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THE IMPACT OF TOBACCO USE ON POSTOPERATIVE COMPLICATIONS

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everything good must come to an end.
Timo Räsänen

SUMMARY

In almost every field of surgery, there have been several reports of an increased frequency of wound healing complications among smokers. There is also evidence of a dramatic drop in the complication rate if a smoking cessation intervention is started 6–8 weeks ahead of orthopaedic surgery. Whether or not this is also true for other surgical procedures has not been studied, and it is not known if even shorter periods of smoking cessation can affect the complication rate. There is little evidence of the long-term efficacy of a perioperative smoking cessation intervention. Very few observations on snus and the rate of postoperative complications have been published. In this thesis, we tried to address these questions and, in addition, we attempted to estimate the impact of obesity on postoperative complications after inguinal hernia surgery and appendectomy. We also estimated the impact of tobacco use and obesity on the perforation rate in appendicitis.

Methods

To study the impact of smoking, snus and obesity on inguinal hernia surgery (Study I) and appendectomy (Study II), we used the Swedish Construction Workers' Cohort linked to the Swedish Inpatient Register. The cohort consists of approximately 361,280 individuals. To study the efficacy of a perioperative smoking cessation intervention (Study III) and the possible effects of that intervention on postoperative complications (Study IV), we performed a randomised controlled trial (n=117). The trial compared a smoking cessation intervention introduced four weeks prior to surgery with standard care. The primary outcome was any postoperative complication and the assessment was blinded.

Results

Our results in the cohort studies show that smokers have an increased risk of postoperative complications after inguinal hernia surgery (OR 1.34; 95% CI 1.04–1.72) and after appendectomy due to non-perforated appendicitis (RR 1.51; 95% CI 1.03–2.22). Smoking was also significantly associated with an increased risk of perforated appendicitis (RR 1.29; 95% CI 1.11–1.50). Obesity was also associated with an increased risk of postoperative complications after appendectomy due to non-perforated appendicitis (RR 2.60; 95% CI 1.71–3.95). Use of snus did not affect the frequency of postoperative complications or the rate of perforations. Smoking cessation intervention proved to be effective in our randomised trial. The overall short-term complication rate in the intervention group was 21% compared to 41% in the control group (p=0.03). The relative risk for the primary outcome of *any postoperative complication* in the intervention group was 0.51 (95% CI 0.27–0.97) and the number needed to treat (NNT) was five (95% CI 3–40). The proportion of abstinent individuals in the intervention group was 58% the week before surgery, the corresponding figure in the control group was 2% (p<0.001). After one year of follow-up one third (33%) of the individuals in the intervention group remained abstinent compared to 15% in the control group (p=0.03).

Conclusion

Smoking increases the risk of postoperative complications even in minor surgery such as inguinal hernia repair. There is also a significant association between smoking and perforated appendicitis. Smoking and obesity are also associated with more postoperative complications after open appendectomy in patients with non-perforated appendicitis. Snus does not seem to affect the complication rate after surgery at all. Smoking cessation programmes can be started successfully four weeks before surgery with long-lasting results. Perioperative smoking cessation is an effective means of reducing postoperative complications even when introduced as late as four weeks prior to surgery.

Key Words: *Smoking, snus, obesity, postoperative complication, appendectomy, hernia, smoking cessation, cohort studies, randomised controlled trials.*

LIST OF ORIGINAL PAPERS

- I. LINDSTRÖM D, SADR AZODI O, BELLOCCO R, WLADIS A, LINDER S, ADAMI J.
The effect of tobacco consumption and body mass index on complications and hospital stay after inguinal hernia surgery. *Hernia* 2007;11(2):117-23.
- II. SADR AZODI O, LINDSTRÖM D, ADAMI J, BELLOCCO R, LINDER S, WLADIS A.
Impact of body mass index and tobacco smoking on outcome after open appendicectomy. *Br J Surg* 2008;95(6):751-7.
- III. SADR AZODI O, LINDSTRÖM D, ADAMI J, TØNNESEN H, NÅSELL H, GILLJAM H, WLADIS A.
The efficacy of a smoking cessation programme in patients undergoing planned surgery - a randomised clinical trial. Accepted for publication, *Anaesthesia*.
- IV. LINDSTRÖM D, SADR AZODI O, WLADIS A, TØNNESEN H, LINDER S, NÅSELL H, PONZER S, ADAMI J. Effects of a perioperative smoking cessation intervention on postoperative complications – a randomised trial. E-pub *Annals of Surgery*, 30 July, 2008.

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LIST OF ABBREVIATIONS

CI	Confidence interval
CO	Carbon monoxide
e.g.	for example (<i>exempli gratia</i>)
ICD	International Classification of Diseases
i.e.	that is (<i>id est</i>)
IL-1 β	Interleukin 1 β
IL-6	Interleukin 6
NNT	Number needed to treat
NRT	Nicotine replacement therapy
OR	Odds ratio
p	Probability, <i>P</i> value
p.o.	per os, by mouth
ppm	parts per million
RCT	Randomised controlled trial
RR	Relative risk
SEK	Swedish kronor (currency)
Snus	Swedish moist oral tobacco
TNF- α	Tumor necrosis factor α
Vs	versus
WHO	World Health Organization

1 AIMS

The aims of the studies in this thesis were the following:

- To investigate the effect of tobacco consumption (smoking and snus) and obesity on the postoperative complication rate after inguinal hernia repair and open appendectomy.
- To determine the impact of tobacco consumption (smoking or snus) and obesity on the risk of perforated appendicitis.
- To investigate the short- and long-term efficacy of a perioperative smoking cessation intervention initiated four weeks preoperatively.
- To assess whether a perioperative smoking cessation intervention, starting four weeks prior to surgery, reduces the risk of postoperative complications.

2 BACKGROUND

Postoperative complications are a major concern after surgery and smoking increases the frequency of such complications. Negative effects on complication rates among smokers have been reported in hernia surgery,^{1,2} gastrointestinal surgery,³⁻⁵ orthopaedic surgery,⁶⁻⁸ plastic reconstructive surgery,⁹⁻¹¹ gynaecological surgery,¹² vascular surgery,¹³ and minor surgical procedures.^{14,15} Major complications influence not only the in-hospital care but also decreases long-term survival.¹⁶ In spite of this evidence, patient-related risk factors for complications are poorly quantified in common standard procedures such as inguinal hernia repair and appendectomy.

The effect of a smoking cessation intervention prior to surgery has also been evaluated in two randomised clinical trials. Smoking cessation initiated 6–8 weeks prior to planned hip and knee arthroplasty reduced the postoperative complication rate by 65%.¹⁷ In contrast, preoperative smoking cessation for 1–3 weeks did not influence the complication rate after colorectal surgery.¹⁸ Some other observational studies have demonstrated positive effects for a preoperative smoking cessation period of four weeks or more.^{19,20}

In summary, there is insufficient evidence concerning how the duration of smoking cessation affects the frequency of postoperative complications.^{21,22} Also, the potential effect of smoking intervention on different types of surgery needs further investigation. Our *a priori* hypothesis was that smoking cessation starting four weeks prior to surgery reduces the risk of postoperative complications. To evaluate this, we performed a randomised trial investigating whether or not an intervention of smoking cessation starting four weeks prior to general and orthopaedic surgery would reduce the frequency of overall postoperative complications.

2.1 PREVALENCE OF TOBACCO USE

WHO estimated in its latest world report on tobacco smoking that there are more than one billion smokers in the world.²³ In Sweden, approximately 16% of the population aged 16–84 years were smokers in the latest 2005 survey (14% among males, 18% among females)²⁴ and, in the Stockholm Capital Region, the figure for 2006 is 13.7 % for males and 15.6 % for females.²⁵ The prevalence of smokers in Sweden is at a uniquely low level; the reason for this has been argued to be the use of snus, Swedish moist oral tobacco. According to the Swedish National Institute of Public Health, in 2005 22% of Swedish men used snus on a daily basis and the corresponding figure for women was 4%.

2.2 HEALTH EFFECTS OF SMOKING AND SNUS

Half of all smokers will die due to their use of tobacco. Non-smokers have on average 10–14 years more of health than smokers. The detrimental effect of smoking has been thoroughly reported both at the individual level and at the public health level.²⁶ Tobacco smoking causes increased costs to society due to the increased need for health care, increased consumption of medications and increased sick leave.²⁷ Tobacco smoking is now the single most important preventable health problem in the world.²³ Snus has, compared to smoking, a very limited impact on public health.²⁸ Still, increasing evidence shows that snus probably causes an increased risk of several types of cancer.²⁹⁻³²

2.3 SMOKING CESSATION

The evidence for the benefit of smoking cessation is solid. There is no doubt about its positive effect on health and on cost-effectiveness. One example is that the cost per saved

life-year is 5000–15,000 SEK with counselling alone and 30,000–80,000 with nicotine replacement therapy (NRT). These figures may be compared with the treatment of high blood pressure, which incurs a cost of 150,000 – 200,000 SEK per life-year saved.³³ Smoking cessation therapy may be based on several steps including motivational counselling,³⁴ information on the health impact of smoking, strategies for successful cessation, information on changes in behaviour and exercise,³⁵ prevention of relapses and different drugs (i.e. NRT, bupropion hydrochlorid (Zyban®), varenicline (Champix®)).³⁶ More advice is more effective than brief advice.³⁷ Smoking cessation is a treatment that could decrease mortality in spite of achieving abstinence only in a minority.³⁸ To stop smoking at the age of 40 increased the life expectancy by 4.6 years in one study.³⁹ There are also many trials in progress, a new Swedish vaccine against smoking is currently being tested (Niccine®, 2008). The effects of different pharmaceutical products are given below. It should be noted that the Cochrane Collaboration has changed its recommendations for reporting pooled estimates. It now recommends relative risk (RR) instead of odds ratio (OR), which, by definition, will be lower if it is not a very uncommon outcome.⁴⁰

