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TOBACCO SMOKING, HIGH BODY MASS INDEX
AND THE OUTCOME AFTER SURGERY: THE ROLE
OF INTERVENTION

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TO MY FATHER

1. ABSTRACT

The negative effects of smoking and obesity on public health are well-known. Despite this knowledge, the smoking-attributable morbidity and mortality is estimated to rise rapidly in the forthcoming years, and obesity has become an emerging worldwide epidemic. In the field of surgery, smokers and the obese constitute important risk groups, prone to develop postoperative complications, ranging from impaired wound healing to deadly cardiovascular and pulmonary events. Abstinence is known to halt the negative effects of smoking. However, the effect of preoperative smoking cessation on postoperative outcomes has only been investigated in a few randomised clinical trials, with differing results. Therefore, the efficacy remains uncertain. Similarly, interventions to reduce weight exist, but the effect of weight reduction on the outcome after planned surgery has not been investigated. The main focus of this thesis was to study the effect of preoperative smoking cessation on the risk of postoperative complications. A secondary aim was to shed light on the magnitude of impact that obesity has on the development of postoperative complications in elective surgery.

Using the large nation-wide Swedish Construction Workers' Cohort, the effect of smoking on the risk of postoperative complications in patients undergoing elective total hip replacement (THR) or open appendectomy (OA) was evaluated. By record linkage, 3,309 male construction workers, who underwent THR between 1971 and 2002, were identified. After controlling for confounders, heavy smoking (>40 pack-years) increased the risk of systemic complications by 121% (Odds ratio (OR) =2.21, 95% Confidence Interval [CI]: 1.28 - 3.82) compared to never-smoking. Being obese (≥ 30 kg/m²) increased this risk by 58% (OR=1.58, 95% CI: 1.06 - 2.35) compared to those of normal weight (18.0-24.9 kg/m²) and also prolonged hospital stay. Neither smoking nor obesity was significantly associated with increased risk of local complications.

There was no effect of smoking on the risk of implant dislocation up to eight years after THR. However, high weight increased the risk of implant dislocation within three years after surgery. Overweight (BMI ≥ 25 kg/m²) increased this risk by 150% (Hazard ratio (HR) = 2.5, 95% CI: 1.1 - 5.5) and obesity increased this risk by 270% (HR = 3.7, 95% CI: 1.5 - 9.3) compared to those of normal weight.

By record linkage, 6,676 male construction workers who underwent OA for acute appendicitis between 1971 and 2004 were identified. Current smokers with more than 10 pack-years of smoking had 29% (RR= 1.29; 95 % CI: 1.11 - 1.50) increased risk of perforated appendicitis (PA) compared to never-smokers. Moreover, in patients with non-perforated appendicitis, current smoking with more than 10 pack-years (RR= 1.51; 95% CI: 1.03 - 2.22) and obesity (RR=2.60; 95% CI: 1.71 - 3.95) were significantly associated with increased risk of overall complications compared to never-smokers and those of normal weight, respectively. There was no significant association between obesity, smoking and overall complications in patients with PA. This was probably due to the high baseline complication frequency, which reduced the risk difference between the subgroups.

In a smoking cessation intervention, 117 patients undergoing elective orthopaedic and general surgery were randomised to intervention (N=55) or control (N=62). Between March 2004 and December 2006, 102 patients, 48 in the intervention group and 52 in control group completed the trial. The intervention group underwent an intensive smoking cessation programme, on average 4 (2 - 7) weeks before surgery, with weekly meetings or phone calls, and was provided with free nicotine replacement therapy. The control group received standard care. According to intention to treat analysis, the risk of postoperative complications was reduced from 30/62 (48%) in the control group to 17/55 (31%) in the intervention group, resulting in a 37% (RR=0.63, 95% CI: 0.40 - 1.02) relative risk reduction. Based on this clinical effect, it was concluded that preoperative smoking cessation, initiated as late as four weeks before surgery, could efficiently be used to reduce the risk of postoperative complications after elective orthopaedic and general surgery.

2. LIST OF PUBLICATIONS

- I. *Sadr Azodi O*, Bellocco R, Eriksson K, Adami J. The impact of tobacco use and body mass index on the length of stay in hospital and the risk of post-operative complications among patients undergoing total hip replacement. *J Bone Joint Surg Br* 2006; 88(10):1316-20.
- II. *Sadr Azodi O*, Adami J, Lindstrom D, Eriksson K, Wladis A, Bellocco R. High body mass index is associated with increased risk of implant dislocation following primary total hip replacement - 2,106 patients followed up to 8 years. *Acta Orthop* 2008 Feb;79(1):141-7
- III. *Sadr Azodi O*, Lindstrom D, Adami J, Bellocco R, Linder S, Wladis A. The impact of body mass index and tobacco smoking on the outcome following open appendectomy. *Br J Surg* 2008 June; 95 (6): 751-757
- IV. Lindstrom 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 Randomized Controlled Trial. Accepted for publication in *Ann Surg*

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4. ABBREVIATIONS

BMI	body mass index
CI	confidence interval
CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
HR	hazard ratio
ICD	International Classification of Disease
NPA	non-perforated appendicitis
NRT	nicotine replacement therapy
OA	open appendectomy
OR	odds ratio
PA	perforated appendicitis
RCT	randomized clinical trial
RR	relative risk
THR	total hip replacement

5. INTRODUCTION

The field of surgery and anaesthesiology has undergone a rapid development during the past decades. This has resulted in improvement of peri- and postoperative outcomes and increased patient safety. The impact of modifiable life-style factors on postoperative complication is an area that is receiving growing attention. Two important life-style factors are smoking and high body mass index (BMI). It is known that smoking cessation can halt the negative effects of smoking. Only a few randomized trials have studied the effect of preoperative smoking cessation on postoperative complications, but with differing results. Similarly, high BMI is associated with increased risk of postoperative complications. Interventions to reduce weight exist, but the effect of weight reduction on the outcome after elective surgery has so far not been investigated.

In this thesis, two common surgical procedures, total hip replacement (THR) in the field of orthopaedic surgery and open appendectomy (OA) in general surgery, were used as models to study the magnitude of the impact that smoking and high BMI have on the risk of postoperative complications. In the final study, an interventional trial was conducted to investigate the effect of preoperative smoking cessation on postoperative complications in elective orthopaedic and general surgery.

6. BACKGROUND

6.1 Smoking: the big picture

The negative effects of smoking on public health are well-known. This awareness has resulted in preventive measures to reduce consumption of smoking-tobacco products in many industrialised countries [1]. In Sweden, with one of the lowest prevalences of smoking in the world, there has been a steady decline in smoking-tobacco consumption for men since the 1980s and for women since the 1990s [2]. In 2006, 13.2% of men and 16.6% of women in Sweden were smokers [2]. However, this declining trend is not shared by many of the developing countries. Between 1970 and 1990, there was a 3.4% yearly growth in tobacco consumption in low- and middle income countries [1]. Today, more than 8 out of 10 smokers live in these countries [1].

In year 2000, 4.8 million deaths in the world were attributed to tobacco smoking [3]. If the changing patterns of tobacco consumption continue, the mortality attributable to smoking in low- and middle income countries alone will increase to 6.8 million in 2030 [4]. Thus, tobacco smoking will remain one of the most important preventable risk factors of public health in the 21st century.

6.2 Smoking and surgery

Smokers constitute an important risk group of patients in the field of surgery. Smoking is associated with postoperative complications, ranging from impaired tissue healing to deadly pulmonary and cardiovascular events.

6.2.1 Tissue healing

Smoking impairs several mechanisms necessary for appropriate tissue healing. Fibroblasts are the main cells responsible of tissue healing. These cells produce collagen, a protein that provides tensile strength to the tissue. The production and turnover of collagen is impeded in smokers [5-7]. Exposure to cigarette smoke lead to changes in the cytoskeleton, resulting in reduced fibroblast migration and assembly in the injured tissue [8-10]. Moreover, smokers have higher quantities of enzymes such as matrix metalloproteinase that degrade proteins (e.g. collagen) compared to non-smokers [11, 12].

The injured tissue is in need of oxygen and nutrition to undergo regeneration. The microcirculatory blood flow [13-15] and oxygen tension is reduced after smoking [16]. In smokers, high levels of carboxyhaemoglobin increase the affinity of oxygen to haemoglobin and impair oxygen delivery to the tissue [17]. Cigarette smoke in vitro decreases growth of new vessels, angiogenesis, in the injured tissue [18, 19].

Smokers were found to be two to four times more likely to develop wound-related complications, mainly infections, in comparison to non-smokers after a variety of surgical procedures [20-25]. Other complications, such as recurrence of groin hernia [26, 27], impaired fracture healing [20], anastomotic leakage after colorectal surgery [28] and incisional hernia following laparotomy [29], all indicators of poor tissue healing, were also two- to four-fold increased in smokers compared to non-smokers.

