OULU 2016
D 1352

ACTA UNIVERSITATIS OULUENSIS

Anna Tuisku

TOBACCO AND HEALTH

A STUDY OF YOUNG ADULTS IN NORTHERN FINLAND

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
LAPLAND CENTRAL HOSPITAL

ACTA UNIVERSITATIS OULUENSIS
D Medica 1352

ANNA TUISKU

TOBACCO AND HEALTH

A study of young adults in Northern Finland

Academic dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium F201 of the Faculty of Medicine, on 22 April 2016, at 12 noon

UNIVERSITY OF OULU, OULU 2016

Acta Univ. Oul. D 1352, 2016

Supervised by
Docent Pentti Nieminen
Professor Vuokko Kinnula

Reviewed by
Docent Anne Pietinalho
Docent Maija Halme

Opponent
Docent Tuula Vasankari

ISBN 978-952-62-1154-1 (Paperback)
ISBN 978-952-62-1156-5 (PDF)

ISSN 0355-3221 (Printed)
ISSN 1796-2234 (Online)

Cover Design
Raimo Ahonen

JUVENES PRINT
TAMPERE 2016

Tuisku, Anna, Tobacco and health. A study of young adults in Northern Finland
University of Oulu Graduate School; University of Oulu, Faculty of Medicine; Lapland Central Hospital
Acta Univ. Oul. D 1352, 2016
University of Oulu, P.O. Box 8000, FI-90014 University of Oulu, Finland

Abstract

Although smoking in adolescents and young adults has been declining in the 21st century in Finland, about 17% of 18-year-olds still smoke on a daily basis. Young adults are in fact one of the age groups that are most likely to smoke in several countries. Nevertheless, a large proportion of them are known to want to quit smoking.

Relatively little is known about the smoking habits of young adults. There are no evidence-based guidelines for smoking cessation in this age group. In many cases, they have been included within studies of adolescents or older adults without any separate analysis. Consequently, smoking cessation interventions demonstrated to be effective in middle-aged smokers are often adapted for young adults even though their culture, somatic features and smoking habits in many ways are different from those of middle-aged people.

This study focused on 18–26-year-olds in northern parts of Finland. Specific aims were 1) to describe their smoking habits, 2) to compare health and lifestyle in tobacco users and non-tobacco users, 3) to study their nicotine dependence and motivation to quit smoking, and 4) to examine the use and effectiveness of smoking cessation pharmacotherapy in this age group.

A total of 1163 male military recruits from northern parts of Finland filled in the study questionnaire. The survey study revealed that young adult males in northern parts of the country used tobacco products relatively often. Their smoking was associated with lower education, higher body mass index, inactivity in sports and impaired physical fitness. In addition, a great part of young smokers displayed symptoms of chronic bronchitis. Although most daily smokers were clearly dependent on nicotine and had previously tried to quit smoking, only 47% of the quitters had utilized any pharmacological aids in their attempts. Snus use seemed to be related to more severe nicotine dependence in smokers.

The prospective study consisted of 314 voluntary young adult daily smokers who were motivated to quit smoking. The study was a randomised, placebo-controlled clinical trial, and the results indicated that varenicline might be more effective than nicotine patches in smoking cessation of young adult heavy smokers, at least in short term. Abstinence rates during the follow-up were similar when the nicotine patch and placebo patch were compared in young adult light smokers.

Keywords: chronic bronchitis, nicotine dependence, physical fitness, smokeless tobacco, smoking, smoking cessation pharmacotherapy, young adults

Tuisku, Anna, Tupakointi ja terveys. Nuoret aikuiset Pohjois-Suomessa
Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Lapin keskussairaala
Acta Univ. Oul. D 1352, 2016
Oulun yliopisto, PL 8000, 90014 Oulun yliopisto

Tiivistelmä

Suomessa nuorten keskuudessa tupakointi on ollut 2000-luvun aikana laskusuuntainen. Kuitenkin arviolta n. 17 % 18-vuotiaista tupakoi edelleen päivittäin. Nuoret aikuiset ovatkin useissa maissa yksi eniten tupakoivia ikäryhmiä. Silti suuren osan tupakoivista nuorista aikuisista on todettu olevan halukkaita lopettamaan tupakoinnin.

Nuorten aikuisten tupakointia on tutkittu verrattain vähän. Heille suunnattuja tieteelliseen näyttöön perustuvia hoitomuotoja tupakoinnin lopettamiseen ei ole. He ovat usein osana teini-ikäisten tai vaihtoehtoisesti vanhempien aikuisten ryhmää tupakointiin liittyvissä tutkimuksissa, eikä heitä yleensä ole analysoitu erikseen. Usein heitä hoidetaankin keski-ikäisiltä aikuisilta saadun tutkimusnäytön pohjalta. Kuitenkin nuorten kulttuuri, biologinen pohja ja tupakointitavat eroavat merkittävästi vanhemmista tupakoitsijoista.

Tämä työ on keskittynyt tutkimaan 18–26-vuotiaita nuoria aikuisia Pohjois-Suomessa. Sen tavoitteina on ollut 1) kuvata heidän tupakointitottumuksiaan, 2) selvittää tupakoinnin yhteyttä terveyteen ja elämäntapaan, 3) tutkia heidän nikotiiniriippuvuuttaan sekä motivaatiota lopettaa tupakointi, sekä 4) selvittää tupakkavieroituslääkkeiden käyttöä ja niiden tehoa tässä ikäryhmässä.

Terveystottumuskyselyymme vastasi 1163 Pohjois-Suomen varusmiestä. Selvisi, että varusmiehet käyttivät tupakkatuotteita Pohjois-Suomessa valtakunnallisia arvioita enemmän. Tupakoinnin todettiin liittyvän varusmiehillä alempaan koulutustasoon, suurentuneeseen painoindeksiin, vähäisempään fyysiseen aktiivisuuteen ja huonompaan aerobiseen suorituskykyyn. Lisäksi tupakoivilla varusmiehillä kroonisen bronkiitin oireet olivat yleisiä. Vaikka valtaosa heistä oli selvästi nikotiiniriippuvaisia ja oli yrittänyt lopettaa tupakointinsa, vain 47% lopetusta yrittäneistä oli kokeillut tupakkavieroituslääkettä. Nuuskan käyttö vaikutti liittyvän vahvempaan nikotiiniriippuvuuteen tupakoitsijoilla.

Prospektiiviseen, satunnaistettuun ja lumekontrolloituun kliiniseen kokeeseen osallistui 314 vapaaehtoista päivittäin tupakoivaa nuorta aikuista, jotka olivat halukkaita tupakoinnin lopetukseen. Tulokset viittasivat siihen, että varenikliini saattaa olla nikotiinilaastaria tehokkaampi tupakoinnista vieroituksessa vahvasti nikotiiniriippuvaisilla nuorilla aikuisilla ainakin lyhyellä aikavälillä. Kevyemmin tupakasta riippuvaisilla nikotiinilaastari ei ollut lumelaastaria tehokkaampi.

Asiasanat: fyysinen kunto, krooninen bronkiitti, nikotiiniriippuvuus, nuoret aikuiset, savuttomat tupakkatuotteet, tupakoinninlopetuslääkkeet, tupakointi

To the memory of Vuokko Kinnula

Acknowledgements

This study was conducted in the Department of Pulmonary Medicine, Lapland Central Hospital in co-operation with the Medical Informatics and Statistics Research Group of University of Oulu from 2008 to 2015.

First, I would like to express my sincere gratitude to my supervisor Associate Professor Pentti Nieminen for his guidance and support during the whole process of preparing this thesis. His calm guidance and inspiring enthusiasm especially about statistical questions have been highly valuable for me.

I express my warmest gratitude to my other supervisor, the late Professor Vuokko Kinnula, MD, PhD, for her supportive guidance and contagious enthusiasm for science. This thesis would not have been initiated without her encouragement.

I would also like to warmly thank Docent Tuula Toljamo, MD, PhD, for her continual support as well as guidance in clinical questions.

Docent Maija Halme, MD, PhD, and Docent Anne Pietinalho, MD, PhD reviewed the manuscript and provided valuable advice on how to improve it.

I thank the members of my follow-up group, Docent Terttu Harju, MD, PhD and Docent Witold Mazur, MD, PhD.

I am very grateful to Ewen MacDonald for the linguistic revision of the original papers and the final version of this thesis, and to Mrs. Maija-Liisa Tarkiainen for her secretarial assistance. I wish to thank information specialist Miia Ulanen, Satakunta Central Hospital, for her professional assistance.

I acknowledge and thank our study nurse Merita Salmela for her crucial contribution to the study and her positive attitude not only towards work but also to life in general.

I owe my special thanks to the Chief of Internal Medicine, Jukka Korpela, PhD, MD, and my other colleagues in Satakunta Central Hospital for their encouragement to finish this thesis while doing my clinical work. I also want to acknowledge and thank Eva Salomaa, MD, Lapland Central Hospital.

I wish to express my appreciation to the collaborators in this work, General, Chief Medical Officer, Pentti Kuronen, MD, PhD, Finnish Defence Forces, Chief Medical Officer Markku Kerola MD, Northern Command, Captain Jyrki Sirkeinen, Jaeger Brigade Sodankylä and Medical Officer Sakari Unga, MD, Jaeger Brigade, Sodankylä. I would also like to thank all the volunteer participants who took part in the study.

I warmly thank my medical school friends Anna, Annika, Elina, Hanne-Kaisa, Lotta, Satu and Susanna as well as my long-term friends Eeva, Jenni, Laura, Miina and Sini for their friendship and support. I also wish to warmly thank my family and relatives. Special thanks to my brother Antti and his family.

Finally, I owe my deepest gratitude to my husband Heikki and my little daughter Selina. Preparing this thesis has not been always easy and has consumed a great deal of my time. It would not have been possible to finish this work without their approval and support.

This study was funded by a governmental subsidy from Ministry of Social Affairs and Health, a governmental subsidy for health science research (EVO, VTR) in Rovaniemi, and the Research Foundation of Pulmonary Diseases, the Finnish Antituberculosis Association Foundation, Finnish Respiratory Society, Yrjö Jahnsson Foundation, Sohlberg Foundation, and the Finnish Medical Society Duodecim, all of which are gratefully acknowledged.

Pori, March 2016 Anna Tuisku née Hamari

Abbreviations

ADHD	attention deficit and hyperactivity disorder
BID	twice a day
BMI	body mass index
CI	confidence interval
cm	centimeter
COPD	chronic obstructive pulmonary disease
CredI	credible interval
e-cigarette	electronic cigarette
eCO	expired-air CO
e.g.	exempli gratia
etc.	et cetera
EU	European Union
g	gram
ETS	environmental tobacco smoke
FEV1/FVC	forced expiratory volume in one second divided by forced vital capacity in spirometry
HSI	Heaviness of Smoking Index
ICD-10	International Classification of Diseases released by World Health Organization, 10th revision
i.e.	id est
IQR	interquartile range
kg	kilogram
K-W test	Kruskal-Wallis test
m	meter
MEF25-75	mid-expiratory flow in spirometry
mg	milligram
ml	milliliter
nAChR	nicotinic acetylcholine receptor
NG	nicotine chewing gum
ng	nanogram
NP	nicotine patch
NRT	nicotine replacement therapy
OR	odds ratio
ppm	parts per million
RR	risk ratio

SD	standard deviation
SLT	smokeless tobacco
SPSS	Statistical Package for the Social Sciences
U.S.	United States
WHO	World Health Organization

List of original publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:

I Tuisku A née Hamari, Toljamo T, Nieminen P & Kinnula VL. (2010) High frequency of chronic cough and sputum production with lowered exercise capacity in young smokers. Ann Med 42(7): 512–20.

II Toljamo T, Tuisku A née Hamari, Nieminen P & Kinnula VL. (2012) Young male daily smokers are nicotine dependent and experience several unsuccessful quit attempts. Scand J Prim Health Care 30(3): 183−188.

III Tuisku AK née Hamari, Toljamo TI, Kinnula VL & Nieminen PA. (2013) Dual use of cigarettes and Swedish snuff (snus) among young adults in Northern Finland. Eur J Public Health 23(5): 768−71.

IV Tuisku A née Hamari, Salmela M, Nieminen P & Toljamo T. (2016) Varenicline and nicotine patch therapies in young adults motivated to quit smoking: randomised, placebo-controlled prospective study. Basic Clin Pharmacol Toxicol. In press.

Papers I and II are included in the PhD thesis by Tuula Toljamo, University of Helsinki.

Contents

1 Introduction

Tobacco is processed from the dried leaves of the tobacco plant, and manufactured into a wide variety of products such as pipe tobacco, cigars, cigarettes, and different forms of smokeless tobacco. However, in Finland and several other western countries, the most common way to consume tobacco is to inhale the smoke from a cigarette. In global terms, the use of tobacco products is one of the greatest public health threats, being responsible for the deaths of up to 6 million people every year.

Although the prevalence of smoking is decreasing in Finland, there is still a lot of work to be done before the country reaches its goal of having a smoke-free nation before the year 2040. For example, national estimates show that about 17% of 18-year-olds in Finland still smoke cigarettes on a daily basis. In addition to the nicotine dependence syndrome caused by smoking, future challenges for health care and science include the increasing number of users of both traditional smoke-free tobacco products such as Swedish snus and the new nicotine-containing electronic cigarettes, neither of which have been adequately studied.

A great part of adult smokers begin to smoke when they are adolescents. The smoking habit often becomes more regular during early adulthood with increasing dependence on nicotine. Fortunately, most of the health damage inflicted by smoking can be prevented if the subject is able to quite the habit before he/she reaches the age of 30. Surprisingly, relatively little is known about the smoking habits of young adults and there is a lack of evidence of the effectiveness of smoking cessation interventions in this age group of smokers.

The aim of this study was to describe the tobacco use habits in young adults in northern parts of Finland, and to compare health and lifestyle in young adult tobacco users and non-tobacco users. In addition, further aims were to study nicotine dependence, motivation to quit, smoking cessation pharmacotherapy use, as well as their effectiveness and safety in young adult smokers.

2 Review of the literature

2.1 Prevalence of tobacco and electronic cigarette use in young adults

2.1.1 Cigarette smoking

As in the adult population (Helldan & Helakorpi 2015), there has been a decreasing trend in cigarette smoking in Finnish adolescents and young adults during the last decades: in males since the 1990s and in females since the 2000s (Kinnunen *et al.* 2015). Nonetheless, smoking is still a common habit in these young people. According to the Finnish nationwide Adolescent Health and Lifestyle Survey, 18% of 18-year-old males and 15% of females smoked daily in 2015 (Kinnunen *et al.* 2015). The number of young adult daily smokers is relatively high when compared to the neighboring country Sweden, where daily snus use is relatively more common: only 7% of 16 to 29 years old males and 9% of females smoked on a daily basis in 2014 (Folkshälsomyndigheten 2015). On the other hand, throughout Europe, smoking is considerably more common in this age group, approximately 29% of 15 to 24-year-olds smoke (Gibson *et al.* 2013).

Most smokers take up the smoking habit before they reach adulthood, and continue to smoke as adults: another national Finnish survey study estimated that approximately 17% of males and 14 % of females were smoking on a daily basis (aged between 15 and 64) in 2014 (Helldan & Helakorpi 2015). In Finland, the typical age to start smoking is between the ages of 12 to 16 (Kinnunen *et al.* 2015).

The prevalence of smoking in adults is known to vary between different parts of the country especially among Finnish males: smoking seems to be more common in the southeast and northern parts of Finland (Helldan & Helakorpi 2015, Luopa *et al.* 2014). However, the regional differences in smoking habits of students in Finnish compulsory schools, vocational schools and high schools are estimated to be considerably smaller than in the Finnish adult population (<5%) (Luopa *et al.* 2014). Education is one factor that is known to associate with the smoking habit: among young Finnish smokers, daily smoking is estimated to be more common in vocational schools (35% males, 37% females), than in compulsory schools (15% males, 12% females) or high schools (8% for females and males) (Luopa *et al.* 2014).

2.1.2 Snus use

Smokeless tobacco (SLT) is mainly used in India, the U.S. (Unites States) and Sweden. The type and composition of smokeless tobacco vary widely between and even within individual countries (Foulds *et al.* 2003). This thesis focuses on "western" SLT products i.e. SLT products that are consumed in the U.S. and in the European Union (EU). In Sweden and Finland, the main form of SLT is Swedish moist snuff, snus.

Sweden and Norway are the only European countries where sales of snus are not banned. In Finland, SLT has been totally banned since the country joined the EU in 1995. However, SLT use has continued even after the sales ban. Unlike smoking, the use of SLT among adolescents and young adults is increasing; in 2015, 47% of Finnish 18-year-old males had experimented with SLT, and 6% were using it every day (Kinnunen *et al.* 2015). SLT users are mainly males, but females seem to be adopting the habit: the corresponding numbers for 18-year old females in Finland are 26% (experimented) and 1% (daily users). Another national survey study in 2013 reported snus use to be generally more common and most common in Finnish vocational schools: daily snus use was reported by 6% of males and 1% of females of compulsory school students, by 10% of males and 0% of females in vocational schools, and by 8% males and 0% females in high schools (Luopa *et al.* 2014). Finnish youngsters gain access to snus mostly from their friends or acquaintances and they buy it themselves on tourist trips to neighbouring countries (Huhtala *et al.* 2006).

Finland is not the only European country where SLT use is increasing in popularity despite a sales ban: in 2010, the prevalence of snus use in Swiss general adult population aged 14 to 65 was 2-3%, but up to 8% in men aged 14 to 19 (Henninger *et al.* 2015). In Norway, where the sales of snus are not banned, the prevalence of snus use (daily + occasional) among young male adults increased from 9% to 33% between the years 1985 and 2013 (Lund & Lund 2014). In Sweden, the prevalence of daily smoking among young adults is somewhat less common than in Finland, but at the same time, daily snus use is relatively more ubiquitous: in 2014 in the age group of 16 to 29 years old, daily snus use was reported by 17% of males and 4% of females (Folkshälsomyndigheten 2015).

2.1.3 Patterns of dual use

The relatively large number of young male dual users i.e. those using both SLT and cigarettes has raised concerns in Sweden, Norway and the U.S. (Galanti *et al.* 2001b, Lund *et al.* 2011, Tomar *et al.* 2010), as well as in Switzerland (Henninger *et al.* 2015). The estimated prevalence of dual use varies widely between the countries, although this may be partly attributable to differences in definitions of snus use and smoking groups, especially in how occasional snus use and smoking have been defined. According to the Public Health Agency of Sweden, in 2014, the values for daily dual use were 2% for males and 0% for females in the age group between years 16 to 29. On the other hand, a survey study of Swedish 9th grade students estimated that among the 19% of respondents reporting at least occasional current snus use, the majority (71%) also stated that they were smoking cigarettes (Galanti *et al.* 2001b). In Norway, 3-11% of young snus users in the age group 16 to 20 years have been estimated to smoke on a daily basis, and 16-35% occasionally (Lund *et al.* 2011). In a Swiss study of military recruits (mean age 20 years), only 21% of those using snus occasionally (less than weekly) and 39% of weekly snus users were non-smokers compared to 56% of non-users of snus (Henninger *et al.* 2015). A Finnish study of young military recruits (median age 19 years; n=16746) found that while the prevalence of occasional/daily exclusive cigarette smoking had declined from 42% to 34% between the years 1999 to 2010, occasional/daily exclusive snus use had increased from 5% to 7%, and occasional/daily dual use from 12% to 13% (Mattila *et al.* 2012).

2.1.4 Electronic cigarette use

While cigarette smoking is a decreasing trend in numerous western countries including Finland, the tobacco industry has launched new smoke-free tobacco imitators, so-called electronic cigarettes (e-cigarettes) in 2006-2007. They are often designed to look like cigarettes. E-cigarettes are battery-powered vaporisers that heat a liquid, so-called e-liquid, which typically contains propylene glycol or glycerol as well as a wide range of additives and flavouring agents. Product engineering and quality control are highly variable (Grana *et al.* 2014). The vapour of heated liquid is inhaled by the users. There are nicotine containing and nicotine-free e-cigarettes available. The nicotine concentration is variable —

nicotine delivery may even exceed that of traditional cigarettes (Ramoa *et al.* 2015).

The regulation of e-cigarettes and e-liquids varies in different countries. The EU has issued a new tobacco products directive to be implemented by May 2016 in the member states that includes recommendations about e-cigarette/e-liquid regulation. It includes regulations and recommendations about the maximum permitted concentration of nicotine in these products as well as a list of prohibited additives, the requirement that there should be a detailed description of ingredients in these products, and health warnings. If the maximum permitted nicotine concentration is exceeded, the products are recommended to be categorized as medicinal products which are subjected to notably more stringent legal regulations. Otherwise, the nicotine-containing products are recommended to be handled under tobacco regulation with marketing and advertising restrictions as for tobacco products. Member states are free to set more strict national regulations for e-cigarette products than in the EU directive.

At the moment in Finland, all nicotine containing e-cigarettes and e-liquids are categorised as medicinal products, and none of the nicotine containing e-cigarette or e-liquids has the trading licence required for medicinal products. In order to obtain this licence, a medicinal product must have evidence of safety and efficacy. Thus, users of these products must buy them from abroad or via online sales.

The advertising of e-cigarettes has rapidly increased in recent years (Duke *et al.* 2014). Despite a national ban on marketing these products, as many as 10% of Finnish adolescents report having seen e-cigarette advertisements, mostly in social media (Kinnunen *et al.* 2014). Although the regular use of e-cigarettes remains rather rare, within only a few years, awareness and experimentations of e-cigarettes have increased rapidly in several countries including Finland: in 2015 13% of Finnish 18-year-olds reported having tried e-cigarettes more than 20 times which was an increase of eight percent points within two years (Kinnunen *et al.* 2015). Finnish adolescents and young adults had mostly experimented with nicotine containing e-cigarettes (Kinnunen *et al.* 2014).

2.2 Health consequences of tobacco and electronic cigarette use

2.2.1 Overview of tobacco related health risks

Smoking and health

Tobacco use is known to be a major health risk; it kills about every other user (Doll *et al.* 2004), and continues to be one of the leading causes of preventable death throughout the world: as many as 6 million deaths are attributable to tobacco each year accounting for 10% of all adult deaths (World Health Organization 2013).

The health consequences in adult smokers have been studied in a prospective study with 50 years' follow-up of British male doctors (n=34439) (Doll *et al.* 2004). It was estimated that regular smokers died 10 years earlier than non-smokers. Fortunately, smoking cessation in early adulthood prevented most of the health harm due to the smoking habit: smoking cessation at the age of 30 almost reduced the risk for premature death to that of nonsmokers, but cessation at age 50 only decreased the risk by half. Half of the premature deaths caused by smoking were due to lung cancer and chronic obstructive pulmonary disease (COPD).

Smoking is known to be the most important cause of COPD in western countries. COPD is a slowly developing, incurable disease and the severity of the disease is strongly dependent on years and frequency of smoking in history, but young age does not protect against the disease development: COPD may develop even after smoking less than 20 pack years (de Marco *et al.* 2011). COPD patients suffer from chronic inflammation in lungs causing obstructive chronic bronchitis (CB) and emphysema with lowered respiratory capacity, impaired physical fitness and deteriorated life quality. COPD has common comorbidities that are often relevant for the prognosis of the patient: respiratory infections, lung cancer, osteoporosis, diabetes, cardiovascular disease, musculoskeletal impairment and depression (Vestbo *et al.* 2013).

In addition, smoking has other well-known health consequences (Gibson *et al.* 2013, U.S. Department of Health and Human Services 2014). Smoking is known to increase the risk not only for lung cancer but also promotes cancers in numerous other organs, especially cancers of mouth, pharynx, pancreas and esophagus. It is known to increase the risk for developing atherosclerosis and

coronary artery disease, myocardial infarction, stroke, peripheral atherosclerosis and congestive heart failure. Smokers more often suffer lung infections as well as gastric and duodenal ulcers, diabetes, rheumatoid arthritis and periodontal diseases. Cigarette smoking is also known to increase the risk for postoperative complications and delayed wound healing. In addition, aging of the skin occurs more rapidly in smokers.

The unwanted health effects of active smoking do not always take decades to develop. During the reproductive age, smoking can reduce fertility and increase the risk for ectopic pregnancy (Mund *et al.* 2013, U.S. Department of Health and Human Services 2014). Smoking is also an independent risk factor for venous thromboembolism, and in female smokers, the risk for venous thrombosis is known to be increased synergistically by oral contraceptive use (Cheng *et al.* 2013). Active smoking at a young age may also alter immune response and cause structural changes in the respiratory tract, and, therefore, increase the risk for respiratory infections (Arcavi & Benowitz 2004). The current evidence also suggests that smoking at a young age increases the risk for asthma and exacerbations of diagnosed asthma (U.S. Department of Health and Human Services 2014). Young smokers display dental caries more often than their non-smoking counterparts, although the evidence for a causal relationship between smoking and caries is only suggestive due to the presence of various confounders such as use of dental services (U.S. Department of Health and Human Services 2014). Smoking can cause skin changes soon after initiating the smoking habit: for example, it causes a yellow discoloration of fingernails and pigmentation of the mouth (Ortiz & Grando 2012). It is also associated with premature graying of hair and early onset hair loss in men (Ortiz & Grando 2012). The association between smoking in young adulthood and respiratory symptoms as well as its association with physical fitness are discussed elsewhere in this thesis.