Cochrane results – drugs compared to placebo. Odds and risk of being able to stop smoking

	Odds and Risk	Year, author
Nicotine replacement	RR 1.6	2008, Stead
Zyban®	OR 1.9	2007, Hughes
Champix®	OR 3.2	2007, Cahill

2.4 METABOLIC AND PHYSIOLOGICAL EFFECTS OF TOBACCO

Cigarette smoke contains more than 4700 chemical compounds distributed in the aqueous, gas and the tar phases of the smoke.⁴¹ In the gas phase, the smoke comprises high concentrations of oxidants, free radicals and nitric oxide. The tar phase of cigarette smoke contains organic radicals, such as long-lived semiquinone radicals.⁴² The aqueous phase of cigarette smoke may undergo redox reactions in the epithelial lining fluid of smokers. Smoking has also been proved to cause oxidative damage in humans.⁴³ Sidestream cigarette smoke (the smoke that comes off a smoldering cigarette and is not inhaled) contains more than a thousand reactive organic compounds per puff, such as carbon monoxide, nicotine, ammonia, formaldehyde, acetaldehyde, crotonaldehyde, acrolein, N-nitrosamines, benzo(a)pyrene, benzene, isoprene, ethane, pentane and other genotoxic and carcinogenic organic compounds. On the other hand, most of the acute effect of smoking comes from nicotine and carbon monoxide (CO). Nicotine has sympathomimetic properties and CO disturbs oxygen delivery. Within 12–48 hrs most of the effect of nicotine and CO are diminished due to the wash-out of CO and degradation of nicotine to the inactive metabolite cotinine.⁴⁴ Swedish snus produces nearly the same peak levels of nicotine as in smoking, but the cotinine levels seem to be higher.⁴⁵ Some other biological effects of smoking are listed below.

2.4.1 Vascular

Perfusion of skin and peripheral tissue decreases during smoking. This is partly due to the vasoconstricting effect of nicotine.⁴⁶⁻⁴⁸ This vasoconstriction may affect the regulation of body temperature, and low body temperature may cause other complications such as shivering. Central haemodynamics are also altered among smokers.⁴⁹ All these vascular effects may disturb the normal physiological effects during anaesthesia. Altered physiology

may be an indirect way to increased morbidity since optimisation of fluids and oxygen delivery have been shown to decrease morbidity.⁵⁰⁻⁵³

2.4.2 *Coagulation*

Nicotine causes increased aggregation of platelets, which may lead to thrombosis.⁵⁴ CO causes hypoxia, which increases the production of red blood cells and the permeability of the endothelium, which in turn leads to higher viscosity and platelet aggregation.^{55,56} Already after two weeks of smoking cessation, platelet functions appear to be partially restored.⁵⁷

2.4.3 *Immune system*

Smoking increases the release of inflammatory markers in the blood^{58,59} and the white blood cells do not function properly.^{60,61} Pulmonary macrophages are altered and lymphocyte suppressor cells are increased. All these findings may facilitate inflammatory processes.

2.4.4 *Oxygenation of tissue*

Smoking decreases the partial pressure of oxygen by 22–48%, which causes a chronic oxygen deficiency in peripheral tissue.⁶² CO occupies the binding sites of oxygen in the haemoglobin molecule and the extent of this is dependent on the amount of tobacco consumed and the time elapsed since last cigarette.⁶³ CO also shifts the oxygen dissociation curve to the left and thereby causes decreased tissue oxygenation. Deoxygenation of tissue has also been associated with an increased risk of postoperative wound infection.⁶⁴ This is supported by the finding that supplemental oxygen may decrease the wound infection frequency.⁶⁵⁻⁶⁷ Global postoperative desaturation is also more common among smokers and desaturation is associated with myocardial ischaemia.⁶⁸ Besides affecting oxygenation in tissues, smoking also causes local pulmonary effects. Everything from chronic obstructive pulmonary disorders⁶⁹ to reduced ciliary movements and changes in surfactant properties⁷⁰ have been observed.

2.4.5 *Wound healing*

Smokers have a distinctly lowered production of collagen. Collagen is of great importance to the wound healing process and collagen synthesis is dependent on oxygen.⁷¹⁻⁷³ There is experimental evidence that the disturbed protein deposition may be restored after ten days of smoking cessation, collagen synthesis does not seem to recover in such short period.⁷⁴ It is not clear which compound in smoking that causes this effect, but it does not seem to be nicotine that impairs wound healing. There are experimental data from a mouse model which indicate that nicotine *per se* may even promote wound healing.⁷⁵ In conflict with these data a small experimental trial on rats showed an increased amount of flap necrosis following exposure to smokeless tobacco.⁷⁶ It is more important, however, that randomised controlled trials of smoking cessation using NRT in the intervention still found a decreased wound complication rate.^{17,77}

2.4.6 *Bone healing*

Smoking is associated with osteoporosis and thereby an increased fracture risk. There is a dose-dependent association and the differences are less pronounced among former smokers, indicating that smoking cessation may be beneficial. Bone healing after a fracture is also impaired.⁷⁸ There is experimental evidence that other substances than nicotine cause the delayed bone healing^{79,80} and a cohort study did not find any evidence of snus delaying bone healing.⁸¹

Since 1944⁸² there has been an increasing wealth of publications regarding the problems caused by smoking in the postoperative period.^{4,17,83 84-86} Besides more clinically established complications such as local wound complications and pulmonary complications, thromboembolism is by some believed⁸⁷ to be caused by smoking although the latter is under debate. Other general negative effects observed are an increased demand for postoperative intensive care⁸⁸ and prolonged hospitalisation periods when complications occur.^{89,90} There is also evidence of behavioural adverse effects such as agitation and non-compliance among smokers in the post-operative period.⁹¹ The possible impact of snus on postoperative complications has not been well described. We only found one cohort study that investigated the effect of snus on bone healing.⁸¹

2.5.1 *Gastrointestinal surgery*

Smokers undergoing surgery have an increased risk of postoperative intensive care admittance^{88,92} and an increased risk of pulmonary complications.^{12,14} The frequency of anastomotic insufficiency is increased after colorectal surgery^{3,93,94} and both smoking and obesity increases complications after colon surgery.⁸³ Delayed wound healing after abdominoperineal resection of rectum has been observed⁹⁵ as well as increased recurrence after anal fistula flap repair.⁹⁶ After gastric bypass surgery, smokers are more prone to develop peptic ulcers⁹⁷ and bacterial infections are more common after surgical procedures in general.⁹⁸ Wound infections after bariatric surgery are more common among smokers.⁹⁹ The number of pack-years smoked can predict the need for postoperative hypoxia and complications after upper GI surgery.¹⁰⁰

2.5.2 *Hernia surgery*

The frequency of primary hernia¹⁰¹ as well as the risk of recurrence of inguinal hernia² is increased among smokers. Tobacco smoking also increases the risk of incisional hernias^{102,103} and increases the risk of wound infection.^{1,104} Also, after internal mesh fixation in abdominal sacral colpoperineopexy, smoking has been shown to predict mesh erosion.¹⁰⁵

2.5.3 *Orthopaedic surgery*

Patients undergoing hip arthroplasty have an increased risk of postoperative complications if they are smokers.⁷ The risk of pseudoarthrosis has been reported to be four times higher for smokers^{8 106} and failed fracture healing is more common after surgical fixation.¹⁰⁷

2.5.4 *Breast cancer surgery*

Wound infections and skin necrosis are more common among smokers undergoing breast cancer surgery.¹⁰⁸⁻¹¹¹ In addition, breast reconstruction following mastectomy entails complications among smokers.