6.2.2 Pulmonary complications

Smoking leads to early destruction of lung parenchyma and is the major cause of chronic obstructive pulmonary disease (COPD) [30]. Even with normal lung function tests smokers have inflammatory and emphysematous changes in lung parenchyma detected by High Resolution CT scan [31] and higher levels of inflammatory cells, such as macrophages and neutrophils, in the lung tissue compared to never-smokers [32, 33].

The increasing level of inflammatory cells is correlated to tissue destruction [32]. The functional response of the immune system against microorganisms is compromised after exposure to tobacco smoke [34].

Mucus produced by the goblet cells, lines airways and traps pathogens and inhaled irritants. Ciliated respiratory epithelium transports the mucus out of the respiratory airways [35]. Compared to non-smokers, goblet cells in smokers are larger in size, number and produce more mucus [36]. Concomitantly, as a result of the reduced ciliary movement [35], transportation of mucus is impeded in smokers [37, 38]. The hypersecretory state along with impaired mucus removal could result in mucus retention and airway obstruction [39].

The increased mucus production was overrepresented in smokers after surgical procedures involving the thoracic cavity [40]. Pneumonia is the most common postoperative pulmonary complication. In a large study of patients, irrespective of the type of surgery, smokers had a 28% (Odds ratio (OR) 1.28; 95% Confidence interval (CI): 1.17-1.42) increased risk of postoperative pneumonia [41] and 24% (OR 1.24; 95% CI: 1.14-1.36) increased risk of respiratory failure compared to non-smokers [42]. These complications were two-fold increased in smokers undergoing surgery involving the thoracic cavity [43-45].

6.2.3 Cardiovascular complications

Smoking promotes atherosclerosis and cardiovascular disease [46]. Endothelial cells, lining the inner layer of blood vessels, have an important role in hemodynamic regulation [47] and endothelial dysfunction is an early sign of atherosclerosis [48]. Some signs of endothelial dysfunction in smokers are reduced coronary vascular dilatation in response to stressful stimuli [49], reduced ability to increase blood flow in peripheral vessels after transient mechanic vasoconstriction [50, 51] and increased vascular wall tension after exposure to smoking [52, 53]. Migration, proliferation and function of the endothelial progenitor cells, important in repair of vascular damage, is impaired in smokers [54]. Moreover, cigarette smoking shifts homeostasis to a more pro-thrombotic state, resulting in lower levels of tissue plasminogen activator [55, 56], increased platelet aggregation through higher expression of platelet-derived thrombin [57, 58], P-selectin [59] and CD40L [60], and increased levels of plasma fibrinogen [61].

Although quite rare, acute vascular events are more commonly occurring in patients undergoing high-risk surgical procedures. In a study of almost 20,000 patients undergoing coronary bypass surgery, the incidence of stroke was 1,4% [62]. In this meta-analysis smokers had 62% (OR 1.62; CI: 1.08-2.43) increased risk of stroke compared non-smokers [62]. Each pack-year (number of cigarettes smoked per day multiplied by years of smoking divided by 20) of smoking increased the overall risk of acute vascular events and death by 4% (OR 1.04; 95% CI: 1.02-1.06) after carotid endarterectomy [63]. In patients with 20 pack-years of smoking, this means more than a two-fold increased risk of such complications compared to non-smokers. Thrombosis and stenosis in hepatic artery after liver transplantation were three times more frequently occurring in smokers compared to non-smokers [64]. Long-term, smokers were more than three times more likely to develop advanced congestive heart failure after aorta valve replacement [65]. Smokers had a two-fold increased likelihood of acute cardiovascular events such as myocardial infarction, stroke [66] and a thirty percent increased risk of allograft failure [67] after renal transplantation compared to non-smokers.

6.3 Smoking cessation

Smoking cessation is an important way to improve public health. From a public health perspective several tools such as increased tax on tobacco products [68-70], deregulation of smoking cessation products [71] and education and information [72, 73] can be used to reduce the prevalence and initiation of smoking in a population. However, only 3 to 5 percent of smokers quit smoking spontaneously and remain abstinent 6 to 12 months after a given quitting attempt [74]. Thus, much effort has been devoted to make smoking cessation more effective and to understand physiological and behavioural determinants of successful smoking cessation.

6.3.1 *Methods of smoking cessation*

There are several methods for smoking cessation. The efficacy of these approaches is dependent on the intensity of the intervention programme and the motivation of the study participants. The results presented below are based on Cochrane reviews that have gathered information from existing randomised clinical trials (RCT) on different smoking cessation approaches.

Contact with health professionals could provide a unique opportunity to initiate smoking cessation. Minimal intervention programmes including advice from a physician with a single follow-up visit lead to smoking cessation in 6% of the intervention group compared to 4% in the controls (OR 1.74; 95% CI: 1.48-2.05) [75]. More intensive programmes including more than one follow-up visit increased the probability of success in the intervention group to more than 10% [75]. Similar results were achieved by intensive intervention programmes in high-risk populations e.g. in those with cardiovascular disease [75]. Interestingly, “teachable moments”, such as being hospitalised due to acute illness or pregnancy, may influence individuals to adopt healthier life-style behaviours [76]. Interventions applied on hospitalised patients with cardiovascular disease resulted in abstinence in almost 37% of the study participants compared to 29% in the controls (OR 1.29; 95% CI: 1.14-1.45) [77]. The high success rate of abstinence in both the intervention and control groups could reflect a combination of the effect of “teachable moments” and the high motivational state of the study participants [76].

Nicotine replacement therapy (NRT) and bupropion are two well-established aids for smoking cessation. Irrespective of the administration form but depending on the intensity of the trial, 10 to 20 % of study participants using NRT succeed to become abstinent [78]. Bupropion, originally an anti-depressive drug, increased the probability of smoking cessation to almost 20% compared to 10% in controls (OR 1.94; 95% CI: 1.72-2.19) [79]. The effect of bupropion is however not through its anti-depressive properties [79]. Studied in only a few RCTs, the effect of bupropion is comparable to those of NRT [79]. Benefits from both of the drugs are not substantially studied in hospitalised settings but it seems that intensive counselling alone without addition of any of these drugs is sufficient to promote a relatively high rate of smoking cessation [80].

Modest increased probability of smoking cessation has been achieved by self-help [81], individual- [82] or group behavioural counselling [83]. Yet, none of these interventional approaches could provide any additive effect to the success of a smoking cessation programme when combined together with other intervention approaches such as NRT or advice from health professionals. There was no significant association between acupuncture [84], anxiolytics [85], exercise [86] or hypnotherapy [87] and success of smoking cessation.

New drugs for promoting smoking cessation are being introduced in the market but more research is needed to confirm their efficacy in promoting abstinence [88-90].

Although still under development, there are efforts to produce a vaccine against nicotine that could lead to immunization against nicotine dependence [91].

Finally, the role of snus (Swedish oral moist snuff) in initiating smoking cessation has been debated. The use of snus has been proposed to have contributed to the low prevalence of smoking and the tobacco-related unhealth in Sweden studied as the decline in the incidence of lung cancer among men during the past decades [92]. In retrospective studies the use of snus has been found to increase the success in becoming abstinent [93, 94]. However, although less harmful than cigarette smoking, the long-term use of snus could increase the risk of some types of gastrointestinal cancer [95, 96] and the incidence of myocardial infarction [97]. Short-term use of snus in promoting smoking cessation warrants prospective studies.

6.3.2 Abstinence and withdrawal symptoms

Abstinence from smoking leads to craving and physiological withdrawal symptoms such as depression [98], sleep disorder [99, 100], irritability [101] and impaired working memory [101, 102]. This presents a challenge to many smokers and may result in relapse. Biologically, cigarette smoking is associated with activation of the limbic system in the brain and the release of dopamine, a neurotransmitter involved in motivation and reward. Smokers have lower availability of dopamine receptors in the limbic areas of the brain [103, 104]. In response to smoking-related cues there is an increased activation of these areas which results in craving [103, 105]. Moreover, smoking during a task performance could improve working memory in abstinent smokers [106]. Another consequence of smoking cessation is weight gain [107, 108]. This side-effect may reduce the probability of smoking cessation initiation [109].

6.3.3 Determinants of effective smoking cessation

Several predictors may affect the success of a smoking cessation attempt. Factors associated with high nicotine dependence [99, 110-112] and depression [113, 114] are frequently found to be negatively related to the success of smoking cessation. Having higher educational level [115, 116], higher socioeconomic status [117], being married [118] or having a partner who does not smoke [117, 118] potentiate abstinence. The advances during the past decade in genetic research have created new opportunities to study and understand biological determinants of smoking cessation. There is some data linking polymorphism in dopamine transporter [119], dopamine receptor- [120, 121], catechol O-methyltransferase (COMT) [122] and nicotine acetylcholine receptor- [123] genes to success in smoking cessation. However, this area of research is new and no firm evidence on the different genotypes' ability to alter success in becoming abstinent is yet available.

