☐	☐	☐	☐	☐	☐

10.02 **Har du antibiotika hjemme?**

☐ Ja ☐ Nei

Hvis JA, er dette etter avtale med lege for å behandle kronisk eller hyppig tilbakevendende sykdom?

☐ Ja ☐ Nei

Hvis Nei, hvordan skaffet du deg dette legemiddelet? (Flere kryss er mulig)

- Kjøpt direkte fra apotek i utlandet ☐
- Kjøpt over Internett ☐
- Rest fra tidligere kur ☐
- Fått av familie/venner ☐
- Andre måter ☐

10.03 **Kan du tenke deg å bruke antibiotika uten å kontakte lege først?**

☐ Ja ☐ Nei

Hvis JA, hvilke tilstander vil du i så fall behandle? (Flere kryss mulig)

- Forkjølelse ☐
- Hoste ☐
- Bronkitt ☐
- Halsbetennelse ☐
- Bihulebetennelse ☐
- Feber ☐
- Influensa ☐
- Ørebetennelse ☐
- Diaré ☐
- Blærebetennelse ☐
- Andre infeksjoner ☐

11. DIN DØGNRYTME

Vi vil stille deg noen spørsmål som handler om dine søvnvaner.

11.01 **Har du hatt skiftarbeid de tre siste månedene?**

☐ Ja ☐ Nei

11.02 **Antall dager i løpet av uken hvor du ikke kan velge fritt når du vil sove (f.eks arbeidsdager)?**

0 1 2 3 4 5 6 7

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Da går jeg til sengs klokken ..... ☐☐:☐☐

Jeg gjør meg klar til å sove klokken ..... ☐☐:☐☐

Antall minutter jeg trenger på å sovne ..... ☐☐

Jeg våkner klokken ..... ☐☐:☐☐

Ved hjelp av: ☐ Vekkeklokke ☐ annen ytre påvirkning *(støy, familie etc)* ☐ av meg selv

Antall minutter jeg trenger på å stå opp ..... ☐☐

11.03 **Antall dager i løpet av uken hvor du fritt kan velge når du vil sove** (f.eks helger eller fridager)

0 1 2 3 4 5 6 7

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Da går jeg til sengs klokken ..... ☐☐:☐☐

Jeg gjør meg klar til å sove klokken ..... ☐☐:☐☐

Antall minutter jeg trenger på å sovne ..... ☐☐

Jeg våkner klokken ..... ☐☐:☐☐

Ved hjelp av: ☐ Vekkeklokke ☐ annen ytre påvirkning *(støy, familie etc)* ☐ av meg selv

Antall minutter jeg trenger på å stå opp ..... ☐☐

12. HUD OG HUDSYKDOMMER

12.01 **Hvor ofte dusjer eller bader du vanligvis?** (sett ett kryss)

- ☐ 2 eller flere ganger daglig
- ☐ 1 gang daglig
- ☐ 4-6 ganger per uke
- ☐ 2-3 ganger per uke
- ☐ 1 gang per uke
- ☐ sjeldnere enn 1 gang per uke

12.02 **Hvor ofte vasker du vanligvis hendene med såpe i løpet av en dag?** (sett ett kryss)

- ☐ 0 ganger
- ☐ 1-5 ganger
- ☐ 6-10 ganger
- ☐ 11-20 ganger
- ☐ Mer enn 20 ganger

12.03 **Har du noen gang fått antibiotikakur (penicillin og liknende medisin) på grunn av en hudlidelse, for eksempel betent eksem, kviser, leggsår som ikke vil gro, tilbakevendende verkebyll?**

☐ Ja ☐ Nei

Hvis JA, hvor mange ganger i gjennomsnitt per år fikk du antibiotika i den perioden du var mest plaget (sett ett kryss)

☐ 1-2 ☐ 3-4 ☐ Mer enn 4 ganger

12.04 **Har du eller har du noen gang hatt følgende hudlidelser?** (sett ett kryss for hver linje)

	Ja	Nei
Psoriasis	☐	☐
Atopisk eksem (barneeksem)	☐	☐
Tilbakevendende håndeksem	☐	☐
Tilbakevendende kviser over flere måneder	☐	☐
Legg- eller fotsår som ikke ville gro i løpet av 3-4 uker	☐	☐

Hvis JA på spørsmål om legg-og/eller fotsår, har du leggsår i dag?