Smoking has a wide potential to harm the health not only of its users but also of other individuals exposed to tobacco smoke. Firstly, smoking during pregnancy is not only a major health risk for the mother but also to the fetus: it is related to several obstetric complications such as stillbirth, chorioamnionitis and preterm birth as well as increased risk for congenital malformations, infantile colic, reduced birth weight, decrease in brain size and impaired pulmonary function and also susceptibility to respiratory infections and asthma in early childhood (Mund *et al.* 2013). Secondly, children who are exposed to environmental tobacco smoke (ETS) are known to be at an increased risk of developing middle ear disease, respiratory symptoms, impaired lung function and lower respiratory illness (U.S.

Department of Health and Human Services 2014). In addition, exposure to ETS in adulthood has been causally linked to same health consequences as active smoking including diseases such as stroke, lung cancer and coronary heart disease (U.S. Department of Health and Human Services 2014).

Although most health effects of smoking are caused by the byproducts of combustion such as carbon monoxide and the multiple carcinogenic compounds present in the smoke, some harmful effects are attributable to nicotine itself (Benowitz 2009, Mund *et al.* 2013). Nicotinic acetylcholine receptors play an important role in the development of the nervous system from pregnancy through adolescence and exposure to exogenous nicotine during the developmental state seems to be crucial in determining the consequences (Dwyer *et al.* 2009). For example, prenatal exposure appears to increase the risk for Attention Deficit and Hyperactivity Disorder (ADHD) and substance abuse in childhood and adolescence, postnatal exposure has been associated with long term defects in auditory cognitive processing, and exposure during adolescence to an enhanced sensitivity to the rewarding effects of nicotine thus increasing vulnerability to nicotine dependence development, as well as the risk for impulsivity and long term mood disorders (Dwyer *et al.* 2009).

Smokeless tobacco use and health

The health consequences of SLT use have not been as extensively studied as those of smoking. In particular, the consequences of long term SLT use from youth to adulthood are unknown. Although the risks related to SLT use are lower than those of smoking (Gartner *et al.* 2007), modern SLT products have been associated with malignant (Boffetta *et al.* 2008) and cardiovascular diseases such as elevated risk of fatal myocardial infarction and stroke (Boffetta & Straif 2009). Modern SLT products may increase the risk for pregnancy complications such as preterm birth, stillbirth, and small for gestational age (Baba *et al.* 2013, Wikstrom *et al.* 2010a, Wikstrom *et al.* 2010b). Snus use is also related to oral health as it is known to cause mucosal changes, gingival recessions and root surface caries (Heikkinen *et al.* 2015). On the other hand, not all studies have found these associations and the health risks attributable to SLT use have been debated (Lee 2013). For example, pancreatic cancer is associated to SLT use in some studies, but meta-analyses on this issue have conflicting or negative results (Maisonneuve & Lowenfels 2015). It is evident that more research is needed to clarify this issue.

Dual use of SLT and cigarettes is relatively common, especially among young people in western countries where SLT is mainly consumed (Galanti *et al.* 2001a, Lund *et al.* 2011, Tomar *et al.* 2010). This must be taken into consideration when evaluating the health risks related to SLT use. On the other hand, a great part of young male snus users have no previous history of smoking (Lund *et al.* 2011, Patja *et al.* 2009), and therefore the health risks of their snus use must be compared to that of non-tobacco users, not with smokers.

2.2.2 Tobacco use and anthropometric measures

Influence of smoking on anthropometric measures

Maternal smoking is known to reduce the linear growth of a newborn baby (Cornelius & Day 2000, Mund *et al.* 2013). However, it is unknown whether active smoking influences the height gained during adolescence and young adulthood; this topic has only occasionally been investigated. Two prospective studies have found significant linear growth reduction among adolescent smokers under the age of 18 (O'Loughlin *et al.* 2008, Stice & Martinez 2005), but another study failed to confirm this association (Fidler *et al.* 2007).

In most adult populations, smoking has been claimed to be responsible for body weight reduction (Akbartabartoori *et al.* 2005, Klesges *et al.* 1989, Marti *et al.* 1989, Molarius *et al.* 1997, Pisinger & Jorgensen 2007), and the difference appears to become more pronounced with increasing number of smoking years (Klesges *et al.* 1989, Marti *et al.* 1989). An increasing frequency of smoking, however, does not seem to lower the body mass index (BMI) linearly, instead there seems to be a U-shaped relationship, with moderate smokers being the leanest (Klesges *et al.* 1989, Marti *et al.* 1989, Molarius *et al.* 1997). In contrast, smoking cessation seems to result in excess weight gain in most adults (Aubin *et al.* 2012, Filozof *et al.* 2004). The underlying mechanisms behind these associations of smoking on body weight appear to be complicated; it has been postulated that nicotine is an appetite suppressant as well as an enhancer of resting metabolic rate (Filozof *et al.* 2004, Jo *et al.* 2002, Perkins 1992).

The studies examining the association between smoking and body weight in adolescents have revealed more conflicting results. In most cross-sectional studies, adolescent smokers have had higher body weights than non-smokers (Potter *et al.* 2004), although there are some prospective studies indicating that

smoking in adolescence might exert a small weight attenuating effect (Fidler *et al.* 2007, Jasuja *et al.* 2008, Klesges *et al.* 1998a, O'Loughlin *et al.* 2008, Potter *et al.* 2004, Stice & Martinez 2005). Therefore, smoking exposure in adolescents may be insufficient to detect the weight attenuating effect of smoking in cross-sectional studies—the process that may take years or even decades. On the other hand, studies have indicated that nicotine accumulation and distribution in the brain is age-dependent (Ilback & Stalhandske 2003), and therefore smoking may cause a differential effect on anthropometric measures of smokers at various ages. There is also a plethora of possibly confounding variables that are difficult to control. For example, education, physical activity, alcohol consumption and diet may all act as confounders. The association may also differ according to gender or race: two cross-sectional studies (Klesges *et al.* 1998b, Sherrill-Mittleman *et al.* 2009) with large sample sizes of young adults (over 30 000 participants, mean age 19 and 20), found a similar negative association between smoking and body weight, especially in white males (approximately -1kg). In addition, the cultural and behavioural differences between nations and various age groups may modify the association between smoking and weight. For example, young people may believe that smoking will confer protection against weight gain and, therefore, take up smoking due to body weight concerns and desire to lose weight (Saarni *et al.* 2004).

Influence of smokeless tobacco use on anthropometric measures

The association between SLT use and weight has been mostly studied in Swedish adult populations. In contrast to smoking, snus use in adults has been associated with heavier weight or no effect at all on weight. Some of the studies have linked snus use to higher body weight (Bolinder *et al.* 1992, Rodu *et al.* 2004, Varga *et al.* 2013), some only in those of heavy snus users (Norberg *et al.* 2006), or those with a smoking habit in addition to snus use (Engstrom *et al.* 2010), but there are two studies that did not find any association at all (Eliasson *et al.* 1995, Wallenfeldt *et al.* 2001). In a Swedish five-year follow-up study, in male adults, snus use was not only related to incident obesity but also to a weight gain during the follow-up period (Hansson *et al.* 2011). In another longitudinal Swedish study, the middle-aged individuals who did not use snus displayed better weight maintenance during a ten-year follow-up (Nafziger *et al.* 2007). Therefore, if anything, snus use seems to be linked to overweight in adults. These conclusions are in conflict with the findings emerging from a Swedish follow-up study that

indicated that snus use could reduce the weight gain associated with smoking cessation at least in adults (Rodu *et al.* 2004). Theoretically, the weight attenuating effect of nicotine encountered in adult smokers should be evident also in adult SLT users as the nicotine concentrations in blood are similar (Foulds *et al.* 2003). However, there may be other factors that overcome this effect in SLT users: for example, U.S. firefighters who were SLT users were more likely to binge drink and consume high fat foods than their non-SLT using colleagues (Jitnarin *et al.* 2013).

Little is known about the association between SLT use and body weight in younger age groups. A Swedish study found that adolescent girls with actual or perceived overweight were at a higher risk to initiate smoking, but among snus users, the same phenomenon was found only among girls with low socio-economic status (Caria *et al.* 2009). Instead, overweight or perceived overweight was not associated with the initiation of tobacco use among male adolescents. In a Finnish twin study, a history of intentional weight loss episodes was not only associated to current smoking in both genders of young adults, but also to current snus use in males (Saarni *et al.* 2004). Based on these findings, young adult snus users could be expected to be heavier than their counterparts who do not use snus. In fact, one U.S. study of military recruits (mean age 20) found that current, former and experimental SLT users had higher body weights than those with no history of SLT use (Vander Weg *et al.* 2005).

2.2.3 Activity in sports and physical fitness in tobacco users

Smoking, activity in sports and physical fitness

There is no consistent evidence about the association of smoking and physical activity. Kaczynski *et al.* (2008) reviewed 50 articles with separate analyses of adults and young people (younger than 18 years). They estimated that there was a negative association between smoking and physical activity in almost 60% of the studies, but the association was somewhat more unclear in adolescents and in males.

The evidence is more convincing about the association of aerobic fitness and smoking. Smoking is known to reduce the lung capacity and increase the risk for cardiovascular diseases (Vestbo *et al.* 2013) and, therefore, to impair the aerobic performance of smokers, at least after several years of smoking. In addition, it has

immediate negative effects that may reduce endurance performance. For example, tobacco smoke contains carbon monoxide that binds to red blood cells and, therefore, decreases oxygen delivery to muscles and other organs. As a result, the muscles of smokers become susceptible to fatigue during endurance performance.

Although it has been shown that smoking is associated with impaired physical fitness at least after several years of smoking, a relatively small number of studies have investigated the relationship between smoking and physical fitness in young smokers. Physical fitness in young adult smokers has been mostly studied in military personnel (Biersner *et al.* 1972, Conway & Cronan 1988, Cooper *et al.* 1968, Jensen 1986, Marti *et al.* 1988, Zadoo *et al.* 1993). The results of these and other studies (Bernaards *et al.* 2003, Montoye *et al.* 1980, Sidney *et al.* 1993) on this issue that have included data gathered from young adults have detected a negative correlation: smoking seems to be related to impaired physical fitness already in young adults.

Smokeless tobacco, activity in sports and physical fitness

SLT is relatively common among athletes especially team sport athletes such as baseball and ice-hockey players (Alaranta *et al.* 2006, Gingiss & Gottlieb 1991, Marclay *et al.* 2011, Rolandsson *et al.* 2006). One reason for this is that SLT is believed to enhance the performance in sports (Connolly *et al.* 1992) as well as lacking the adverse effects of cigarettes on the respiratory system. Indeed SLT has been placed on World Anti-Doping Agency Monitoring Programme 2012 in order to detect patterns of abuse in athletes.

In a study of Swiss military male recruits (mean age 20), snus use was associated with high level of physical activity and even more clearly with activity in sports and exercise (Henninger *et al.* 2015). Accordingly, a Finnish survey study of young military recruits (aged 18 to 29; n=16746) found that exclusive use of snus was linked with higher activity in sports, especially team sports such as ice hockey (Mattila *et al.* 2012). This was the reverse of the association between physical activity and cigarette smoking.

SLT has a theoretical potential to boost the sport performance as nicotine is known to activate the sympathetic nervous system leading to increased heart rate, greater heart contractility, vasoconstriction, elevation in blood pressure and increased blood flow to the muscles as well as improvements in several aspects of cognitive function such as memory, reaction time and fine motor ability (Pesta *et al.* 2013). However, very few studies have investigated the direct effect of

smokeless tobacco use on aerobic performance. Snus use before physical performance in football players who had no previous regular tobacco use was observed to increase mental load and fatigue level as well as reducing the perceived readiness level and heart rate variability without causing any significant effect on performance in physical test or physical fatigue level (Morente-Sanchez *et al.* 2015). Additionally, a Swedish study on healthy, physically-trained middle-aged men found that long term snus use did not exert a significant effect on their exercise capacity (Bolinder *et al.* 1997). Therefore, although nicotine is known to activate the sympathetic nervous system and evoke a theoretical positive influence on aerobic fitness performance, more studies are needed to clarify whether or not SLT possesses this property in real life.

2.2.4 Symptoms of chronic bronchitis in smokers

Bronchitis is an inflammatory process in the bronchia. The symptoms of bronchitis include cough, increased bronchial mucus production, dyspnea, and chest tightness. Bronchitis is divided into two groups, acute and chronic conditions, which have different etiologies. Acute bronchitis typically lasts for about three weeks and it is usually caused by a viral infection (Albert 2010). There are some differences in the definitions of CB between studies, but one widely used definition of CB is as follows: chronic cough with sputum production for at least three months per year for at least two successive years in the absence of other conditions that may explain the symptoms (Kim & Criner 2013, Ramos *et al.* 2014). The reproductive cough in CB is caused by chronic airway irritation and increased number of goblet cells and enlarged submucosal glands with mucus overproduction and decreased mucus elimination (Ramos *et al.* 2014, Vestbo *et al.* 2013).

CB is a common condition in general populations but there are large variations in its prevalence: a review of population-based studies summarised the prevalence to range from 3.4% to 22.0% in adults (Kim & Criner 2013). The most common cause of CB is smoking (Heath & Mongia 1998, Ramos *et al.* 2014). In fact, there is a clear dose-response relationship between the symptoms and the smoking history (Forey *et al.* 2011). A large Finnish adult twin study revealed that the risk of CB increased by about 1.5 fold of each amount category of daily cigarettes, and also that not only moderate and heavy, but also former and light smokers had a significant risk for CB (Hukkinen *et al.* 2009). A Finnish study of men living in rural areas (n=1711) found that 30-year cumulative incidence of CB

was 42% in continuous smokers, 26% in ex-smokers and 22% in never-smokers (Pelkonen *et al.* 2006). Therefore, about 40% of smokers seem to develop CB, at least in rural areas. There are other known risk factors for CB e.g. organic and inorganic dust, combustion byproducts and fumes, but also gastroesophageal reflux disease seems to increase the risk for CB (Ramos *et al.* 2014).

The symptoms of CB are common in COPD patients: there are major variations in the estimates ranging from 14% up to a significant majority (74%) of COPD patients suffer from CB (Kim & Criner 2013). Therefore, CB is considered as one of the main manifestations of COPD. The other main manifestations of COPD include development of emphysema and not fully reversible airway limitation.

The early signs of COPD development can be detected even in young smokers: a dose-response relationship has been described between smoking in adolescents and already lowered FEV% (FEV1/FVC; forced expiratory volume in one second divided by forced vital capacity) and mid-expiratory flows (MEF25-75) which is evidence of early airway obstruction and small airway disease (Gold *et al.* 1996). Young adults in their twenties or thirties may have smoking histories of over 10-15 years which may well be long enough to allow the development of COPD. Unfortunately, the diagnosis of COPD is often made when the disease is already at an advanced stage. The mechanisms behind individual vulnerability for future COPD development are largely unknown, and one challenge for the future is to identify those smokers who are developing the disease (Vestbo *et al.* 2013). CB is one condition that has been proposed to be a sign of early disease development, because it has been associated not only to decreased lung capacity, but also with a higher risk of future COPD development and increased mortality in adult smokers, including young adults (de Marco *et al.* 2004, de Marco *et al.* 2007, Guerra *et al.* 2009, Pelkonen *et al.* 2006).

2.2.5 Health risks related to electronic cigarette use

The health consequences of e-cigarette use are largely unknown, especially with long term use, and these may differ between the products because of the large diversity in the additives and other compounds present in the product as well as in quality control. Nonetheless, there is increasing evidence that use of these products has health consequences (Grana *et al.* 2014). At present, e-cigarettes have been found to contain some carcinogenic and cytotoxic compounds although in lower amounts than in cigarette smoke, and they may cause eye and respiratory

irritation. Users have reported throat and mouth irritation, as well as cough, nausea and vomiting after e-cigarette use. They have also caused injuries such as explosions and fires. E-cigarettes have also been associated to some specific respiratory diseases. For example, there is a case report of acute lipoid pneumonia secondary to recurrent exposure to the glycerine-based oils found in e-cigarette vapour (McCauley *et al.* 2012). Inhalation of buttering flavouring chemicals, especially diacetyl, that have been included in e-cigarette liquids, has been associated to respiratory diseases such as bronchiolitis obliterans –a potentially severe disease with irreversible loss of pulmonary function that may even require a lung transplant (Allen *et al.* 2015).

2.3 Nicotine dependence in tobacco users

2.3.1 Tobacco dependence syndrome

Tobacco dependence is classified as a disease in ICD-10 (International Classification of Diseases released by WHO, 10th revision; F17 Nicotine addiction). In ICD-10, the dependence syndrome is described as "a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state" (World Health Organization 2014). Nicotine is the main component in tobacco products responsible for the dependence syndrome (Benowitz 2010, Dwyer *et al.* 2009, Placzek *et al.* 2009).

2.3.2 Nicotine dependence development

The development of the nicotine dependence is a complex process. When nicotine is absorbed into the bloodstream from any tobacco product, the alkaloid moves to brain from the bloodstream and binds to nicotine acetylcholine receptors (nAChRs), triggering the release of dopamine and other neurotransmitters. These neurotransmitters cause the positive feedback attributable to tobacco use with perceptions of pleasure and reward. When repeatedly exposed to nicotine, neuroadaptation and desensitization of nAChRs occur in a receptor subtype-

specific manner and tolerance develops. This has been suggested to evoke withdrawal symptoms related to nicotine: anxiety, stress, depression, difficulty to concentrate, irritability and anhedonia during abstinence. Nicotine administration relieves these symptoms, and the dependence to nicotine develops. Repeated exposure to nicotine also results to neural plasticity with long term alterations in the properties of nAChRs, reinforcing addictive behaviour and behavioural conditioning. Through behavioural conditioning, tobacco is associated with specific environmental factors, situations or moods in its users. These associations can also trigger withdrawal symptoms and complicate attempts to quit smoking. (Benowitz 2009, Benowitz 2010, Placzek *et al.* 2009).

2.3.3 Individual vulnerability to nicotine dependence

There are genetic and environmental factors that influence smoking behaviour. The vulnerability to nicotine dependence and to take up smoking is shown to be partly inheritable (Benowitz 2009, Lessov-Schlaggar *et al.* 2008), and this inherited susceptibility seems to be pronounced in higher risk environments, for example in rural areas and in individuals with a lower socioeconomic status (Lessov-Schlaggar *et al.* 2008). There is genetic variability in the genes coding for the nicotine receptors that can affect the individual vulnerability to nicotine dependence (Brunzell *et al.* 2015, Tobacco and Genetics Consortium 2010). On the other hand, nicotine is metabolised to cotinine mostly by liver enzyme CYP2A6, and genetic polymorphism in this enzyme has been related to individual vulnerability of nicotine dependence (Benowitz 2010, Lessov-Schlaggar *et al.* 2008). Women are generally more rapid metabolisers, and this fast metabolism of nicotine is associated with more severe dependence (Benowitz 2010). The effects of nicotine seem to be age-dependent, young individuals display a higher sensitivity to nicotine dependence development (Benowitz 2010, Dwyer *et al.* 2009, Placzek *et al.* 2009). Female adolescents seem to experience symptoms of dependence more frequently and might have more difficulties to quit smoking than males (DiFranza *et al.* 2002, Lessov-Schlaggar *et al.* 2008) –possibly partly because of their rapid nicotine metabolism.

In addition to genetic factors and age, several other factors have been recognised to be related to increased risk for nicotine dependence and the initiation of a regular smoking habit in young people. They include social, psychological and environmental factors such as parental smoking or having friends that smoke (Hoffman *et al.* 2006, Schepis & Rao 2005), lower

socioeconomic status (Doku *et al.* 2010, Hanson & Chen 2007), and psychiatric co-morbidity (Sihvola *et al.* 2008) as well as exposure to cigarette smoke during pregnancy (Dwyer *et al.* 2009).

2.3.4 Nicotine dependence in young cigarette smokers

Nicotine delivery to the brain takes only a couple of seconds after inhaling cigarette smoke. Nicotine has a half-life of two hours and during the day when the user smokes regularly, the blood nicotine level accumulates and then declines during the night. The pharmacokinetics of nicotine with fast delivery and accumulation during the day enhance nicotine dependence development. The first cigarette in the morning is commonly considered as the most addictive by a great part of dependent smokers since this causes the largest change in the brain nicotine concentration in brain for the entire day. (Benowitz 2009).

At the vulnerable age of 12 to 16, when the smoking habit is usually adopted and the neural system is still developing, symptoms of nicotine dependence occur soon after intermittent use of cigarettes: half of those who have symptoms of dependence have smoked fewer than 10 cigarettes per month (DiFranza *et al.* 2002, DiFranza *et al.* 2007). In the most sensitive adolescents, symptoms of nicotine dependence can be detected soon after inhaling the first cigarette (DiFranza *et al.* 2007, Gervais *et al.* 2006).

Young adults are one of the age groups that are most likely to smoke in several western countries, and in comparison with adolescents, they smoke more often on a regular basis and more frequently during the day (Bachmann *et al.* 2012, Hammond 2005). As a result, young smokers are increasingly likely to become addicted to the habit as they enter their adulthood (Hammond 2005).

2.3.5 Nicotine dependence in young smokeless tobacco users

The pharmacokinetics of nicotine in SLT products display some differences compared to those of smoked cigarettes. In SLT, nicotine absorption is slower and high levels of nicotine can be sustained for a considerably longer time than when smoking cigarettes (Benowitz 1988). Even though peak blood nicotine levels in snus users are often lower than in smokers, the differences in pharmacokinetics result in an even higher amount of nicotine being absorbed per dose than can be achieved with cigarettes (Benowitz 1988, Foulds *et al.* 2003). Consequently, snus use can result in nicotine dependence at least comparable to that of smoking.

A few studies have examined the nicotine dependence in young SLT users, and the dependence of dual users using cigarettes and SLT. According to a Swedish study, it seems that young dual users are a group of smokers that are more dependent on nicotine than exclusive smokers or exclusive snus users i.e. even though dual users consumed fewer cigarettes weekly than exclusive smokers, these individuals seemed to exhibit greater nicotine dependence than exclusive smokers, based on the commonly-used indicators such as time to first cigarette in the morning (Post *et al.* 2010). In that study, exclusive smokers and dual users had similar patterns of unsuccessful quit attempts in their history. A Finnish study on adolescent smokers who smoked weekly showed that the more the subject had experimented with snus, the more nicotine addicted that individual would be (Haukkala *et al.* 2006).

Furthermore, a U.S. survey study of middle and high school students found that using at least two other tobacco products in addition to cigarettes was associated with nicotine dependence (Lee *et al.* 2015). According to the trajectories of tobacco use in Swedish adolescents, dual users of snus and cigarettes were a high-risk group for tobacco dependence (Rosendahl *et al.* 2008). Another U.S. study found that among young adult smokers, the consumption of more than one tobacco product was associated with more severe nicotine dependence (Timberlake 2008).

2.4 Smoking cessation with focus on young adults

Despite the increase in cigarette consumption and nicotine dependence among smokers from adolescence to early adulthood, it has been estimated that more than half of the young adult smokers want to quit smoking, and over 60% have made a previous quit attempt according to studies conducted in Canada, the U.S and Switzerland (Bachmann *et al.* 2012, Hammond 2005, Solberg *et al.* 2007). The attempt to quit had been mostly unassisted (85%) among young adults in Switzerland (Bachmann *et al.* 2012). In the U.S study in which all respondents were health plan members, the number of unassisted quit attempts was reported to be lower, about 51% (Solberg *et al.* 2007). A previous smoking abstinence with a duration of at least one month has been recorded by 1-6% of adolescents and 10-12% of young adult smokers (Bachmann *et al.* 2012, Hammond 2005).

Solberg *et al.* (2007) compared 18 to 24 years old smokers to older smokers, and found young adult smokers were as likely to be motivated to quit and even more likely to report a quit attempt in the past year than older smokers (60% vs.

50%). However, the quit attempts were also more likely to have been unassisted in the young adults (51% vs. 34%). In a Finnish study investigating the history of smoking cessation from teenage years to adulthood, only one third of all adolescent smokers had quit, with an annual quitting rate of 2.3% between ages 15 and 28 (Paavola *et al.* 2001). Therefore, a great part of young smokers continue to smoke as an adult although it is probable that several of them have had previous quit attempts, mostly unassisted.

Multiple predictors of smoking cessation in young people have been recognised. A systematic review (Cengelli *et al.* 2012) summarised five main predictors associated to smoking cessation and successful abstinence for at least six months among adolescent and young adult smokers:

1. Not having friends who smoke.
2. Not having intentions to smoke in the future.
3. Resisting peer pressure to smoke.
4. Being older when first using cigarettes.
5. Having negative beliefs about smoking.

Although there is not a large number of studies investigating smoking cessation intervention for adolescent smokers, the number is even smaller for the studies focusing on young adults —despite the fact that they have several behavioral and somatic features that differ from smokers in other age groups. Therefore, there are no evidence-based guidelines for smoking cessation in young smokers (Bailey *et al.* 2012, Kim *et al.* 2011, Stanton & Grimshaw 2013, Working group set up by the Finnish Medical Society Duodecim and the Finnish Association for General Practice 2012).