6.3.4 Smoking cessation and physiological adaptation

Smoking cessation results in progressive functional restoration of different organ systems, some of which occur within weeks after abstinence and some take decades to become restored. Interestingly, long-term abstinence from smoking reduces the risk of several types of cancers to levels comparable to non-smokers [124, 125].

6.3.4.1 Pulmonary system

The inflammatory activity in the lung tissue is reduced after smoking cessation. Animal studies have shown reduction of inflammatory cells and markers in response to cessation of smoke-exposure [126, 127]. Previous smokers with COPD had lower quantities of macrophages producing matrix metalloproteinase compared to current smokers with

COPD [11]. Several years of smoking cessation resulted in structural changes in the bronchial structure with reduction of epithelial mucin stores, squamous cell metaplasia and fewer number of proliferating cells [128].

A few weeks of abstinence improved cough sensitivity [129], reduced use of broncodilating medicine in asthmatics [130] and occurrence of airway symptoms [131]. Hyper-responsiveness of the airways to irritative substances was reduced three [132] to six months [133] after smoking cessation. Improvement in lung function was exhibited only six weeks after smoking cessation [134]. This improvement was found to continue up to several years after sustained smoking cessation in a young cohort [135]. In elderly individuals with higher life-time tobacco use the decline in the lung function was slower in abstained smokers compared to current smokers [136].

6.3.4.2 Cardiovascular system

Smoking cessation improves endothelial function. Myocardial blood flow in response to stressful stimuli was normalised after one month [137] and arterial stiffness was reduced after two months of smoking cessation [138]. This improvement of the endothelial function was also evident after smoking cessation in individuals who suffered from myocardial infarction [139]. The number of endothelial progenitor cells increased after only two weeks of smoking cessation and reached the same level as non-smokers after four weeks of abstinence [140].

Beginning with 5 years after smoking cessation, the level of pro-inflammatory markers, such as C-reactive protein, fibrinogen and tissue plasminogen activator reduced in former smokers compared to current smokers [141]. Arterial stiffness decreased after a decade of smoking cessation to levels comparable to never-smokers [142]. Likewise, a decade of abstinence reduced mortality in stroke and coronary heart disease to more than half in comparison to current smokers, a level which was comparable to never-smokers [143].

6.3.5 Cost-effectiveness

Not only improving health, different smoking cessation interventions are proven to be cost-efficient. Physician advice, use of NRT or Bupropion to promote smoking cessation are cost saving in primary and secondary prevention of cardiovascular disease [144]. Through the financial savings secondary to the reduced tobacco-related illness, one-time smoking cessation counselling is estimated to save 65 US \$ per every smoker advised to stop smoking [145]. Repeated counselling was estimated to save >500 US \$ per smoker counselled [145]. The cost of a life-year saved after twelve weeks of treatment with nicotine patch was estimated to be between 400 – 800 UK £ [146]. The same cost when using Parvastatin, a cholesterol lowering drug, was over 8,000 UK £ [147]. Prevention of smoking in pregnant mothers saved 3 US \$ for every US dollar invested [148]. The earlier smoking cessation was established, the greater was the lifetime cost savings in terms of reduced costs secondary to tobacco-attributed morbidity, mortality and loss of productivity [149]. As an example, abstinence in a 35-year-old female smoker resulted in lifetime cost savings between 25 000 to almost 50 000 € whereas abstinence in a 65-year-old female led to cost savings below 10 000 € [149].

6.3.6 Smoking cessation and surgery

Smoking cessation has long been advocated prior to coronary artery bypass surgery [150], plastic surgery [151] and lung cancer surgery [152]. Several surgical series have shown preoperative smoking cessation before elective surgery to be efficient to reduce the risk of postoperative complications [64, 153-155]. Only three RCTs have tested the

effect of preoperative smoking cessation on the outcome after surgery [156-158]. The first studied the risk of wound-related complications after incisional wounds were made in the skin of study participants [156]. The intervention started four weeks before the “surgical procedure” and the intervention group was provided with NRT during the study period. At the end of follow-up 1 wound of 86 (1%) in those who became abstinent and 10 wounds of 36 (28%) in those who smoked developed wound infection ($p < 0.01$). The risk of infection in those who managed to become abstinent was comparable to the risk of never-smokers. In the second study, Moller *et al* studied the effect of 6-8 weeks of preoperative smoking cessation intervention provided by weekly counselling sessions with a study nurse and NRT on the short-term outcome after knee- and hip replacement [157]. The overall risk of complications dropped from 52% in the control group to 18% in the intervention group (OR 0.34; 95% CI 0.17-0.58). The corresponding figures for the risk of wound-related complications were 31% and 5% (OR 0.16; 95% CI: 0.05-0.52) [157]. In the third study, Sorensen *et al* used a less intensive smoking cessation programme which started 2-3 weeks before colorectal cancer surgery. The intervention did not affect the risk of postoperative complications in comparison to the controls (OR 0.90; 95% CI: 0.31-2.58) [158]. Detailed information about the latter two studies is shown in Table 1.

Based on the existing evidence, it still remains unclear how factors such as the type of surgery, the length of preoperative smoking cessation or the type of intervention could affect the success of preoperative smoking cessation and its impact on the postoperative complications.

Furthermore, the efficacy of preoperative smoking cessation to promote abstinence has been tested only in a few randomised clinical trials, all of which have been successful in reducing the prevalence of smoking in short-term perspectives [158-162] (Table 1). However, the majority of the studies have not been able to maintain these results long-term.

6.4 Obesity, a growing epidemic

The World Health Organization (WHO) has defined a BMI [calculated as weight (kg) / height (m²)] ≥ 25 as overweight and ≥ 30 as obesity. The prevalence of overweight and obesity have increased rapidly in many parts of the world. One third of all Americans are obese [163]. In China, the prevalence of overweight and obesity increased from 14.6% in 1992 to 21.8% in 2002 [164]. The increasing weight is unfortunately growing in younger ages and will continue to increase if no measures to reduce this trend are undertaken [165]. Thus, overweight and obesity have now become a global threat to human health.

Obesity and overweight are associated to insulin resistance and metabolic syndrome [166], cardiovascular disease [167] and hyperlipidemia [168]. Obesity increases mortality in cardiovascular disease and cancer [169]. As with smokers, the obese have increased risks of wound-related [170, 171] and cardiopulmonary complications [172, 173] after surgical procedures.

6.4.1 Methods for weight reduction

There are several possible approaches to reduce weight, and most efficient way is obesity surgery. This surgery is performed on individuals who are either morbidly obese (BMI ≥ 40 kg/m²) or have a BMI ≥ 35 kg/m² together with co-morbidities. In a meta-analysis, obesity surgery resulted in a reduction of BMI by on average 14 units over a two-year period [174]. Alongside this improvement, co-morbidities such as diabetes, hypertension and hyperlipidemia resolved in the majority of patients [174]. These results are consistent after a decade of follow-up [175]. However, as described above, the indications for surgery leaves out patients with a BMI less than 35 kg/m².

Other interventional approaches to reduce weight are less efficient. Pharmacological therapy of obesity results in a mean weight reduction of 5 kg or less and a modest improvement of glycemic control and lipid values after at least one year of follow-up [176]. Comparatively, increased physical activity [177] and change of diet [178, 179] alone or in combination was found to modestly reduce weight, improve glycemic control and lipid levels. Psychological interventions has been proposed to reduce weight in overweight and obese individuals, but again the results of such interventions are modest even when combined with physical activity or dietary interventions [180]. The effect of these interventional approaches on the outcome after surgical treatments remains to be investigated.