2.5.5 *Plastic surgery*

Reconstructive surgery is particularly vulnerable to smoking effects. Muscular flaps among smokers have a doubled risk of entailing necrosis and smokers require on average one extra procedure before healing occurs.^{112,113} The risk of flap complications among smokers is so common that preoperative cessation has already been proposed.^{10,114} Wound healing after breast reduction is disturbed.^{19,115,116} A minor adverse effect that may be of importance to many patients is increased scarring; post-laparotomy smokers developed significantly more ugly scars.¹¹⁷ After performing skin-flap procedures smokers have an increased risk of wound complications⁸⁴ and after face-lifts complication rates are massively increased among smokers¹¹⁸ as well as after aesthetic abdominoplasties.¹¹⁹ There

is evidence of a dose-response relationship in which a serum cotinine level of above 10 ng/ml has been shown to be associated with complications after head and neck flap reconstructions.¹²⁰

2.5.6 Cardiovascular and vascular surgery

There is massive evidence showing that virtually every vascular surgery procedure has a poorer outcome and patency among tobacco smokers. This applies to both cardiac¹²¹⁻¹²⁴ and vascular surgery.¹²⁵⁻¹²⁸

2.5.7 Day care surgery

There is some evidence that smoking increases wound infections and pulmonary complications even after minor day-care surgery.¹⁴ Even in minor diagnostic skin biopsies adverse effects of smoking have been seen.¹²⁹

2.6 EFFICACY OF SMOKING CESSATION IN THE PREOPERATIVE PERIOD

There is not so much evidence to choose from when it comes to *preoperative* smoking cessation. The scheduled face-to-face consultation combined with NRT is the method that has the best documentation of efficacy.¹⁷ Other more low-intensity protocols have not achieved as high frequency of abstainers.^{18,130,131} A Cochrane review of in-hospital interventions concluded that intensive counselling lasting at least one month after discharge was effective, and in addition, NRT seemed to improve quit rates.¹³² There are two long-term (one year) efficacy reports on preoperative smoking cessation interventions: in one RCT 27% in the intervention group were still abstinent one year after surgery compared to 26% in the control group.¹³³ The other trial recently published a 22% abstinence rate in the intervention group compared to 3% in the control group.¹³⁴ The latest reviews concludes that preoperative intervention is effective, in the short-term perspective, but longer follow-ups are needed.^{135,136}

2.7 EFFECT OF SMOKING CESSATION ON POSTOPERATIVE COMPLICATIONS

In spite of the deleterious effects of smoking on complications, preoperative smoking cessation has not sufficiently been explored.²¹ How long does a smoking cessation period need to be, to prove efficient in preventing complications, has been heavily debated.^{22,137,138} Studies with different designs trying to explore a shorter cessation period of three weeks have shown diverging results.^{18,20,139,140} The most cited and influential study in the field by Møller et al. consisted of a RCT investigating whether 6–8 weeks of preoperative smoking cessation intervention were effective in preventing complications.¹⁷ The study comprised planned hip and knee arthroplasties and the results were impressive. Those in the intervention group reduced their complication rate by more than half; the number needed to treat (NNT) was 3. The intervention group had a complication rate of 18% compared to 52% among controls; the effect was strongest in wound complications (5% vs 31%). This intervention was also shown to be cost-effective.¹⁴¹ Whether a preoperative smoking cessation period of less than 6–8 weeks can reduce complications is not clear.^{140,142} There is only one RCT that evaluates a short-term smoking cessation period of 2–3 weeks. This trial included patients undergoing colorectal surgery and no difference in complications was found.¹⁸ Another experimental randomised trial with skin biopsies did find a beneficial effect after four weeks of cessation.⁷⁷ There is no evidence that a *reduction* of smoking could be beneficial; a complete stop seems to be necessary.¹⁷

2.8 BENEFITS OF SMOKING IN RELATION TO COMPLICATIONS

Although one can expect a severe publication bias, there is not much evidence of any protective effect of smoking. The only evidence-based effect that there is something good about it is a reduced risk of postoperative nausea and vomiting. The mechanism behind this has been debated,¹⁴³ but probably stems from an anti-emetic effect of nicotine.¹⁴⁴ There are occasional reports of improved wound healing among smokers,¹⁴⁵ but not in any adequately powered and performed trials.

2.9 HARM FROM PREOPERATIVE SMOKING CESSATION

There has been an old belief that smokers are more prone to complications if they quit smoking in connection with surgery. Modern trials have not been able to confirm this; in fact, the only finding in controlled trials is rather the opposite, i.e. that cessation is protective or harmless. There is a side effect in weight gain¹⁴⁶ although the health impact of this is negligible compared to continued smoking. In a randomised trial of preoperative smoking cessation the weight gain one year after surgery was on average 1 kilogram.¹³⁴ Then there are some possible adverse events that might occur as a result of pharmaceutical treatment, such as seizures from Zyban® or worsened depression by Champix®, but these may not be related to smoking cessation *per se*.

2.10 EFFECT OF OBESITY ON POSTOPERATIVE COMPLICATIONS

Obesity seems to increase complications in a wide range of surgical procedures. This might be due to technical, surgical difficulties but also to physiological mechanisms such as insulin resistance, increased susceptibility to infections and deoxygenation. Malnourished patients with a low BMI also have an increased risk of a poor outcome.¹⁴⁷ Some authors have argued that the obese have no excess risk in routine surgery.¹⁴⁸ The reason for conflicting results might be that the risk is U-shaped rather than linear, meaning that the slimmest and the fattest have the highest risk.¹⁴⁹ Several reports show that obese patients generally have an increased risk of wound infections¹⁵⁰⁻¹⁵² and thromboembolism.^{153,154} There are several types of procedures in which obesity has been associated with an increased complication frequency, including prosthesis complications,¹⁵⁵ spine surgery,¹⁵⁶ gastric cancer,¹⁵⁷ tracheostomy¹⁵⁸ and breast reconstruction.^{159,160} Also in a minor procedure such as open appendectomy, obesity has been shown to increase the operating time and postoperative pain.¹⁶¹ There is a possible link between smoking cessation and obesity in that women in particular may prefer smoking in fear of a possible weight gain if they quit.¹⁶²

2.11 LACK OF EVIDENCE

Major surgical procedures have always attracted surgeons the most and this is probably the reason why they have been studied the most. When it comes to minor surgical procedures with low mortality rates, the data on morbidity are scarce.

The relationship of smoking and obesity to postoperative complications in routine procedures such as inguinal hernia surgery and appendectomy has not been reported.

Few studies investigating the impact of patient-related factors on perforation in appendicitis have been published.

The impact of snus on postoperative complications in general is not known.

Preoperative smoking cessation interventions shorter than six to eight weeks have been investigated in only one small RCT.¹⁸ The same trial is also the only one including general surgery patients.

Reporting on the long-term efficacy of preoperative smoking cessation is sparse. There are only two trials that have reported cessation rates at one year.^{21,133,134}

3 STUDY I AND II

3.1 METHOD STUDIES I & II

The Swedish Construction Worker's Cohort

The Swedish Construction Industry's Organisation for Working Environment Safety and Health (Bygghälsan), established in 1968, provided outpatient medical services to construction workers all over Sweden from 1969 through 1992.^{163,164} The organisation was a joint venture launched by the construction trade unions and the corresponding employer's association. The basic units were stationary and mobile clinics, typically staffed by a few nurses and a physician. The main activity was preventive health check-ups, offered to all blue- and white-collar workers in the building industry through regular (every other year during the first years, every three years thereafter) personal invitations and visits to outpatient clinics or advertisements at virtually all major building sites. Since 1971, data from these health check-ups have been compiled in a computerised central register. In all, 361,280 individuals had records of at least one visit between 1971 and 1993. Since less than 5% of the participants were women, we restricted our investigation to male workers (n=343,822). Our studies on this cohort were approved by the Ethics Committee at Umeå University, Sweden (No. 03-191).

Exposure assessment

Before every visit, each worker filled in a self-administered questionnaire seeking exposure information. On an average, each cohort member underwent three health check-ups, each 2–3 years apart. To avoid misunderstandings or inconsistencies, the answers were double-checked by a nurse at the time of the visit. The questionnaires were extensive and comprised almost 200 items, including, among other things, a detailed tobacco consumption history, anthropometric measurements and occupational coding in 200 categories. The quality of the smoking data has been reviewed in a previous study by Nyrén et al.¹⁶⁵ Missing information on smoking duration was noted in 1.3% of current and 1.4% of previous smokers. Inconsistencies (e.g. when subjects who indicated that they were current or ex-smokers in the first questionnaire asserted that they had never smoked in the second questionnaire) were found in 2.6% of the cases. Perfect concordance between reports on smoking status 2–3 years apart was found in 89%.

In order to attain the most complete tobacco exposure status, we strived to use the questionnaire information from the period 1978 and later. During 1976 and 1977 no smoking data were collected. Exposure data from 1978–1992 were only collected from the first visit due to a flaw in registration if workers came on a return visit. With regard to the information collected in 1971–75, it has subsequently been noted that non-smokers could not actively deny smoking in the questionnaire. Instead, they were instructed to simply skip the smoking questions. All cohort members without answers to these questions were coded as non-smokers. Thus, the never-smoker category might have contained some smokers who skipped the smoking questions for other reasons. During the 1978–92 period, information on smoking and use of snus was obtained through personal interviews by nurses.²⁹ When assessing the total amount of tobacco smoked by a patient every day, we assumed cigarettes to contain 1 gram of tobacco and cigars 6 grams of tobacco. Pipe smokers reported the amount of tobacco in grams consumed every week. In order to calculate pack years of tobacco use, we multiplied the total amount of tobacco smoked every day by the length of time the patient had been smoking, and divided by 20.

Swedish Inpatient Register

The Swedish Inpatient Register has collected data on individual hospital discharges since 1964 and has complete national coverage from 1987 onwards. National health care in Sweden is based on administratively independent county councils and is funded mainly by local taxes. The private sector is small and provides mainly planned care.¹⁶⁶ The Register stores patient discharge data from all publicly funded hospitals in Sweden, which make up the vast majority. It should be noted is that most day-care surgery is not included. Each patient record corresponds to one hospital admission and contains, in addition to the national personal identification number, the dates of admission and discharge, information about the type of admission (scheduled/emergency), discharge destination (home, other hospitals or departments, senior citizens home, death) and discharge diagnoses coded according to the Swedish version of ICD. Each patient record also lists up to 12 surgical codes assigned according to the Swedish Classification of Operations and Major Procedures. The Register has been evaluated for validity and completeness, and the codes for the main diagnoses were correct at the three-digit level for 92–94% of the records on surgical patients. For surgical procedures (excluding endoscopies and biopsies), the codes were incorrect for 2% of the records and were missing for 5.4%.^{167 168} Another validation study made on patients with hip fractures found an estimated error level of the diagnoses of less than 1%.¹⁶⁹ We were able to follow each patient until 31 December 2004.