☐ Ja ☐ Nei

12.05 **Har du ofte eller bestandig noen av følgende plager?** (sett ett kryss for hver linje)

	Ja	Nei
Hevelse i ankler og legger, særlig om kvelden	☐	☐
Åreknuter	☐	☐
Eksem (rødt, kløende utslett) på leggene	☐	☐
Smerter i beina når du går, men som forsvinner når du står stille	☐	☐

12.06 **Har du noen gang fått følgende diagnoser av lege?** (sett ett kryss for hver linje)

	Ja	Nei
Psoriasis	☐	☐
Atopisk eksem	☐	☐
Rosacea	☐	☐

12.07 **Har du tilbakevendende store kviser/ verkebyller som er ømme/smertefulle og som ofte tilheler med arr på følgende steder?** (sett ett kryss for hver linje)

	Ja	Nei
Armhulene	☐	☐
Under brystene	☐	☐
Magefolden/navlen	☐	☐
Rundt kjønnsorganet	☐	☐
Rundt endetarmsåpningen	☐	☐
Lyskene	☐	☐

Hvis JA, har du noen gang oppsøkt lege på grunn av verkebyller?

☐ Ja ☐ Nei

Hvis JA, fikk du da noen av følgende behandlinger? (sett ett kryss for hver linje)

	Ja	Nei
Antibiotika salve/krem	☐	☐
Antibiotika tabletter	☐	☐
Kirurgisk åpning/tømming	☐	☐
Større kirurgisk inngrep med fjerning av hud	☐	☐
Kirurgisk laserbehandling	☐	☐

Oppfølgingsspørsmål

INFORMASJON TIL OPPFØLGINGSSPØRSMÅL

De neste sidene med spørsmål skal ikke besvares av alle. Dersom du har svart ja på ett eller flere av spørsmålene under, ber vi deg om å gå videre til oppfølgingsspørsmål om emnet eller emnene du har svart ja på. De fire første emnene er fra det første spørreskjemaet og det siste spørsmålet er fra dette skjemaet.

Vi har for enkelhetsskyld markert emnene med ulike farger slik at du lett skal finne frem til de spørsmålene som gjelder for deg.

Dersom du svarte JA på at du har: langvarige eller stadig tilbakevendende smerter som har vart i 3 måneder eller mer, ber vi deg svare på spørsmålene på side 19 og 20. Margen er markert med grønn.

Dersom du svarte JA på at du har gjennomgått noen form for operasjon i løpet av de siste 3 årene, ber vi deg svare på spørsmålene på side 21 og 22. Margen er markert med lilla.

Dersom du svarte JA på at du arbeider utendørs minst 25% av tiden, eller i lokaler med lav temperatur, som for eksempel lager/industrihaller, ber vi deg svare på spørsmålene på side 23. Margen er markert med rød.

Dersom du svarte JA på at du har brukt reseptfrie smertestillende medisiner, ber vi deg svare på spørsmålene på side 24. Margen er markert med orange.

Dersom du svarte JA på at du har eller noen gang har hatt plager med hud (som psoriasis, atopisk eksem, legg- eller fotsår som ikke vil gro, tilbakevendende håndeksem, kviser eller verkebyll), ber vi deg svare på spørsmålene på side 25. Margen er markert med gul.

Har du svart **NEI** på disse fem spørsmålene, er du ferdig med besvarelsen din. Spørreskjemaet returneres i svarkonvolutten du fikk utlevert på undersøkelsen. Portoen er allerede betalt.

Skulle du ønske å gi oss en skriftlig tilbakemelding om enten spørreskjema eller Tromsøundersøkelsen generelt, er du hjertelig velkommen til det på side 26.

Har du noen spørsmål, kan du ta kontakt med oss på telefon eller på e-post. Du finner kontaktinformasjon på baksiden av skjemaet. **TUSEN TAKK** for at du tok deg tid til undersøkelsen og til å svare på spørsmålene fra oss.

13. OPPFØLGINGSSPØRSMÅL OM SMERTE

Du svarte i det første spørreskjemaet at du har langvarige eller stadig tilbakevendende smerter som har vart i 3 måneder eller mer. Her ber vi deg beskrive de smertene litt nærmere.