Table 1. Characteristics of studies investigating the efficacy of preoperative smoking cessation intervention

Authors	No patients	Timing of intervention	Intervention provided	Length of follow-up	Cessation validated	Dropout	Abstinence data
Wolfenden <i>et al</i> 2005	210	1–2 w before surgery	IG [†] : 1) Computed-based 2) tailored self-help material 3) telephone counselling 4) 1–2 w of NRT CG [‡] : NRT at staff's discretion	3 months after surgery	No	IG: 16 of 124 (13%)* CG: no dropout	78% of IG and 65% of CG at the time of surgery (p=0.04) 19% of IG and 12% of CG at 3 months after surgery (p=0.18)
Ratner <i>et al</i> 2004	237	1–3 w before surgery	IG: 1) Two face-to face counselling sessions 2) one telephone counselling session 3) NRT and self-help material CG: 1) standard care	12 months after surgery	Yes	IG: 6 of 117 (5%) at the time of surgery 24 of 117 (21%) at 6 months after surgery 36 of 117 (31%) at 12 months after surgery CG: 3 of 120 (3%) at the time of surgery 11 of 120 (9%) at 6 months after surgery 32 of 120 (27%) at 12 months after surgery	73% of IG and 53% of CG at the time of surgery (p<0.01) 31% of IG and 20% of CG at 6 months after surgery were abstinent (p=0.10) 27% of IG and 26% of CG at 12 months after surgery (p=1.0)
Myles <i>et al</i> 2004	47	8 w before surgery	IG: 1) Bupropion during 8 w CG: 2) standard care	6 months after surgery	Yes	IG: 6 of 24 (25%) after 3w 10 of 24 (42%) after 6w 10 of 24 (42%) after 6 months CG: 11 of 23 (48%) after 3w 13 of 23 (57%) after 6w 15 of 23 (65%) after 6 months	38% of IG and 9% of CG after 3 w (p=0.04) 25% of IG and 9% of CG at 6 w (p=0.25) 13% of IG and 5% of CG at 6 months (p=0.61)

Table 1 (cont). Characteristics of studies investigating the efficacy of preoperative smoking cessation intervention

Authors	No patients	Timing of intervention	Intervention provided	Length of follow-up	Cessation validated	Dropout	Abstinence data
Sorensen <i>et al</i> 2003	60	2-3 w before surgery	1) face-to-face visit, 2) telephone support 3) NRT up to 24 hours before surgery CG: 1) Asked to continue smoking	30 days after surgery	Yes	IG: 3 of 30 (10%) CG: no dropout	89% of IG and 13% of CG at the time of surgery (p<0.01) [‡] 93% of IG and 50% of CG one week after surgery (p<0.01)
Moller <i>et al</i> 2002	120	6-8 w before surgery	IG: 1) Weekly meetings with a study nurse 2) NRT provided CG: standard care	10 days after surgery	Yes	IG: 4 of 60 (7%) at 10 days after surgery CG: 8 of 60 (13%) at 10 days after surgery No further dropout 12 months after surgery	64% of IG and 8% of CG at the end of follow-up (p<0.01) 23% of IG and 4% of CG at 12 months after surgery (p<0.01)

† Intervention group

± Control group

* Not specifying the exact timing of dropout

‡ Including those who reduced their daily cigarette consumption to half.

7. AIMS

The main aim of this thesis was to study the role of smoking and high BMI on the risk of development of postoperative complications.

The specific aims were:

- To study the impact of smoking and high BMI on the risk of postoperative complications up to 60 days after elective THR.
- To evaluate the long-term effects of smoking and high BMI on the risk of implant dislocation up to 8 years after elective THR.
- To investigate the impact of smoking and high BMI on the risk of postoperative complications up to 30 days after acute OA.
- To evaluate the effect of preoperative smoking cessation on the risk of postoperative complications up to 30 days after elective orthopaedic or general surgery.

8. MATERIALS AND METHODS

8.1 The Swedish Construction Workers' Cohort (Study I – III)

The Construction Industry's Organization for Working Environment Safety and Health (Bygghälsan), established in 1968, provided outpatient medical services to construction workers all over Sweden from 1969 through 1992. The organization was a joint venture launched by the construction trade unions and sub-sectors and the corresponding employers' associations. 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 2nd year during the first years, every 3rd year thereafter) personal invitations and through visits to outpatient clinics or advertisements at virtually all major building sites. Beginning with visits in 1971, data from these health check-ups were compiled in a computerised central register. The resulting cohort consisted of more than 386,000 construction workers, most of whom were male (95%).

From 1971 to 1976, each cohort member filled out a self-administered 200-item questionnaire which included a detailed smoking history and data on weight and length. To avoid misunderstandings or inconsistencies, the answers were double-checked by the attending staff. This questionnaire was not used during 1976 through 1977, but was resumed and expanded in 1978 to record an even more detailed smoking history now recorded directly by the staff. On average, each cohort member underwent three health check-ups, each occurring 2-3 years apart. The quality of the smoking data has been validated. Inconsistencies were found in 2.6% of the cases e.g., subjects who indicated that they were current or ex-smokers in the first questionnaire asserted that they had never smoked in the second questionnaire [181].

8.2 The Swedish Inpatient Register (study I – III)

Established in 1964, the National Board of Health and Welfare has collected data on individual hospital discharges in the Swedish Inpatient Register. The national coverage of this register was 60% in 1969, 85% in 1983 and 100% in 1987 and onwards. Besides the national registration number (NRN) (uniquely identifying each resident in Sweden), each record contains as many as eight discharge diagnoses coded according to the current International Classification of Disease (ICD) and up to twelve 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 three-digit level for 92-94% of the records on surgical patients. For surgical procedures (excluding endoscopies or biopsies), the codes were incorrect in 2% of the records and were missing in 5.3% [182].

8.3 Cohort identification (study I – III)

Using the NRN, linkage between the Swedish Construction Workers' Cohort and the Swedish Inpatient Register was made to identify all construction workers who were discharged from hospitals with a procedure code of THR (study I-II) or OA (study III).

8.1.1 Study I

Figure 1 shows the process of identifying the cohort in study I. By merging the two cohorts, males undergoing THR were identified (codes according to the Swedish Classification of Operations and Major Procedures: <1997: 8411, 8414; ≥1997: NFB29-NFB49). Only the first THR was included in the cohort. To reduce confounding, the

cohort was limited to those with primary osteoarthritis of the hip and those with previous orthopaedic procedures on the lower spine, pelvis and lower extremity were excluded.

8.1.2 Study II

The same procedure for including subjects as in study I was used. Due to more precise coding of *implant dislocation* from 1997, the cohort in study II was limited to those who underwent THR in 1997 or later.

8.1.3 Study III

In this study, cases of OA (Swedish Classification of Operations and Major Procedures: <1997: 4510, 4511; ≥1997: JEA00, JEA10) due to acute appendicitis were identified. Only procedures that occurred after recruitment to the Swedish Construction Workers' Cohort were included. Those with colonic cancer and inflammatory bowel disease were excluded. Owing to small numbers, all cases of laparoscopic appendectomies were excluded (n= 202).

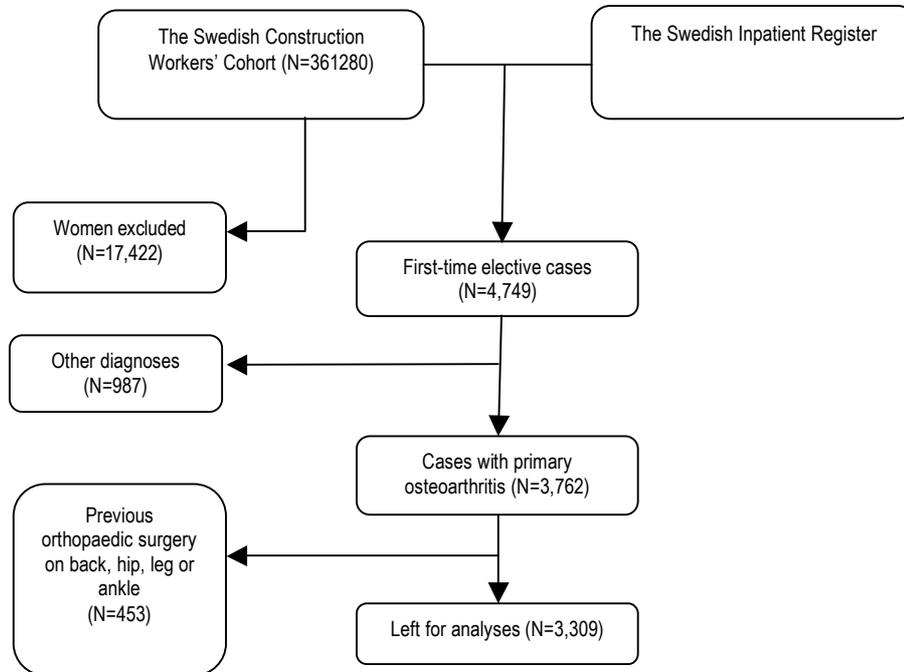
8.4 Smoking Cessation Study (Rökstoppsstudien) (study IV)

This RCT was conducted at four university-affiliated hospitals in Stockholm, Sweden. Between March 2004 and December 2006, active daily smokers (>2 cigarettes per day during at least one year prior to inclusion), aged 18 to 79 years old, scheduled to undergo elective hip or knee replacement, elective inguinal- or umbilical hernia repair or laparoscopic cholecystectomy were invited to participate in this study. Current alcohol or drug abuse, pregnancy, severe mental illness, dementia or poor proficiency in the Swedish language were excluding factors. Patients were enrolled after giving their informed consent by the study nurses or the treating surgeons, none of whom took part in the randomization procedure.