Cohort identification Study I

Using the personal identification number, we linked our cohort to the Inpatient Register. All construction workers discharged from hospital with a procedure code for open inguinal hernia repair were identified. We selected inguinal hernias with open suture repair or with open mesh repair. In all, 23,812 cohort members had undergone inguinal hernia repair. We selected only the first-time inguinal hernia procedure and thus 4,316 observations were excluded. Further exclusions included women, exposure data missing (individuals retained if data on tobacco were available but not specified in dosage), surgery before entry into the cohort, patients with an other main diagnosis than inguinal hernia, those with erroneous personal identification numbers (in the whole cohort, $n=570$) and patients who underwent another major surgical procedure at the same time. Excluded procedures were for instance; incisional hernias, appendectomies, endoscopic prostatic surgery, cancer surgery, hip prosthesis. Those retained were those that could possibly be a complication to hernia surgery; i.e. small bowel obstruction, stomas and reoperations. Finally, we counted subjects with repeated hospitalisations in conjunction with the same hernia repair only once. The final cohort consisted of 12,697 male subjects. The majority had an open suture repair ($n=11,198$, 88.2%) and 1,499 had an open mesh repair. The exposure data in this study came from the following time periods: 4,176 patients had exposure information from 1978 onwards, 66 individuals had exposure status from 1975 and the rest from before 1971–1974.

Cohort Identification Study II

We selected all appendectomies with the procedure code of open appendectomy between 1971 and 2004. We excluded all cases with colon cancers or inflammatory bowel disease. Due to the low number of observations, all women in the cohort ($N=197$) were excluded. The final cohort consisted of 6,676 male patients. We used the Swedish version of ICD-8 to ICD-10 to identify perforation status of appendicitis.

Study outcomes

POSTOPERATIVE COMPLICATIONS

We went through the Swedish Inpatient Register using the Swedish versions of ICD-8 to ICD-10 and the Swedish Classification of Operations and Major Procedures in order to collect information on postoperative complications that had occurred from the day of surgery and 30 days onwards. All deaths within 30 days were identified using information from the Swedish Death Register. Since 1952 the National Board of Health and Welfare has kept the Death Register comprising all deceased persons registered in the country at the time of death. The Register provides information on underlying and contributing causes of death, the date of death, and age at death. All causes of death are reported by the attending physician or coroner and are coded in accordance with the International Classification of Diseases, Injuries, and Causes of Death (ICD). The number of missing cases is low, less than 0.5%.¹⁷⁰

In addition to obvious complications such as wound infection or myocardial infarction, any adverse event which could be regarded as a complication to surgery was included. General complications such as peptic ulcer, fever of unknown origin and small bowel obstruction were placed in the Systemic group. Patients could be registered for more than one complication during the follow-up. In order to have more stable groups in terms of sample size, we grouped all complications, including cases of death within 30 days, into a single category (*Any complication*).

LENGTH OF HOSPITAL STAY STUDY I

Every individual was followed until the day of discharge home. Patients (n =621) who were discharged from one clinic and admitted to another one on the same day were considered to still be undergoing treatment or observation due to the hernia procedure and were followed until discharged home.

Statistical analyses Study I

We used stratified categorical data analysis and a logistic regression model to study the probability of developing complications within 30 days from surgery. In order to avoid multicollinearity, we analysed different tobacco-related exposure factors separately, thereby achieving different final models. We used logistic regression to estimate the adjusted OR and its 95% confidence interval. We employed descriptive statistics to summarise the hospital stay. We applied natural log transformation to improve symmetry and normality when performing multiple linear regressions. We used the multivariable *F test* to assess the significance of each simple variable added to the model (we considered a *P* value (*p*) of less than 0.05 significant). The overall *Goodness of fit* of the model was studied by means of the *adjusted R²*; residual analyses (based on both crude and studentized residuals) were performed to assess the validity of assumptions in the linear regression, and diagnostics analyses were performed to identify possible outlying patients. Stata 9.1 was used to perform the statistical analyses (StataCorp 2005. *Stata Statistical Software*. Release 9. College Station, TX: StataCorp LP).

Statistical analyses Study II

We summarised the association between tobacco use and BMI and the risk of (a) perforated appendicitis and (b) 30-day postoperative complications in terms of RR and the corresponding 95% CI using binomial logistic regression. We performed univariable (results not shown) and multivariable binomial logistic regression analyses to study the

effect of BMI and tobacco smoking on the risk of perforated appendicitis. In the multivariable analyses, we adjusted also for age and calendar period. We performed the same analyses to study the impact of BMI and tobacco smoking on the risk of postoperative complications when stratified by perforation status. We used the *Hosmer-Lemeshow* goodness-of-fit test to assess the fit of the models. Stata 9.1 was used to perform the statistical analyses (StataCorp 2005. *Stata Statistical Software*: Release 9. College Station, TX: StataCorp LP).

3.2 RESULTS STUDY I

Postoperative complications

The entire cohort of 12,697 subjects had a mean age of 56.5 years and a mean BMI of 24.6. Current smokers constituted 39.3%, previous smokers 24.3% and never smokers 36.4%. Ever snus users accounted for 20.9% and never users 79.1%. The overall complication rate was 2.9%.

After adjusting for the other covariates in the multivariable logistic regression analysis, current smokers had an increased risk of postoperative complications compared to never smokers (OR, 1.34; 95% CI, 1.04–1.72, Table 1). Snus and pack-years of tobacco smoking were not found to be significantly associated with an increased risk of postoperative complications.

BMI was also associated with postoperative complications ($p=0.04$). The underweighted had an increased risk of complications (OR, 2.94; 95% CI, 1.15–7.51). There was a trend to an increase in the risk of postoperative complications in connection with obesity ($p=0.07$). Obese patients had an increased risk of postoperative complications in comparison with the normally weighted reference group (OR, 1.57; 95% CI, 0.96–2.57).

Table 1. Adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) of the rate of postoperative complications according to tobacco exposure and BMI category obtained from logistic regression analyses

^a Each tobacco-related exposure variable was fitted separately. All final models were adjusted for age, calendar period, BMI and acute surgery.

^b The final model for BMI was adjusted for age, calendar period, smoking status and acute surgery.

	<i>Any complication</i>			
	<i>OR</i>	<i>95% CI</i>	<i>P-value</i>	<i>Overall P-value</i>
<i>Overall smoking status^a</i>				0.02
Never	Ref	Ref		
Previous	0.95	0.71–1.28	0.75	
Current	1.34	1.04–1.72	0.02	
<i>Smus status^a</i>				0.62
Never	Ref	Ref		
Ever	0.93	0.71–1.22	0.62	
<i>Pack years of smoking^a</i>				0.43
Never-tobacco smokers	Ref	Ref		
>0–9.9	1.11	0.83–1.48	0.47	
10–19.9	1.34	1.00–1.81	0.05	
20–29.9	1.12	0.74–1.73	0.58	
30–max	1.14	0.74–1.76	0.54	
<i>Body mass index^b</i>				0.04
<18.5	2.94	1.15–7.51	0.02	
18.5–24.9	Ref	Ref		
25–29.9	1.16	0.92–1.46	0.20	
30–max	1.57	0.96–2.57	0.07	

3.3 RESULTS STUDY II

Perforation status

A total of 5,536 (82.9%) patients underwent open appendectomy due to non-perforated appendicitis. The mean age at the time of surgery was 41.4 (standard deviation [SD] 15.1) for patients with non-perforated appendicitis and 49.8 (SD: 16.7) for those with perforated appendicitis. The mean BMI was almost the same for patients with non-perforated appendicitis and perforated appendicitis (24.4 (SD: 3.1) and 24.9 (SD: 3.2), respectively).

The impact of BMI and tobacco smoking on the risk of perforated appendicitis is shown in Table 2. Current smoking was found to be significantly associated with an increased risk of perforation. The risk of perforation increased up to 29% (RR 1.29; CI 1.11–1.50) among current smokers with >10 pack-years of tobacco use compared to never tobacco-smokers. Increasing age was also found to be an independent predictor of the risk of perforation (p<0.01). The risk of perforation was increased threefold (RR 3.37; CI 2.72–4.19) among those older than 70 as compared to patients aged 16–30 years. A high BMI was not significantly associated with an increased risk of perforated appendicitis (p=0.55).

Table 2: Adjusted odds ratios and corresponding 95% confidence intervals (CIs) for changes in the rates of perforated appendicitis according to age, tobacco use and BMI category. Multivariable logistic analyses

^a The final model for age was adjusted for calendar period, smoking status and BMI.

^b The final model for BMI was adjusted for calendar period, age and smoking status.

^c Smoking status and snuff status were fitted separately. Both final models were adjusted for calendar period, age and BMI.