13.01 **Hvor lenge har du hatt disse smertene?**

Antall år..... ☐☐ måneder..... ☐☐

13.02 **Hvor ofte har du vanligvis disse smertene?**

- ☐ Hver dag
- ☐ En eller flere ganger i uken
- ☐ En eller flere ganger i måneden
- ☐ Sjeldnere enn 1 gang i måneden

13.03 **Hvor er det vondt?** (Kryss av for alle steder der du har langvarige eller stadig tilbakevendende smerter)

- ☐ Hode/ansikt
- ☐ Kjeve/kjeveledd
- ☐ Nakke
- ☐ Rygg
- ☐ Skulder
- ☐ Arm/albue
- ☐ Hånd
- ☐ Hofte
- ☐ Lår/kne/legg
- ☐ Ankel/fot
- ☐ Bryst
- ☐ Mage
- ☐ Underliv/kjønnsorganer
- ☐ Hud
- ☐ Annet sted

13.04 **Hva mener du er årsaken til smertene?** (Kryss av for alle kjente årsaker)

- ☐ Ulykke/akutt skade
- ☐ Langvarig belastning
- ☐ Kirurgisk inngrep/operasjon
- ☐ Skiveutglidning *(prolaps)*/lumbago
- ☐ Nakkesleng *(whiplash)*
- ☐ Migrene/hodepine
- ☐ Slitasjegikt *(artrose)*
- ☐ Leddgikt
- ☐ Bechterews sykdom
- ☐ Fibromyalgi
- ☐ Angina pectoris *(hjertekrampe)*
- ☐ Dårlig blodsirkulasjon
- ☐ Kreft
- ☐ Nerveskade/nevropati
- ☐ Infeksjon
- ☐ Helvetesild
- ☐ Annen årsak *(beskriv under)*
- ☐ Vet ikke

Beskriv annen årsak:

.....

13.05 **Hvilke former for behandling har du fått for smertene?** (Kryss av for alle typer smertebehandling du har mottatt)

- ☐ Ingen behandling
- ☐ Smertestillende medisiner
- ☐ Fysioterapi/kiropraktikk
- ☐ Behandling ved smerteklinikk
- ☐ Operasjon
- ☐ Smerteskole/avspenning/psykoterapi
- ☐ Akupunktur
- ☐ Alternativ behandling *(homøopati, healing, aromaterapi, m.m.)*
- ☐ Annen behandling

13.06 **På en skala fra 0 til 10, der 0 tilsvarer ingen smerte og 10 tilsvarer den verst tenkelige smerten du kan forestille deg:**

Hvor sterke vil du si at smertene vanligvis er?	Ingen smerte	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	Verst tenkelige smerte
Hvor sterke er smertene når de er på sitt sterkeste?	Ingen smerte	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	Verst tenkelige smerte
I hvor stor grad påvirker smertene søvnen din?	Påvirker ikke	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	Umulig å få sove
I hvor stor grad hindrer smertene deg i å utføre vanlige aktiviteter hjemme og i arbeid?	Påvirker ikke	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	Kan ikke gjøre noe

14. OPPFØLGINGSSPØRSMÅL OM OPERASJON

I det første spørreskjemaet svarte du at du har gjennomgått en operasjon i løpet av de siste 3 årene.

14.01 **Hvor mange operasjoner har du totalt gjennomgått de siste 3 årene?**

Antall ..... ☐☐

Nedenfor ber vi deg beskrive operasjonen. Dersom du har gjennomgått flere operasjoner i løpet av de siste 3 årene gjelder disse spørsmålene den siste operasjonen du gjennomgikk.