8.1.4 Randomization

Randomization was made at the day of inclusion by the nurse providing the smoking cessation. Patients were randomised in a 1:1 ratio to the control or the intervention group, using opaque, sealed envelopes in blocks of ten, stratified by the type of the surgical procedure and the treating clinic. These envelopes were prepared by the nurse providing the smoking cessation. The treating physician and other medical staff were blinded to the allocation status. Patients in the intervention group were scheduled to undergo an intensive smoking cessation programme as described below and participants in the control group received standard care which meant brief or no information about smoking cessation before surgery.

Figure 1: Flow-chart for study I



8.1.5 Intervention

The smoking cessation programme was intended to start four weeks before the elective surgery and lasted up to four weeks after surgery. The intervention included weekly meetings or telephone counselling with a nurse professionally trained in smoking cessation therapy. In addition, patients received a telephone number to the national smoking cessation helpline in case they needed further counselling or support. All participants in the intervention group were offered free NRT administered as self-adhesive patches, chewing gum or microtabs based on patient preferences. NRT was the only pharmaceutical cessation therapy offered. The main goal was to remain abstinent three weeks preoperatively and four weeks after surgery.

8.1.6 Recorded data

Each patient completed a self-administered questionnaire, providing background information on patient-related, socioeconomic and life-style factors. Obesity was categorised as BMI ≥ 30 kg/m² and BMI < 30 kg/m² was defined as not obese. The monthly average alcohol consumption was registered as 0-31 or ≥ 32 drinks per month. Tobacco use was categorised in pack years of smoking. The Fagerström tolerance questionnaire [183] was used to measure nicotine dependence. Information on regular exercise, snus (Swedish smokeless tobacco) use, the participants' marital status, the smoking habits of their partners, the level of education and occupational status was also registered.

Preoperative health evaluation provided the rated American Society of Anaesthesiology classification (ASA) [184], the level of exhaled carbon monoxide (CO)

(Micro™ Smokerlyzer®, Bedfont Scientific Ltd, Rochester, UK) at the time of inclusion and occurrence of co-morbidities.

8.1.7 Sample size calculation

Power calculation was based on the results of previous randomized trials [157, 158]. The baseline complication risk was set to be 30% and the treatment effect was estimated to be a 30% (from 30% to 21%) reduction in the risk of postoperative complications compared to no intervention at all. Using a two-sided α -level of 0.05 and statistical power of 90%, almost 600 patients were planned to be recruited. Since the recruitment of patients was very slow, the inclusion was terminated in December 2006 before the estimated number was met. No interim analysis was done.

8.5 Outcome measures

8.1.8 Length of hospital stay (Study I)

In order to study the length of hospital stay, each patient was followed up until the day they returned home. Five patients died in the immediate post-operative period and were excluded from the final analysis. Length of hospital stay at readmissions after being discharged was not added to this variable.

8.1.9 Postoperative complications (Study I)

Using the Swedish versions of ICD-8 to ICD-10 and the Swedish Classification of Operations and Major Procedures, complications that occurred within a 60-day period after admission to the hospital were recorded. These complications were categorised into local or systemic. Wound-related and prosthesis-related complications were categorised as local complications while systemic complications comprised all others including death.

8.1.10 Implant dislocation (Study II)

The primary outcome was the first-time event of implant dislocation corrected by a non-surgical repositioning. Study subjects were also followed until the end of follow-up up to 8 years after surgery, emigration, or death—as provided through linkage with the Swedish Emigration Register and the Swedish Cause of Death Register—whichever occurred first. Moreover, patients were censored at the time of admission to hospital if they underwent reoperation due to prosthesis-related complications. The information about which hip (right or left) that had undergone THR was missing for the majority of the subjects (91%). Therefore, patients were also censored at the time of a new THR or other hip prosthesis surgery. The cohort was followed for a maximum of 8 years, up to the end of 2004.

8.1.11 Perforation status (Study III)

The Swedish versions of ICD-8 to ICD-10 were used to identify the appendicitis perforation status. PA was defined as cases with the discharge diagnosis codes 540.00–03 (ICD-8), 540A-B (ICD-9) or K35.0–1 (ICD-10). Non-perforated appendicitis (NPA) was defined as cases having the ICD discharge code 540.90–99 (ICD-8), 540X (ICD-9) or K35.9 (ICD-10).

8.1.12 Postoperative complications (Study III)

Complications that occurred within 30 days after hospital admission were recorded using the Swedish versions of ICD-8 to ICD-10 and the Swedish Classification of Operations

and Major Procedures. All deaths within 30 days were identified through linkage to the Swedish Cause of Death Register.

8.1.13 Smoking status (Study IV)

Smoking status of the intervention group was assessed on self-reported basis at weekly face-to-face meetings or through telephone calls before and after surgery. Smoking status of the intervention and control group was objectively assessed once at the next visit to hospital two to four weeks after surgery by measurement of the level of exhaled CO. At this follow-up, the control group self-reported their smoking status. Successful abstinence during the whole intervention period was considered only if 1) participants reported no use of cigarettes at least one week prior to surgery, 2) remained abstinent until four weeks after the surgical procedure and 3) if the level of exhaled CO measured at the next visit to the hospital, two to four weeks postoperatively, was ≤ 10 ppm.

Long-term smoking status was assessed using a self-reported questionnaire mailed to all participants approximately twelve months after surgery. If the questionnaire was not returned, smoking data was retrieved by telephone calls. The long-term smoking status twelve months after surgery was not validated by measurement of exhaled CO.

8.1.14 Postoperative outcome (Study IV)

The primary outcome in study IV was the development of any postoperative complications that occurred within 30 days after surgery. The secondary outcome was occurrence of wound-related complications during the same follow-up period. A complication was defined as an unexpected event causing additional medical or surgical treatment, investigations (radiography, laboratory tests), prolonged hospital stay or unscheduled postoperative check-ups at the out-patient department. Complications were recorded by the study nurse at the clinical follow-up two to four weeks after surgery and also by a telephone interview four weeks postoperatively using a predefined study protocol (Table 2). All study nurses were given the same information and training on how to record possible complications. The recorded complications were double-checked by the authors reviewing the medical records without knowledge of the allocation status. This was arranged as a panel discussion to reach consensus on the status of each possible complication.

Table 2. Pre-specified definitions of postoperative complications

Type of complication	Definition and management
<i>Wound complications</i>	
Seroma or hematoma	Wound revision, wound drainage or repeated wound dressings
Superficial wound infection	Antibiotics or repeated wound dressings
Deep wound infection	Surgical debridement
Wound dehiscence	Reoperation
Pressure wounds or skin necrosis	Wound revision or repeated wound dressings
<i>Urinary tract complications</i>	
Urinary retention	Catheterization after surgery (>24 h after surgery)
Urinary tract infection	Antibiotics
Renal failure	Oliguria <500 ml/24h or increase in creatinine with more than 30%
<i>Gastrointestinal complications</i>	
Nausea and vomiting	Intolerance to nutrition and prolonged need of iv fluids (>24 h after surgery)
Small bowel obstruction	Gastrointestinal X-ray series or reoperation
Biliary leakage	Reoperation or endoscopic retrograde cholangiography (ERC)
<i>Pulmonary complications</i>	
Pneumonia or bronchitis	Antibiotics
Respiratory insufficiency	Postoperative ventilator support (>24 h after surgery)
<i>Cardiovascular complications</i>	
Myocardial infarction/Angina pectoris/Heart Failure/Arrhythmias	Medication, prolonged observation or additional diagnostics
Stroke or transient ischemic attack	Medication, prolonged observation or additional diagnostics
Deep Venous Thrombosis	Verified with Duplex or flebography and treated with anticoagulant drugs
Pulmonary Embolism	Verified with computerized tomography and treated with anticoagulant drugs
<i>Prosthesis related</i>	
Fracture of prosthesis	Verified by X-ray
Dislocation of prosthesis	Verified by X-ray
Peripheral nerve injury	Clinical or Neurophysiologic diagnosis
<i>Other</i>	
Fever of unknown origin	Antibiotics and/or additional investigations
Reoperation	Type
Death	Cause
Other complication(s)	Type

9. STATISTICAL ANALYSIS

9.1 Linear regression (study I)

Multiple linear regression analysis was used to estimate adjusted associations between length of hospital stay (continuous variable) and BMI and smoking status. To improve the symmetry of the outcome, natural log transformation was applied. Interpretation of the log-transformed outcome is the percentage increase in the average value of the outcome per unit increase in the predictor calculated as $100(e^{\beta} - 1)$ where β is the coefficient.

9.2 Binomial regression (study I, III and IV)

Unconditional multivariable logistic regression modelling was used to study how patient characteristics simultaneously affected the likelihood of developing postoperative complications (dichotomous variable) within 60 days after surgery. The measure of association was ORs and their corresponding 95% CI.