Although young adults may have been included in numerous cessation trials, the outcomes have not been analysed separately from that of older adult smokers. Suls *et al.* (2012) aimed to resolve this problem by contacting authors to differentiate young adults from the original data. Fourteen studies were analysed with heterogeneous interventions including some pharmacological intervention [nicotine replacement therapy (NRT)/bupropion/nortriptyline] and/or psychological support. Encouragingly, the meta-analysis indicated that cessation interventions should be as effective for young adults as they are for general adult population, but there were too few studies to investigate the benefits of any particular type of intervention.

In another review with a focus on young adults, Villanti *et al.* (2010) systematically surveyed 14 clinical trials including various interventions. They

concluded that there is little evidence of efficacy of smoking cessation interventions targeted to U.S young adults i.e. 18 to 24 years olds. They found promising results for brief interventions with extended support via the telephone and electronic media, and for personalisation of the intervention to conform to the interests of the participant. Pharmacologic interventions were not included in the review because they found no eligible studies of pharmacologic interventions in young adults.

In a small number of trials focusing on young smokers, young adults have not been separately analysed from adolescent smokers. The results of these trials will be described in more detail in the subsequent sections of specific interventions in this thesis. Generally, a great part of smoking cessation trials on adolescent and young adult smokers have reported problems in recruiting enough participants, and these have been accentuated by low compliance rates and incomplete follow-up adherence. In some studies, lower doses and/or a shorter length of pharmacologic treatment than recommended for adult smokers have been applied, possibly to the detriment of efficacy. In addition, definitions of smokers and non-smokers have varied between studies, making it rather difficult to compare and summarise the results. These issues restrict the confidence of the results of the smoking cessation trials focusing on young smokers that are also too few in number to allow any definitive conclusions to be drawn.

In summary, there is a clear need for more studies to investigate interventions on smoking cessation in young smokers, especially in young adults.

2.4.1 Smoking cessation interventions for groups

Tobacco control campaigns which include mass media interventions through television, radio, newspapers, billboards, posters, leaflets and booklets targeted to adults are thought to reduce smoking (Bala *et al.* 2013). In addition, internet-based interventions, especially those that have been tailored to individuals or have interactive components, seem to help adults to quit smoking (Civljak *et al.* 2013). Telephone quit lines for adult smokers also seem to support these individuals in their attempts to quit smoking (Stead *et al.* 2013b). In addition, print-based self-help materials have a small increasing effect on the quit rate of smoking, at least in adults (Hartmann-Boyce *et al.* 2014). Instead, competitions and incentives for smoking cessation have not been shown to have any remarkable effect to support adult smokers to quit in the long term (Cahill & Perera 2008, Cahill & Perera 2011).

Behavioural therapy in groups of adults has been shown to be more effective than self-help, but there is no evidence that group behavioural therapy would be more effective than individual counselling of a similar intensity (Stead & Lancaster 2005).

2.4.2 Simple advice and counselling for smoking cessation

Simple advice from a medical practitioner has been shown to exert a small but cost-effective positive effect on the smoking cessation rate (Law & Tang 1995, Stead *et al.* 2013a). Accordingly, in a Cochrane review (Lancaster & Stead 2005) individual counselling for over 10 minutes by a trained therapist outside of routine clinical care was found to be effective in helping adult smokers to quit smoking.

If behavioural support is provided in combination with smoking cessation pharmacotherapy (NRT, bupropion or varenicline) for adults trying to quit smoking, the chances of successful smoking abstinence are increased when compared to minimal intervention or usual care (Stead & Lancaster 2012b). Increasing the intensity of behavioural support as adjuncts to pharmacotherapy seems to increase the chances of success by about 10% to 25% (Stead & Lancaster 2012a).

There is one Cochrane review which has summarised smoking cessation interventions on young individuals aged under 20 (about 6000 people; 28 controlled trials). Several of the trials included in the meta-analysis had complex interventions, with the majority using motivational enhancement with some kind of psychological support, and three of them involved a pharmacological intervention. The authors concluded that complex approaches showed promise, especially those that included sensitiveness to stage of change and motivational enhancement and supported behavioural change, but it stressed that more good quality studies were needed on this issue (Stanton & Grimshaw 2013).

2.4.3 Smoking cessation pharmacotherapy

The three smoking cessation pharmacotherapies commonly used around the world are varenicline, NRT and bupropion. All these three treatments have been proven to enhance the odds for smoking abstinence in adults (Cahill *et al.* 2013), but their efficacy has been less extensively studied in younger age groups as will be described in detail below.

Varenicline

Varenicline is an α4β2 nicotine acetylcholine receptor partial agonist. Since it possesses antagonistic properties, it blocks α4β2 nicotine acetylcholine receptors from binding nicotine since it has a higher affinity for the receptor and therefore partially prevents the stimulating effect of nicotine on the mesolimbic dopamine system, reducing the pleasure obtained after the use of a tobacco product. However, it has also agonist properties which are weaker than nicotine itself but these are thought to be sufficient to relieve the withdrawal symptoms in abstinent tobacco users without evoking the pleasure linked with tobacco product use.

The regular dosing schedule for varenicline is 0.5 mg once daily for three days, then 0.5 mg twice daily for four days and then 1 mg twice daily for 11 weeks. The patient is expected to set the exact date when he/she will stop smoking and varenicline therapy is initiated one to two weeks before that date. If quitting is successful after 12 weeks of varenicline use, it is recommended to continue the treatment with 1 mg twice daily for another 12 weeks.

Varenicline has been extensively studied in adult smokers and it is claimed to be the most effective smoking cessation pharmacotherapy available at the moment: it has been estimated that varenicline more than doubles the chances of long term abstinence (six months or longer) at the standard dose when compared to placebo treatment (OR 2.88; 95% CredI 2.40-3.47), and it is more effective than bupropion (OR 1.59; 95% CredI 1.29-1.96) or any single form of NRT (OR 1.57; 95% CredI 1.29-1.91) (Cahill *et al.* 2013). The efficacy seems to be similar at achieving long term abstinence when compared to combination NRT i.e. nicotine transdermal patches (NP) combined with some other form of NRT (OR 1.06; 95% CredI 0.75-1.48) (Cahill *et al.* 2013).

Varenicline seems to be well-tolerated, and the most common adverse events are nausea, insomnia, abnormal dreams and headache (Cahill *et al.* 2012, Cahill *et al.* 2013). Because of concerns raised from post-marketing safety data, the Pharmaceutical Medication Centre in Finland and other countries do not recommend that varenicline should be given to subjects with unstable mental illness or to those estimated to have an increased risk for suicidal behaviour. Post-marketing surveillance has also raised concerns about possibly increased risk for cardiovascular events in varenicline users. However, recent reports from clinical trials have not detected any increased risk for neuropsychiatric nor cardiac events in adult varenicline users but caution is still recommended when prescribing the drug (Cahill *et al.* 2012, Cahill *et al.* 2013).

So far, no placebo-controlled studies focusing on the efficacy of varenicline have been conducted in adolescent smokers. In addition, young adults have not been separately analysed from older adults even though they differ in several ways from adults not only in their dependence to nicotine but also in other behaviours related to smoking as stated elsewhere in this thesis. One study (Faessel *et al.* 2009) has provided preliminary results on the tolerability and safety of the drug in adolescent smokers. Varenicline was associated with adverse events similar to those described in adults, but no discontinuations were reported because of adverse events. One small randomised trial (n=29; age 15 to 20 years) compared varenicline to bupropion (Gray *et al.* 2012) without reporting any serious adverse events; the end-of-treatment abstinence rates after 8 weeks of treatment were 27% for varenicline and 14% for bupropion but after 12 weeks, none of the subjects in the varenicline group were still abstinent and only one in bupropion group.

Nicotine replacement therapy

NRT is based on nicotine containing products that relieve the symptoms of nicotine dependence by releasing nicotine to bind to the nAChRs. They do not contain the other unhealthy compounds present in tobacco products. NRT is available in multiple forms: there are nicotine chewing gums (NG), NPs, inhalers, oral and nasal sprays, sublingual tablets and lozenges. Most studies have been conducted with NGs and NPs. Nicotine delivery differs between the different forms of NRT: NPs deliver nicotine slowly to the brain, but delivery is more rapid with NGs, inhalers, sprays, nicotine tablets and lozenges —although not as quickly as can be obtained after smoking a cigarette (Stead *et al.* 2012), and therefore the positive feedback of nicotine in dependent subjects is somewhat more mild in NRT.

NPs contain multiple different doses of nicotine; from 5mg to over 50mg. The usual dosing is 7 to 10mg per day in milder patches and 15 to 21 mg in stronger patches. The patches are recommended to be used for 16 to 24 hours depending on the brand of the patch. NGs are commonly available in 2 mg and 4 mg doses, and lozenges/sublingual tablets in one to four milligrams per portion. Oral sprays commonly contain 1mg of nicotine per single dose. One inhaler usually contains 10 to 15 mg of nicotine per cartridge, and 3-12 cartridges are recommended to be used in one day, depending on the symptoms of nicotine dependence.

There is no clear evidence showing that one dosage form of NRT would be better than the others, but there is some evidence in support of the concept that heavily dependent smokers may benefit from stronger doses of NGs and NPs (Cahill *et al.* 2013, Stead *et al.* 2012). A Cochrane review summarised evidence from previous studies; it concluded that the duration of NRT has varied widely between the reviewed studies, from two weeks to three months, with no major effects for efficacy of the treatment (Stead *et al.* 2012). The usual recommended duration of NRT is two to three months with a tapering of the dose at the end of the treatment. However, a recent Canadian study indicated that NRT use for less than four weeks may even be related to a lower abstinence rate compared to those that do not use NRT at all, and the adherence to NRT for 8-12 weeks rather than 4-8 weeks may increase the likelihood of abstinence in the general population (Zhang *et al.* 2015).

The most commonly reported adverse events for NP are skin sensitivity and local irritation, for NG they are hiccoughs, gastrointestinal disturbances and jaw pain, for nicotine inhalers and sprays local irritation at the side of the administration and hiccoughs and burning feeling in mouth have been described after the use of nicotine tablets (Cahill *et al.* 2013). The adverse events are generally mild; NRT may increase the occurrence of chest pain and heart palpitation –although it seems to be well-tolerated also in patients with cardiac disease (Cahill *et al.* 2013). The manufacturers recommend that NRT should not be provided to patients with instable ischemic heart disease, or those with severe arrhythmias or after an acute stroke.

All forms of NRT have been shown to improve long term (six months or longer) smoking abstinence with similar efficacies compared to placebo in adult smokers: they seem to increase the chances of successful quitting by about 80% (OR 1.84; 95% CredI 1.71 to 1.99) (Cahill *et al.* 2013, Stead *et al.* 2012). The combination of NPs and an NRT with more rapid nicotine delivery seems to be more effective than a single form of NRT (RR 1.34; 95% CI 1.18-1.15) (Cahill *et al.* 2013, Stead *et al.* 2012). Even though it does not seem to be as effective as varenicline, the efficacy is similar to bupropion (OR 0.99; 95% CredI 0.86 to 1.13) (Cahill *et al.* 2013). The combination of bupropion with NRT may increase the success rate in smoking abstinence (RR 1.24; 95% CI 1.06 to 1.45) (Stead *et al.* 2012).

NRT has been less extensively studied in young smokers. Some clinical trials have analysed NRT in young smokers (aged 13 to 21; n=40-257) reporting the following findings: end-of-treatment abstinence rates: 0% for nasal spray

(Rubinstein *et al.* 2008), 6.5% for NG (Moolchan *et al.* 2005) and 0-28% for NP (Hanson *et al.* 2003, Moolchan *et al.* 2005, Roddy *et al.* 2006, Scherphof *et al.* 2014), and after 26-weeks' follow-up, 9% for NG and 21% for NP (Moolchan *et al.* 2005). Although these studies have not shown that NRT to be more effective than placebo in young smokers in general, two of these studies have provided some evidence that NRT could be more effective than placebo in the short term. Moolchan *et al.* (2005) found that the NP was more effective than placebo at the end of the treatment (nicotine patch group 18% vs. placebo 3%). The difference was no longer statistically significant at the 26 week follow-up. In addition, Scherphof *et al.* (2014) reported that NP was significantly more effective than placebo at the end of the treatment only in the "high-compliant"-group (OR 1.09; 95% CI 1.01-1.17).

Bupropion

Bupropion hydrochloride is a selective catecholamine neuronal (norepinephrine and dopamine) reuptake inhibitor. The therapeutic indications for bupropion are depression and smoking cessation. Its mechanism of action as smoking cessation therapy is unknown.

Regular dosing for bupropion is 150 mg daily for six days, and then 150mg twice daily for seven to twelve weeks. Drug therapy is started when patient is still smoking. The patient is encouraged to set a date when he/she will quit smoking, and bupropion use is started 1-2 weeks before that date.

The most common adverse events reported by bupropion users are insomnia, dry mouth and nausea (Cahill *et al.* 2013). Bupropion increases risk for seizures (seizure rate 1:1000 of users) (Cahill *et al.* 2013), and therefore it is not recommended to be used in patients with known seizure liabilities. Other contraindications for bupropion are severe liver cirrhosis, eating disorder and bipolar disorder.

Bupropion increases the long term abstinence rate in adult smokers trying to quit smoking compared to placebo treatment by about 80% (OR 1.82; 95% CredI 1.60 to 2.06) (Cahill *et al.* 2013). As described elsewhere in this thesis, bupropion seems to be as effective as NRT, but not as effective as varenicline treatment in smoking cessation (Cahill *et al.* 2013).

Some studies have investigated bupropion as smoking cessation aid in young individuals. The end-of-treatment abstinence rates in four randomised clinical studies (Gray *et al.* 2011, Killen *et al.* 2004, Muramoto *et al.* 2007, Niederhofer &

Huber 2004) (aged 12 to 21; n=22-312) have ranged from 8% to 55% with two studies reporting a significant difference compared to placebo (Muramoto *et al.* 2007, Niederhofer & Huber 2004). After 26 weeks, the abstinence rates were less impressive i.e. 3% to 14% (Killen *et al.* 2004, Muramoto *et al.* 2007) without any statistically significant difference compared to placebo.

Other pharmacotherapies tested on smoking cessation

In addition to the above three treatments licenced for smoking cessation in the EU and the U.S, multiple other drugs have been studied for effectiveness as smoking cessation therapy: for example, cytisine (similar to varenicline; nicotine cholinergic receptor partial agonist), antidepressants such as nortriptyline, some anxiolytics, rimonabant (cannabinoid receptor antagonist), clonidine (centrally acting sympatholytic drug), lobeline (an alkaloid present in Indian tobacco leaves), mecamylamine (nicotine antagonist), and opioid antagonists. These other options have generally been less studied than varenicline, NRT and bupropion, but there is evidence that cytisine (RR 3.98; 95% CI 2.01 to 7.87), nortriptyline (RR 2.03; 95% CI 1.48 to 2.78), and clonidine (RR 1.63; 95% CI 1.22 to 2.18) increase the chances of quitting (Cahill *et al.* 2013). Cytisine is licensed for smoking cessation in Russia and some other former socialist economy countries. Nortriptyline is licensed for smoking cessation in New Zealand, but it is recommended to be used as a second line therapy in several other countries including Finland (Working group set up by the Finnish Medical Society Duodecim and the Finnish Association for General Practice 2012). The use of clonidine as a smoking cessation therapy is limited by its adverse events (Cahill *et al.* 2013). A nicotine vaccine, designed to block nicotine access to the central nervous system, has been tested, but there is no current evidence of its effectiveness (Cahill *et al.* 2013, Hartmann-Boyce *et al.* 2012).

2.4.4 Smokeless tobacco and smoking cessation

SLT has been a focus of interest as a tool to help in smoking cessation as well as a harm reduction tool, especially in Sweden where adult male smoking and smoking related diseases have decreased and this has been suggested to be at least partly attributable to "switching" from cigarettes to snus (Foulds *et al.* 2003). Nonetheless, it has been debated whether the "Swedish model" could or even should be replicated in other western countries i.e. whether snus use could be

marketed for smokers as a smoking cessation aid and, therefore, snus use could act as a harm-reduction tool in other countries besides Sweden (Melikian & Hoffmann 2009).

As described before in this thesis, a great part of young snus users are also smoking cigarettes. These young smokers do not seem to use snus primarily for smoking cessation purposes but as an addicting behaviour similar to cigarettes: for example, a Norwegian study has described that only a low number of adolescent and young adult snus users are ex-smokers when compared to older adults (Lund *et al.* 2011). The relatively large number of dual user may partly be attributable to the use of snus in the increasing number of situations where smoking is not allowed. On the other hand, the studies examining whether smokeless tobacco can act as a gateway to the more unhealthy habit of cigarette smoking in the young have been inconclusive (Haddock *et al.* 2001, O'Connor *et al.* 2003, Severson *et al.* 2007, Timberlake *et al.* 2009, Tomar 2003). One Swedish prospective study found that those adolescents experimenting with snus had an increased risk to initiate smoking (Galanti *et al.* 2008). A Finnish prospective study investigating adolescents revealed that experimenting with snus in the 7th grade predicted weekly smoking by the 9th grade (Haukkala *et al.* 2006). These findings may reflect the association found in some studies that SLT and cigarette smoking have some common predictors e.g. risk-taking behaviour, binge-drinking, and poor school achievement (Engstrom *et al.* 2010, Galanti *et al.* 2001b, O'Connor *et al.* 2003, Timberlake *et al.* 2009). In all, the role of snus use to reduce smoking related health harm in young is highly questionable.

2.4.5 Electronic cigarettes and smoking cessation

E-cigarettes have been marketed as a healthier option than cigarettes as well as a smoking cessation tool, and users have often assimilated this claim (Grana & Ling 2014, Pepper *et al.* 2014). In fact, population-based studies in several countries have reported that e-cigarettes are primarily used to replace conventional cigarettes in places where smoking is not allowed, or to cut down on smoking cigarettes, followed by a way of trying to quit smoking (Grana *et al.* 2014). However, not only the evidence about their safety but also their claims of efficacy in smoking cessation are insufficient to allow drawing of any reliable conclusions: a recent Cochrane review found that there was evidence from two trials indicating that e-cigarettes would be superior than placebo in long term smoking abstinence of adults, and one trial indicating that the efficacy of e-

cigarettes was similar to nicotine patches in smoking cessation (McRobbie *et al.* 2014). However, according to the reviewers, the low number of good quality studies, the low event rates and the wide confidence intervals decreased the confidence in the results to a low level. In line with the Cochrane review, another recent review combined evidence of four longitudinal studies, four clinical trials and one cross-sectional study and came to the conclusion that e-cigarettes did not seem to be associated with successful quitting of smoking in general population-based samples of smokers (Grana *et al.* 2014).

Dual use of e-cigarettes and conventional cigarettes is common among young and adult e-cigarette users in several countries i.e. a great part of e-cigarette users also smoke conventional cigarettes (Grana *et al.* 2014). Because there is no consistent evidence that e-cigarettes are an effective smoking reduction or cessation therapy, wide dual use raises concerns that e-cigarette use may even lead to an increase in tobacco consumption. In a Finnish survey (n=3535), e-cigarette use in adolescents was associated with some common risk factors with conventional cigarette smoking such as parental smoking and poor school achievement, and, interestingly, the experimentations among young daily smokers were not linked with any interest in quitting smoking (Kinnunen *et al.* 2014). Furthermore, a Polish study (Goniewicz *et al.* 2014) comparing two cross-sectional samples of 15 to 19-year-olds found evidence that e-cigarettes may not play any role in reducing smoking conventional cigarettes in young people: they observed an increase not only in the prevalence of e-cigarette use (6% vs. 30%) but also a simultaneous increase in the prevalence of smoking conventional cigarettes (24% vs. 38%) as well as in the dual use of these products in the period from 2010-2011 to 2013-14.

Although a great part of the adolescents and young adults experimenting with e-cigarettes are current smokers, a significant proportion of them have never smoked conventional cigarettes (Carroll Chapman & Wu 2014, Grana *et al.* 2014). To date, we do not know whether their e-cigarette use increases their risk to initiate smoking conventional cigarettes in the future. A small prospective U.S. study investigated 16 to 26 years old e-cigarette users with no previous history of tobacco use; their preliminary finding was that e-cigarette use was an independent risk factor for conventional cigarette use during the one year follow-up period, even after controlling for sex, age, ethnicity, parental smoking, maternal education, sensation-seeking tendency, and cigarette smoking among friends (Primack *et al.* 2015). The majority, 11 out of 16 e-cigarette users, progressed to cigarette smoking during the follow-up period.

As a conclusion, while e-cigarette users are rapidly increasing in number and there is evidence that e-cigarettes are highly addictive, it is far from clear that e-cigarettes should be viewed as a smoking related harm reduction tool aiding smokers, especially young smokers, to cut down smoking and ultimately to quit smoking —as commonly believed by the e-cigarette users. Fortunately, studies of e-cigarettes are rapidly growing in number.

2.4.6 Others

Biomedical risk assessment e.g. lung function or exhaled-air carbon monoxide (eCO) measurement, ultrasonography of arteries and photographs of plaques or genetic susceptibility in addition to some counselling have been tested as smoking cessation strategies, but with little evidence of their efficacy. There is a Cochrane review (Bize *et al.* 2012) that summarised the results of 15 studies on this issue, only two found that biomedical risk assessment could increase statistically significantly smoking abstinence rates in middle-aged smokers in the long term. The first positive study tested lung function in smokers with the results being explained to the test subjects and compared the quit rate to smokers without any explanation of the results. The second study found light smokers to be more likely to quit smoking when images of their arteries were shown to them.

Some specific techniques have been claimed to help people to quit smoking such as acupuncture, acupressure and laser stimulation as well as hypnotherapy, but there is no consistent, bias-free evidence to support the effectiveness of these approaches (Barnes *et al.* 2010, White *et al.* 2014).

2.5 Definitions and biochemical verification of smoking abstinence

Definitions of successful smoking abstinence have differed in the various clinical smoking cessation trials making it more difficult to compare the results. Fortunately, there are some definitions that are most commonly used for assessing smoking abstinence (Cahill *et al.* 2013, Lancaster & Stead 2005, Stanton & Grimshaw 2013). One commonly used measure is seven-day or 30-day point prevalence i.e. the proportion of subjects that have not smoked during the past seven or 30 days. Another, more restricted definition is continuous abstinence i.e. the proportion of subjects that have been abstinent from the beginning of the follow-up. The third commonly used definition, prolonged abstinence, is defined as abstinence following occasional relapse in the two weeks post-treatment grace

period. Abstinence rates are often reported at the end of treatment and six months or longer after the beginning of an intervention (so-called long term smoking abstinence).

Biochemical verification of self-reported smoking abstinence is considered the golden standard in smoking cessation trials (West *et al.* 2005). The commonly used biochemical verification tests are eCO and cotinine analysis from samples of blood, urine, or saliva. eCO is only indicative for recent smoking as it has a half-life of about four hours (Ryter & Choi 2013), and is limited to smoking as it cannot detect SLT use. In clinical trials, cut-off values have been variable, ranging up to eCO <10 ppm (Lancaster & Stead 2005, Stanton & Grimshaw 2013). In most recent studies, the proposed eCO cut-off values for a non-smoker have been more stringent, from ≤5 to 6.5 ppm, as environmental exposure to CO has decreased in several western countries (Marrone *et al.* 2010, Ryter & Choi 2013). Nonetheless, values exceeding these limits have been measured in non-smokers living in heavily urbanized areas (Ryter & Choi 2013).

Cotinine is the main metabolite of nicotine (Benowitz *et al.* 2009b). It has remarkably longer half-life than eCO, approximately 16 hours (Benowitz *et al.* 2009b). Therefore, in many cases, it is a more useful indicator than eCO for verification of self-reported smoking abstinence since it can detect nicotine exposure over the past 3-4 days. It is also a highly sensitive and specific marker (Benowitz *et al.* 2009b), but cannot distinguish between smokers, SLT users and those using NRT. The cotinine concentration depends on the body fluid that is sampled: blood, serum, and saliva cotinine concentrations are similar, but urinary cotinine concentrations can be even five times higher (Benowitz *et al.* 2009a). Saliva is believed to be the most useful sampling procedure as it is the least invasive and has the better sensitivity values when compared to urine and blood samples (Connor Gorber *et al.* 2009, Stevens & Muñoz 2004).

In a systematic review, substantial heterogeneity was found among the cut-off values in measured cotinine concentrations used to separate non-smokers from smokers, ranging from 50 to 500 ng/ml in urine, from 8 to 100 ng/ml in serum and from 7 to 44 ng/ml in saliva (Connor Gorber *et al.* 2009). The authors emphasized the need for standardization of the cut-off values. Recently, there have been suggestions to make cotinine cut-off values more stringent as smokers are more often light/occasional smokers and, on the other hand, exposure to ETS has decreased in western countries (Benowitz *et al.* 2009a, Jarvis *et al.* 2008). In addition, it has been speculated that some specific subgroup populations may require alternative cut-off values such as different racial/ethnic groups, pregnant

women, and those populations with notably differing levels of exposure to second hand smoke (Benowitz *et al.* 2009a, Connor Gorber *et al.* 2009, Jarvis *et al.* 2008). For example, in the U.S., the optimal cut-off value recently recommended for serum cotinine varied from 5.92 ng/ml for non-Hispanic black adults to 0.84 ng/ml for Mexican Americans, in comparison to the value of 3 ng/ml for the overall U.S. population (Benowitz *et al.* 2009a).