	OR	95% CI	P value
<i>Age Category^a</i>			
16–30	1.00	Ref	Ref
31–40	1.30	1.04–1.78	0.02
41–50	1.97	1.55–2.50	<0.001
51–60	2.46	1.90–3.18	<0.001
61–70	3.44	2.59–4.57	<0.001
71–92	4.89	3.66–6.54	<0.001
<i>Body Mass Index Category^b</i>			
18.5–24.9	1.00	Ref	Ref
25–27.4	1.04	0.89–1.23	0.60
27.5–29.9	1.10	0.87–1.38	0.42
30–max	1.17	0.88–1.55	0.29
<i>Smoking status, Pack-years of tobacco use^c</i>			
Never-tobacco smokers	1.00	Ref	Ref
Previous, 0–9.9	0.94	0.75–1.19	0.62
Previous, ≥10	1.16	0.86–1.58	0.33
Current, 0–9.9	1.21	1.01–1.45	0.04
Current, ≥10	1.44	1.16–1.78	<0.01
<i>Snus status^c</i>			
Never	1.00	Ref	Ref
Ever	0.89	0.77–1.03	0.12

Postoperative complications

In total, 241 patients (4.4%) with non-perforated appendicitis and 75 (6.6%) with perforated appendicitis had one or more events of postoperative complications. The most common complication in both groups was wound infection occurring in 163 (2.9%) and 22 (1.9%) cases of non-perforated and perforated appendicitis, respectively. A total number of 26 (9.9%) obese patients with non perforated appendicitis developed one or more postoperative complications as compared to 123 (3.6%) patients among those of normal weight. The corresponding figures among patients with perforated appendicitis were 7 (8.9%) and 37 (6.0%).

The results from multivariable binomial logistic regression analyses are presented in Table 3. Having a high BMI was found to be significantly associated with an increased risk of postoperative complications among patients with non-perforated appendicitis ($p < 0.01$). Among current smokers with >10 pack-years and non-perforated appendicitis, the risk of postoperative complications was increased by 51% (RR 1.51; CI 1.03–2.22). None of the predictors mentioned above were significantly associated with an increased risk of postoperative complications in perforated appendicitis.

Table 3: Adjusted OR and corresponding 95%CI for changes of rates of postoperative complications according to tobacco exposure and BMI category. Multivariable logistic analyses.

*Including individuals (N=90) with BMI <18.5

^a The final model for BMI was adjusted for age, calendar period and smoking status.

^b Smoking status and snus status were fitted separately. Both final models were adjusted for calendar period, age and BMI.

	<i>Non-Perforated</i>			<i>Perforated</i>		
	<i>OR</i>	<i>95% CI</i>	<i>P value</i>	<i>OR</i>	<i>95% CI</i>	<i>P value</i>
<i>Body Mass Index: Category^a</i>						
18.5*–24.9	1.00	Ref	Ref	1.00	Ref	Ref
25–27.4	1.11	0.80–1.55	0.54	1.03	0.57–1.84	0.93
27.5–29.9	1.74	1.15–2.67	0.01	1.22	0.57–2.62	0.61
30–max	2.80	1.76–4.45	<0.001	1.33	0.55–3.20	0.53
<i>Smoking status, Pack-years of smoking^b</i>						
Never-smokers	1.00	Ref	Ref	1.00	Ref	Ref
Previous, 0–9.9	0.99	0.63–1.57	0.97	0.56	0.20–1.52	0.25
Previous, ≥10	0.85	0.44–1.64	0.63	0.49	0.16–1.53	0.22
Current, 0–9.9	1.02	0.71–1.47	0.93	1.01	0.50–2.03	0.97
Current, ≥10	1.55	1.02–2.34	0.04	1.30	0.67–2.55	0.44
<i>Snus status^b</i>						
Never user	1.00	Ref	Ref	1.00	Ref	Ref
Ever user	0.84	0.62–1.11	0.23	0.77	0.43–1.37	0.37

4 STUDIES III AND IV

4.1 METHOD STUDIES III AND IV

Study Setting

A randomised clinical trial conducted at four university-affiliated hospitals in the Stockholm region, Sweden. The study was planned according to the International Conference on Harmonisation Guidelines for good clinical practice and it was approved by the Ethics Committee of the Karolinska Institute (Ref. No. 03-214, 215) Stockholm, and registered at Clinicaltrials.gov (ID NCT00533000). This trial was performed and reported according to guidelines provided by the CONSORT group.¹⁷¹

Patients

Patients scheduled for primary inguinal and umbilical hernia repair, laparoscopic cholecystectomy or a hip or knee prosthesis were asked to participate in the study. To be eligible, patients had to be daily smokers (for at least one year prior to inclusion) and aged 18 to 79 years. Patients with overt alcohol or drug abuse, pregnancy, severe mental illness, dementia or poor Swedish language proficiency were excluded.

Assignment

Patients were enrolled after giving their informed consent by study nurses in the hospitals or by the treating surgeons, none of whom took part in the randomisation procedure. The nurse administering the smoking cessation intervention did the randomisation on the day of inclusion. Patients were randomised in a 1:1 ratio to a control group or intervention group, using opaque, sealed envelopes in blocks of ten, stratified by type of surgical procedure and clinic. The allocation was blinded to the treating surgeon, study nurses evaluating outcomes and other medical staff.

Intervention

The intervention was intended to start four weeks prior to surgery and last for four weeks after surgery. The intervention included weekly meetings or telephone counselling with a nurse trained in smoking cessation therapy, the telephone number to a hot line providing smoking cessation advice, and free nicotine substitution (Nicorette[®]) offered with an individual schedule for the whole intervention period. We offered nicotine replacement therapy in the form of self-adhesive patches, chewing gum or microtabs based on patient preferences. The intervention was aimed at keeping the patients completely smoke-free from four weeks preoperatively until four weeks postoperatively. The control group received standard care, which, besides the neutral information given on the consent form, included little or no information about smoking cessation or the potential harm of tobacco smoking.

Baseline data

Each patient filled in a questionnaire upon inclusion providing background information on marital status, occupation and education level. We recorded the average alcohol consumption per week and the previous smoking history was categorised in pack-years. The Fagerström score¹⁷² is a validated measure of nicotine dependency and was used to grade nicotine dependency. We also recorded information on regular exercise and body mass index (BMI). A preoperative health evaluation determined the ASA class,¹⁷³ forced expiratory volume (FEV 1.0), the presence of comorbidities and any medications. The

smoking status of all participants was evaluated preoperatively by both self-administered questionnaires and measurements of carbon monoxide (CO) in the expired air (Micro™ Smokerlyzer®, Bedford Scientific Ltd, Rochester, UK). The Smokerlyzer measures CO in the Range 0–200 with an accuracy of $\pm 2\%$. Following inhalation, CO displaces oxygen in the erythrocyte to form carboxyhemoglobin (COHb). In this form, CO has a half-life of about 5 to 6 h and may remain in the blood for up to 24 h depending on a number of factors, such as gender, physical activity, and ventilation rate.

Follow-up data

In the intervention group, smoking status, nicotine and tobacco consumption were recorded each week during the intervention. Smoking habits were validated by CO measurements at follow-up at the clinic two to three weeks postoperatively. In the *per protocol* analysis in Study IV, patients were divided into three groups. They were judged to be successful in smoking cessation if they reported smoking zero cigarettes for the minimum period of three weeks prior to surgery until four weeks postoperatively and if the postoperative level of exhaled CO was ≤ 10 parts per million (ppm). The cutoff level of 10 was based on previous findings.¹⁷⁴ The second group consisted of patients who reported smoking zero cigarettes for the period of 1–2 weeks prior to surgery until four weeks postoperatively, with a postoperative CO of ≤ 10 ppm. The last group was those who continued to smoke or only reduced smoking.

Outcome assessment Study III

Successful short-term abstinence was considered only if participants reported no use of cigarettes at least three weeks prior to surgery, remained abstinent until four weeks after the surgical procedure and if the level of exhaled carbon monoxide (CO) measured at the next visit to the hospital, 2–3 weeks postoperatively (median 14 days), was ≤ 10 ppm. To assess the outcome in smoking cessation one year after surgery, a questionnaire was posted to all participants. If the questionnaire was not returned, we retrieved smoking data by phone. All individuals with missing data were considered to be smokers.

Outcome measures Study IV

The main outcome measure was the frequency of any postoperative complication within 30 days. The secondary outcome was the frequency of any wound complication during the same follow-up period. The study nurse recorded complications at the two to three-week clinical follow-up and via a telephone interview at four weeks postoperatively. We predefined complications in the study protocol (Table 4) and instructed all study nurses with the same information and training in how to record possible complications on the case record form (CRF). The study group double-checked each complication recorded on the CRF by the study nurse, reviewing the medical record. A complication was defined as any unexpected event causing additional medical or surgical treatment, additional investigations (radiography, laboratory tests), a prolonged hospital stay or unscheduled postoperative check-ups at the out-patient department. The study group evaluated all complications without prior knowledge of group allocation.