The association between postoperative outcome and exposure factors was summarized in terms of relative risk (RR) with the corresponding 95 % CI by means of binomial logistic regression. Due to the small size of the cohort in study IV, only factors of baseline characteristics that affected the outcome >10% were included in the multivariable model.

9.3 Cox regression (study II)

The Kaplan-Meier method was used to estimate the crude cause-specific survival distribution of time from surgery to the event of implant dislocation. Both log-rank and Wilcoxon test were used to study the effect of BMI and smoking on the risk of implant dislocation. Cox proportional hazards regression model was used to test the null hypothesis of no effect of BMI and smoking status, while taking into account the simultaneous and independent effects of age at the time of surgery, calendar period, and fixation principle (use of cement or not). Parameter estimates (Hazard Ratio (HR)) and 95% CI were obtained by maximizing the partial log-likelihood.

9.4 Intention to treat analysis (Study IV)

Primary analyses were performed according to intention to treat and exploratory analyses were performed using per protocol information. When analysing the data according to intention to treat those not completing the study and follow-up were considered to still be smokers. Comparatively, when studying the effect of intervention on the outcome after surgery those who did not complete the follow-up were considered to have developed postoperative complications. The level of statistical significance was set at $P < 0.05$ and tests were two-sided.

10. RESULTS

10.1 Study I

A total of 3,309 male patients undergoing unilateral THR due to primary osteoarthritis of the hip were identified. There was a difference of on average 16 years (0.1 – 31) between recruitment to the Construction Workers' Cohort and the time of surgery. This means that the calculated post-estimates were based on exposure information collected almost two decades before the time of surgery. The mean age at the time of surgery was 65.6 (33 – 89).

In a multivariable model, the length of hospital stay was significantly longer among the overweight and obese. In obese mean the length of hospital stay was ½-1 day (7% (95% CI: 2.9-11.1)) longer in-hospital treatment compared to those of normal weight who had on average 9 days of hospital stay.

There were 268 (8.1%) of 3,309 patients who developed one or more systemic postoperative complications and 128 (3.9%) who suffered from prosthesis- or wound-related complications. In multivariable models previous and current smoking, high level of life-time smoking (>20 pack-years) and obesity were significantly associated with the increased risk of systemic postoperative complications (Table 3). In addition, overweight and obesity significantly increased the risk of local complications. However, this association was stronger for the overweight compared to those who were obese.

Table 3. The risk of postoperative complications according to smoking status, life-time tobacco smoking and BMI calculated by adjusted OR and 95% CI.

	Systemic complications			Local complications		
	OR	95% CI	Overall p-value	OR	95% CI	Overall p-value
BMI (kg/m²) †			0.08			0.12
18.5-24.9	1	Ref		1	Ref	
25.0-29.9	1.12	0.84 – 1.51		1.55	1.01 – 2.38	
≥30	1.58	1.06 – 2.35		1.24	1.24 – 2.35	
		p-trend 0.04			p-trend = 0.22	
Smoking status*			0.01			0.87
Never	1	Ref		1	Ref	
Previous	1.43	1.04 – 1.97		1.13	0.72 – 1.75	
Current	1.56	1.14 – 2.14		1.03	0.66 – 1.60	
		p-trend <0.01			p-trend = 0.88	
Pack-years of smoking*			<0.01			0.87
Never	1	Ref		1	Ref	
>0-19.9	1.35	0.99 – 1.84		1.11	0.74 – 1.68	
20-39.9	1.78	1.21 – 2.60		0.92	0.50 – 1.68	
≥40	2.21	1.28 – 3.82		1.26	0.55 – 2.91	
		p-trend <0.01			p-trend = 0.80	

* Each tobacco-related exposure variable was fitted separately. All final models were adjusted for age at the time of surgery, calendar period, body mass index, medical region and co-morbidities

† The final model for BMI was adjusted for age at the time of surgery, calendar period, medical region, smoking status and co-morbidities

10.1.1 Supplementary analyses

As in study III (discussed below), smoking status and life-time tobacco consumption were combined into a single variable. The effect of this variable on the outcome after THR is presented in Table 4. Combination of BMI and smoking status resulted in small subgroups of patients with imprecise results and was therefore not shown. Stratification of the results over calendar period did not change the estimates.

Table 4. The risk of postoperative complications according to life-time tobacco exposure calculated by adjusted OR and 95% CI.

Smoking status (pack-years)*	Systemic complications			Local complications		
	OR	95% CI	Overall p-value	OR	95% CI	Overall p-value
Never	1	Ref	<0.01	1	Ref	0.96
Previous, 0-19.9	1.48	1.04 – 2.11		1.11	0.68 – 1.83	
Previous, ≥20	1.60	0.98 – 2.63		1.12	0.53 – 2.34	
Current, 0-19.9	1.19	0.81 – 1.74		1.20	0.73 – 1.98	
Current, ≥20	2.07	1.40 – 3.06		1.00	0.53 – 1.87	
		p-trend <0.01			p-trend = 0.96	

* The final model was adjusted for age at the time of surgery, BMI and calendar period

10.2 Study II

In study II, 2,106 males underwent unilateral THR between 1997 and 2004 due to primary osteoarthritis of the hip. Mean age at the time of surgery was 65.7 (36 – 89) and as in Study I, the exposure data was collected almost two decades before the time of surgery. The mean time of follow-up was 3 years (0 – 8) resulting in a total of 6,474 person-years of follow-up. The follow-up was divided into two time periods 1) 0–3 years and 2) 3–8 years. All 2,106 patients were available for the first study period, which began at the day of admission to the hospital to undergo THR and continued until implant dislocation or censoring had occurred, or up to 3 years after surgery. 53 (2.5%) patients had implant dislocation within three years after surgery. In the second follow-up period, 897 patients, who were not censored, were followed up to eight years after THR. There were only two cases of implant dislocation that occurred during the second follow-up period. Thus, no bivariable or multivariable Cox-regression analyses could be performed for the second follow-up period.

The main finding of this study was a significant association between the risk of implant dislocation and high BMI occurring within 0-3 years after admission to hospital (Table 5). There was no significant association between smoking and the risk of implant dislocation.

Table 5. The risk of implant dislocation in relation to BMI and smoking status 0 to 3 years after primary THR calculated by adjusted HR and 95% CI.

BMI (kg/m ²) †	Implant dislocation		
	HR	95% CI	Overall p-value
18.5-24.9	1	Ref	0.01
25.0-29.9	2.50	1.14 – 5.49	
≥30	3.74	1.50 – 9.33	
		p-trend <0.01	
<u>Smoking status*</u>			0.07
Never	1	Ref	
Previous	0.70	0.31 – 1.57	
Current	1.69	0.90 – 3.18	
		p-trend =0.10	
<u>Pack-years of smoking*</u>			0.83
Never	1	Ref	
>0-19.9	1.22	0.65 – 2.31	
≥ 20	1.44	0.66 – 3.18	
		p-trend =0.35	

† The final model for BMI was adjusted for age at the time of surgery, calendar period, smoking status, and fixation principle *each tobacco-related exposure variable was fitted separately. All final models were adjusted for age at the time of surgery, calendar period, BMI, and fixation principle

10.2.1 Supplementary analyses

The impact of smoking status and high BMI (overweight and obese subgroups collapsed) on the risk of implant dislocation is shown below (Table 6). Due to too few events of implant dislocation in different subgroups no further multivariable modelling was performed.

Table 6. The risk of implant dislocation in combined relation to smoking status and BMI.

BMI (kg/m ²)	Smoking status		
	Never	Previous	Current
18.5-24.9	1 (0.6%)	1 (1.3%)	7 (4.3%)
≥25.0	18 (5.8%)	8 (3.2%)	18 (6.7%)

P-value= 0.02

10.3 Study III

The majority of patients in this study were treated for NPA (5,536 (82.9%)). The median age at the time of surgery due to NPA was 41.3 years (16 - 89). Those who developed PA were in median 49.8 years (18 - 92). Exposure data was on average assessed 9 years (0 - 33) before the time of surgery.

In multivariable analysis, current smoking was found to be significantly associated with increased risk of being discharged with a diagnosis code of PA (Table 7).

Table 7. The risk of perforated appendicitis in relation to BMI and smoking status calculated by adjusted RR and 95% CI.

BMI (kg/m ²) †	Perforated appendicitis		
	RR	95% CI	Overall p-value
18.5-24.9	1	Ref	0.82
25.0-27.4	1.02	0.90 - 1.15	
27.5-29.9	1.09	0.92 - 1.28	
≥30	1.13	0.93 - 1.39	
		p-trend = 0.77	
<u>Smoking status (pack-years)*</u>			<0.01
Never	1	Ref	
Previous, 0-9.9	0.96	0.80 - 1.15	
Previous, ≥10	1.12	0.90 - 1.38	
Current, 0-9.9	1.17	1.01 - 1.35	
Current, ≥10	1.29	1.11 - 1.50	
		p-trend <0.01	

† The final model for BMI was adjusted for age at the time of surgery, calendar period and smoking status

* The final model for smoking status was adjusted for BMI, age at the time of surgery and calendar period

Postoperative complications occurred in 241 (4.4%) patients with NPA and 75 (6.6%) of those with PA. A BMI ≥27.5 kg/m² and tobacco-smoking ≥10 pack-years were significantly associated with increased risk of overall postoperative complications.