3 Aims of the present study

Smoking is one of the leading causes of preventable mortality and morbidity in the world. Finland has set a national goal to achieve a totally smokeless nation before the year 2040. Although a declining trend has been seen in younger age groups after the turn of the century, still about 20% of Finnish young adults smoke on a daily basis.

To reach the goal of a smokeless Finland before the year 2040, it is not only crucial to prevent young people from starting to smoke, but also to find more effective strategies to help young smokers to quit smoking. Relatively little is known about smoking habits, nicotine addiction propensities and the optimal means of smoking cessation in young adults. Therefore, it is important to obtain more knowledge about tobacco use in this age group on the cusp of adulthood: related life style factors, characteristics of smoking cessation, and effectiveness of smoking cessation interventions in this age group.

The specific aims were:

1. To describe tobacco use habits in a cross-sectional study of young adults.
2. To compare health and lifestyle in young adult tobacco users and non-tobacco users.
3. To study nicotine dependence and motivation to quit in young adult tobacco users.
4. To examine use of smoking cessation pharmacotherapy as well as their effectiveness and safety in young adults.

4 Materials and methods

4.1 Tobacco use in a cross-sectional study of military recruits in Northern Finland

4.1.1 Subjects (I-III)

A cross-sectional survey study was conducted in Northern Finland during autumn 2008 to spring 2009. The military recruits came from the two most northern regions of Finland, Lapland and Northern Ostrobothnia. They were surveyed at the beginning of their military service with a high response rate (80%). At the time of the survey, approximately 81-82% of an age group of males were recruited for military service each year.

A total of 1186 subjects were surveyed. Female recruits (n=12) were excluded because of their small number. Subjects with incomplete filling in crucial study questions or unreliable answers were excluded (n=11-23 depending on the study).

4.1.2 Data collection (I-III)

All study subjects were asked to fill in a specific questionnaire about their sex, age, height, weight, education, tobacco use habits, physical fitness, daily exposure to ETS, and symptoms of CB. It also included questions about whether they considered themselves to be nicotine dependent, number of previous quit attempts and experimentations of pharmacological help in smoking cessation. The questions about the smoking and snus use habits were based on a Finnish nationwide study questionnaire, the Adolescent Health and Lifestyle Survey (Rimpelä *et al.* 2007).

4.1.3 Definition of smoking and snus usage groups (I-III)

In studies I and III, the main analysis strategy to answer the research questions was to compare education, anthropometric, health, and lifestyle variables between different smoking and snus usage status groups. In study II, nicotine dependence variables were compared in daily smokers by whether they had attempted to quit

smoking and whether pharmacological help had been previously used. For these purposes, we created three smoking subgroups and three snus use subgroups.

A daily smoker was defined as a subject who currently smoked at least one cigarette daily (studies I-III). An occasional smoker was a subject who reported smoking less than daily or who had smoked over 50 cigarettes in the past (studies I and III). A non-smoker was a person who had smoked <50 times in his lifetime and did not consider himself as a smoker (I and III). Ex-smokers were subjects who reported that they had stopped smoking (I and III).

In study III, subjects were divided into three subgroups according to their snus usage. Daily users of snus were those who reported using snus on a daily basis. Occasional users were those stating that they used snus occasionally or who had experimented with snus more than once. Subjects with no snus use had not experimented with snus on more than a single occasion.

4.1.4 Outcome variables (I-III)

Three educational groups were made: 1) compulsory school (i.e. grades 1-9), 2) vocational school, and 3) graduates from either high school or higher academic institutions. For the linear and multinomial logistic regression analyses, education was categorized into two groups. The lower education group included subjects who had attended compulsory school or vocational school. The higher education group had graduated from the high school or had an academic degree.

Both body weight and height were self-reported in the questionnaire. BMI was the body weight (kg) divided by the square of height (m).

Physical activity level was assessed with a question 'How would you describe yourself as a sportsmen?' The options were 'I compete in some sport', 'I'm very active in sports, but I don't compete', 'I'm a "couch potato" –I only do sports if I have to' and 'Something else, what?' Subjects were divided into subgroups 'Active', 'Moderate' and 'Passive'. Subjects who competed or were otherwise active in sports were considered as 'Active'. Based on specific descriptions given by subjects, the term 'Moderate' was given to those subjects who answered 'Something else'. "Couch potatoes" were considered as 'Passive'.

The result of a Cooper's test, a measure used in study I, was self-reported in the questionnaire. The Cooper's test is a 12-minute running test for physical fitness that all conscripts were required to undertake at the beginning of their military service if there was no health reason for exemption. Subjects run as far as possible within 12 minutes around a running track. The running distance was

recorded by the army personnel. The recruits were encouraged to do their best since they could obtain extra leave if the test result exceed 3000 metres. Alternatively, a poor result meant that the recruit had to participate in an extra fitness enhancing programme, something they were keen to avoid.

Symptoms of CB were assessed by the question 'Have you had cough with sputum production on most days or nights for at least three months yearly?'

Detailed tobacco use habits were assessed. Daily grams of tobacco were asked and one pack year was defined as 20g of tobacco smoked per day for one year. The time to the first cigarette in the morning was inquired (≤5, 6-30, 31-60, or >60 minutes after waking up), and nicotine dependence in smokers was assessed by the Heaviness of Smoking Index (HSI) (Etter *et al.* 1999, Heatherton *et al.* 1991). HSI grading is based on two questions that are as follows: 1. how soon after you wake up do you have your first cigarette? A. within 5 minutes (3 points), B. 6-30 minutes (2 points), C. 31-60 minutes (1 point), D. after 60 minutes (0 points). 2. How many cigarettes do you typically smoke per day? A. 31 or more (3 points), B. 21-30 (2 points), C. 11-20 (1 point), D. 10 or fewer (0 points). The more that the subject scores in HSI, the more dependent he or she is.

Dependence to snus was enquired by the question: Which describes you the best? "I think I'm addicted to snus": 1) not at all, 2) to some extent, 3) quite a lot, or 4) very much. According to the answers, snus dependence was categorised as 1) no dependence, 2) mild, 3) moderate, or 4) strong dependence. Two groups of perceived dependence were formed: 1) no dependence or mild dependence, and 2) moderate to strong dependence.

4.1.5 Statistical methods (I-III)

Studies I and III described the tobacco use habits of the subjects. Study I investigated the relationship between smoking habits and education, body weight and height, BMI, activity in sports, physical fitness (Cooper's test result), and symptoms of CB. The relationships between snus use habits and education, body weight and BMI were also examined (study III).

Study II investigated nicotine dependence, previous quit attempts and use of smoking cessation pharmacotherapy in daily smokers.

In study III, the association was examined between snus use habits and nicotine dependence in smokers.

The distributions of subject characteristics and outcome variables were compared in smoking and snus usage subgroups. For the categorical variables, the

statistical significance of the differences between groups was tested by chi-square test or Fisher's test when the assumptions of chi-square test were not fulfilled. To compare the mean values of continuous variables with normal distributions, an independent samples t-test was employed between two groups and one-way analysis of variance between more than two groups. Tukey's post-hoc test was performed for the pairwise comparisons of mean values. Kruskal-Wallis test (K-W test) was used to evaluate the statistical significance in comparing median values of skewed continuous variables between smoking or snus usage groups. The relationship between BMI and daily tobacco usage variables was evaluated with scatter-plot diagrams and Spearman's correlation coefficient (r(s)).

Linear regression was used to evaluate the relationship between the Cooper's test result and smoking with adjustment for potential confounding factors. Potential collinearity between explanatory variables was evaluated using variance inflation factors (VIF) (Armitage *et al.* 2002). Scatter-plot diagrams and Spearman's correlation coefficient (r(s)) were used to illustrate the correlation of the Cooper's test result to daily tobacco usage, smoking years and pack years. Multinomial logistic regression was used to evaluate the relationship between self-reported symptoms of CB and smoking habits with analysis of potential confounders (BMI, age, education and physical activity). All data analyses were performed using IBM SPSS Statistics software.

4.1.6 Ethics (I-III)

The study was approved by the Ethical Committee of the Lapland Central Hospital in Rovaniemi, Finland.

4.2 Prospective study of young adult smokers motivated to quit smoking

4.2.1 Subjects (IV)

In study IV, subjects were recruited during spring 2012 until spring 2014 via community media and face-to-face contact mainly by a study nurse from three levels of vocational educational establishments, i.e. vocational schools, vocational colleges, vocational higher educational institutes as well as the army in northern parts of Finland (cities of Rovaniemi, Kemi and Tornio, municipality of

Sodankylä). Recruited subjects were 18 to 26 year-old volunteering men and women. To be included in the study, recruits had to have smoked daily for at least the past month and to have smoked 100 or more cigarettes in his/her life, be motivated to try to quit smoking and be willing to participate in the 52 week follow-up with the associated monitoring visits arranged in Lapland Central Hospital in the city of Rovaniemi. Exclusion criteria at the point of the recruitment were current drug or alcohol abuse, known allergy towards medications used in the study, lactation, pregnancy or intention to become pregnant during the study period.

Although subjects using psychiatric medication on a daily basis were included into the study during recruitment of the study subjects, they were excluded from randomisation and analysis because the Pharmaceutical Medication Centre in Finland does not recommend that varenicline should be given to subjects with unstable mental illness or to those estimated to have an increased risk for suicidal behaviour.

The targeted sample size was estimated on the basis of findings from Cochrane systematic reviews (Stead *et al.* 2012, Stead & Lancaster 2012b). The standard placebo smoking cessation treatment methods achieve a good outcome in about 10% of the smokers. It was postulated that if the tested nicotine patch 10mg/16h treatment could increase the success by up to 24% and varenicline by up to 28%, this would be clinically important. An increase of this size with a two-tailed p-value of 0.05 and power 0.80 would require a total sample size of 300 young adult daily smokers which became the target sample size. The placebo to the nicotine patch 10mg/16h comparison would require 180 smokers with mild to moderate nicotine dependence and the nicotine patch 15mg/16h to varenicline comparison would need 120 smokers with strong nicotine dependence.

4.2.2 Study visits and data collection (IV)

Figure 1 describes the time line of the study contacts. The same study nurse that had recruited the study subjects conducted all study contacts with them during the study. In study IV, the data emerging from 26 weeks' follow-up was analysed.

The comprehensive questionnaire was completed at baseline that not only included the two HSI questions and detailed smoking habits, but also basic personal information, questions about medications in use, asthmatic or allergic diseases, symptoms of CB, exposure to ETS, parental smoking, snus/e-cigarette/water pipe use, previous attempts to quit smoking, smoking cessation

pharmacotherapy previously used, questions of self-perceived stress by Cohen (Cohen *et al.* 1983) and Life Satisfaction Scale (Koivumaa-Honkanen *et al.* 2000). At the baseline visit, first counselling visit and the initiation of smoking cessation attempt was scheduled. The first counselling visit was also the starting point of the study treatment i.e. week 0.

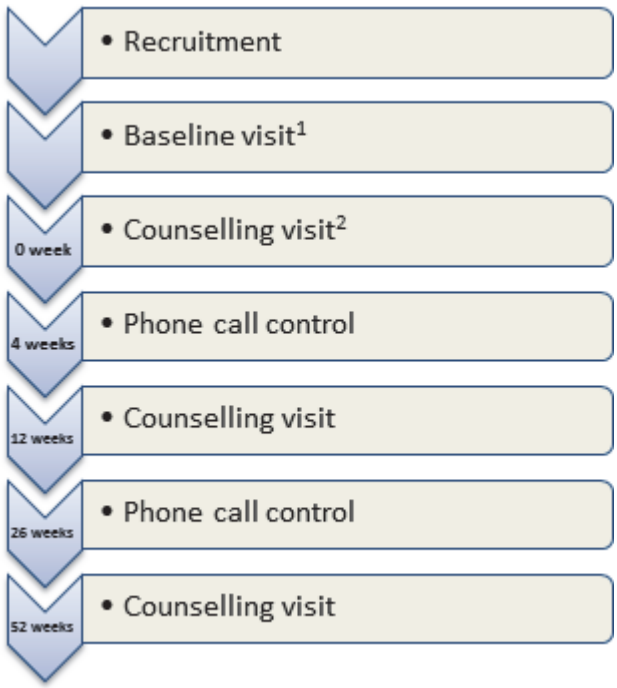

Fig. 1. Study flow in follow-up study of young adult daily smokers. [1]Heaviness of Smoking Index assessment and randomisation. [2]Starting point of the treatment.

Phone call controls were carried out at weeks 4 and 26, and follow-up counselling visits at weeks 12 and 52. All contacts with the study nurse after week 0 involved completion of the modified baseline questionnaire which included questions about current smoking and snus use status, use of withdrawal medicine, possible adverse effects and other concerns about withdrawal medicine asked via an open question, as well as the HSI assessment. A subject was also asked to assess his/her motivation to quit smoking on a scale from 1 to 10 points (1=very low motivation, 10=very high motivation) during the study contacts. All counselling visits (at week 0, 12 and 52) included an individualised smoking cessation

counselling (30 min) by the study nurse using the technique of a Motivational Interview (Dunn *et al.* 2001).

Flow-volume spirometry before and after bronchodilation (0.4mg salbutamol) were conducted at the baseline, 12 weeks and 52 weeks visit, and saliva cotinine level determinations (SalivaNicAlert®) at 12 and 52 weeks. Body weight was measured at all visits.

4.2.3 Study groups (IV)

Current nicotine dependence of the recruited subjects was assessed with the two questions of HSI (Heatherton *et al.* 1989, Heatherton *et al.* 1991). In study IV, subjects were divided into a group of light smokers (HSI 0-2 points i.e. mild-to-moderate nicotine dependence) and a group of heavy smokers (HSI 3-6 points i.e. strong to very strong nicotine dependence).

Figure 2 shows randomised study groups after HSI calculation. Light smokers were randomly assigned into two treatment groups: placebo patch for 8 weeks or nicotine patch 10mg/16h for 8 weeks. Heavy smokers were randomised to receive nicotine patches 15mg/16h for 8 weeks or 12 weeks of varenicline treatment with one week of dose titration.

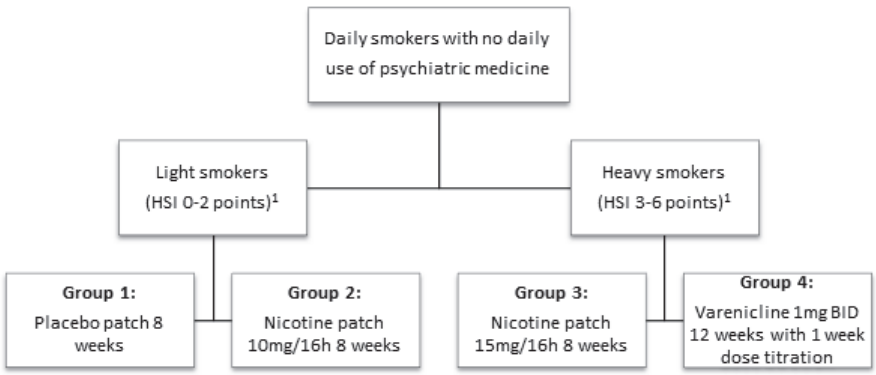

Fig. 2. Study groups subdivided by their score in the Heaviness of Smoking Index. HSI=Heaviness of Smoking Index. BID=twice a day. [1]Randomisation.

Snus dependence was assessed with HSI questions modified for snus use i.e. two questions: 1. how soon after you wake up do you have your first snus? 2. How

much snus do you typically use every day? The grading was the same as in the HSI. One gram of snus was estimated to be one portion. If a subject reported mild-to-moderate dependence for cigarettes (HSI 0-2), but strong-to-very-strong dependence for Swedish moist snuff (snus), then the HSI grading to be used in the randomisation was raised to the more severe dependence level (HSI 3-6) to avoid underestimating the dependence to nicotine.

4.2.4 Randomisation (IV)

Simple randomisation with a computer-generated random list (allocation ratio 1:1) was used to allocate study subjects into different treatment groups after the baseline visit. Randomisation was conducted by a professional from the Medical Informatics and Statistics Research Group in the University of Oulu who was not otherwise part of the study group.

4.2.5 Study medication (IV)

In summary, the follow-up study (study IV) included four treatment groups: placebo patch group, nicotine patch 10mg/16h group, nicotine patch 15mg/16h group and varenicline group. The four study groups chosen to be used in this study were based on clinical experience and previous studies. In clinical practice, nicotine patch dosing is adjusted according to nicotine dependence level: for more dependent patients the recommended dosing is higher. Nonetheless, there is no consistent evidence that one dosing would be more effective than the other in a subgroup of smokers (Stead *et al.* 2012). HSI was used to assess the nicotine dependence, and it was decided to give those subjects with mild-to-moderate nicotine dependence 10mg/16h nicotine patches, whereas those with strong-to-very-strong dependence received 15mg/16h patches. The duration of placebo and nicotine patch therapy was eight weeks. A Cochrane review found no evidence supporting a longer treatment period than 8 weeks for nicotine patches (Stead *et al.* 2012).

In the clinic, on the other hand, varenicline is mainly prescribed for smokers with strong nicotine dependence. Therefore, it was deemed best to compare nicotine patch 15mg/16h to varenicline only in the group of heavy smokers (HSI 3-6).

The first week of varenicline use included dose titration: 0.5mg once daily for three days and then 0.5mg twice a day until the end of the first week. From the

2nd week until the end of the 12th week, the dosing was 1mg twice a day. The dosing and the duration of varenicline treatment followed the manufacturer's recommendations.

The placebo patch (Leukomed T®) was not identical to the nicotine patch, but chosen since it did resemble a medication-type patch. It was packed into packages each containing 56 patches without the trade name. The nicotine patch was removed from its original packaging, and replaced into boxes also containing 56 patches. The trade name of the nicotine patch was printed on the patches. Each subject was recommended to change the patch daily. Varenicline (Champix®) was supplied in the original package.

4.2.6 Outcome assessment (IV)

Study IV compared the efficacy of placebo patches to 10mg/16h nicotine patches in young adult light smokers, and on the other hand, 15mg/16h nicotine patches to varenicline in young adult heavy smokers. Smoking abstinence at 4, 12 and 26 weeks was recorded if the subject reported that he/she had quit smoking and had not smoked for about one week. The primary outcome variable in study IV was self-reported smoking abstinence at week 12 i.e. after the treatment period. Secondary outcome variables were self-reported smoking abstinence at 4 and 26 weeks, and self-reported smoking abstinence as verified by saliva cotinine level ≤10 ng/ml (Cooke *et al.* 2008, Montalto & Wells 2007) at week 12.

4.2.7 Statistical methods (IV)

All statistical analyses were conducted using IBM SPSS Statistics version 21 software. The distribution of categorical variables between the study groups was compared with cross-tabulation. The difference between the observed proportions of abstinence (with 95% CI) in the study groups was used as the effect size measure. The statistical significances of differences in tobacco abstinence rates (primary and secondary outcomes) and compliance were further evaluated with chi-square test. Distributions of body height, smoking initiation age, the duration of smoking and HSI-points between the study groups were compared using mean values and standard deviations. Because of the right-skewed distribution, the study groups were compared in terms of age, body weight, BMI, motivation to quit smoking and number of daily cigarettes with medians and interquartile ranges. Those subjects who were lost to follow-up were considered as continuing

to smoke. If a subject missed a control visit, but attended subsequent controls, his/her smoking status at the missed control was assumed to be the same as that recorded at the next time when he/she came to the control session. All randomised subjects were analysed according to the intent-to-treat principle.

4.2.8 Ethics (IV)

The study was approved by the Ethical Committee of the Northern Ostrobothnia Hospital District. All subjects provided written informed consent.

5 Results

5.1 Tobacco use habits in young adults in Northern Finland

5.1.1 Subject characteristics and smoking in the study of military recruits (I, III)

The final study population consisted of a total number of 1130 male subjects (study I). The mean age of the study population was 19.4 years (min 18, max 25); of the 1130 subjects, 525 (46.5%) were daily smokers, 197 (17.4%) occasional smokers and 408 (36.1%) non-smokers. There was also a small group of ex-smokers (n=33 in study I and n=27 in study III).

The median pack year in daily smokers was 3.6 (IQR 4.0). Approximately 10% of them had already smoked at least 10 pack years. The mean age to start the smoking habit was 14.6 years in daily smokers with a normal distribution (SD 2.1). In occasional smokers who reported the age when they had initiated smoking (n=79), the distribution was left-skewed with median of 16.0 years (IQR 3.0).

The mean age did not differ statistically significantly between the smoking groups (F-test p=0.196): the mean age for non- and occasional smokers was 19.4 years (SD 0.8 and 0.6) and for daily smokers 19.5 years (SD 0.9) (study I). Furthermore, mean age did not differ significantly between the snus use groups (study III): the mean age for those with no snus use or occasional snus use was 19.4 years (SD 0.9 and 0.7), and 19.5 years (SD 0.9) for daily snus users (F-test p=0.507).

Smokers had generally lower education than non-smokers: smokers had less commonly graduated from high school or had an academic degree and more frequently had completed vocational school or only compulsory school than non-smokers (Figure 3; chi-square test $p<0.001$).

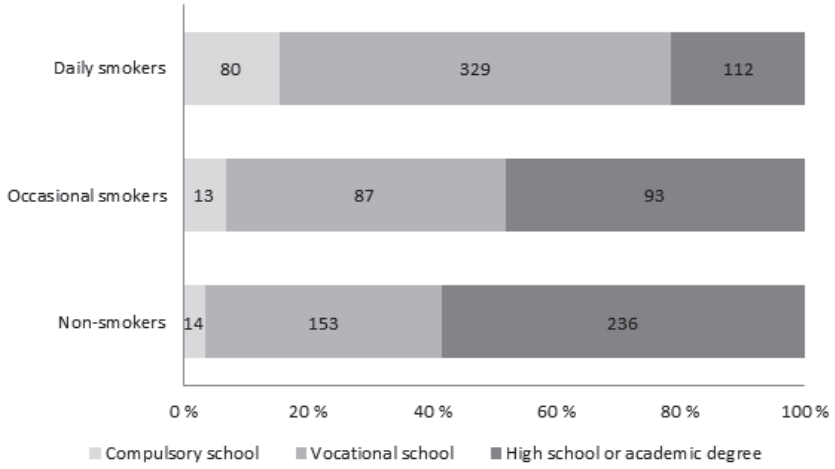

Fig. 3. Education according to smoking status in a study of young military recruits.

Furthermore, snus use seemed to be related to a lower educational level (Figure 4; chi-square test $p<0.001$): those who had not used snus were more often high school graduates or had an academic degree (52.6%) compared to individuals who were daily or occasional snus users (33.0% and 30.8%).

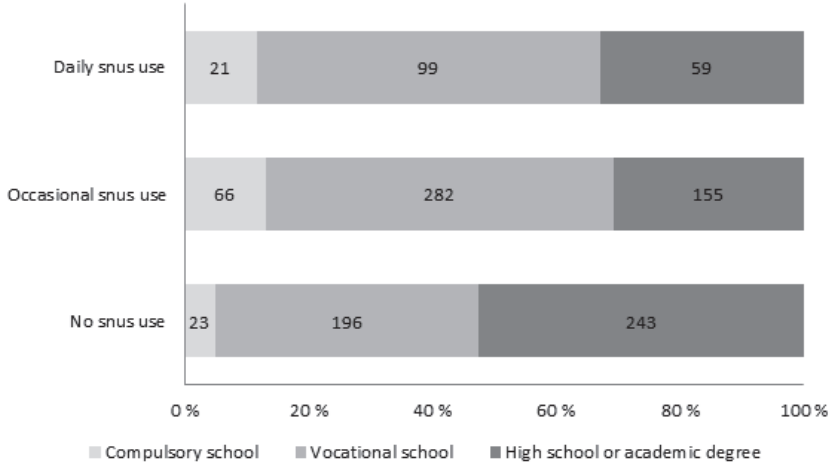

Fig. 4. Education in snus use subgroups.

5.1.2 Snus use among military recruits (III)

Figure 5 presents the distribution of snus use according to the severity of the smoking habit. As many as 15.6% of male military recruits reported daily snus use, and 6.9% were dual users i.e. they consumed both products on a daily basis. Daily snus use was common among smokers: 15.1% of daily smokers and 30.1% of occasional smokers used snus on a daily basis. In comparison, 7.8% of non-smokers used snus daily, while most of them did not use snus (77.2%). The prevalence with no snus use was remarkably lower among smokers (18.5-24.4%) and ex-smokers (22.2%). In the small group of former smokers (n=27), as many as 37.0% were using snus on a daily basis.