Table 4: Prespecified Definitions of Postoperative Complications

<p>Wound complications</p> <p>Seroma (wound revision, wound drainage or need for repeated wound dressings)</p> <p>Superficial wound infection (infection treated with antibiotics or repeated wound dressings)</p> <p>Deep wound infection (treated with surgical debridement)</p> <p>Heamatoma (treated with surgical intervention, blood transfusion or extra wound checks)</p> <p>Wound dehiscence (redo surgery)</p> <p>Skin necrosis (surgical wound revision or repeated wound checks)</p> <p>Pressure wounds (wound revision or need for repeated wound dressings)</p>
<p>Urinary tract complications</p> <p>Urinary retention (need for catheterisation after surgery)</p> <p>Urinary tract infection (treated with antibiotics)</p> <p>Renal failure (oliguria <500 ml/24h or increase in creatinine by more than 30%)</p>
<p>Gastrointestinal complications</p> <p>Intolerance to oral nutrition and prolonged need for intravenous fluids (>24 h)</p> <p>Small bowel obstruction (redo surgery or gastrointestinal X-ray series)</p> <p>Biliary leakage (redo surgery or endoscopic retrograde cholangiography)</p>
<p>Pulmonary complications</p> <p>Pneumonia or bronchitis (treated with antibiotics)</p> <p>Respiratory insufficiency (postoperative need for ventilator support, postoperative need for oxygen more than 24 h or other respiratory treatments)</p>
<p>Cardiovascular complications</p> <p>Myocardial infarction/Angina pectoris/Heart failure/Arrhythmias (causing treatment, prolonged observation or additional diagnostic work-up)</p> <p>Stroke/TIA (Neurological symptoms causing treatment, prolonged observation or additional diagnostic work-up)</p> <p>Deep venous thrombosis (treated and verified with duplex scanning or phlebography)</p> <p>Pulmonary embolism (treated and verified with computerised tomography)</p>
<p>Other infectious complications</p> <p>Fever of unknown origin (treated with antibiotics or additional investigations)</p> <p>Sepsis (blood-borne infection treated with antibiotics)</p>
<p>Prosthesis-related</p> <p>Fracture of prosthesis (X-ray verified)</p> <p>Dislocation of prosthesis (X-ray verified)</p> <p>Peripheral nerve injury (clinical or neurophysiologic diagnosis)</p>
<p>Other</p> <p>Redo surgery (cause)</p> <p>Death (cause)</p> <p>Other complication (specify)</p> <p>Any complication (Yes/No)</p>

Power Calculation

The power calculation was based on the results of previous randomised trials^{17,77} and was performed using a two-tailed test. We made a conservative estimate of a baseline complication rate of 30% and a treatment effect of 30% reduction of complications. We planned to include 586 patients in total to identify a 30% reduction (from 30% down to 21%) in the complication rate with a statistical power of 80% ($\beta=0.20$) at the significance level of 0.05 (α). We terminated the inclusion in December 2006 before the estimated number because recruitment was slowing down. No interim analysis was done.

Statistics Study III

The association between different factors pertaining to baseline characteristics and short and long-term abstinence from smoking was analysed using *Fisher's exact test*. We used multivariable logistic regression modelling to study how the participants' characteristics could simultaneously affect the likelihood of abstinence one year after surgery. Variables were included in the multivariable model if the *P* value of the univariable analyses was $p < 0.15$. Results from the multivariable logistic regression analysis are presented as odds ratios using 95% CIs. SPSS version 16.0.2 was used to perform the statistical analyses (SPSS, Chicago, IL, USA).

Statistics Study IV

Our primary analyses were performed according to intention to treat and secondary analyses were *per protocol*. We used *Fisher's exact test* for dichotomous data and *Mann-Whitney* when applicable. The level of statistical significance was set at $p < 0.05$ and tests were always two-sided. We also calculated the absolute and relative risk reduction and the numbers of patients needed to treat (NNI). As we could not recruit the estimated number of patients in the power calculation, we performed further analyses. We used binomial logistic regression to study potential confounders due to the differences between the two groups at baseline. Logistic regression was not performed since the outcome was so common ($>10\%$) that the odds ratio would be an overestimation if (incorrectly) interpreted as relative risk.⁴⁰ First, we introduced a univariable analysis with randomisation status as the only explanatory variable and we assessed parameter estimates with *Wald's test*. Secondly, we added each additional variable at baseline to the model one at a time. A variable was *a priori* considered to be a confounder if the RR for randomisation status changed by more than 10% when the new variable was added to the model. Data were analysed in SPSS version 15.0 (SPSS, Chicago, IL, USA).

4.2 RESULTS STUDY III

Between 16 February 2004 and 21 December 2006, 117 patients agreed to participate, 55 of which were randomised to the intervention group and 62 to the control group. Information on smoking status was collected until January 2008. Seven patients in the intervention group and eight in the control group did not complete the study as shown in Figure 1 (Study III). Reasons were that they did not meet the inclusion criteria ($n=5$), or that they did not undergo surgery within the period allowed by the study plan ($n=8$), or that they withdrew consent ($n=2$). Five patients were incorrectly randomized since they did not meet the inclusion criteria (pipe smoker, cheroot smoker, bilateral hip prosthesis, bilateral knee prosthesis, and recurrent hernia). Data collection was only complete for those who followed the study protocol (per-protocol analysis). The smoking cessation programme started at a median of 4 (SD: 1.3) weeks prior to planned surgery and lasted until four weeks after the surgical procedure. Each patient in the intervention group participated in a mean of 7 (SD: 1.8) meetings or telephone calls. Most patients, 41/48

(85.4%) patients in the intervention group used NRT products. No patient started using snus.

Short-term smoking abstinence

The short- and long-term success in abstinence by both *intention to treat* and *per protocol* is shown in table 5. According to the intention to treat analysis, 20 of 55 (36%) patients in the intervention group and 1 of 62 (2%) in the control group were completely abstinent for the minimum period of three weeks before surgery until four weeks after surgery ($p < 0.001$). Corresponding figures for the *per protocol data* were 19 of 48 (40%) and 1 of 54 (2%) ($p < 0.001$). Among those receiving the intervention in the *per protocol* analysis, the proportion of abstinent individuals increased from 40% three weeks before surgery to 58% the week before surgery. There were no missing data in the *per protocol* analysis.

Among those 15 not included in the *per protocol* analysis, smoking data were missing for four ($n=4$) in the intervention group and five ($n=5$) in the control group. They were all categorised as smokers.

One year smoking abstinence

Information on smoking status at one year was available for 48/55 (87%) of the intervention group and 52/62 (84%) of the control group. This information was retrieved in average 13 months (SD 2.8) after surgery. One death due to pancreatic cancer occurred in the control group seven months after surgery. Long-term success rate in the intervention group was 18 of 55 (33%) compared to 9 of 62 (15%) in the control group ($p=0.03$). Corresponding values in the *per protocol* analysis was 17 of 48 (35%) and 9 of 54 (17%) ($p=0.04$). Patients who were abstinent at the short-term follow-up were more likely to be abstinent at the one-year follow-up, 43% vs 19% ($p=0.02$).

Table 5. *Abstinence at different points of follow-up as a result of allocation status*

<i>Abstinence</i>	Randomization status		
	<i>Intervention, n (%)</i>	<i>Control, n (%)</i>	<i>P-value</i>
Perioperative* - intention-to-treat**	20/55 (36)	1/62 (2)	<0.001
Perioperative* - per-protocol	19/48 (40)	1/54 (2)	<0.001
One year after surgery – intention-to-treat**	18/55 (33)	9 /62 (15)	0.03
One year after surgery – per-protocol**	17/48 (35)	9 /54 (17)	0.04

4.3 RESULTS STUDY IV

The follow up for the primary outcome was complete March 5, 2007. There were no losses to follow-up, but seven patients in the intervention group and eight patients in the control group were not included in the analysis (*see 4.2*); no patient in the intervention group discontinued intervention. In total 102 patients remained for analysis, for details see CONSORT flow chart in Fig. 1 (StudyIV). Details of baseline demographics are presented in Table 1(Study IV). The mean age was 55 years and 53% ($n=54$) were men. The majority (64%) underwent a general surgery procedure and 36% an orthopedic surgery procedure. Hernia procedures had the highest complication rates (42%), compared

to knee prosthesis (33%), hip prosthesis (24%), and laparoscopic cholecystectomy (22%). These differences between the types of surgical procedures were not significant ($p=0.29$).

Intention to treat analysis

The outcome according to intention to treat is presented in Table 6. The overall complication rate in the intervention group was significantly reduced compared to the control group, 21% and 41% ($p=0.03$), respectively. The relative risk for the primary outcome of *any postoperative complication* in the intervention group was 0.51 (95% CI 0.27–0.97) and the number needed to treat was 5 (95% CI, 3 to 40). The secondary outcome, *wound complication rate*, was 13% in the intervention group and 26% in the control group ($p=0.13$). The relative risk for the secondary outcome of *any wound complication* in the intervention group was 0.48 (95% CI 0.20–1.16). The intervention group had a clinically interesting reduction of complications in most subgroups of complications except gastrointestinal and cardiovascular complications, but the small numbers prevented further analysis of these data. No adverse events related to intervention were observed.

Table 6. *Intention to treat analysis. Postoperative complications within 30 days and hospital stay.*

^a Fisher's exact test (two-sided)

	<i>Intervention group (n=48)</i>	<i>Control group (n=54)</i>	<i>P Value a</i>
Haematoma, No. (%)	3 (6)	7 (13)	0.33
Wound infection, No. (%)	2 (4)	4 (7)	0.68
Seroma, No. (%)	3 (6)	5 (9)	0.72
Other wound complication, No. (%)	2 (4)	4 (7)	0.68
Any wound complication, No. (%)	6 (13)	14 (26)	0.13
Urinary tract complication, No. (%)	4 (8)	9 (17)	0.25
Pulmonary complication, No. (%)	0 (0)	1 (2)	1.00
Cardiovascular complication, No. (%)	1 (2)	1 (2)	1.00
Gastrointestinal complication, No. (%)	3 (6)	0 (0)	0.10
Fever of unknown origin, No. (%)	0 (0)	1 (2)	1.0
Any complication, No. (%)	10 (21)	22 (41)	0.03

Per protocol analysis

There was a difference, although not statistically significant, between smokers who stopped ≥ 3 weeks preoperatively, 1–2 weeks preoperatively, and those who continued smoking. The frequencies of any complication according to the analysis *per protocol* were 15%, 22% and 37%, respectively ($p=0.14$, Table 4, Study IV). The trend of the effect seen in the *per protocol* analysis was almost the same as in the intention to treat analysis. The self-reported quit-rate was supported by measurements of CO in exhaled air: abstainers exhaled 1.0 ppm (0–10) on a median and the corresponding value for those who reduced or continued their smoking was 9.0 ppm (0–35) $p<0.001$.