Table 8. The risk of postoperative complications in relation to BMI and smoking status calculated by adjusted RR and 95% CI.

	NPA			PA		
	RR	95% CI	Overall p-value	RR	95% CI	Overall p-value
<u>BMI (kg/m²) †</u>			<0.01			0.90
18.5-24.9	1	Ref		1	Ref	
25.0-27.4	1.11	0.80 – 1.52		1.04	0.61 – 1.76	
27.5-29.9	1.69	1.14 – 2.51		1.24	0.63 – 2.43	
≥30	2.60	1.71 – 3.95		1.26	0.57 – 2.77	
		p-trend <0.01			p-trend =0.72	
<u>Smoking status (pack-years)*</u>			0.20			0.35
Never	1	Ref		1	Ref	
Previous, 0-9.9	1.00	0.64 – 1.54		0.58	0.23 – 1.50	
Previous, ≥10	0.88	0.47 – 1.62		0.53	0.18 – 1.53	
Current, 0-9.9	1.02	0.72 – 1.44		1.02	0.54 – 1.95	
Current, ≥10	1.51	1.03 – 2.22		1.25	0.69 – 2.28	
		p-trend = 0.08			p-trend =0.74	

† The final model for BMI was adjusted for age at the time of surgery, calendar period and smoking status

* The final model for smoking status was adjusted for BMI, age at the time of surgery and calendar period

10.4 Study IV

Between February 2004 and December 2006, 117 patients were enrolled in this study. Information of postoperative outcomes was collected until March 2007. Seven patients in the intervention group and eight in the control group did not complete the study due to reasons stated in Figure 2. Baseline characteristics for those who completed the trial are shown in Table 9.

Table 9: Baseline characteristics of patients according to the randomization status

	Randomization status	
	Intervention (N=48)	Control(N=54)
<u>Patient-related factors</u>	N (%)	N (%)
Male gender	30 (62)	24 (44)
Age (median, IQR ^a)	55 (46 – 60)	57.5 (49 – 64)
ASA classification (1 – 2)	44 (92)	46 (85)
Alcohol use (<32 drinks /month)	44 (92)	45 (83)
BMI (kg/m ²)	26 (24 - 30)	25 (23 - 29)
<u>Co-morbidities</u>		
Diabetes	0 (0)	2 (4)
Chronic heart disease	1 (2)	8 (15)
COPD	6 (13)	6 (11)
<u>Preoperative laboratory test</u>		
Haemoglobin (n=100)	144 (134 - 153)	142 (134 – 153)
FEV ₁ (n=99)	2.5 (2.2 – 3.5)	2.5 (2.0 – 3.2)
<u>Smoking status</u>		
Cigarettes/ day (median, IQR)	15 (10 – 20)	15 (10 – 20)
Years of smoking (median, IQR)	35 (25 – 42)	37 (30 – 45)
CO in the expired air (IQR)	15 (8 – 22)	14 (8 – 22)
Snus use	5 (10)	4 (7)
<u>Type of surgery*</u>		
Hernia surgery	21 (44)	17 (32)
Laparoscopic cholecystectomy	9 (19)	18 (33)
Hip replacement	10 (21)	15 (28)
Knee replacement	8 (16)	4 (7)
<u>Perioperative data</u>		
Duration of surgery (minutes)	80 (61 – 102)	73.5 (50 – 95)
Preoperative antibiotics	25 (52)	29 (54)
Day care surgery	16 (33)	8 (15)
Surgeon in training (resident)	14 (29%)	14 (26%)

a. Interquartile range

* Column percentages

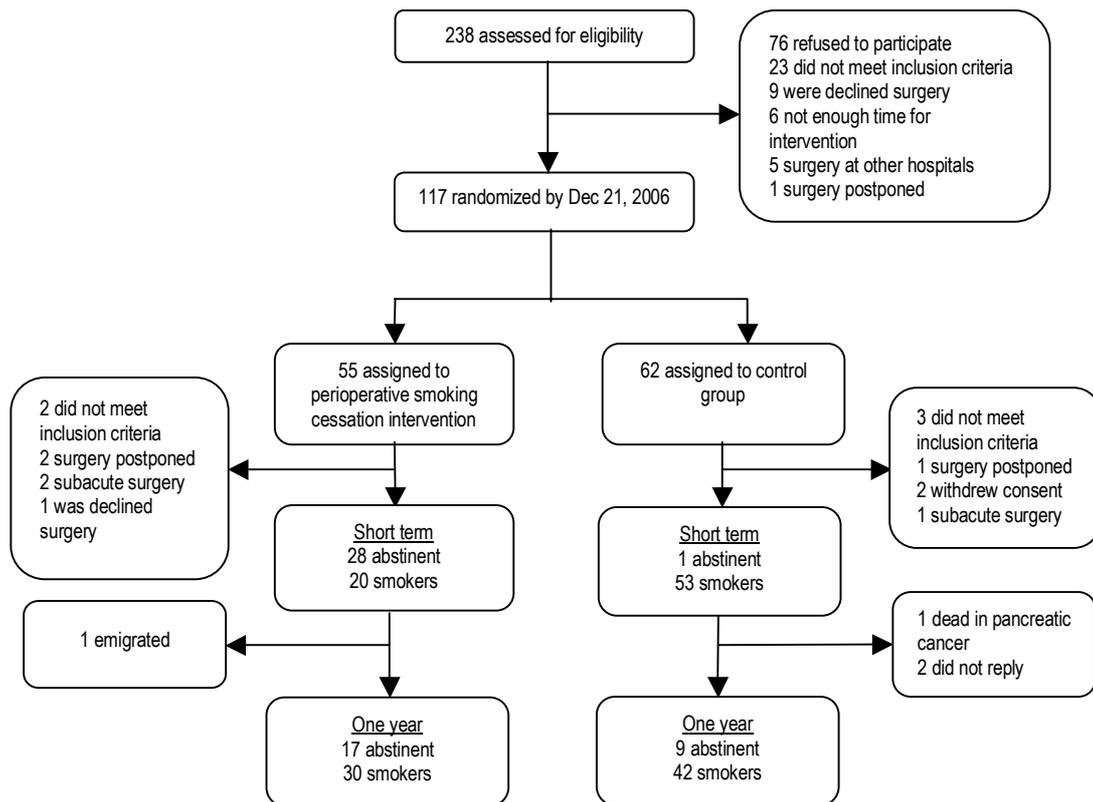
10.4.1 Intervention

The smoking cessation programme started a median of 4 (Interquartile range (IQR): 3 - 5) weeks prior to surgery and lasted until four weeks after the surgical procedure. Each patient in the intervention group participated in a median of 8 (IQR: 7 - 9) meetings or telephone interviews. Most patients, 41/48 (85.4%) in the intervention group used NRT products. No patient started using snus.

10.4.2 Smoking status

As a result, 28/48 (58.3%) patients in the intervention group became abstinent before surgery and remained so throughout the intervention period until four weeks after surgery. 19 (39.6%) of these patients became abstinent ≥ 3 weeks before surgery and the remaining 9 (18.7%) < 3 weeks preoperatively. In the control group only one (1.9%) person managed to become abstinent preoperatively and remain so until four weeks after surgery. No adverse events related to NRT were reported.

Figure 2: Trial profile



10.4.3 Postoperative complications

Table 10 summarizes the event of postoperative complications that occurred within 30 days after surgery. According to intention to treat analysis the overall risk of postoperative complications dropped 37% (RR= 0.63; 95% CI: 0.40 – 1.02) from 30/62 (48%) in the control group to 17/55 (31%) in the intervention group. This risk was reduced by 53% (RR=0.47; 95% CI 0.20 – 1.09) in those who adhered to the intervention (5/29 (17%) and became abstinent compared to those who continued smoking (27/73 (37%)). The risk of wound complications was also lower in the intervention group (intention to treat: RR=0.67; 95% CI: 0.37 – 1.19, per-protocol: RR=0.28; 95% CI: 0.07 – 1.13). None of the factors of baseline characteristics altered the point estimates by >10% in either direction. Thus, no multivariable modelling was performed.