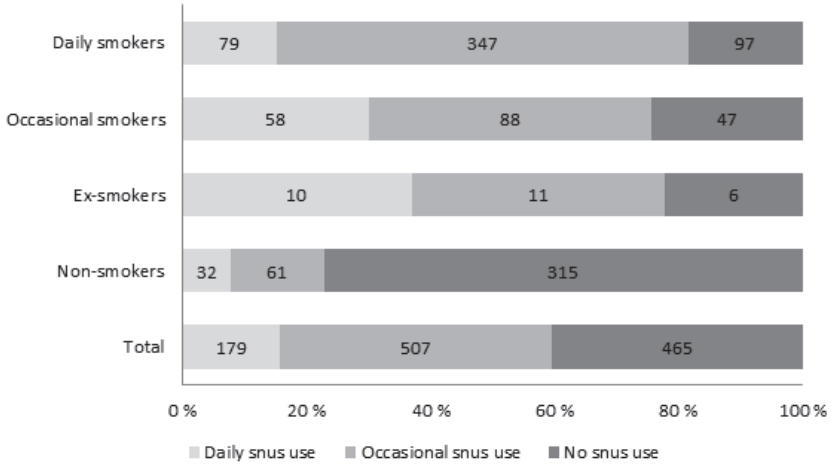

Fig. 5. Distribution of snus use according to smoking status.

5.2 Health and lifestyle related to tobacco use in young adults

5.2.1 Anthropometric measures in tobacco users (I, III)

Anthropometric measures in smoking subgroups

Table 1 presents the anthropometric measures in the smoking subgroups. Mean height and mean body weight were similar in daily, occasional and non-smokers, but the BMI was statistically significantly greater in daily smokers than in non-

smokers (p=0.035). Instead, the BMI of non-smokers and occasional smokers did not differ significantly from each other. BMI did not correlate with daily tobacco usage or calendar years of smoking, but BMI had a weak positive correlation with pack years [r(s) =0.103, p=0.022, weak visual positive correlation].

Table 1. Anthropometric measures according to smoking status.

Parameters	Daily smokers			Occasional smokers			Non-smokers			Total			P-value[1]
	n	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD	
Height (cm)	524	177.9	6.8	196	178.3	6.4	408	178.0	6.3	1128	178.0	6.5	0.723
Weight (kg)	523	74.7	10.3	197	74.7	9.8	408	73.4	9.6	1128	74.2	9.9	0.118
BMI (kg/m^2)	523	23.6	2.7	196	23.5	2.6	408	23.1	2.5	1127	23.4	2.6	0.042[2]

[1]P-value of F-test (One-way ANOVA). [2]Daily smokers compared to non-smokers Tukey's post-hoc test p=0.035.

Anthropometric measures in snus use groups

Table 2 presents the anthropometric measures according to snus use. The snus use subgroups had statistically insignificant differences in body height, but the differences were statistically significant with respect to body weight and BMI: daily snus users were heavier than occasional snus users (p=0.048), and the difference was even more significant when daily snus users were compared to those with no snus use (p=0.002). In addition, the value of BMI in daily snus users was higher than that of occasional snus users (p=0.018), or those with no snus use in their history (p<0.001).

Table 2. Anthropometric measures in snus use subgroups.

Parameters	Daily snus use			Occasional snus use			No snus use			Total			P-value[1]
	n	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD	
Height (cm)	179	177.8	6.1	505	177.8	6.7	465	178.1	6.5	1149	178.0	6.5	0.786
Weight (kg)	179	76.3	10.7	506	74.3	10.2	464	73.3	9.3	1149	74.2	9.9	0.002[2,3]
BMI (kg/m^2)	179	24.1	2.7	505	23.5	2.7	464	23.1	2.5	1148	23.4	2.6	<0.001[4,5]

[1]P-value of F-test (One-way ANOVA). [2]Daily vs. occasional snus use Tukey's test p=0.048. [3]Daily vs. no snus use Tukey's test p=0.002. [4]Daily vs. occasional snus use Tukey's test p=0.018. [5]Daily vs. no snus use Tukey's test p<0.001.

5.2.2 Activity in sports and physical fitness in smokers (I)

Physical activity differed statistically significantly between the smoking subgroups (Table 3). Daily smokers were statistically significantly less active in sports than non-smokers. Among the daily smokers, the median of pack years was 2.78 with subjects defined as 'Active', 3.6 for 'Moderate' and 4.50 for 'Passive'. The median of daily amount of tobacco was 14.0 for 'Active', 16.0 for 'Moderate', and 20.0 for 'Passive'. The median of years of smoking was 4.0 for 'Active', 4.0 for 'Moderate', and 5.0 for 'Passive' (K-W test p-value for all three variables <0.001). Therefore, the more active the subjects were, the less they smoked daily and the fewer were their smoking years and pack years in their history.

Table 3. Activity in sports according to smoking status.

Activity in	Daily smokers		Occasional smokers		Non-smokers		Total	
sports	n	%	n	%	n	%	n	%
Active	168	32.4	96	48.7	210	52.0	474	42.3
Moderate	155	29.9	61	31.0	82	20.3	298	26.6
Passive	196	37.8	40	20.3	112	27.7	348	31.1
Total	519	100.0	197	100.0	404	100.0	1120	100.0

Chi-square test p<0.001.

Smoking seemed to have impaired the physical fitness in these young military recruits: the performance of daily smokers in the Cooper's test was worse than their occasionally or non-smoking counterparts (Table 4, p<0.001). The mean results of occasional smokers and non-smokers did not differ statistically significantly.

Table 4. Cooper's test result in metres according to smoking group.

Cooper's	Daily smoker			Occasional smoker			Non-smoker			Total		
test result	n	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD
Metres	508	2376.6	405.0	188	2510.7	325.5	396	2537.1	355.4	1092	2457.9	382.0

One-way ANOVA F-test p<0.001: Daily vs. occasional smokers Tukey's test p<0.001. Daily vs. non-smokers Tukey's test p<0.001.

The linear regression analysis revealed that smoking and BMI were negatively correlated with the distance covered in the running test (Table 5). As expected, the more active that the subjects were in sports, the better was the test result.

Education also had a strong positive association with test performance –the result was better in subjects who had graduated from high school or had an academic degree than in those who had graduated from vocational school or only compulsory school. The strongest influence was noted for the physical activity, the next being education and the third with smoking and BMI, with the last two factors having similar magnitudes of effect. The extent of collinearity between explanatory variables was not high as estimated by the VIF statistic.

Table 5. Results of linear regression analysis with Cooper's test result (m) as dependent variable (I, published by permission of Informa Healthcare).

Parameters	Unstandardized coefficients		P-value	Collinearity statistics
	B	SE		VIF
(Constant)	2975.2	244.6	<0.001	
Smoking	-33.1	11.6	0.004	1.2
Activity in sports	198.0	11.9	<0.001	1.1
BMI	-37.0	3.7	<0.001	1.0
Education	70.5	21.7	0.001	1.2
Age	7.1	12.2	0.56	1.0

The mean distance covered in the Cooper's test did not correlate to daily grams of tobacco or smoking years in daily smokers, but there was a weak negative relation to the pack years ($r(s)=-0.113$, $p=0.013$) i.e. the more pack years in their history, the shorter distance they ran in the Cooper's test.

5.2.3 Symptoms of chronic bronchitis (I)

Table 6 lists the symptoms of CB in the subgroups of smokers. Symptoms were frequent and the groups differed statistically significantly: they were more common in daily smokers than in occasional smokers (40.7% vs. 26.9%), and least common in non-smokers (12.0 %; $p<0.001$). The difference between the smoking subgroups remained highly significant ($p<0.001$) after taking into account the potential confounders (BMI, age, education, physical activity) in the multinomial logistic regression analysis.

Table 6. Answer to the question: 'Have you had cough with sputum production on most days or nights for at least three months yearly?' in smoking subgroups.

Symptoms of chronic bronchitis	Daily smokers		Occasional smokers		Non-smokers		Total	
	n	%	n	%	n	%	n	%
'Yes'	212	40.7	53	26.9	49	12.0	314	27.9
'No'	187	35.9	116	58.9	308	75.7	611	54.3
'I do not know'	122	23.4	28	14.2	50	12.3	200	17.8
Total	521	100.0	197	100.0	407	100.0	1125	100.0

Chi-square test p<0.001.

Table 7 presents medians of daily tobacco (g), years of smoking and pack years in daily smokers according to the symptoms of CB. Those daily smokers reporting to have symptoms of CB had statistically significantly higher daily tobacco consumption (daily tobacco grams), more years of smoking and more pack years in their history.

Table 7. Medians of daily tobacco amount, smoking years and pack years according to the question's answer 'Have you had cough with sputum production on most days or nights for at least 3 months yearly?' in daily smokers.

Smoking values	'Yes'			'No'			'I do not know'			Total			P-value[1]
	n	median	IQR	n	median	IQR	n	median	IQR	n	median	IQR	
Daily tobacco (g)	202	18	11.3	181	15	10.0	117	16	14.5	500	15	10.0	<0.001
Smoking years	211	5.0	3.0	185	4.0	3.0	121	4.0	3.0	517	5.0	3.0	0.007
Pack years	201	4.5	4.6	179	3.0	4.1	116	3.85	4.0	496	3.6	4.0	<0.001

[1]Kruskal-Wallis test p-value.

Among non-smokers, 22.4% (n=91/406) had had daily exposure to ETS. Of these exposed non-smokers, only six had one to five hours of exposure daily and none had had more than 5 hours of exposure. The prevalence of symptoms of CB in exposed non-smokers did not differ significantly from non-exposed non-smokers (chi-square test p=0.625).

5.3 Nicotine dependence and motivation to quit smoking

5.3.1 Nicotine dependence and quit attempts in smokers (II)

Nearly all daily smokers (95.3%; 95% CI 93.1-96.8) felt that they were nicotine dependent to some extent, and the majority of them (71.4%; 95% CI 67.3-75.2) had moderate to very strong nicotine dependence according to the HSI (2-6 points). The majority of daily smokers (55.4%) had tried to quit smoking. The stronger the feeling of nicotine dependence, the more likely the individual had tried to quit (chi-square test p=0.022): even 40.0% of those who did not feel themselves dependent on nicotine at all had tried to quit, although this was less than the 65.6% of those totally agreeing that they were nicotine dependent. In contrast, those daily smokers who had tried to quit did not differ statistically significantly in terms of HSI (chi-square test p=0.572), the time of smoking the first cigarette in the morning (chi-square test p=0.915) or pack years in history (chi-square test p=0.147) from those daily smokers who had not tried to quit smoking.

5.3.2 Nicotine dependence and quit attempts in snus users (III)

About one in six (18.2%) of daily snus users claimed that they had no dependence on snus, but 35.3% perceived that they had mild dependence, 34.1% had moderate and 12.4% strong dependence on snus. Occasional smokers who used snus on a daily basis were more likely to suffer from moderate to strong dependence to snus (60.3%) than non- or daily smokers with daily snus use (35.5% and 38.9%).

The influence of snus use on cigarette consumption and dependence in cigarette smokers was also analysed. Daily smokers who also used snus daily in fact smoked a similar number of cigarettes per day as the other daily smokers: the median value in daily tobacco grams smoked was 15.5 (IQR 10) in those daily smokers who used snus daily compared to 15.0 (IQR 10) in those with occasional snus use or with no snus use (K-W test p=0.452). Figures 6 and 7 describe the distribution of the first cigarette in the morning and HSI, and figure 8 describes the number of previous unsuccessful quit attempts in daily smokers according to their snus use habits. None of these three variables correlated statistically significantly with the snus use habit in daily smokers. However, some trends of specific interest were noted. For example, dual daily users seemed to be more

likely to smoke their first cigarette in the morning within 30 minutes compared to smokers without snus use (49.4% vs. 39.4%; Figure 6). This was reflected also in HSI: it seemed that dual daily users had less often mild dependence in HSI grading than daily smokers without snus use (HSI 0-1 30.7% vs. 37.1%; Figure 7). In addition, dual daily users had less commonly attempted to quit smoking than smokers without snus use (51.5% vs. 64.9%, chi-square test p=0.147). Among those who had tried to quit, dual users seemed to have had a higher number of unsuccessful quit attempts (≥5 quit attempts 18.6% vs. 9.1%; Figure 8, p=0.725). In all, these findings might indicate that dual users were more dependent on nicotine than exclusive smokers although the differences did not reach statistical significance in this study.

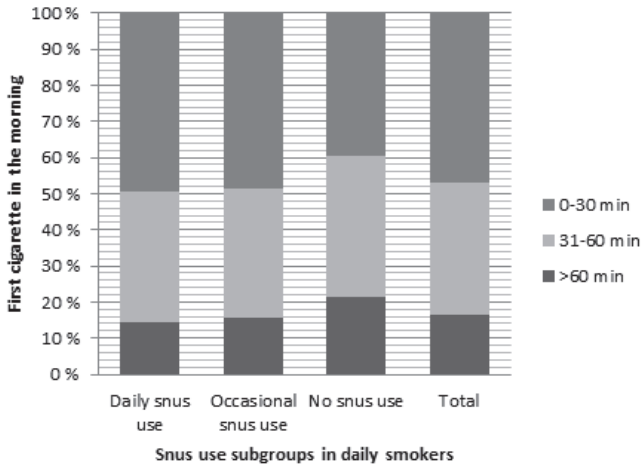

Fig. 6. First cigarette in the morning according to snus use in daily smokers. Chi-square test p=0.492.

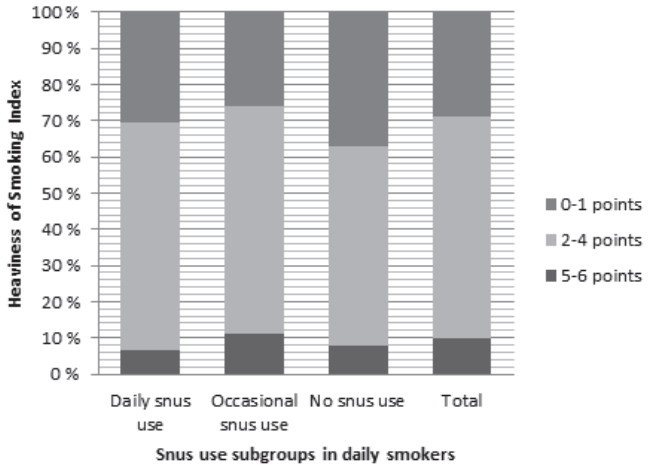

Fig. 7. Heaviness of Smoking Index according to snus use in daily smokers. Chi-square test p=0.244.

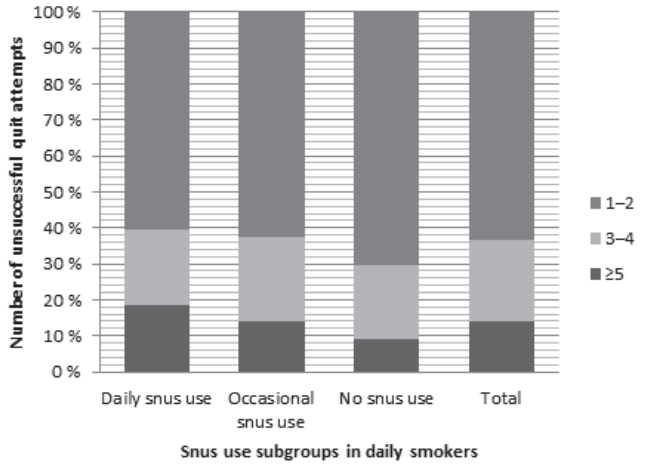

Fig. 8. Number of previous unsuccessful quit attempts according to snus use in daily smokers. Chi-square test p=0.725.

5.4 Smoking cessation pharmacotherapy use in young adult smokers (II)

The majority of daily young adult male smokers had tried to quit smoking in study II, 47.2% (n=146) of those who had previously tried to quit smoking had utilized some pharmacological aid for that purpose: two of them had used bupropion and all others NRT in its different forms. None of them reported having used varenicline during their previous smoking cessation attempts. Those who had experimented with some kind of pharmacological therapy in their previous attempt to quit smoking were more likely to smoke earlier in the morning (chi-square test $p=0.026$), to have more pack years in history (chi-square test $p=0.002$), to have had more quit attempts in their smoking history (chi-square test $p=0.025$) and to feel themselves dependent on nicotine (chi-square test $p<0.001$), but HSI did not differ significantly in terms of previously having experimented with smoking cessation pharmacological therapy or not (chi-square test $p=0.085$).

5.5 Effectiveness and safety of varenicline and nicotine patch in smoking cessation of young adults

5.5.1 Subject characteristics in the prospective study of young adults (IV)

In the follow-up study of voluntary daily smokers (study IV), a total of 416 young adults were recruited: 102 were now non-smokers and 314 were daily smokers. Twenty-three smokers had to be excluded from the analysis and were not randomised: one subject had quit smoking before randomisation, one had moved to another city, one was lost early to follow-up, and 20 subjects had a daily use of some psychiatric medicine.

From the 291 randomised and analysed subjects, three subjects were not treated with study medication: one subject who was randomised to nicotine patch 15mg/16h refused to use NRT, one subject in nicotine patch 15mg/16h did not arrive for the first counselling visit where study medication was scheduled to be started as randomised, and one subject was not treated for some undetermined reason. Therefore, a total number of 288 daily smokers were treated. Because the study followed the intent-to-treat principle, all randomised subjects were analysed (n=291).

Table 8 describes the participation rate of the subjects during the study contacts of the 26 weeks' follow-up. The participation rate at the end of the follow-up was 75.9%. If a subject did not come for the control or answer to the nurse phone call at once, the study nurse tried to call repeatedly and finally tried to contact the subject via e-mail. Some of the subjects did not attend the study controls, but reported some specific reason for non-attendance to study nurse via phone or e-mail. The specific reasons were as follows: being abroad (n=2), illness (n=2), being in another city (n=1), moved to other city (n=2), and lack of motivation (n=4). The remainder, who were not contacted even after repeated phone calls or e-mail, were lost to follow-up.

Table 8. Participation to counselling visits and phone call controls during the 26 weeks follow-up by study group.

Study control	Placebo patch		Nicotine patch 10mg/16h		Nicotine patch 15mg/16h		Varenicline		Total	
	n	%	n	%	n	%	n	%	n	%
Baseline										
Visit	86	100.0	94	100.0	51	100.0	60	100.0	291	100.0
Week 0										
Visit	86	100.0	93	99.0	49	96.1	60	100.0	288	99.0
Week 4										
Phone call	78	90.7	88	93.6	45	88.2	60	100.0	271	93.1
Lost to follow-up	8	9.3	5	5.3	4	7.8	0	0.0	17	5.8
Week 12										
Visit	43	50.0	53	56.4	23	45.1	38	63.3	157	54.0
Phone call	22	25.6	21	22.3	13	25.5	13	21.7	69	23.7
Lost to follow-up	19	22.1	14	14.9	13	25.5	8	13.3	54	18.6
Non-attendance	2	2.3	5	5.3	0	0.0	1	1.7	8	2.7
Week 26										
Phone call	64	74.4	75	79.8	38	74.5	44	73.3	221	75.9
Lost to follow-up	22	25.6	15	16.0	9	17.6	15	25.0	61	21.0
Non-attendance	0	0.0	3	3.2	2	3.9	1	1.7	6	2.1

Tables 9a and 9b describe the characteristics of the subjects in the four study treatment groups. The median age was 21. The study groups were similar in terms of age, weight, BMI, height, baseline motivation to quit smoking, proportion of female sex, and educational level (Table 9a and 9b; Figure 9 and 10). In contrast, heavy smokers seemed to have more years of smoking in their history and had

begun to smoke at a younger age than light smokers (Table 9b). As expected, heavy smokers smoked generally more cigarettes daily and had more severe dependence according to HSI compared to light smokers (Table 9a and 9b).

Table 9a. Subject characteristics of study groups in the prospective study of young adult smokers motivated to quit smoking (IV, published by permission of John Wiley & Sons Ltd.).

Parameters	Placebo patch n=86		Nicotine patch 10mg/16h n=94		Nicotine patch 15mg/16h n=51		Varenicline n=60		Total n=291	
	median	IQR	median	IQR	median	IQR	median	IQR	median	IQR
Age (years)	20.0	18.0-23.3	21.0	19.0-23.0	22.0	19.0-24.0	21.0	19.0-23.8	21.0	19.0-23.0
Weight (kg)	70.1	61.0-82.7	70.5	62.0-78.2	71.2	61.5-82.9	72.6	62.2-79.7	70.7	61.7-80.5
BMI (kg/m^2)	24.4	21.4-27.2	24.0	21.3-27.4	24.7	21.0-28.3	24.0	22.0-27.0	24.0	21.4-27.5
Baseline motivation to quit (1-10)[1]	8.0	7.0-8.0	7.0	6.0-8.0	7.0	6.0-8.0	7.0	6.0-8.0	7.0	6.0-8.0
Number of daily cigarettes	10	8.0-15.0	10	7.0-14.3	18	15.0-20.0	18	15.0-20.0	14	10.0-20.0

BMI=body mass index; IQR=interquartile range. [1]Two missing values in nicotine patch 15mg/16h group.

Table 9b. Subject characteristics of study groups in the prospective study of young adult smokers motivated to quit smoking (IV, published by permission of John Wiley & Sons Ltd.).

Parameters	Placebo patch n=86		Nicotine patch 10mg/16h n=94		Nicotine patch 15mg/16h n=51		Varenicline n=60		Total n=291	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
Height (cm)	170.6	8.7	170.1	8.9	171.7	10.3	169.9	7.8	170.5	8.9
Smoking initiation age (years)	14.8	2.3	15.3	2.0	14.4	2.0	14.1	1.9	14.7	2.1
Duration of smoking (years)	5.8	3.1	5.9	3.0	7.0	2.7	7.3	2.8	6.4	3.0
HSI (points)	1.3	0.8	1.3	0.8	3.3	0.9	3.5	0.7	2.1	1.3

HSI=Heaviness of smoking index; SD=standard deviation.

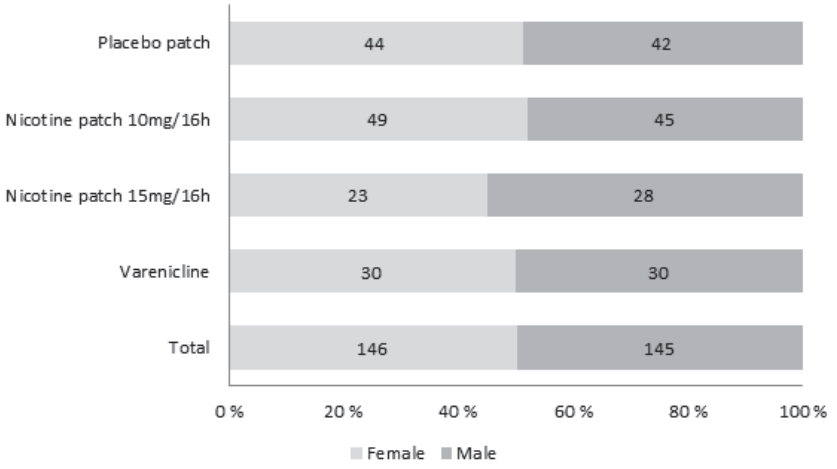

Fig. 9. Distribution of genders in four study groups of young adult smokers.

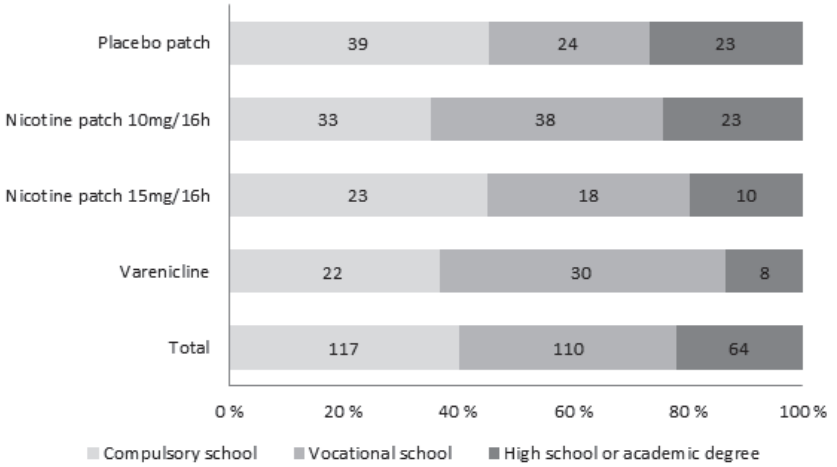

Fig. 10. Education in four study groups of young adult smokers.

5.5.2 Self-reported smoking abstinence rates during the 26 weeks' follow-up (IV)

Self-reported abstinence at week 4

Figure 11 presents smoking abstinence rate at week 4. A total of 96 (33.0%) subjects had quit smoking. There were no statistically significant differences in the abstinence rates between the two following groups of light smokers- placebo and nicotine patch 10mg/16h [p=0.296; effect size 6.8% (95% CI -5.6 to 18.8)], but varenicline was significantly more effective than nicotine patch 15mg/16h treatment in heavy smokers at this time point [p<0.001; effect size 53.7% (95% CI 35.9 to 66.6)]. The smoking abstinence rates at week 4 were as follows: placebo patch group 19.8%; nicotine patch 10mg/16h 26.6%; nicotine patch 15mg/16h 19.6%; varenicline 73.3%.