14.02 **Hvor i kroppen ble du operert?** (Dersom du samtidig ble operert flere steder i kroppen, settes flere kryss)

Operasjon i hode/nakke/rygg
- · Hode/ansikt ☐
- · Nakke/hals ☐
- · Rygg ☐

Operasjon i brystregionen
- · Hjerte ☐
- · Lunger ☐
- · Bryster ☐
- · Annen operasjon i brystregionen ☐

Operasjon i mage/underliv
- · Mage/tarm ☐
- · Lyskebrokk ☐
- · Urinveier/kjønnsorganer ☐
- · Galleblære/galleveier ☐
- · Annen operasjon i mage/underliv ☐

Operasjon i hofte/ben
- · Hofte/lår ☐
- · Kne/legg ☐
- · Ankel/fot ☐
- · Amputasjon ☐

Operasjon i skulder og arm
- · Skulder/overarm ☐
- · Albue/underarm ☐
- · Hånd ☐
- · Amputasjon ☐

14.03 **Bakgrunn for operasjonen:**
- Akutt sykdom/skade ☐
- Planlagt ikke-kosmetisk operasjon ☐
- Planlagt kosmetisk operasjon ☐

14.04 **Hvor ble du operert?**
- Sykehuset i Tromsø ☐
- Sykehuset i Harstad ☐
- Annet offentlig sykehus ☐
- Privat klinikk ☐

14.05 **Hvor lenge er det siden du gjennomgikk operasjonen?**

Antall år ..... ☐☐ måneder ..... ☐☐

14.06 **Har du nedsatt følsomhet i et område nær operasjonsarret?**

☐ Ja ☐ Nei

14.07 **Er du overfølsom for berøring, varme eller kulde i et område nær operasjonsarret?**

☐ Ja ☐ Nei

14.08 **Kan lett berøring av klær, dusj og lignende fremkalle ubehag/smerte?**

☐ Ja ☐ Nei

14.09 **Hvis du hadde smerter på operasjonsstedet før du ble operert, har du samme type smerte nå?**

☐ Ja ☐ Nei

14.10 **Smerte fra operasjonsstedet:** Svar på en skala fra 0 til 10, hvor 0=ingen smerte og 10=verst tenkelige smerte

Hvor sterke smerter hadde du fra operasjonsstedet før operasjonen.....	Ingen smerte	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	Verst tenkelige smerte
Hvor sterke smerter har du vanligvis fra operasjonsstedet nå.....	Ingen smerte	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	Verst tenkelige smerte
Hvor sterke smerter har du nå fra operasjonsstedet når smertene er på det sterkeste.....	Ingen smerte	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	Verst tenkelige smerte

15. OPPFØLGINGSSPØRSMÅL OM ARBEID I KALDT KLIMA

I det første spørreskjemaet svarte du ja på at du arbeidet i kaldt klima. Her er noen oppfølgingsspørsmål vi håper du vil svare på.

15.01 **Fryser du på jobb?**

☐ Ja, ofte
☐ Ja, noen ganger
☐ Nei, aldri

15.02 **Hvor lenge har du vært utsatt for kalde omgivelser under 0°C sist vinter?**

Fritid/hobby *(timer/uke)* ..... ☐☐
Arbeid *(timer/uke)* ..... ☐☐
Utendørs, godt kledd *(timer/uke)* ..... ☐☐
Utendørs, tynnkledd *(timer/uke)* ..... ☐☐
Innendørs, uten oppvarming *(timer/uke)* ..... ☐☐
I kalde omgivelser, med våte klær *(timer/uke)* ..... ☐☐
Kontakt med kalde gjenstander/ verktøy *(timer/uke)* ..... ☐☐

15.03 **Hvilken omgivelsestemperatur forhindrer deg i å:**

	Under °C
Arbeide utendørs	☐☐
Trene utendørs	☐☐
Utføre andre aktiviteter utendørs	☐☐

15.04 **Har du hatt forfrysninger siste 12 måneder, med blemmer, sår eller skader i huden?**

☐ Ja ☐ Nei

Hvis JA, hvor mange ganger? ..... ☐☐

15.05 **Har du opplevd kløe og/eller utslett i forbindelse med kulde?**

☐ Ja ☐ Nei

15.06 **Har du i løpet av de siste 12 måneder vært involvert i ulykke som krevde medisinsk behandling der kulde var en viktig faktor?**

	Ja	Nei
På arbeid	☐	☐
I fritiden	☐	☐

15.07 **Opplever du noen av følgende symptomer mens du oppholder deg i kalde omgivelser? I så fall, ved hvilken temperatur oppstår symptomene?**