Binomial regression analysis

A binomial logistic regression analysis did not show any confounding effects on the results, explained by the differences between the two groups seen at baseline in Table 1 (Study IV). Regression modelling was performed only on the intention-to-treat analysis and with the primary outcome of any postoperative complication. The RR of being in the intervention group as the only explanatory variable in the model was 0.51 (95% CI, 0.27–0.97, $p=0.04$). None of the variables at baseline affected the RR of 0.51 by more than 10% in either direction and we performed no further analyses.

5 DISCUSSION

5.1 METHODOLOGICAL CONSIDERATIONS

5.1.1 *Information bias*

In studies I and II the low overall frequency of postoperative complications within 30 days (2.9% and 6.6%) is largely due to the failure of complete registration in the Swedish Inpatient Register. The true number is likely to be in the range 10–20%, which matches the overall complication frequency reported in the Swedish Hernia Registry¹⁷⁵ and appendectomy studies.¹⁷⁶ Nearly half of the reoperations due to surgical complications are not reported in the Swedish Inpatient Register, and the frequency of missing data on minor complications such as a wound infection is even higher.¹⁷⁷ This should not affect the results of this study as we have no reason to believe that a low reporting frequency is related to smoking or BMI, i.e., any misclassification is most likely non-differential. This is true if not smoking is associated with more serious complications which may be registered in a higher degree.

In study II there was a sudden increase in the rate of perforated appendicitis from 6.1% during the calendar period 1972–1984 to 17.3% during 1985–1989, probably due to the updating of ICD codes. The Swedish version of ICD-9 was introduced in 1987 and resulted in an increase in the rate of perforated appendicitis recorded in the Swedish Inpatient Register, from 5.9% in 1986 to 20.4% in 1987. ICD-10 was introduced in 1997 and resulted in an increased rate of perforated appendicitis, from 20.9% in 1996 to 27.6% in 1997. Therefore, in the present study there could be patients with perforated appendicitis who are misclassified as having non-perforated appendicitis. However, it is not likely that such misclassification is related to tobacco and BMI. Also, the accuracy of an appendicitis diagnosis has been found to be falsely positive in 10 per cent of cases compared to the pathology report.¹⁷⁸ It is unlikely that such misclassification is dependent on BMI or smoking status.

As reported after our cohort studies were conducted, the never-smoker category might have contained some smokers who skipped the smoking questions for other reasons.²⁹ This would in turn bias the point estimate towards zero and, in that case, our results would be an underestimation of the true risk of smoking.

In Study III, we did not verify smoking status one year after surgery by measuring CO in exhaled air. The self-reported smoking status one year after surgery did correlate with the short-term smoking status, which we confirmed by measuring CO in the expired air.

In Study IV there is a possible information bias due to the fact that the blinding of the outcome assessors may not have been perfect. Some of the patients might have revealed their randomisation status. In order to avoid this possible bias, the study physicians arranged panel discussions in order to reach a consensus on each complication without prior knowledge of the particular group allocation. Furthermore, the study nurses may have recorded complications differently. We tried to avoid this by training and by giving the same information to all of them and by having written, prespecified definitions of complications (see 4.1, Table 4).

Our high rate of postoperative complications (31%) might be a result of our definition of a complication (i.e. any unexpected event that necessitates treatment, extra investigation or

prolonged care) and a rigorous follow-up. This wide definition should not weaken the results as we used the same criteria for a complication in both groups, so any misclassification is most likely non-differential. Minor complications that may be disregarded in trials due to a small influence on morbidity may still have a significant impact on health-economic evaluations. One should also remember that all patients in Study IV are smokers, a group that has a higher baseline risk of complications.

5.1.2 *Selection bias*

In Study III and IV, two patients in the control group withdrew consent. This may have caused a selection bias since the lack of follow-up may be related to the fact that they were randomised to controls. In addition, not all patients randomised were included in the final analyses in Study IV. Other reasons for exclusion were not related to the patients' baseline characteristics or randomisation status. Hence, we do not believe that excluding these patients from the final analyses has biased our results.

5.1.3 *Confounding*

In Study I, being underweight increased the complication rate. The increased risk of postoperative complications among underweight patients could be due to confounding factors, especially malignant diseases. Another theoretical possibility in Studies I and II is that BMI could be in the causal pathway as an effect of smoking. To test this hypothesis, analyses of smoking unadjusted for BMI could have been, but were not, performed. Furthermore, snus use in relation to smoking categories is more difficult to interpret, the reason being that probably any person using snus and classified as an ex-smoker would probably be exposed to less cigarette smoke than other ex-smokers and this could be a residual (negative) confounder.

In Studies I and II, alcohol is a possible confounder that has been shown to be associated with an increased risk of postoperative complications.^{83,91,179} Most patients in these studies were active workers at the time of surgery and, with regard to the low mortality rate in the cohort; the present results are unlikely to be explained by alcohol consumption.

In Studies III and IV, there might be some residual confounding from baseline characteristics due to the relatively small numbers included. We controlled for all known confounders at baseline with our regression analyses and we saw no such significant effect, i.e. no difference at baseline changed the relative risk by more than 10% in any direction.

5.1.4 *Validity and precision*

In Studies I and II there may be a healthy worker effect that could keep the frequency of complications low in general, which may in turn affect generalizability.

In Study II, current smoking of more than 10 pack-years and being in the upper overweight or obese category were associated with an increased risk of postoperative complications among patients following open appendectomy. However, this increased risk was statistically significant only in patients with non-perforated appendicitis. Patients with perforated appendicitis had a higher baseline risk of complications, which reduced the risk difference for different types of exposure, and our study might have been too small to capture a possible existing association in this group.

In Studies III and IV, the frequency of patients who declined participation may affect the external validity. In our attempt to reduce the refusal rate, we tried different approaches to

patients during the process of inclusion. Nevertheless, we still found a significant proportion of patients who were not interested in smoking cessation. Common reasons for refusal were: no interest in giving up smoking or a need to focus on the forthcoming surgical procedure. We still believe the generalizability to be high since we have included a wide spectrum of surgical procedures and ages and tried to minimise exclusion criteria. We believe that the participants in this study represent a population of motivated smokers amenable to smoking cessation intervention and that the results of the study could be generalizable to them.

The relatively small number of patients may also increase the risk of a type II error, i.e. overlooking other possible effects of the intervention. Especially the impact on our secondary outcome in study IV, wound complications, may have suffered from the limited sample size since the relative size of the effect was as strong as we expected. In addition, Study III was not primarily designed to investigate predictors of successful smoking cessation. Therefore, some of the results could suffer from type II error and be false negative.

5.2 INTERPRETATION

Discussion Study I

In this study, we found smoking to be associated with postoperative complications after inguinal hernia surgery. Smoking was also an independent risk factor for postoperative infection ($p=0.02$, data not shown), but the numbers were too small to determine if this was due to wound infections or systemic infections. Use of snus did not affect the complication rate.

This study has the advantage of using prospectively collected information on tobacco exposure and is based on a very large sample. It also benefits from a unique quality of data on tobacco: the type of tobacco used and the dose and duration of use, as well as the use of snus have been recorded. Furthermore, our mortality rate of 0.1% is consistent with earlier findings of postoperative mortality after inguinal hernia repair.¹⁸⁰ Also in our study, acute hernia surgery had a much higher frequency of complications than scheduled surgery, which has been demonstrated previously.¹⁸¹ Complications increase with the calendar period, which is an expected effect of increased demands on the registration of multiple diagnoses in the health economics system used in Sweden.

Discussion Study II

This study shows that smoking is associated with an increased risk of perforated appendicitis. If the relationship is causal, this finding may reflect a more rapid progression of appendicitis to perforation among smokers. Smoking modulates the immune system,^{59,61,182-184} and this might increase the likelihood of perforated appendicitis. The association found between age and risk of perforated appendicitis is in agreement with some previous studies.^{185,186} But the high proportion of perforations in the elderly is probably a mere consequence of the relatively low incidence of non-perforated appendicitis among these patients.¹⁸⁷ This view is supported by a stable incidence of perforations over age. Relatively few patients in this study developed postoperative complications (4.4% and 6.6% among patients with non-perforated and perforated appendicitis, respectively). This may be due to the fact that many minor postoperative complications are treated on an outpatient basis, so that they do not appear in the discharge register. In addition, many in-hospital complications are simply not recorded.¹⁷⁷ In addition, this study may have included a selected group of healthy workers who were less likely to have complications following

appendectomy. Mortality rates of up to 1.8% have been reported previously.¹⁷⁶ The low mortality rates in the present study (0.1% for non-perforated appendicitis and 0.5% for perforated appendicitis) might support this hypothesis.