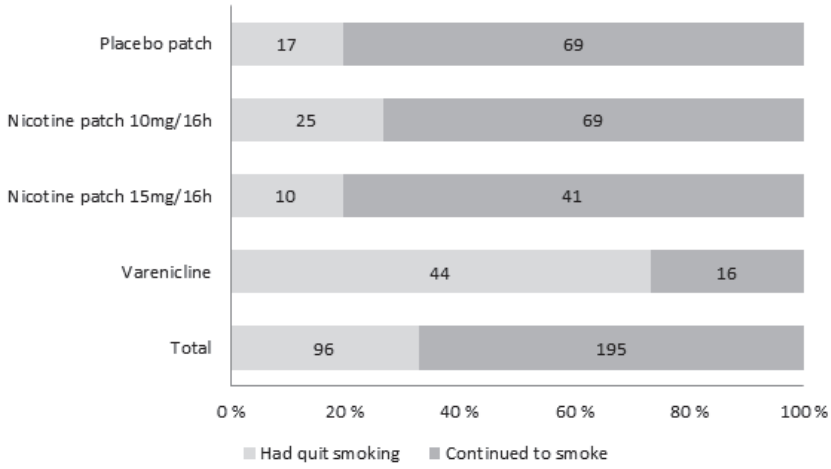

Fig. 11. Distribution of the outcome variable (self-reported smoking abstinence) at week 4 by study groups. Placebo vs. nicotine patch 10mg/16h p=0.296. Nicotine patch 15mg/16h vs. varenicline p<0.001.

Self-reported abstinence at week 12

Figure 12 presents smoking abstinence rates at week 12. A total of 67 (23.0%) had quit smoking. There were no statistically significant differences between the treatment groups of light smokers in self-reported smoking abstinence [17.4-

23.4%; p=0.360; effect size 6.0% (-6.0 to 17.5)], but the differences were significant between the groups of heavy smokers [p=0.018; effect size 21.0% (95% CI 4.4 to 25.7)]: in the varenicline group 36.7% had been successful in achieving smoking abstinence whereas those treated with the nicotine patch 15mg/16h displayed a significantly lower smoking abstinence rate, 15.7%.

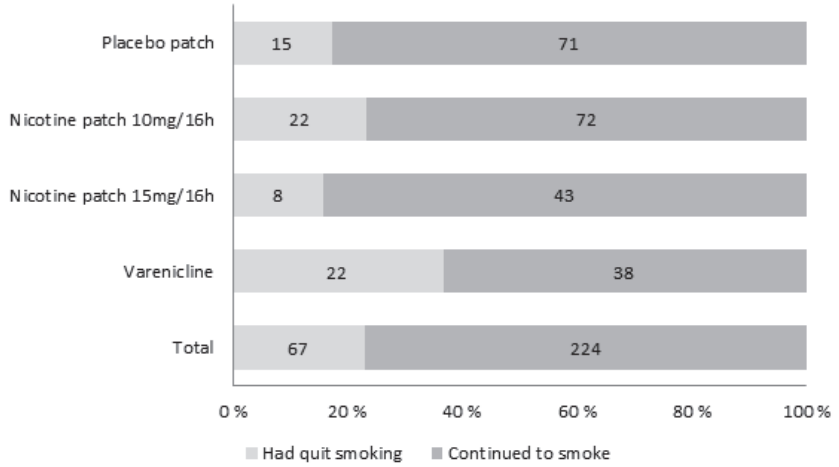

Fig. 12. Distribution of the outcome variable (self-reported smoking abstinence) at week 12 by study groups. Placebo vs. nicotine patch 10mg/16h p=0.360. Nicotine patch 15mg/16h vs. varenicline p=0.018.

Self-reported abstinence at week 26

Figure 13 shows the smoking abstinence rates at week 26 as subdivided by the study groups. At this control point, 48 (16.5% had) quit smoking. The group specific smoking abstinence rates were as follows: placebo patch 15.1%; nicotine patch 10mg/16h 20.2%; nicotine patch 15mg/16h 9.8%; varenicline 18.3%, and there were no statistically significant differences between the two groups of light [p=0.437; effect size 5.1% (95% CI -6.3 to 16.1)] or heavy smokers [p=0.280; effect size 8.5% (95% CI -5.1 to 21.4].

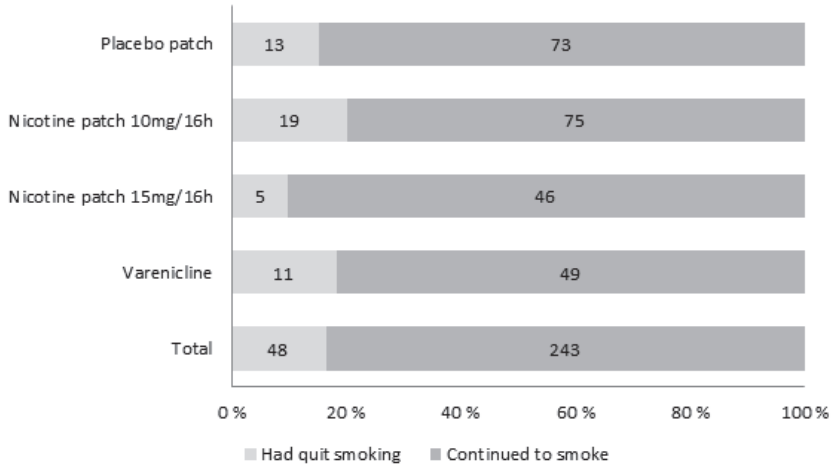

Fig. 13. Distribution of the outcome variable (self-reported smoking abstinence) at week 26 in the different study groups. Placebo vs. nicotine patch 10mg/16h p=0.437. Nicotine patch 15mg/16h vs. varenicline p=0.280.

5.5.3 Smoking abstinence verified by saliva cotinine test with additional eCO-level assessment after the treatment (week 12) (IV)

Out of a total of 67 smoking abstinent subjects, 52 (77.6%) came to the counselling visit conducted on week 12. Saliva cotinine was measured from 50 of these subjects. Four subjects reported using NG at the time of the saliva cotinine measurement and two spontaneously reported having been recently exposed to ETS although exposure to ETS was not specifically asked at the 12 week control session. Fourteen subjects participating in the 12 week control visit reported that they had quit smoking but were using snus, although often infrequently. The eCO level was measured in 11 of these 14 snus users, all had eCO levels ≤5ppm confirming their self-reported abstinence of smoking.

Therefore, 30 self-reporting smoking abstinent subjects did not report any confounding factor which could have interfered with the saliva cotinine assay. Nonetheless, self-reported smoking abstinence poorly correlated with measures of saliva cotinine. Only 7 subjects had self-reported smoking abstinence confirmed by saliva cotinine level ≤10ng/ml: two subjects in placebo group, one in nicotine patch 10mg/16h group, one in the nicotine patch 15mg/16h group, and three in

the varenicline group. A low-positive (10-30ng/ml) was measured in 20 of these subjects. Three subjects exhibited a clearly positive saliva cotinine test value (30-100ng/ml n=2; 100-200ng/ml n=1). The eCO level was measured in eight low-positive subjects and one with a definite positive test result (saliva cotinine 30-100ng/ml), and all had eCO level ≤5ppm supporting their self-reported smoking abstinence.

5.5.4 Compliance, adverse events and safety (IV)

The most compliant group was the subjects receiving varenicline: 76.7% used the drug for over two weeks and 20.0% completed the treatment. The corresponding numbers for placebo patch were 36.1% and 10.5%, for nicotine patch 10mg/16h 51.1% and 21.3%, and for nicotine patch 15mg/16h 37.3% and 9.8%. The varenicline group was statistically significantly more compliant than nicotine patch 15mg/16h group (chi-square exact test $p<0.001$). There were no statistically significant differences in terms of compliance between the placebo and nicotine 10mg/16h patch groups (chi-square exact test $p=0.136$).

The majority of varenicline users (60.0%) reported experiencing some degree of adverse events, but most of them did not stop using the medicine because of suffering an adverse event. However, treatment discontinuations were most common in the varenicline group (13.3% for varenicline group, 5.9-8.5% for nicotine patch groups, and 3.5% for placebo group; Table 10). Adverse events were less common in those in nicotine patch (27.7-31.4%) and placebo groups (17.4%). No serious adverse events were reported.

Table 10. Reported adverse events 4 weeks after beginning of the smoking cessation pharmacotherapy and adverse events leading to discontinuation of the treatment.

Adverse events	Placebo patch		Nicotine patch 10mg/16h		Nicotine patch 15mg/16h		Varenicline	
	n	%	n	%	n	%	n	%
Any adverse event	15	17.4	26	27.7	16	31.4	36	60.0
Nausea	1	1.2	5	5.3	1	2.0	25	41.7
Abnormal dreams	-		-		-		11	18.3
Abdominal pain	-		-		-		5	8.3
Cutaneous irritation	7	8.1	19	20.2	8	15.7	1	1.7
Pain at the side of the patch	-		2	2.1	3	5.9	-	
Nervousness	6	7.0	-		-		-	
Paraesthesia	-		1	1.0	2	3.9	-	
Insomnia	3	3.5	-		-		4	6.7
Other	11	12.8	2	2.1	3	5.9	13	21.7
Adverse event leading to discontinuation of the treatment	3	3.5	8	8.5	3	5.9	8	13.3
Nausea	-		-		-		6	10.0
Shift of moods	-		-		-		1	1.7
Abdominal pain	-		-		-		1	1.7
Cutaneous irritation	2	2.3	7	7.4	3	5.9	-	
Pain at the site of the patch	-		1	1.0	-		-	
Unsteady feeling	1	1.2	-		-		-	

5.6 Summary of the main results

The main study findings related to the designated aims were:

1. There was a high prevalence of young adult males in northern parts of Finland that use tobacco products, and a notable part of these young men are dual users of cigarettes and snus.
2. Smoking was related to lower education, higher BMI, physical inactivity and impaired physical fitness as well as a high prevalence of symptoms of chronic bronchitis among young adult males.
3. They had generally a high nicotine dependence level, and dual users seemed to be a subgroup of smokers that were even more nicotine dependent than exclusive smokers. The majority of them had tried to quit smoking.
4. Smoking cessation pharmacotherapies are underused by young adult smokers trying to quit. Varenicline may be effective in helping them in their attempts to quit smoking.

6 Discussion

6.1 Major findings of the studies

6.1.1 Tobacco use habits in young adult males in northern parts of Finland (I, III)

In the present study, the mean age when the subjects started to smoke was 15 years corresponding to the national estimates (Kinnunen *et al.* 2015), but the number of daily smokers was relatively high: 47% in our study of young adult males from northern parts of Finland vs. 28% of 18 years old males in a nationwide survey study conducted in the same year i.e. 2009 (Kinnunen *et al.* 2015). This may indicate that there is greater variability in smoking habits of adolescents and young adults in different parts of the country than previously estimated (Luopa *et al.* 2014). In comparison, Mattila *et al*. (2012) analysed data obtained from the nationwide Finnish Conscript Health Survey for the years 1999 to 2010; they found that the percentage of smokers in 2010 was 48% in this national sample of military recruits when not only daily smokers but also occasional smokers were taken into account. In the present study, as many as 64% of military recruits were either occasional or daily smokers. The differences in definitions of smoking groups may not fully explain the differences in the prevalence of smoking. It may also reflect the variability in smoking habits of young adults inside the country, but also raises question of whether undertaking national service in the army may increase the smoking prevalence in males. In any case, it is clear that a significant number of military recruits are exposed to highly addictive nicotine.

Recent estimates reveal that the prevalence of smoking in young adolescents and young adults has decreased remarkably: in the past 10 years, the habit of daily smoking has decreased by 16 percentage points in 18-year-old males and by 18 percentage points in females at the same age (Kinnunen *et al.* 2015). However, it is concerning that at the same time, more and more young people seem to be adopting the use of alternate nicotine-containing substances such as snus and electronic cigarettes (Kinnunen *et al.* 2015). In the present study, snus use was relatively common: as many as 16% of young male adults in Northern Finland were consuming snus daily in 2009. National estimates for daily snus use at the time as the present study were considerably lower for 18-year-old males, about

2% (Rainio *et al.* 2009). In addition, the number is relatively high when compared to the national sample of military recruits (Mattila *et al.* 2012) in which 20% of the recruits reported occasional or daily snus use in 2010. The authors did not report the number of daily snus use separately from occasional use, instead they combined these groups, because the number of daily snus users was considered to be low. One reason for the relatively high number of daily snus use is that in northern parts of Finland snus is readily available due to the close access to the Swedish border where sales of snus are not banned. It is also possible that being in the army somehow influences the use of snus to some extent, but this cannot fully explain the difference when the findings of Mattila *et al.* are taken into consideration. On the other hand, the present response rate was relatively high (80%) compared to that of National Health and Lifestyle Survey study (38% to 56% between years 2009 and 2015) (Kinnunen *et al.* 2015), and therefore the risk for underestimating the prevalence of tobacco use might be lower.

The dual use of cigarettes and snus was common among male recruits: only 20% of smokers had experimented with snus not more than on one occasion, and a significant number, 7%, were using both cigarettes and snus on a daily basis. If one compares the results to the neighbouring country Sweden, then 22% of Swedish 16-29-year-old men used snus daily but the number of daily dual users was lower than here: only 2% were daily dual users of snus and cigarettes according to the Swedish National Institute of Public Health in 2009 (Folkshälsomyndigheten 2015). Swedish tobacco use habits are somewhat exceptional since the country has a long tradition of snus use, a relatively large number of snus users and on the other hand, a low number of daily smokers also in the younger age groups. Nonetheless, the relatively large numbers of dual users of snus and cigarettes among young have raised concerns also in Norway (Lund *et al.* 2011), the U.S (Tomar *et al.* 2010) and Switzerland (Henninger *et al.* 2015), but also among Swedish youth (Galanti *et al.* 2001b). Accordingly, snus use does not seem to primarily act as a smoking cessation aid in young males either in these countries or in Finland.

Association of tobacco use and education

In the present study group of young military recruits, not only smoking, but also snus use was more common in military recruits with a lower educational level. A previous Finnish study detected a similar association of smoking, i.e. being more common among youngsters in compulsory schools than in vocational or high

schools (Luopa *et al.* 2014). In fact, smoking has been related to lower socioeconomic status not only in Finland, but in several other westerns countries (Hanson & Chen 2007). In agreement with the present results, snus use (exclusive and dual use) was also associated with a lower educational level in a Swedish study of adults (Engstrom *et al.* 2010). In a Norwegian study, adolescents' and young adults' exclusive snus use was not associated with education, but dual use did associate with schooling – and furthermore exclusive smokers were the most likely to be less educated (Overland *et al.* 2010). As a result of these findings, tobacco related disease especially that of smoking, can be expected to cluster in individuals with lower socioeconomic status also in the future if these young people continue to smoke during their adult life. This is unfortunately likely to generate inequality in Finnish society.

6.1.2 Impaired physical fitness and symptoms of chronic bronchitis in young adult smokers (I, III)

Elevated body mass index and inactive lifestyle in young adult tobacco users

Mean body height did not seem to associate with smoking or snus use habit in this study. Previous prospective reports (Fidler *et al.* 2007, O'Loughlin *et al.* 2008, Stice & Martinez 2005) on the association of linear growth and smoking have included mainly 11 to 17 years old adolescents with relatively small numbers of daily smokers, and two of them indicated that smoking might exert a small effect to impair growth. This present study evaluated young adults with remarkably longer smoking histories, so that these subjects had mostly completed their linear growth. If active smoking really had a substantial effect on linear growth during adolescence and young adulthood, one would predict that young adult smokers would be significantly shorter than non-smokers. According to the present findings, smoking has no major effect on the height of young smokers. Nonetheless, our cross-sectional study is a crude estimate, and multiple confounding variables exist that have not been taken into consideration, such as the nutritional state and genetic factors that are known to associate with linear growth.

In addition to cigarette smoking, being overweight is a major risk factor contributing the overall burden of disease worldwide with the main adverse

consequences such as cardiovascular disease, type II diabetes, and several cancers (Haslam & James 2005). In this cross-sectional study of young male adults, the BMI was significantly higher not only in daily smokers but also in daily snus users in comparison to those with no tobacco use. Although BMI in smokers did not correlate with daily tobacco usage or years of smoking, the more the subject had pack years in his history, the higher the body weight. Therefore, daily tobacco use seemed be related to higher weight in young adult males. This association is in line with most other cross-sectional studies which have detected a positive relationship between smoking and body weight in young smokers. It may be partly explained by the fact that these young smokers have not been exposed to cigarette smoke for a sufficiently long time that it would evoke the weight loss encountered in older smokers, but it is more likely to be a complex association since there are several other contributors such as possible higher alcohol consumption, high fat diet and physical inactivity. On the other hand, tobacco use could hypothetically have a weight increasing metabolic effect in growing adolescents, an effect which could later be reversed in adulthood. In fact, a prospective twin study (Saarni *et al.* 2009) concluded that smoking in adolescence was a risk factor for abdominal obesity in early adulthood in both genders. Several confounders (physical activity, education, dietary behaviour) did not fully explain the association. Because causality cannot be investigated in a cross-sectional study, overweight young adults could also be at a higher risk to start smoking: smoking has been utilized as a weight control strategy especially in white young females (Potter *et al.* 2004), and has been associated to recurrent intentional weight loss episodes in young adults (Saarni *et al.* 2004).

Studies on the association between weight and SLT use have mainly included older adults indicating that smokeless tobacco use may be related to overweight, but the results are somewhat conflicting (Bolinder *et al.* 1992, Eliasson *et al.* 1995, Engstrom *et al.* 2010, Hansson *et al.* 2011, Nafziger *et al.* 2007, Norberg *et al.* 2006, Rodu *et al.* 2004, Varga *et al.* 2013). Rather few studies have examined this association in younger SLT users. A U.S. study of young military recruits found a similar association of weight and smokeless tobacco use (Vander Weg *et al.* 2005). Nonetheless, the higher BMI in snus users is somewhat surprising, since SLT use is known to be more common among young adult athletes (Alaranta *et al.* 2006). The higher BMI may therefore partly reflect the higher muscle mass in these snus users. On the other hand, previous studies have indicated that not only smokers but also young smokeless tobacco users with perceived or actual overweight may be more likely to utilize smokeless tobacco

(Caria *et al.* 2009, Saarni *et al.* 2004) which may also partly explain the present results.

Smokers were less active in sports. In addition, the more that the subject had consumed cigarettes, the more likely that he would be inactive in sports. Previous investigations into the association between smoking and physical activity have reported conflicting results especially in young and males, but most studies have found a negative association, as in the present study (Kaczynski *et al.* 2008). The conflicting results in previous studies may partly result from their various definitions of physical activity, but also cultural differences that affect tobacco use habits may influence this association. However, the finding about the negative association between smoking and activity in sports in Finnish young male adults was confirmed in a nationwide sample of young Finnish military recruits: Mattila et al. (2012) found that those recruits who were active in sports were less likely to smoke. The level of physical inactivity among Finnish young adult smokers is concerning as this has been shown to be an independent risk factor for several health problems such as cardiovascular diseases, obesity, mental health problems, sleeping problems and premature death –the magnitude of the health consequences has even been compared to that of smoking (Helajarvi *et al.* 2015).

In the present study, young adult male smokers were not only less active in sports, but they had also poorer performance in the Cooper's test i.e. their aerobic fitness was already impaired compared to their counterparts even when confounding for physical activity, education and BMI. This result is in line with previous studies investigating the relationship between smoking and aerobic fitness in relatively young populations (Bernaards *et al.* 2003, Biersner *et al.* 1972, Conway & Cronan 1988, Cooper *et al.* 1968, Jensen 1986, Marti *et al.* 1988, Montoye *et al.* 1980, Sidney *et al.* 1993, Zadoo *et al.* 1993). When detailed smoking history was evaluated here, the result of the Cooper's test was shown to be inversely related to pack years, although the association was not strong. A stronger association between smoking history and aerobic fitness has been reported (Marti *et al.* 1988): Cooper's test performance was inversely related to daily cigarette consumption and years of smoking in young adult smokers, and impaired performance was seen even in light smokers (1-10 cigarettes/day) with less than two years in their smoking history.

In summary, tobacco use seems to be relatively common among young males in northern parts of Finland, and their smoking habit is just one contributor to a cluster of health hazards i.e. elevated BMI, sedentary lifestyle and poor physical

fitness. These additional health hazards are likely to increase the risks related to smoking. It is recommended that health care professionals not only encourage young smokers to quit smoking but also question these individuals about other aspects of their life-style such as sports activity and dietary habits, and describe how best they can adopt more healthy practices in general. In addition, it has been claimed that increased physical activity level may even help some smokers to quit smoking (Ussher *et al.* 2014).

Symptoms of chronic bronchitis

Study I revealed that the symptoms of self-reported CB were very common already in young male smokers: about 40% of daily smokers complained of these symptoms compared to 12% of non-smokers. The symptoms of CB displayed a strong association to the smoking history: the more a subject had smoked, the more likely he would exhibit these symptoms.

The high prevalence of these symptoms in young smokers is alarming, because these symptoms have been associated with impaired future health: Guerra et al. (2009) found that chronic cough and sputum production represent early markers for future COPD development and increased mortality in smokers aged 50 years or less. Another large study (de Marco *et al.* 2004) found that active smoking was strongly related to the symptoms of CB without airway limitation in 20 to 44 year-old smokers, and the presence of these symptoms also significantly predicted COPD development (de Marco *et al.* 2007). Interestingly, those smokers suffering the chronic symptoms without signs of airway limitation, i.e. not having a diagnosis of COPD, nonetheless were very likely to consume healthcare resources for respiratory problems, and in this respect, there was no statistically significant difference compared to those already having COPD (de Marco *et al.* 2004).

Previously it has been estimated that 40% of smokers will develop CB in long term (Pelkonen *et al.* 2006). Therefore, symptoms of CB were relatively common in these young adult smokers. The symptoms of CB in study I were relatively common also in non-smokers and this could not be explained by ETS. The high numbers of symptoms in this cross-sectional study may be attributable to several reasons, one of those being the awareness of these pulmonary problems: all subjects had attended an information/lecture about the effects of smoking during their first weeks of military service; this may have affected the final answers to the questionnaire. Infectious respiratory epidemics are frequent in

the army, especially during the winter period, and could be partly responsible for the high number of respiratory symptoms reported by both smokers and non-smokers. In addition, approximately, 5-10% of draftees have a diagnosis of asthma (Kotaniemi *et al.* 2001). The present study did not include exact information about the subjects' known allergies or asthma nor were spirometric tests conducted that are needed for recognition of undiagnosed asthma. These diseases commonly include the same symptoms as CB and may therefore explain why the incidence of these symptoms was so high.

6.1.3 Nicotine dependence, readiness to quit and smoking cessation in young adults (II-IV)

Nicotine dependence and readiness to quit in tobacco users

Young adult male daily smokers in Northern Finland were highly dependent on nicotine: over 70% of them were moderately to very strongly dependent on nicotine according to HSI. Nevertheless, most of them had tried to quit smoking, in fact, the more dependent they felt that they were, the more likely they had tried to quit. Nonetheless, the number of successful quitters (ex-smokers) was very small (2.3-2.8%, n=27-33 depending on the study). Young adult snus users were commonly nicotine dependent as well: about 80% of daily snus users felt themselves addicted to snus to some extent, and over half of them graded their dependence to be moderate-to-strong.

Those smokers with dual use of cigarettes and snus smoked a similar number of cigarettes each day as daily smokers who did not use snus i.e. dual use did not seem to decrease the number of cigarettes smoked per day in these daily smokers. One could speculate that individuals who otherwise would have been the heaviest smokers were more likely to consume snus and this reduced the number of cigarettes they smoked each day to the same level as smokers without snus use. However, considering also the relatively widespread dual use among young adult males, it seems that snus use does not have a role at reducing the health harm related to cigarette smoking in these young adults.

Nonetheless, those smokers with snus use seemed to have a stronger dependence on cigarettes—although the difference did not reach statistical significance. If daily smokers were trying to substitute cigarettes by taking snus, it would be anticipated that those who use snus would also smoke their first

cigarette later in the morning than the smokers who were not snus users. However, in daily smokers, the pattern of smoking the first cigarette in the morning did not differ significantly according to their snus use habits. In fact, there was trend that dual users smoked their first cigarette earlier in the morning, reflecting the higher HSI values in dual users than in daily smokers without snus use. Dual users appeared less likely to make quit attempts, although this trend was also statistically insignificant. In summary, it seemed that dual users were more dependent on nicotine than smokers without snus use, but the statistical power of the present study could not reveal statistical significance for this difference. This is in line with the U.S and Swedish studies in which polytobacco use has been associated with stronger nicotine dependence in adolescent and young adult smokers (Lee *et al.* 2015, Post *et al.* 2010, Rosendahl *et al.* 2008, Timberlake 2008). Therefore, dual users may be a subgroup of smokers that need even more intensive interventions to achieve successful smoking cessation than exclusive smokers.