	Ja	Nei	Under °C
Pusteproblemer	☐	☐	☐☐
Pipende pust	☐	☐	☐☐
Slim fra lungene	☐	☐	☐☐
Brystsmerter	☐	☐	☐☐
Forstyrrelse i hjerterytmen	☐	☐	☐☐
Nedsatt blodsirkulasjon i hender/føtter	☐	☐	☐☐
Synsforstyrrelse *(kortvarig/ forbigående)*	☐	☐	☐☐
Migrene *(kortvarig/forbigående)*	☐	☐	☐☐
Hvite fingre *(kortvarig/ forbigående)*	☐	☐	☐☐
Blå, blå-røde fingre *(kortvarig/forbigående)*	☐	☐	☐☐

15.08 **Hvordan påvirker kalde omgivelser og kulderelaterte symptomer din yteevne?**

	Nedsatt	Uforandret	Forbedret
Konsentrasjon	☐	☐	☐
Hukommelse	☐	☐	☐
Fingerfølsomhet *(følelse)*	☐	☐	☐
Fingerferdighet *(motorikk)*	☐	☐	☐
Kontroll av bevegelse *(for eksempel skjelving)*	☐	☐	☐
Tungt fysisk arbeid	☐	☐	☐
Langvarig fysisk arbeid	☐	☐	☐

16. BRUK AV RESEPTFRIE SMERTESTILLENDE LEGEMIDLER

I det første spørreskjemaet svarte du at du hadde brukt reseptfrie smertestillende legemidler de siste 4 ukene. Her er noen oppfølgingsspørsmål vi håper du vil svare på.

16.01 **Hvilke typer reseptfrie smertestillende legemidler har du brukt?**

Paracetamol: *(Pamol, Panodil, Paracet, Paracetamol, Pinex)*

- ☐ Ikke brukt
- ☐ Sjeldnere enn hver uke
- ☐ Hver uke, men ikke daglig
- ☐ Daglig

Hvor mye tar du vanligvis daglig når du bruker midlene?
(Antall tabletter, stikkpiller)..... ☐☐

Acetylsalisylsyre: (*Aspirin,Dispril, Globoid)*

- ☐ Ikke brukt
- ☐ Sjeldnere enn hver uke
- ☐ Hver uke, men ikke daglig
- ☐ Daglig

Hvor mye tar du vanligvis daglig når du bruker midlene?
(Antall tabletter)..... ☐☐

Ibuprofen: *(Ibumetin, Ibuprofen, Ibuprox, Ibux)*

- ☐ Ikke brukt
- ☐ Sjeldnere enn hver uke
- ☐ Hver uke, men ikke daglig
- ☐ Daglig

Hvor mye tar du vanligvis daglig når du bruker midlene?
(Antall tabletter, stikkpiller)..... ☐☐

Naproksen: *(Ledox, Naproxen)*

- ☐ Ikke brukt
- ☐ Sjeldnere enn hver uke
- ☐ Hver uke, men ikke daglig
- ☐ Daglig

Hvor mye tar du vanligvis daglig når du bruker midlene?
(Antall tabletter)..... ☐☐

Fenazon med koffein: *(Antineuralgica ,Fanalgin Fenazon-koffein, Fenazon-koffein sterke)*

- ☐ Ikke brukt
- ☐ Sjeldnere enn hver uke
- ☐ Hver uke, men ikke daglig
- ☐ Daglig

Hvor mye tar du vanligvis daglig når du bruker midlene?
(Antall tabletter)..... ☐☐

16.02 **Mot hvilke plager bruker du reseptfrie smertestillende midler: (**Flere kryss er mulig)

- ☐ Hodepine
- ☐ Menssmerter
- ☐ Migrene
- ☐ Ryggsmerter
- ☐ Muskelsmerter/leddsmerter
- ☐ Tannsmerter
- ☐ Annet

16.03 **Mener du å ha opplevd bivirkninger av noen av legemidlene?** (sett ett kryss for hver linje)

	Ja	Nei
Paracetamol	☐	☐
Acetylsalisylsyre	☐	☐
Ibuprofen	☐	☐
Naproksen	☐	☐
Fenazon med koffein	☐	☐

16.04 **Hvor pleier du å kjøpe slike legemidler?**

- ☐ Apotek
- ☐ Dagligvare
- ☐ Bensinstasjon
- ☐ Utenlands
- ☐ Internett

16.05 **Kombinerer du behandlingen med bruk av reseptbelagte smertestillende midler?**

☐ Ja ☐ Nei

17. OPPFØLGINGSSPØRSMÅL OM HUDSYKDOMMER

På side 15 i dette spørreskjemaet svarte du at du har eller har hatt en hudsykdom. Her er noen oppfølgingsspørsmål vi håper du vil svare på.