Discussion Study III

This study shows that a preoperative smoking cessation intervention with individual counselling and NRT is effective in achieving abstinence. The proportion of abstinent individuals among those receiving the intervention increased from 40% three weeks before surgery to 58% the week before surgery. The probability of being abstinent in the intervention group was comparable to the result by Moller et al.¹⁷ where preoperative smoking cessation six to eight weeks prior to scheduled hip and knee arthroplasty led to abstinence in 64% of the patients in the intervention group. The one-year abstinence proportion of 33% is higher than what has been reported with NRT in the non-surgical setting.¹⁸⁸⁻¹⁹⁰ It is also slightly higher than what has been published in the other two RCTs reporting one-year abstinence rates.^{133,134} Our intervention was more effective than what has been observed in some low-intensity-protocols¹³⁰ not using repeated personal contacts and NRT during the whole study period. The relatively high probability of successful smoking cessation might reflect the motivating effects of surgery¹⁹¹ and suggests that the preoperative period might be optimal for initiating smoking cessation interventions. The relatively large proportion of individuals who became abstinent in the control group could also be supportive of this hypothesis. High nicotine dependence affected the likelihood of remaining abstinent one year after surgery which is in accord with the results reported by Villebro et al.¹³⁴ It has been suggested that nicotine dependence should be regarded as a chronic disorder and longer periods of intervention may be necessary for some individuals to remain abstinent.¹⁹² Obesity was also associated with success in smoking cessation, this finding has been proposed to arise from an increased health concern among those with overweight.¹⁹³

Discussion Study IV

This study shows that perioperative smoking intervention initiated as late as four weeks prior to scheduled surgery reduces the risk of postoperative complications. This is an important finding for patients undergoing surgical procedures for diagnoses that do not allow the six to eight weeks of smoking cessation¹⁹⁴ previously shown to be effective in reducing complication rates. This finding is in line with previous trials,^{17,77} but the effect has not been demonstrated in a clinical trial for such a short preoperative time frame. The *per protocol* analysis supports the effect of abstinence *per se* in reducing complication rates, but these data must be interpreted with caution considering the low statistical precision and the non-randomised nature of the data. The finding, although not statistically significant, that those who really were abstinent throughout the study period had fewer complications, suggests that there is a causal connection between abstaining and fewer complications. The strong effect of smoking cessation could partly be explained by a higher oxygen delivery to the healing tissues. This hypothesis is supported indirectly by the positive effect seen with supplementary oxygen delivery.^{65,66} Smoking also alters the immune system^{58,59,195} and disturbs white blood cells,^{60,61} elevated white blood cell counts has been shown to be a reversible condition.¹⁸² As expected, the control group had more wound complications. Besides the expected elevated frequency of wound infection, haematomas were also more common among smokers, which has also been found in another recent retrospective study.¹⁹⁶ The strength of our study is, besides the randomised nature of the data, the blinded outcome assessment and the structured follow-up.

The cost of impaired health due to smoking is substantial. Smoking increases the need for health care, the need for medication and for sick-leave.²⁷ Smoking is number one among preventable causes of morbidity and mortality in the public health perspective.^{23,33} Reduction of postoperative complications is of great importance for decreasing suffering among patients, decreasing the need for health care and medication and reducing the frequency of sick-leave. Between 20% and 40% of all surgical patients in the Western world are smokers. For example, in Sweden nearly 20,000 operations on inguinal hernia are performed annually,¹⁷⁵ with smokers constituting somewhere around 20–30% of the patients. The total postoperative complication frequency *among smokers* is probably at least 20%. This means that only in the field of inguinal hernia surgery in Sweden, there are hundreds of complications each year that are potentially preventable with an inexpensive and harmless treatment. This does not take into account the fact that some of those who quit in connection with a surgical procedure will stop permanently. Permanent cessation has a major positive influence on life expectancy and costs to society. ***There is no longer any need for more evidence; there is a need for more action.*** Every surgical department should have a routine for providing qualified smoking cessation advice to all patients undergoing surgery. As expected, a recent trial found that surgeons underestimate the positive effect of preoperative smoking cessation.¹⁹⁷ One month of preoperative smoking cessation is possible before most types of scheduled surgery and should be implemented. Even shorter periods of smoking cessation may be effective but there are no direct evidence supporting that.

5.4 ONGOING AND FUTURE STUDIES

Although the evidence for smoking cessation as a means to reduce complications is accumulating, the pathophysiological background of this effect deserves to be elucidated. In an ongoing study we are investigating the effect of smoking cessation on inflammatory cytokines (IL-1 β , IL-6, TNF- α). In the same study we will also evaluate the effect of smoking cessation on glutaredoxin and thioredoxin,¹⁹⁸ two major antioxidant enzymes in human cells which may be of importance for the effects of smoking.¹⁹⁹

In the RCT we also collected data on Quality of life (EuroQol) and we aim to calculate QALY's and the cost-effectiveness of perioperative smoking cessation intervention. In addition, there could be an impact of perioperative smoking cessation on postoperative pain. The effect of nicotine on postoperative pain is not clearly understood and it is not known if smoking cessation can affect postoperative pain and the need for pain medication.^{200,201} In order to assess this, we used a pain diary in the RCT in which patients recorded postoperative pain on a visual analogue scale (VAS) for the first two postoperative weeks.

Another paper concerns the experience of patients randomised to the control group. Ideally, all patients would participate in an RCT out of altruism, but there is evidence that most people accept trials out of self-interest.²⁰² For this reason, we conducted a study with in-depth interviews of patients randomised to the control group. We used a structured questionnaire in which they could describe their expectancies of the study and their feelings when allocated to the control group.

In a parallel RCT, our colleagues in the orthopaedic department are studying the efficacy of a smoking cessation intervention offered to patients undergoing acute fracture surgery. The effect of that intervention on postoperative complications is also under investigation.

Smoking cessation is an inexpensive treatment with a potential to affect many surgical conditions. Conditions associated with smoking have a particularly high potential. The impact of smoking cessation on cancer surgery remains to be explored. Also in the field of vascular surgery, evidence for smoking cessation intervention is sparse. Smoking cessation offered to patients with small abdominal aortic aneurysms might, for instance, decrease the growth rate. The implication of this is that smoking cessation has the potential to postpone both death from the disease and death from treatment.

6 CONCLUSIONS

- Smoking increases the risk of postoperative complications even in minor surgical procedures such as inguinal hernia repair.
- Smoking increases the risk of perforated appendicitis.
- Smoking and obesity are associated with postoperative complications after open appendectomy.
- Snus does not affect the frequency of complications after inguinal hernia surgery and appendectomy.
- Smoking cessation intervention starting four weeks before surgery results in a high abstinence frequency, in both the short- and long-term.
- Perioperative smoking cessation is an effective means of reducing postoperative complications in both general and orthopaedic surgery. A strong reduction of complications is accomplished, even if smoking cessation is introduced as late as four weeks prior to surgery.

7 POPULÄRVETENSKAPLIG SAMMANFATTNING (SWEDISH SUMMARY)

Komplikationer efter operationer innebär ett lidande för patienterna, men är också bekymmersamma för sjukvården. Komplikationerna leder till ett ökat vårdbehov i form av förlängda vårdtider, ökat läkemedelsbehov och fler reoperationer. Det leder också till ökade samhällskostnader i form av längre sjukskrivningar och ökat hjälpmedelsbehov. Komplikationerna kan även undergräva förtroendet för sjukvården. Det är visat i en rad olika studier efter större kirurgiska ingrepp att rökare oftare drabbas av komplikationer än icke-rökare. Huruvida snusare har en ökad risk för komplikationer är mycket lite studerat.

På senare år har det visat sig att även ett kortare rökstopp på 6–8 veckor inför operation kan medföra kraftig reduktion av komplikationerna. Om ett *ännu* kortare rökstopp inför operation skulle kunna löna sig har varit oklart.

Målet med de två första studierna i denna avhandling har varit att undersöka om rökare drabbas av fler komplikationer även efter mindre rutinoperationer såsom ljumskbräck eller blindtarmsoperation. Målet var också att undersöka om snus och övervikt påverkade komplikationsrisken efter dessa operationer.

Målet med de två sista studierna i avhandlingen var att ta reda på om det lönar sig att sluta röka så sent som fyra veckor inför en operation. Målet var också att ta reda på hur många som klarar av att sluta inför sin operation om de får kvalificerad hjälp och hur många av dessa som förblir rökfria efter ett år. Detta testade vi genom att lotta hälften av rökarna till en kontrollgrupp som fick fortsätta röka om de ville och hälften till rökavvänjningsbehandling.

Våra studier visar att rökare har en ökad risk för komplikationer både efter bräckoperation och blindtarmsoperation. Vi fann inga tecken till att snus skulle öka risken för komplikationer. Fetma gav en måttlig riskökning för komplikationer efter dessa ingrepp. Blindtarmsstudien visade också att rökare har en ökad risk att drabbas av brusten blindtarmsinflammation, detta var inte tidigare känt.

Vår studie med rökavvänjning fyra veckor inför operation visade en mycket kraftig reduktion av komplikationer hos dem som fick rökavvänjningshjälp. De som fortsatte röka i kontrollgruppen hade ungefär dubbelt så många komplikationer, detta trots att alla i behandlingsgruppen inte slutade röka. Ungefär 58 % av patienterna som fick rökavvänjningshjälp lyckades sluta inför och efter operation. Detta är en mycket bra siffra i jämförelse med andra rökavvänjningsprogram. Ett år efter operationen var fortfarande 33 % rökfria vilket även det är ett mycket bra resultat.

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