About 55% of young adult male daily smokers in this cross-sectional study reported that they had previously tried to quit smoking. However, little less than half of the quitters had tried any pharmacological help in their previous quit attempts. The proportion of those that had sought pharmacological help is relatively small considering that there is easy access to NRT products in Finland since they are sold in grocery stores to people aged 18 or older. Most of these individuals had tried NRT but none of them had tried varenicline even though this compound is considered to be the most effective pharmacotherapy available for smoking cessation, at least according to smoking cessations studies conducted in older adult smokers (Cahill *et al.* 2013), and it is available with a prescription also for young adults in Finland. Although there are no evidence-based guidelines for smoking cessation pharmacotherapy use in young adults, it is reasonable to argue that if they truly want to help these young smokers with generally high dependence level, then health care professionals should be more active in recommending pharmacological anti-smoking therapies.

Varenicline and nicotine patch therapies in young adults motivated to quit smoking

Study IV indicated that varenicline for 12 weeks might be more effective than a nicotine patch 15mg/16h for 8 weeks in helping young adult heavy smokers to quit smoking in the short term (at week 4 and 12) based on self-reported smoking

status of the subjects. However, cotinine-verified smoking abstinence did not support this finding. The treatments had equal efficacy at the end of the follow-up period (week 26). On the other hand, the nicotine patch 10mg/16h did not seem to be any more effective than placebo in promoting smoking abstinence in young adult light smokers trying to quit smoking. No serious adverse events were reported. Both nicotine patches and varenicline seemed to be well tolerated. Unfortunately, these young smokers had generally low compliance to both of the treatments; low compliance is a problem that is often encountered in smoking cessation trials focusing on young smokers (Bailey *et al.* 2012).

Although the nicotine patch has been found to be effective in smoking cessation of adult smokers even with long term follow-up, helping about 80% more people to quit compared to placebo treatment (Cahill *et al.* 2013), it is not known whether nicotine patch therapy is effective in young smokers, especially in young adults (Bailey *et al.* 2012, Kim *et al.* 2011, Stanton & Grimshaw 2013). In the present study, nicotine patch did not seem to enhance the chances of successful quitting in either the short or long term. Varenicline has been shown to be even more effective than nicotine patch in adults as about 50% more smokers quit smoking when having varenicline treatment compared to nicotine patch treatment (Cahill *et al.* 2013). As far as is known, there is only one previous study (n=29; age 15 to 20 years) (Gray *et al.* 2012) investigating varenicline as a treatment for smoking cessation in a group of young smokers. The trial compared varenicline to bupropion, and only one individual was abstinent after 12 weeks. Our preliminary results showing that varenicline might be more effective than NRT at least in the short term in smoking cessation of young smokers based on their own reports of smoking status are promising, but more randomised, placebo-controlled, double-blinded clinical trials will be needed to confirm the finding.

6.2 Limitations and strengths of the studies

6.2.1 Cross-sectional study of young military recruits (I-III)

One obvious limitation of this study of military recruits is its cross-sectional design. More longitudinal studies are needed to investigate the causal relationships related to dual use, dependence and smoking cessation in young adults. Another limitation is that only the current use of snus was inquired, and a

more detailed snus use history was not obtained e.g. duration of snus use, daily snus consumption, or previous SLT use (ex-snus use). In addition, military service itself might have some influence on the tobacco use habits of the recruits, considering that the military service differs in several ways from everyday life outside the military environment. However, in order to minimise this effect, the study questionnaire was filled in soon after the beginning of the military service. In addition, the present sample might be a slightly selected population since at the time of the study about 20% of this age group of males did not undertake military service. One major reason for not participating in army service is that the young man is suffering from psychiatric problems –a factor also known to exhibit a positive association with smoking prevalence (Sihvola *et al.* 2008).

On the other hand, the study has some strengths. The sample size was relatively large and it conducted a detailed assessment of smoking history enabling a more profound analysis of factors related to smoking habits. Furthermore, the response rate was good, 80%, and consisted of an age group of young people that are otherwise often difficult to contact successfully in health-related topics. In addition, there were some double-check questions in the questionnaire that partly enabled the assessment of trustworthy of the subjects' answers in general. However, very few of the responses needed to be excluded from the analysis because of unreliable answers or incomplete filling of the questionnaire, another strength of the study.

6.2.2 Prospective study of young adults motivated to quit smoking (IV)

Study IV has some limitations that need to be considered when evaluating its results. Firstly, the study was not conducted in a truly blinded manner. Secondly, the nicotine and placebo patches were not identical, although the placebo patch was chosen to resemble a medicinal patch. In fact, the subjects rarely reported any suspicion of receiving placebo treatment. On the other hand, the study did not include similar looking placebo tablets as the varenicline tablets despite efforts to obtain them for this study. Randomised, double-blinded and placebo-controlled trials on young adult smokers are needed to confirm these preliminary results that varenicline seems to be an effective smoking cessation aid in this age group at least in the short term.

In study IV, the saliva cotinine concentration was assayed to verify self-reported abstinence after the treatment period at week 12. Only seven subjects

gave a negative saliva cotinine test result to confirm their self-reported smoking abstinence. One reason for this is that 23.7% (n=69) stated that they were unable to come to the control visit at week 12 but participated over the phone. On the other hand, the subjects were not asked to report all confounding factors which might have interfered with this measurement such as recent exposure to ETS or whether they were continuing to use of nicotine replacement therapy. Furthermore, some smoking abstinent subjects continued to use snus, at least to some extent. After noting this problem, it was decided to measure the eCO level from all of those exhibiting a positive saliva cotinine test result. These results did indicate that the individuals claiming to have stopped smoking were reliable, as none of them had an eCO level over 5ppm.

However, the lack of comprehensive verification of self-reported smoking abstinence with an eCO level assessment is an important limitation of this study. In particular, the continuous use of snus or NRT by some individuals in the sample limited the usefulness of saliva cotinine measurement as a way to confirm smoking abstinence. Therefore, eCO level measurement could have been more useful in this sample of young adults.

This study included nicotine patch 10mg/16h and 15mg/16h treatment for 8 weeks. The dosing and the duration of varenicline therapy used were those recommended by the drug manufacturer. Therefore, it should be noted that the varenicline group received treatment for a longer period than the nicotine patch groups. However, previous studies on adults have not revealed any consistent evidence that a longer duration or higher dosing of the patches would improve smoking abstinence rates —although some individuals might benefit from longer duration or higher dosing of NRT to achieve smoking abstinence (Stead *et al.* 2012). On the other hand, by combining an NRT with a more rapid nicotine delivery such as NGs to NPs in the study, it might have been possible to achieve a better effect in helping young adults to quit smoking, as this combination is known to be more effective in adults than NP therapy alone (Cahill *et al.* 2013). In addition, more studies will be needed to investigate the efficacy and safety of varenicline and nicotine patch treatment in young adult smokers with daily psychiatric medication or concomitant drug/alcohol abuse —subgroups that were not included on the present trial.

Finally, compliance in the present study was generally low. Even though compliance was moderate after two weeks of treatment, only about 10-20% fully

completed the treatment as recommended, possibly to the detriment of study treatment efficacy.

In general, the process of preparing and enrolling a clinical trial has been instructive for our research group. Despite the challenges encountered during the process, it has some strengths that should be mentioned. Study IV was a real life study with a relatively large sample size of volunteering young adult smokers with comparably good follow-up adherence despite the young age. Although there were some limitations, it did provide novel information about the pros and cons of pharmacotherapy in young adults –an age group of smokers that despite their obvious importance, have been omitted from most previous anti-smoking trials.

7 Conclusions and future aspects

To conclude, there is extensive variability in the smoking habits of young adults in different parts of one country, even in Europe. Dual use of cigarettes and snus is very common in young adults, but only a few have quit smoking with or without snus use. In fact, snus use does not seem to substitute for cigarettes in young adult daily smokers, instead snus seems to be additional unhealthy habit in these individuals.

Despite their young age, in general the physical fitness of smokers was already poorer than their non-smoking peers and furthermore there was an association between smoking history, sedentary life style and elevated BMI. Young male smokers in their twenties commonly reported signs of chronic bronchitis, which is alarming since this symptom has been linked not only with a higher risk to develop COPD in the future but also an increased mortality rate.

Although the prevalence of smoking in young adults is declining, continuous efforts should be made to prevent youngsters from acquiring a smoking habit and to find evidence-based guidelines for effective smoking cessation programs targeted especially to young smokers. This may well include the promotion of effective pharmacological interventions to help young people to quit smoking as soon as possible and, therefore, to prevent most of the smoking related health harm. This present study revealed that varenicline might be more effective than nicotine patch only in helping young adults to quit smoking in the short term. As far as is known, very few previous studies have been conducted on the use of varenicline in young smokers motivated to quit smoking. The study has some limitations, and the result should be considered as a preliminary finding. More good quality clinical trials will be needed to confirm this outcome as well as to evaluate the efficacy and safety of other therapies targeted to young smokers motivated to quit smoking.

Future challenge in reducing tobacco use include the use of alternate tobacco products, such as smokeless tobacco and e-cigarettes, which are becoming more and more commonly used by young people. The health consequences and other important clinical knowledge about these products are still largely unknown. The situation will be clarified when the growing numbers of studies focusing on alternate tobacco products, especially e-cigarettes, are published. Hopefully, these future studies will make it clear whether these alternate tobacco products really have any role at all in helping young smokers to quit the smoking habit.

References

Akbartabartoori M, Lean ME & Hankey CR. (2005) Relationships between cigarette smoking, body size and body shape. Int J Obes (Lond) 29(2): 236-243.

Alaranta A, Alaranta H, Patja K, Palmu P, Prattala R, Martelin T & Helenius I. (2006) Snuff use and smoking in Finnish olympic athletes. Int J Sports Med 27(7): 581-586.

Albert RH. (2010) Diagnosis and treatment of acute bronchitis. Am Fam Physician 82(11): 1345-1350.

Allen JG, Flanigan SS, LeBlanc M, Vallarino J, MacNaughton P, Stewart JH & Christiani DC. (In press) Flavoring Chemicals in E-Cigarettes: Diacetyl, 2,3-Pentanedione, and Acetoin in a Sample of 51 Products, Including Fruit-, Candy-, and Cocktail-Flavored E-Cigarettes. Environ Health Perspect.

Arcavi L & Benowitz NL. (2004) Cigarette smoking and infection. Arch Intern Med 164(20): 2206-2216.

Armitage P, Berry G & Matthews JNS. (2002) Checking the Model. In: Brown A & Pattison F (eds) Statistical Methods in Medical Research. Oxford: Blackwell Science: 359.

Aubin HJ, Farley A, Lycett D, Lahmek P & Aveyard P. (2012) Weight gain in smokers after quitting cigarettes: meta-analysis. BMJ 345: e4439.

Baba S, Wikstrom AK, Stephansson O & Cnattingius S. (2013) Changes in snuff and smoking habits in Swedish pregnant women and risk for small for gestational age births. BJOG 120(4): 456-462.

Bachmann MS, Znoj H & Brodbeck J. (2012) Smoking behaviour, former quit attempts and intention to quit in urban adolescents and young adults: a five-year longitudinal study. Public Health 126(12): 1044-1050.

Bailey SR, Crew EE, Riske EC, Ammerman S, Robinson TN & Killen JD. (2012) Efficacy and tolerability of pharmacotherapies to aid smoking cessation in adolescents. Paediatr Drugs 14(2): 91-108.

Bala MM, Strzeszynski L, Topor-Madry R & Cahill K. (2013) Mass media interventions for smoking cessation in adults. Cochrane Database Syst Rev (6): CD004704.

Barnes J, Dong CY, McRobbie H, Walker N, Mehta M & Stead LF. (2010) Hypnotherapy for smoking cessation. Cochrane Database Syst Rev (10): CD001008.

Benowitz NL. (1988) Nicotine and smokeless tobacco. CA Cancer J Clin 38(4): 244-247.

Benowitz NL. (2009) Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. Annu Rev Pharmacol Toxicol 49: 57-71.

Benowitz NL. (2010) Nicotine addiction. N Engl J Med 362(24): 2295-2303.

Benowitz NL, Bernert JT, Caraballo RS, Holiday DB & Wang J. (2009a) Optimal serum cotinine levels for distinguishing cigarette smokers and nonsmokers within different racial/ethnic groups in the United States between 1999 and 2004. Am J Epidemiol 169(2): 236-248.

Benowitz NL, Hukkanen J & Jacob P,3rd. (2009b) Nicotine chemistry, metabolism, kinetics and biomarkers. Handb Exp Pharmacol (192): 29-60.

Bernaards CM, Twisk JW, Van Mechelen W, Snel J & Kemper HC. (2003) A longitudinal study on smoking in relationship to fitness and heart rate response. Med Sci Sports Exerc 35(5): 793-800.

Biersner RJ, Gunderson EK & Rahe RH. (1972) Relationships of sports interests and smoking to physical fitness. J Sports Med Phys Fitness 12(2): 124-127.

Bize R, Burnand B, Mueller Y, Rege-Walther M, Camain JY & Cornuz J. (2012) Biomedical risk assessment as an aid for smoking cessation. Cochrane Database Syst Rev (12): CD004705.

Boffetta P, Hecht S, Gray N, Gupta P & Straif K. (2008) Smokeless tobacco and cancer. Lancet Oncol 9(7): 667-675.

Boffetta P & Straif K. (2009) Use of smokeless tobacco and risk of myocardial infarction and stroke: systematic review with meta-analysis. BMJ 339: b3060.

Bolinder G, Noren A, Wahren J & De Faire U. (1997) Long-term use of smokeless tobacco and physical performance in middle-aged men. Eur J Clin Invest 27(5): 427-433.

Bolinder GM, Ahlborg BO & Lindell JH. (1992) Use of smokeless tobacco: blood pressure elevation and other health hazards found in a large-scale population survey. J Intern Med 232(4): 327-334.

Brunzell DH, Stafford AM & Dixon CI. (2015) Nicotinic receptor contributions to smoking: insights from human studies and animal models. Curr Addict Rep 2(1): 33-46.

Cahill K & Perera R. (2008) Quit and Win contests for smoking cessation. Cochrane Database Syst Rev (4): CD004986.

Cahill K & Perera R. (2011) Competitions and incentives for smoking cessation. Cochrane Database Syst Rev (4): CD004307.

Cahill K, Stead LF & Lancaster T. (2012) Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev (4): CD006103.

Cahill K, Stevens S, Perera R & Lancaster T. (2013) Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev (5): CD009329.

Caria MP, Bellocco R, Zambon A, Horton NJ & Galanti MR. (2009) Overweight and perception of overweight as predictors of smokeless tobacco use and of cigarette smoking in a cohort of Swedish adolescents. Addiction 104(4): 661-668.

Carroll Chapman SL & Wu LT. (2014) E-cigarette prevalence and correlates of use among adolescents versus adults: a review and comparison. J Psychiatr Res 54: 43-54.

Cengelli S, O'Loughlin J, Lauzon B & Cornuz J. (2012) A systematic review of longitudinal population-based studies on the predictors of smoking cessation in adolescent and young adult smokers. Tob Control 21(3): 355-362.

Cheng YJ, Liu ZH, Yao FJ, Zeng WT, Zheng DD, Dong YG & Wu SH. (2013) Current and former smoking and risk for venous thromboembolism: a systematic review and meta-analysis. PLoS Med 10(9): e1001515.

Civljak M, Stead LF, Hartmann-Boyce J, Sheikh A & Car J. (2013) Internet-based interventions for smoking cessation. Cochrane Database Syst Rev (7): CD007078.

Cohen S, Kamarck T & Mermelstein R. (1983) A global measure of perceived stress. J Health Soc Behav 24(4): 385-396.

Connolly GN, Orleans CT & Blum A. (1992) Snuffing tobacco out of sport. Am J Public Health 82(3): 351-353.

Connor Gorber S, Schofield-Hurwitz S, Hardt J, Levasseur G & Tremblay M. (2009) The accuracy of self-reported smoking: a systematic review of the relationship between self-reported and cotinine-assessed smoking status. Nicotine Tob Res 11(1): 12-24.

Conway TL & Cronan TA. (1988) Smoking and physical fitness among Navy shipboard men. Mil Med 153(11): 589-594.

Cooke F, Bullen C, Whittaker R, McRobbie H, Chen MH & Walker N. (2008) Diagnostic accuracy of NicAlert cotinine test strips in saliva for verifying smoking status. Nicotine Tob Res 10(4): 607-612.

Cooper KH, Gey GO & Bottenberg RA. (1968) Effects of cigarette smoking on endurance performance. JAMA 203(3): 189-192.

Cornelius MD & Day NL. (2000) The effects of tobacco use during and after pregnancy on exposed children. Alcohol Res Health 24(4): 242-249.

de Marco R, Accordini S, Cerveri I, Corsico A, Anto JM, Kunzli N, Janson C, Sunyer J, Jarvis D, Chinn S, Vermeire P, Svanes C, Ackermann-Liebrich U, Gislason T, Heinrich J, Leynaert B, Neukirch F, Schouten JP, Wjst M & Burney P. (2007) Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm. Am J Respir Crit Care Med 175(1): 32-39.

de Marco R, Accordini S, Cerveri I, Corsico A, Sunyer J, Neukirch F, Kunzli N, Leynaert B, Janson C, Gislason T, Vermeire P, Svanes C, Anto JM, Burney P & European Community Respiratory Health Survey Study Group. (2004) An international survey of chronic obstructive pulmonary disease in young adults according to GOLD stages. Thorax 59(2): 120-125.

de Marco R, Accordini S, Marcon A, Cerveri I, Anto JM, Gislason T, Heinrich J, Janson C, Jarvis D, Kuenzli N, Leynaert B, Sunyer J, Svanes C, Wjst M, Burney P & European Community Respiratory Health Survey (ECRHS). (2011) Risk factors for chronic obstructive pulmonary disease in a European cohort of young adults. Am J Respir Crit Care Med 183(7): 891-897.

DiFranza JR, Savageau JA, Fletcher K, O'Loughlin J, Pbert L, Ockene JK, McNeill AD, Hazelton J, Friedman K, Dussault G, Wood C & Wellman RJ. (2007) Symptoms of tobacco dependence after brief intermittent use: the Development and Assessment of Nicotine Dependence in Youth-2 study. Arch Pediatr Adolesc Med 161(7): 704-710.

DiFranza JR, Savageau JA, Rigotti NA, Fletcher K, Ockene JK, McNeill AD, Coleman M & Wood C. (2002) Development of symptoms of tobacco dependence in youths: 30 month follow up data from the DANDY study. Tob Control 11(3): 228-235.

Doku D, Koivusilta L, Rainio S & Rimpela A. (2010) Socioeconomic differences in smoking among Finnish adolescents from 1977 to 2007. J Adolesc Health 47(5): 479-487.

Doll R, Peto R, Boreham J & Sutherland I. (2004) Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ 328(7455): 1519.

Duke JC, Lee YO, Kim AE, Watson KA, Arnold KY, Nonnemaker JM & Porter L. (2014) Exposure to electronic cigarette television advertisements among youth and young adults. Pediatrics 134(1): e29-36.

Dunn C, Deroo L & Rivara FP. (2001) The use of brief interventions adapted from motivational interviewing across behavioral domains: a systematic review. Addiction 96(12): 1725-1742.

Dwyer JB, McQuown SC & Leslie FM. (2009) The dynamic effects of nicotine on the developing brain. Pharmacol Ther 122(2): 125-139.

Eliasson M, Asplund K, Evrin PE & Lundblad D. (1995) Relationship of cigarette smoking and snuff dipping to plasma fibrinogen, fibrinolytic variables and serum insulin. The Northern Sweden MONICA Study. Atherosclerosis 113(1): 41-53.

Engstrom K, Magnusson C & Galanti MR. (2010) Socio-demographic, lifestyle and health characteristics among snus users and dual tobacco users in Stockholm County, Sweden. BMC Public Health 10: 619.

Etter JF, Duc TV & Perneger TV. (1999) Validity of the Fagerstrom test for nicotine dependence and of the Heaviness of Smoking Index among relatively light smokers. Addiction 94(2): 269-281.

Faessel H, Ravva P & Williams K. (2009) Pharmacokinetics, safety, and tolerability of varenicline in healthy adolescent smokers: a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther 31(1): 177-189.

Fidler JA, West R, Van Jaarsveld CH, Jarvis MJ & Wardle J. (2007) Does smoking in adolescence affect body mass index, waist or height? Findings from a longitudinal study. Addiction 102(9): 1493-1501.

Filozof C, Fernandez Pinilla MC & Fernandez-Cruz A. (2004) Smoking cessation and weight gain. Obes Rev 5(2): 95-103.

Folkshälsomyndigheten. (2015) Tobaksvanor. URl: http://www.folkhalsomyndigheten.se/amnesomraden/statistik-och-undersokningar/enkater-och-undersokningar/nationella-folkhalsoenkaten/levnadsvanor/tobaksvanor/. Cited 2015/10/23.

Forey BA, Thornton AJ & Lee PN. (2011) Systematic review with meta-analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis and emphysema. BMC Pulm Med 11: 36-2466-11-36.

Foulds J, Ramstrom L, Burke M & Fagerstrom K. (2003) Effect of smokeless tobacco (snus) on smoking and public health in Sweden. Tob Control 12(4): 349-359.

Galanti MR, Rosendahl I, Post A & Gilljam H. (2001a) Early gender differences in adolescent tobacco use--the experience of a Swedish cohort. Scand J Public Health 29(4): 314-317.

Galanti MR, Rosendahl I & Wickholm S. (2008) The development of tobacco use in adolescence among "snus starters" and "cigarette starters": an analysis of the Swedish "BROMS" cohort. Nicotine Tob Res 10(2): 315-323.

Galanti MR, Wickholm S & Gilljam H. (2001b) Between harm and dangers. Oral snuff use, cigarette smoking and problem behaviours in a survey of Swedish male adolescents. Eur J Public Health 11(3): 340-345.

Gartner CE, Hall WD, Vos T, Bertram MY, Wallace AL & Lim SS. (2007) Assessment of Swedish snus for tobacco harm reduction: an epidemiological modelling study. Lancet 369(9578): 2010-2014.

Gervais A, O'Loughlin J, Meshefedjian G, Bancej C & Tremblay M. (2006) Milestones in the natural course of onset of cigarette use among adolescents. CMAJ 175(3): 255-261.

Gibson G, Loddenkemper R, Sibille Y & Lundbäck B. (2013) European Lung White Book. Sheffield: European Respiratory Society.

Gingiss PL & Gottlieb NH. (1991) A comparison of smokeless tobacco and smoking practices of university varsity and intramural baseball players. Addict Behav 16(5): 335-340.

Gold DR, Wang X, Wypij D, Speizer FE, Ware JH & Dockery DW. (1996) Effects of cigarette smoking on lung function in adolescent boys and girls. N Engl J Med 335(13): 931-937.

Goniewicz ML, Gawron M, Nadolska J, Balwicki L & Sobczak A. (2014) Rise in electronic cigarette use among adolescents in Poland. J Adolesc Health 55(5): 713-715.

Grana R, Benowitz N & Glantz SA. (2014) E-cigarettes: a scientific review. Circulation 129(19): 1972-1986.

Grana R & Ling P. (2014) "Smoking revolution": a content analysis of electronic cigarette retail websites. Am J Prev Med 46(4): 395-403.

Gray KM, Carpenter MJ, Baker NL, Hartwell KJ, Lewis AL, Hiott DW, Deas D & Upadhyaya HP. (2011) Bupropion SR and contingency management for adolescent smoking cessation. J Subst Abuse Treat 40(1): 77-86.

Gray KM, Carpenter MJ, Lewis AL, Klintworth EM & Upadhyaya HP. (2012) Varenicline versus bupropion XL for smoking cessation in older adolescents: a randomized, double-blind pilot trial. Nicotine Tob Res 14(2): 234-239.

Guerra S, Sherrill DL, Venker C, Ceccato CM, Halonen M & Martinez FD. (2009) Chronic bronchitis before age 50 years predicts incident airflow limitation and mortality risk. Thorax 64(10): 894-900.

Haddock CK, Weg MV, DeBon M, Klesges RC, Talcott GW, Lando H & Peterson A. (2001) Evidence that smokeless tobacco use is a gateway for smoking initiation in young adult males. Prev Med 32(3): 262-267.

Hammond D. (2005) Smoking behaviour among young adults: beyond youth prevention. Tob Control 14(3): 181-185.

Hanson K, Allen S, Jensen S & Hatsukami D. (2003) Treatment of adolescent smokers with the nicotine patch. Nicotine Tob Res 5(4): 515-526.

Hanson MD & Chen E. (2007) Socioeconomic status and health behaviors in adolescence: a review of the literature. J Behav Med 30(3): 263-285.