Svar på en skala fra 0 til 10, der 0 tilsvarer ingen plager og 10 tilsvarer verst tenkelige plager. Dersom du svarte JA på at du har eller har hatt:

Ingen plager 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelige plager

17.01 **Psoriasis**
- Hvor mye plaget er du av din psoriasis i dag? ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
- Hvor mye plaget er du av din psoriasis når den er som verst? ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

17.02 **Atopisk eksem**
- Hvor mye plaget er du av ditt atopiske eksem i dag? ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
- Hvor mye plaget er du av ditt atopiske eksem når det er som verst? ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

17.03 **Håndeksem**
- Hvor mye plaget er du av ditt håndeksem i dag? ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
- Hvor mye plaget er du av ditt håndeksem når det er som verst? ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

17.04 **Kviser**
- Hvor mye plaget er du av dine kviser i dag? ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
- Hvor mye plaget er du av dine kviser når de er som verst? ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

17.05 **Verkebyller**
- Hvor mye plaget er du av dine verkebyller i dag? ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
- Hvor mye plaget er du av dine verkebyller når de er som verst? ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

17.06 **Her er en liste over faktorer som kan tenkes å utløse eller forverre verkebyller, kryss av for hva du synes gjelder for deg:**

	Ja	Nei
Stress/psykisk påkjenning	☐	☐
Trange/tette klær	☐	☐
Menstruasjonssyklus	☐	☐
Svangerskap	☐	☐
Annet	☐	☐

17.07 **Hvor mange utbrudd av verkebyller har du vanligvis i løpet av ett år?** (sett ett kryss)

☐ 0-1 ☐ 4-6
☐ 2-3 ☐ Mer enn 6

17.08 **Hvor gammel var du da du fikk verkebyller første gang?**

☐ 0-12 år ☐ 26-35 år
☐ 13-19 år ☐ 36-50 år
☐ 20-25 år ☐ Over 50 år

17.09 **Dersom du ikke lenger har verkebyller, hvor gammel var du da plagene forsvant?**

☐ 0-12 år ☐ 26-35 år
☐ 13-19 år ☐ 36-50 år
☐ 20-25 år ☐ Over 50 år

TILBAKEMELDING

Skulle du ønske å gi oss en skriftlig tilbakemelding om enten spørreskjema eller Tromsøundersøkelsen generelt, er du hjertelig velkommen til det her:

Takk for hjelpen!

LUNDBLAD MEDIA AS · FOTO: TORGER GRYTA

Tromsø-undersøkelsen

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Appendix C

Interview-questions related to the Tromsø Staph and Skin Study in the 6th Tromsø Study

English translation

Interview–questions related to The Tromsø Staph and Skin Study

Interview Phase 1

ANTIBIOTICS:

Have you taken any antibiotics (tablets, injections or oral suspensions, nasal ointments, eye drops or eye ointment) the last 24 hours? Yes / No

If you have taken any antibiotics the last 24 hours:

1. What brand (included strength) did you take?
2. Administration form?
3. Numbers of tablets, milliliter of suspension etc. last time?
4. Total number of tablets, doses of suspensions etc during the last 24 hours?
5. How many hours since you took the last dose?

LIGHT/SUN EXPOSURE:

Have you used a solarium or any form of light therapy during the last 7 days? Yes / No

Have you been travelling to the south (for instance South-Europe) during the last 4 weeks? Yes / No

INFECTIONS AND EXPOSURE TO HEALTHCARE SERVICES:

Have you been suffering from persistent coughing during the last 24 hours? Yes / No

Have you been suffering from nasal discharge during the last 24 hours? Yes / No

Have you been hospitalized during the last 12 months? Yes / No

Does anyone in your household work in health care services (hospital, nursing home, senior care service, GP's office, public health center)? Yes / No

Have you ever had a tonsillectomy? Yes / No / Don’t know

Interview Phase 2

ANTIBIOTICS:

Have you taken any antibiotics (tablets, injections or oral suspensions, nasal ointments, eye drops or eye ointment) the last 24 hours? Yes / No

If you have taken any antibiotics the last 24 hours:

1. What brand (included strength) did you take?
2. Administration form?
3. Numbers of tablets, milliliter of suspension etc. last time?
4. Total number of tablets, doses of suspensions etc during the last 24 hours?
5. How many hours since you took the last dose?

LIGHT/SUN EXPOSURE:

Have you used a solarium or any form of light therapy during the last 7 days? Yes / No

Have you been travelling to the south (for instance South-Europe) during the last 4 weeks? Yes / No

INFECTIONS AND EXPOSURE TO HEALTHCARE SERVICES:

Do you work in health care services (hospital, nursing home, senior care service, GP's office, public health center)? Yes / No

Have you been suffering from persistent coughing during the last 24 hours? Yes / No

Have you been suffering from nasal discharge during the last 24 hours? Yes / No

Have you been hospitalized since last attendance (survey)? Yes / No

Appendix D

Interview-questions related to the Tromsø Staph and Skin Study in the 6th Tromsø Study

Original questionnaire

Intervjuspørsmål til Tromsø Staph and Skin Study

Intervju Fase 1:

ANTIBIOTIKA:

Har du brukt antibiotika enten i form av tabletter/mikstur, injeksjoner, nesesalve, hudsalve, øyedråper eller øyesalve i løpet av de siste 24 timene? Ja / Nei

Hvis du har tatt antibiotika siste 24 timer:

1. Hvilken type (inkludert styrke) har du brukt?
2. Hvilken inntaksmåte?
3. Hvor mange tabletter, milliliter suspensjon etc. tok du ved siste dose?
4. Hvilken totaldose av tabletter, suspensjon etc. har du tatt siste 24 timer?
5. Hvor mange timer er det siden du tok siste dose?

SOLARIUM / SOLEKSPONERING:

Har du tatt solarium eller lysbehandling de siste 7 dagene? Ja / Nei

Har du vært på reise til sydligere breddegrader (tilsvarende Sør-Europa) i løpet av de siste 4 ukene? Ja / Nei

INFEKSJONER / EKSPONERING FRA HELSEVESENET:

Har du vært forkjøla i halsen i løpet av de siste 24 timene? Ja / Nei

Har du vært forkjøla i nesen i løpet av de siste 24 timene? Ja / Nei

Har du vært innlagt på sjukehus i løpet av de siste 12 månedene? Ja / Nei

Arbeider noen i din husstand i helsevesenet (sjukehus, sjukehjem, hjemmetjenesten, legekontor, helsestasjon)? Ja / Nei

Har du tidligere fått fjernet mandlene? Ja / Nei / Vet ikke

Intervju Fase 2:

ANTIBIOTIKA:

Har du brukt antibiotika enten i form av tabletter/mikstur, injeksjoner, nesesalve, hudsalve, øyedråper eller øyesalve i løpet av de siste 24 timene? Ja / Nei

Hvis du har tatt antibiotika siste 24 timer:

1. Hvilken type (inkludert styrke) har du brukt?
2. Hvilken inntaksmåte?
3. Hvor mange tabletter, milliliter suspensjon etc. tok du ved siste dose?
4. Hvilken totaldose av tabletter, suspensjon etc. har du tatt siste 24 timer?
5. Hvor mange timer er det siden du tok siste dose?

SOLARIUM/ SOLEKSPONERING:

Har du tatt solarium eller lysbehandling de siste 7 dagene? Ja / Nei

Har du vært på reise til sydligere breddegrader (tilsvarende Sør-Europa) i løpet av de siste 4 ukene? Ja / Nei

INFEKSJONER/ EKSPONERING FRA HELSEVESENET:

Arbeider du i helsevesenet (sjukehus, sjukehjem, hjemmetjenesten, legekontor, helsestasjon)? Ja / Nei

Har du vært forkjøla i halsen i løpet av de siste 24 timene? Ja / Nei

Har du vært forkjøla i nesen i løpet av de siste 24 timene? Ja / Nei

Har du vært innlagt på sjukehus siden siste fremmøte/undersøkelse? Ja / Nei

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