Hansson J, Galanti MR, Magnusson C & Hergens MP. (2011) Weight gain and incident obesity among male snus users. BMC Public Health 11: 371.
Hartmann-Boyce J, Cahill K, Hatsukami D & Cornuz J. (2012) Nicotine vaccines for smoking cessation. Cochrane Database Syst Rev (8): CD007072.
Hartmann-Boyce J, Lancaster T & Stead LF. (2014) Print-based self-help interventions for smoking cessation. Cochrane Database Syst Rev (6): CD001118.
Haslam DW & James WP. (2005) Obesity. Lancet 366(9492): 1197-1209.
Haukkala A, Vartiainen E & de Vries H. (2006) Progression of oral snuff use among Finnish 13-16-year-old students and its relation to smoking behaviour. Addiction 101(4): 581-589.
Heath JM & Mongia R. (1998) Chronic bronchitis: primary care management. Am Fam Physician 57(10): 2365-72, 2376-8.
Heatherton TF, Kozlowski LT, Frecker RC & Fagerstrom KO. (1991) The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict 86(9): 1119-1127.
Heatherton TF, Kozlowski LT, Frecker RC, Rickert W & Robinson J. (1989) Measuring the heaviness of smoking: using self-reported time to the first cigarette of the day and number of cigarettes smoked per day. Br J Addict 84(7): 791-799.
Heikkinen AM, Meurman JH & Sorsa T. (2015) Tupakka, nuuska ja suun terveys. Duodecim 131(21): 1975-1980.
Helajarvi H, Lindholm H, Vasankari T & Heinonen OJ. (2015) Health hazards of physical inactivity. Duodecim 131(18): 1713-1718.
Helldan A & Helakorpi S. (2015) Health behaviour and health among the Finnish adult population, spring 2014. National Institute for Health and Welfare 6/2015.
Henninger S, Fischer R, Cornuz J, Studer J & Gmel G. (2015) Physical Activity and Snus: Is There a Link? Int J Environ Res Public Health 12(7): 7185-7198.
Hoffman BR, Sussman S, Unger JB & Valente TW. (2006) Peer influences on adolescent cigarette smoking: a theoretical review of the literature. Subst Use Misuse 41(1): 103-155.
Huhtala HS, Rainio SU & Rimpela AH. (2006) Adolescent snus use in Finland in 1981-2003: trend, total sales ban and acquisition. Tob Control 15(5): 392-397.
Hukkinen M, Korhonen T, Broms U, Koskenvuo M & Kaprio J. (2009) Long-term smoking behavior patterns predicting self-reported chronic bronchitis. COPD 6(4): 242-249.
Ilback NG & Stalhandske T. (2003) Nicotine accumulation in the mouse brain is age-dependent and is quantitatively different in various segments. Toxicol Lett 143(2): 175-184.
Jarvis MJ, Fidler J, Mindell J, Feyerabend C & West R. (2008) Assessing smoking status in children, adolescents and adults: cotinine cut-points revisited. Addiction 103(9): 1553-1561.
Jasuja GK, Chou CP, Riggs NR & Pentz MA. (2008) Early cigarette use and psychological distress as predictors of obesity risk in adulthood. Nicotine Tob Res 10(2): 325-335.

Jensen RG. (1986) The effect of cigarette smoking on Army Physical Readiness Test performance of enlisted Army medical department personnel. Mil Med 151(2): 83-85.
Jitnarin N, Haddock CK, Poston WS & Jahnke S. (2013) Smokeless tobacco and dual use among firefighters in the central United States. J Environ Public Health 2013: 675426.
Jo YH, Talmage DA & Role LW. (2002) Nicotinic receptor-mediated effects on appetite and food intake. J Neurobiol 53(4): 618-632.
Kaczynski AT, Manske SR, Mannell RC & Grewal K. (2008) Smoking and physical activity: a systematic review. Am J Health Behav 32(1): 93-110.
Killen JD, Robinson TN, Ammerman S, Hayward C, Rogers J, Stone C, Samuels D, Levin SK, Green S & Schatzberg AF. (2004) Randomized clinical trial of the efficacy of bupropion combined with nicotine patch in the treatment of adolescent smokers. J Consult Clin Psychol 72(4): 729-735.
Kim V & Criner GJ. (2013) Chronic bronchitis and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 187(3): 228-237.
Kim Y, Myung SK, Jeon YJ, Lee EH, Park CH, Seo HG & Huh BY. (2011) Effectiveness of pharmacologic therapy for smoking cessation in adolescent smokers: Meta-analysis of randomized controlled trials. Am J Health Syst Pharm 68(3): 219-226.
Kinnunen J, Pere L, Lindfors P, Ollila H & Rimpelä A. (2015) The Adolescent Health and Lifestyle Survey 2015. Adolescent smoking, alcohol and substance use in 1977-2015. Reports of the Ministry of Social Affairs and Health 31/2015.
Kinnunen JM, Ollila H, El-Amin SE, Pere LA, Lindfors PL & Rimpela AH. (2014) Awareness and determinants of electronic cigarette use among Finnish adolescents in 2013: a population-based study. Tob Control 24(e4): e264-70.
Klesges RC, Meyers AW, Klesges LM & La Vasque ME. (1989) Smoking, body weight, and their effects on smoking behavior: a comprehensive review of the literature. Psychol Bull 106(2): 204-230.
Klesges RC, Ward KD, Ray JW, Cutter G, Jacobs DR,Jr & Wagenknecht LE. (1998a) The prospective relationships between smoking and weight in a young, biracial cohort: the Coronary Artery Risk Development in Young Adults Study. J Consult Clin Psychol 66(6): 987-993.
Klesges RC, Zbikowski SM, Lando HA, Haddock CK, Talcott GW & Robinson LA. (1998b) The relationship between smoking and body weight in a population of young military personnel. Health Psychol 17(5): 454-458.
Koivumaa-Honkanen H, Honkanen R, Viinamaki H, Heikkila K, Kaprio J & Koskenvuo M. (2000) Self-reported life satisfaction and 20-year mortality in healthy Finnish adults. Am J Epidemiol 152(10): 983-991.
Kotaniemi JT, Lundback B, Nieminen MM, Sovijarvi AR & Laitinen LA. (2001) Increase of asthma in adults in northern Finland?--a report from the FinEsS study. Allergy 56(2): 169-174.
Lancaster T & Stead LF. (2005) Individual behavioural counselling for smoking cessation. Cochrane Database Syst Rev (2): CD001292.

Law M & Tang JL. (1995) An analysis of the effectiveness of interventions intended to help people stop smoking. Arch Intern Med 155(18): 1933-1941.
Lee PN. (2013) Epidemiological evidence relating snus to health--an updated review based on recent publications. Harm Reduct J 10: 36-7517-10-36.
Lee YO, Hebert CJ, Nonnemaker JM & Kim AE. (2015) Youth tobacco product use in the United States. Pediatrics 135(3): 409-415.
Lessov-Schlaggar CN, Pergadia ML, Khroyan TV & Swan GE. (2008) Genetics of nicotine dependence and pharmacotherapy. Biochem Pharmacol 75(1): 178-195.
Lund I & Lund KE. (2014) How has the availability of snus influenced cigarette smoking in Norway? Int J Environ Res Public Health 11(11): 11705-11717.
Lund KE, Scheffels J & McNeill A. (2011) The association between use of snus and quit rates for smoking: results from seven Norwegian cross-sectional studies. Addiction 106(1): 162-167.
Luopa P, Kivimäki H, Matikka A, Vilkki S, Jokela S, Laukkarinen E & Paananen R. (2014) Wellbeing of adolescents in Finland 2000-2013. The results of the School Health Promotion study. National Institute for Health and Welfare 25/2014.
Maisonneuve P & Lowenfels AB. (2015) Risk factors for pancreatic cancer: a summary review of meta-analytical studies. Int J Epidemiol 44(1): 186-198.
Marclay F, Grata E, Perrenoud L & Saugy M. (2011) A one-year monitoring of nicotine use in sport: frontier between potential performance enhancement and addiction issues. Forensic Sci Int 213(1-3): 73-84.
Marrone GF, Paulpillai M, Evans RJ, Singleton EG & Heishman SJ. (2010) Breath carbon monoxide and semiquantitative saliva cotinine as biomarkers for smoking. Hum Psychopharmacol 25(1): 80-83.
Marti B, Abelin T, Minder CE & Vader JP. (1988) Smoking, alcohol consumption, and endurance capacity: an analysis of 6,500 19-year-old conscripts and 4,100 joggers. Prev Med 17(1): 79-92.
Marti B, Tuomilehto J, Korhonen HJ, Kartovaara L, Vartiainen E, Pietinen P & Puska P. (1989) Smoking and leanness: evidence for change in Finland. BMJ 298(6683): 1287-1290.
Mattila VM, Raisamo S, Pihlajamaki H, Mantysaari M & Rimpela A. (2012) Sports activity and the use of cigarettes and snus among young males in Finland in 1999-2010. BMC Public Health 12: 230.
McCauley L, Markin C & Hosmer D. (2012) An unexpected consequence of electronic cigarette use. Chest 141(4): 1110-1113.
McRobbie H, Bullen C, Hartmann-Boyce J & Hajek P. (2014) Electronic cigarettes for smoking cessation and reduction. Cochrane Database Syst Rev (12): CD010216.
Melikian AA & Hoffmann D. (2009) Smokeless tobacco: a gateway to smoking or a way away from smoking. Biomarkers 14 Suppl 1: 85-89.
Molarius A, Seidell JC, Kuulasmaa K, Dobson AJ & Sans S. (1997) Smoking and relative body weight: an international perspective from the WHO MONICA Project. J Epidemiol Community Health 51(3): 252-260.

Montalto NJ & Wells WO. (2007) Validation of self-reported smoking status using saliva cotinine: a rapid semiquantitative dipstick method. Cancer Epidemiol Biomarkers Prev 16(9): 1858-1862.

Montoye HJ, Gayle R & Higgins M. (1980) Smoking habits, alcohol consumption and maximal oxygen uptake. Med Sci Sports Exerc 12(5): 316-321.

Moolchan ET, Robinson ML, Ernst M, Cadet JL, Pickworth WB, Heishman SJ & Schroeder JR. (2005) Safety and efficacy of the nicotine patch and gum for the treatment of adolescent tobacco addiction. Pediatrics 115(4): e407-14.

Morente-Sanchez J, Zandonai T, Mateo-March M, Sanabria D, Sanchez-Munoz C, Chiamulera C & Zabala Diaz M. (2015) Acute effect of Snus on physical performance and perceived cognitive load on amateur footballers. Scand J Med Sci Sports 25(4): e423-31.

Mund M, Louwen F, Klingelhoefer D & Gerber A. (2013) Smoking and pregnancy--a review on the first major environmental risk factor of the unborn. Int J Environ Res Public Health 10(12): 6485-6499.

Muramoto ML, Leischow SJ, Sherrill D, Matthews E & Strayer LJ. (2007) Randomized, double-blind, placebo-controlled trial of 2 dosages of sustained-release bupropion for adolescent smoking cessation. Arch Pediatr Adolesc Med 161(11): 1068-1074.

Nafziger AN, Lindvall K, Norberg M, Stenlund H, Wall S, Jenkins PL, Pearson TA & Weinehall L. (2007) Who is maintaining weight in a middle-aged population in Sweden? A longitudinal analysis over 10 years. BMC Public Health 7: 108.

Niederhofer H & Huber M. (2004) Bupropion may support psychosocial treatment of nicotine-dependent adolescents: preliminary results. Pharmacotherapy 24(11): 1524-1528.

Norberg M, Stenlund H, Lindahl B, Boman K & Weinehall L. (2006) Contribution of Swedish moist snuff to the metabolic syndrome: a wolf in sheep's clothing? Scand J Public Health 34(6): 576-583.

O'Connor RJ, Flaherty BP, Quinio Edwards B & Kozlowski LT. (2003) Regular smokeless tobacco use is not a reliable predictor of smoking onset when psychosocial predictors are included in the model. Nicotine Tob Res 5(4): 535-543.

O'Loughlin J, Karp I, Henderson M & Gray-Donald K. (2008) Does cigarette use influence adiposity or height in adolescence? Ann Epidemiol 18(5): 395-402.

Ortiz A & Grando SA. (2012) Smoking and the skin. Int J Dermatol 51(3): 250-262.

Overland S, Tjora T, Hetland J & Aaro LE. (2010) Associations between adolescent socioeducational status and use of snus and smoking. Tob Control 19(4): 291-296.

Paavola M, Vartiainen E & Puska P. (2001) Smoking cessation between teenage years and adulthood. Health Educ Res 16(1): 49-57.

Patja K, Hakala SM, Bostrom G, Nordgren P & Haglund M. (2009) Trends of tobacco use in Sweden and Finland: do differences in tobacco policy relate to tobacco use? Scand J Public Health 37(2): 153-160.

Pelkonen M, Notkola IL, Nissinen A, Tukiainen H & Koskela H. (2006) Thirty-year cumulative incidence of chronic bronchitis and COPD in relation to 30-year pulmonary function and 40-year mortality: a follow-up in middle-aged rural men. Chest 130(4): 1129-1137.

Pepper JK, Ribisl KM, Emery SL & Brewer NT. (2014) Reasons for starting and stopping electronic cigarette use. Int J Environ Res Public Health 11(10): 10345-10361.

Perkins KA. (1992) Metabolic effects of cigarette smoking. J Appl Physiol 72(2): 401-409.

Pesta DH, Angadi SS, Burtscher M & Roberts CK. (2013) The effects of caffeine, nicotine, ethanol, and tetrahydrocannabinol on exercise performance. Nutr Metab (Lond) 10(1): 71.

Pisinger C & Jorgensen T. (2007) Weight concerns and smoking in a general population: the Inter99 study. Prev Med 44(4): 283-289.

Placzek AN, Zhang TA & Dani JA. (2009) Age dependent nicotinic influences over dopamine neuron synaptic plasticity. Biochem Pharmacol 78(7): 686-692.

Post A, Gilljam H, Rosendahl I, Bremberg S & Galanti MR. (2010) Symptoms of nicotine dependence in a cohort of Swedish youths: a comparison between smokers, smokeless tobacco users and dual tobacco users. Addiction 105(4): 740-746.

Potter BK, Pederson LL, Chan SS, Aubut JA & Koval JJ. (2004) Does a relationship exist between body weight, concerns about weight, and smoking among adolescents? An integration of the literature with an emphasis on gender. Nicotine Tob Res 6(3): 397-425.

Primack BA, Soneji S, Stoolmiller M, Fine MJ & Sargent JD. (2015) Progression to Traditional Cigarette Smoking After Electronic Cigarette Use Among US Adolescents and Young Adults. JAMA Pediatr 169(11): 1018-23.

Rainio S, Pere L, Lindfors P, Lavikainen H, Saarni L & Rimpelä A. (2009) The Adolescent Health and Lifestyle Survey 2009. Adolescent smoking, alcohol and substance use in 1977–2009. Ministry of Social Affairs and Health, University of Tampere, School of Public Health 47.

Ramoa CP, Hiler MM, Spindle TR, Lopez AA, Karaoghlanian N, Lipato T, Breland AB, Shihadeh A & Eissenberg T. (In press) Electronic cigarette nicotine delivery can exceed that of combustible cigarettes: a preliminary report. Tob Control.

Ramos FL, Krahnke JS & Kim V. (2014) Clinical issues of mucus accumulation in COPD. Int J Chron Obstruct Pulmon Dis 9: 139-150.

Rimpelä A, Rainio S, Huhtala H, Lavikainen H, Pere L & Rimpelä M. (2007) The Adolescent Health and Lifestyle Survey 2007. Adolescent smoking, alcohol and substance use in 1977–2007. Reports of the Ministry of Social Affairs 63.

Roddy E, Romilly N, Challenger A, Lewis S & Britton J. (2006) Use of nicotine replacement therapy in socioeconomically deprived young smokers: a community-based pilot randomised controlled trial. Tob Control 15(5): 373-376.

Rodu B, Stegmayr B, Nasic S, Cole P & Asplund K. (2004) The influence of smoking and smokeless tobacco use on weight amongst men. J Intern Med 255(1): 102-107.

Rolandsson M, Hallberg LR & Hugoson A. (2006) Influence of the ice-hockey environment on taking up snuff: an interview study among young males. Acta Odontol Scand 64(1): 47-54.

Rosendahl KI, Galanti MR & Gilljam H. (2008) Trajectories of smokeless tobacco use and of cigarette smoking in a cohort of Swedish adolescents: differences and implications. Nicotine Tob Res 10(6): 1021-1027.

Rubinstein ML, Benowitz NL, Auerback GM & Moscicki AB. (2008) A randomized trial of nicotine nasal spray in adolescent smokers. Pediatrics 122(3): e595-600.

Ryter SW & Choi AM. (2013) Carbon monoxide in exhaled breath testing and therapeutics. J Breath Res 7(1): 017111.

Saarni SE, Pietilainen K, Kantonen S, Rissanen A & Kaprio J. (2009) Association of smoking in adolescence with abdominal obesity in adulthood: a follow-up study of 5 birth cohorts of Finnish twins. Am J Public Health 99(2): 348-354.

Saarni SE, Silventoinen K, Rissanen A, Sarlio-Lahteenkorva S & Kaprio J. (2004) Intentional weight loss and smoking in young adults. Int J Obes Relat Metab Disord 28(6): 796-802.

Schepis TS & Rao U. (2005) Epidemiology and etiology of adolescent smoking. Curr Opin Pediatr 17(5): 607-612.

Scherphof CS, van den Eijnden RJ, Engels RC & Vollebergh WA. (2014) Short-term efficacy of nicotine replacement therapy for smoking cessation in adolescents: A randomized controlled trial. J Subst Abuse Treat 46(2): 120-127.

Severson HH, Forrester KK & Biglan A. (2007) Use of smokeless tobacco is a risk factor for cigarette smoking. Nicotine Tob Res 9(12): 1331-1337.

Sherrill-Mittleman D, Klesges RC, Massey V, Vander Weg MW & DeBon M. (2009) Relationship between smoking status and body weight in a military population of young adults. Addict Behav 34(4): 400-402.

Sidney S, Sternfeld B, Gidding SS, Jacobs DR,Jr, Bild DE, Oberman A, Haskell WL, Crow RS & Gardin JM. (1993) Cigarette smoking and submaximal exercise test duration in a biracial population of young adults: the CARDIA study. Med Sci Sports Exerc 25(8): 911-916.

Sihvola E, Rose RJ, Dick DM, Pulkkinen L, Marttunen M & Kaprio J. (2008) Early-onset depressive disorders predict the use of addictive substances in adolescence: a prospective study of adolescent Finnish twins. Addiction 103(12): 2045-2053.

Solberg LI, Boyle RG, McCarty M, Asche SE & Thoele MJ. (2007) Young adult smokers: are they different? Am J Manag Care 13(11): 626-632.

Stanton A & Grimshaw G. (2013) Tobacco cessation interventions for young people. Cochrane Database Syst Rev (8): CD003289.

Stead LF, Buitrago D, Preciado N, Sanchez G, Hartmann-Boyce J & Lancaster T. (2013a) Physician advice for smoking cessation. Cochrane Database Syst Rev (5): CD000165.

Stead LF, Hartmann-Boyce J, Perera R & Lancaster T. (2013b) Telephone counselling for smoking cessation. Cochrane Database Syst Rev (8): CD002850.

Stead LF & Lancaster T. (2005) Group behaviour therapy programmes for smoking cessation. Cochrane Database Syst Rev (2): CD001007.
Stead LF & Lancaster T. (2012a) Behavioural interventions as adjuncts to pharmacotherapy for smoking cessation. Cochrane Database Syst Rev (12): CD009670.
Stead LF & Lancaster T. (2012b) Combined pharmacotherapy and behavioural interventions for smoking cessation. Cochrane Database Syst Rev (10): CD008286.
Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K & Lancaster T. (2012) Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev (11): CD000146.
Stevens KR & Muñoz LR. (2004) Cigarette smoking: Evidence to guide measurement. Res Nurs Health 27(4): 281-292.
Stice E & Martinez EE. (2005) Cigarette smoking prospectively predicts retarded physical growth among female adolescents. J Adolesc Health 37(5): 363-370.
Suls JM, Luger TM, Curry SJ, Mermelstein RJ, Sporer AK & An LC. (2012) Efficacy of smoking-cessation interventions for young adults: a meta-analysis. Am J Prev Med 42(6): 655-662.
Timberlake DS. (2008) A latent class analysis of nicotine-dependence criteria and use of alternate tobacco. J Stud Alcohol Drugs 69(5): 709-717.
Timberlake DS, Huh J & Lakon CM. (2009) Use of propensity score matching in evaluating smokeless tobacco as a gateway to smoking. Nicotine Tob Res 11(4): 455-462.
Tobacco and Genetics Consortium. (2010) Genome-wide meta-analyses identify multiple loci associated with smoking behavior. Nat Genet 42(5): 441-447.
Tomar SL. (2003) Is use of smokeless tobacco a risk factor for cigarette smoking? The U.S. experience. Nicotine Tob Res 5(4): 561-569.
Tomar SL, Alpert HR & Connolly GN. (2010) Patterns of dual use of cigarettes and smokeless tobacco among US males: findings from national surveys. Tob Control 19(2): 104-109.
U.S. Department of Health and Human Services. (2014) The health consequences of smoking – 50 years of progress: a report of the Surgeon General.
Ussher MH, Taylor AH & Faulkner GE. (2014) Exercise interventions for smoking cessation. Cochrane Database Syst Rev (8): CD002295.
Vander Weg MW, Klesges RC & DeBon M. (2005) Relationship between smokeless tobacco use and body weight in young adult military recruits. Nicotine Tob Res 7(2): 301-305.
Varga TV, Hallmans G, Hu FB, Renstrom F & Franks PW. (2013) Smoking status, snus use, and variation at the CHRNA5-CHRNA3-CHRNB4 locus in relation to obesity: the GLACIER study. Am J Epidemiol 178(1): 31-37.

Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, Stockley RA, Sin DD & Rodriguez-Roisin R. (2013) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 187(4): 347-365.

Villanti AC, McKay HS, Abrams DB, Holtgrave DR & Bowie JV. (2010) Smoking-cessation interventions for U.S. young adults: a systematic review. Am J Prev Med 39(6): 564-574.

Wallenfeldt K, Hulthe J, Bokemark L, Wikstrand J & Fagerberg B. (2001) Carotid and femoral atherosclerosis, cardiovascular risk factors and C-reactive protein in relation to smokeless tobacco use or smoking in 58-year-old men. J Intern Med 250(6): 492-501.

West R, Hajek P, Stead L & Stapleton J. (2005) Outcome criteria in smoking cessation trials: proposal for a common standard. Addiction 100(3): 299-303.

White AR, Rampes H, Liu JP, Stead LF & Campbell J. (2014) Acupuncture and related interventions for smoking cessation. Cochrane Database Syst Rev (1): CD000009.

Wikstrom AK, Cnattingius S, Galanti MR, Kieler H & Stephansson O. (2010a) Effect of Swedish snuff (snus) on preterm birth. BJOG 117(8): 1005-1010.

Wikstrom AK, Cnattingius S & Stephansson O. (2010b) Maternal use of Swedish snuff (snus) and risk of stillbirth. Epidemiology 21(6): 772-778.

Working group set up by the Finnish Medical Society Duodecim and the Finnish Association for General Practice. (2012) Tobacco Dependence and Cessation: Current Care Guidelines. URl: http://www.kaypahoito.fi. Cited 2014/09/07.

World Health Organization. (2013) WHO report on the global tobacco epidemic, 2013. URI: http://www.who.int/tobacco/mpower/en/index.html. Cited 2014/01/31.

World Health Organization. (2014) International Classification of Diseases. URI: http://www.who.int/classifications/icd/en/. Cited 2014/11/05.

Zadoo V, Fengler S & Catterson M. (1993) The effects of alcohol and tobacco use on troop readiness. Mil Med 158(7): 480-484.

Zhang B, Cohen JE, Bondy SJ & Selby P. (2015) Duration of nicotine replacement therapy use and smoking cessation: a population-based longitudinal study. Am J Epidemiol 181(7): 513-520.

Original articles

I Hamari A, Toljamo T, Nieminen P, Kinnula VL. (2010) High frequency of chronic cough and sputum production with lowered exercise capacity in young smokers. Ann Med 42(7): 512–20.

II Toljamo T, Hamari A, Nieminen P, Kinnula VL. (2012) Young male daily smokers are nicotine dependent and experience several unsuccessful quit attempts. Scand J Prim Health Care 30(3): 183−188.

III Hamari AK, Toljamo TI, Kinnula VL, Nieminen PA. (2013) Dual use of cigarettes and Swedish snuff (snus) among young adults in Northern Finland. Eur J Public Health 23(5): 768−71.

IV Tuisku A, Salmela M, Nieminen P, Toljamo T. (2016) Varenicline and nicotine patch therapies in young adults motivated to quit smoking: randomised, placebo-controlled prospective study. Basic Clin Pharmacol Toxicol. In press.

Original publications are not included in the electronic version of the dissertation.

Book orders:
Granum: Virtual book store
http://granum.uta.fi/granum/

UNIVERSITY OF OULU P.O. Box 8000 FI-90014 UNIVERSITY OF OULU FINLAND

ACTA UNIVERSITATIS OULUENSIS

UNIVERSITY of OULU
OULUN YLIOPISTO

ISBN 978-952-62-1154-1 (Paperback)
ISBN 978-952-62-1156-5 (PDF)
ISSN 0355-3221 (Print)
ISSN 1796-2234 (Online)