Table 10. Postoperative complications according to allocation status

	Randomization status	
	Intervention (N=48)	Control (N=52)
<i>Wound-related complications</i>		
Hematoma	3 (6%)	7 (13%)
Wound infection	2 (4%)	4 (7%)
Seroma	3 (6%)	5 (9%)
Other wound complications	2 (4%)	4 (7%)
<i>Any wound complication</i>	6 (13%)	14 (26%)
Urinary tract complication	4 (8%)	9 (17%)
Pulmonary complication	0 (0%)	1 (2%)
Cardiovascular complication	1 (2%)	1 (2%)
Gastrointestinal complication	3 (6%)	0 (0%)
Fever of unknown origin	0 (0%)	1 (2%)
<i>Any complication</i>	11 (21%)	22 (41%)

10.4.4 Supplementary analyses

The efficacy of the smoking cessation programme to promote smoking cessation was studied using data from the clinical follow-up visit 2 to 4 weeks (self-reported smoking status and measurement of CO in the expired air) and the one year (self-reported smoking status) follow-up after surgery. Almost two thirds of the intervention group managed to become abstinent compared to one fifth of the control group after 2 to 4 weeks of follow-up. The proportion of the abstinent individuals declined one year after surgery in the intervention group. Due to small subgroups no meaningful stratified analyses could be performed.

Table 11. Abstinence at different points of follow-up as a result of allocation status

Abstinence	Randomization status			
	Intervention N (%)	Control N (%)	RR	95% CI
2-4 weeks after surgery - intent-to-treat	35/55 (64)	11/62 (18)	0.44	0.31 – 0.64
2-4 weeks after surgery - per-protocol	35/48 (73)	11/54 (20)	0.34	0.21 – 0.55
One year after surgery – intent-to-treat	15/55 (27)	9 /62 (17)	0.85	0.70 – 1.03
One year after surgery – per-protocol	15/47 (32)	9 /52 (17)	0.83	0.66 – 1.03

11. METHODOLOGICAL CONSIDERATIONS

To study associations between exposure and outcome in a population, the most ideal scenario is to have information on all individuals in that population. However, this is impractical and very expensive in large populations. Therefore, samples are drawn from the population of interest and the observed associations are assumed to be applicable to the population that the sample was drawn from. In order to make correct inferences, the validity of the observed associations should be analysed.

11.1 Validity

In the epidemiological context *bias* leads to lack of study validity. Bias is defined as *systematic errors in collecting or interpreting data such that there is deviation of results or inferences from the truth*. Three types of biases are often discussed in epidemiology, namely *selection bias*, *information bias* and *confounding*.

11.1.1 Selection bias

Selection bias is the result of errors due to systematic differences in characteristics between those selected for the study and the population from which the study sample was drawn. Selection bias is often an issue in case-control studies. Retrospective cohort studies may also be susceptible to this kind of bias, when selection of the exposed and un-exposed is related to their disease status. Since the outcome has yet not occurred in prospective studies, these are not subject to selection bias.

In study II death was a censoring factor that occurred significantly more frequent in current and former smokers compared to never-smokers. This differential loss to follow-up is known as *informative censoring*. Hypothetically those who will die (normally due to chronic illness) are becoming less mobile over a period of time before death. Thus, those patients will have a lower probability of implant dislocation since this complication is related to the level of physical activity. Yet, only 47 out of 2,108 patients in the cohort were censored due to death, of which 35 deaths occurred within the first 3 years after surgery. Thus, if any, the magnitude of the bias introduced by this censoring will be quite small.

Some diseases, such as acute appendicitis, have a spectrum of clinical presentations ranging from spontaneously resolving diffuse abdominal pain to perforation and general peritonitis [185]. In study III, only individuals undergoing appendectomies were studied. Thus, there was no information about those who had appendicitis that resolved spontaneously or those treated by other means than surgery. This limitation should be considered when interpreting the association between smoking and the risk of PA.

11.1.2 Information bias

Information bias is the result of errors in measuring exposure or disease. Case-control and cohort studies (both prospective and retrospective) could be subject to information bias. When the existence of misclassification of exposure or outcome is independent of the other axis it is referred to as *non-differential*. A non-differential misclassification of exposure or outcome will normally underestimate the results and bias the association towards the null. Exposure information in study I-III was collected at least one to two decades before the outcome. Using the entire Construction Workers' cohort, individuals' smoking behaviour and BMI could be followed prospectively for up to 17 years (Table 13 and 14).

Table 13. Changes of smoking status in males comparing smoking status at the time of inclusion to the Constructions Workers' cohort 17 (9 – 21) years later

<u>Day of inclusion</u>	<u>17 years later</u>			
	Never	Previous	Current	Total
<i>Smoking status</i>				
Never	5,135 (84.1%)	520 (8.5%)	451 (7.4%)	6,106 (100%)
Previous	0 (0.0%)	2,470 (87.8%)	344 (12.2%)	2,903 (100%)
Current	1 (0.0%)	2,249 (42.3%)	3,067 (57.7%)	5,317 (100%)

To evaluate the possible type of bias in study I-III introduced by the changes in smoking, sensitivity analysis was performed. The association between smoking and the risk of systemic complications in study I was chosen as a model to evaluate the bias resulting from a possible misclassification of smoking status. For each smoking subgroup, uniformly distributed random numbers between 0 and 100 were generated. Assuming that individuals in study I had the same dynamics in smoking behaviour as the rest of the Construction Workers' Cohort, new smoking variables were generated that displayed the distribution of the proportions in Table 13. The median OR (univariate) for the association between current smoking and systemic complications, based on 500 calculations, was 1.36 (95% CI: 0.97 – 1.92). This result was in line with the previously calculated univariate result 1.39 (95% CI: 1.02 – 1.89). Thus, possible changes in smoking status seemed not to affect the results substantially.

Table 14. Changes of BMI in male individuals comparing smoking status at the time of inclusion to the Constructions Workers' cohort and on average 10 (4 – 21) and 16 (8 – 21) years later

<u>Day of inclusion</u>	<u>16 years later</u>			
	18.5 – 24.9	25.0 – 29.9	≥30	Total
<i>BMI (kg/m²)</i>				
18.5-24.9	8,599 (59.3%)	5,733 (39.6%)	151 (1.0%)	14483 (100%)
25.0-29.9	506 (8.1%)	4,643 (74.3%)	1,103 (17.6%)	6252 (100%)
≥30	6 (0.9%)	153 (22.8%)	512 (76.3%)	671 (100%)

Similar procedures were used to perform sensitivity analysis on the association between BMI and postoperative complications. Study II was used as the model. After sensitivity analysis, the median HR for the association between obesity and the risk of implant dislocation was 2.34 (95% CI: 0.92 – 5.79). This could be compared to a HR of 3.45 (95% CI: 1.39 – 8.58) in study II. Hence, the association between BMI and the risk of postoperative complications in study I-III could have overestimated the true association.

It is known that registration of surgical complications in the Swedish Inpatient Register might suffer from missing data [186]. Based on the relatively low complication rate in study I and III there is the possibility that many in-hospital complications were not recorded. Moreover, complications treated on an outpatient basis will not have been recorded in this register either, which increases the likelihood of outcome misclassification. Nevertheless, such lack of data is unlikely to be related to the exposure status, i.e., BMI or smoking status. Thus, this non-differential misclassification is biasing the results towards null.

Differential misclassification is in contrast to non-differential misclassification a serious problem for the validity of a study. In case-control studies this misclassification is more often due to errors in exposure assessment which is likely to occur for diseased individuals than the non-diseased (e.g. recall bias). In cohort studies, differential misclassification of disease is a consequence of differing accuracy in the outcome assessment related to participant's exposure status. In study IV, there was a possibility that participants, particularly those in the intervention group, felt obligated to report that they were abstinent even if not actually being so. Such

reporting bias would have biased the results of the per-protocol analysis. However, when validating the smoking status, only one person in the intervention group who reported being abstinent during the whole study-period had a level of CO in exhaled breath >10 ppm. Thus, the information on smoking status could be judged as valid. The assessment of postoperative complications in study I-III was not related to the participant's exposure status. Thus, there was no differential misclassification of outcome occurring in these studies.

11.1.3 Confounding

Confounding is a mixing of effects. A confounder is defined as a third factor that is 1) a risk factor for the outcome 2) is associated with the exposure 3) is not an intermediate step in the causal pathway between exposure and outcome. All three criteria must be met in order to consider a factor to be a confounder.

One limitation of using a register-based cohort may be the lack of information of potential confounders. The level of alcohol use is one important possible confounder missing in the Construction Workers' Cohort (studies I-III). The diagnosis code for alcohol abuse is seldomly used in the Swedish Inpatient Register. Thus, the results of the three first studies should be interpreted with some caution.

When planning patients for elective surgery, there is a possibility that the surgeon will be more reluctant to admit those with multiple risk factors and diseases for surgery. Yet if admitted, the indication for such surgical procedure in these patients could be a more handicapping condition compared to the indication for healthier individuals. In this case, the indication for surgery will become a confounder related to the treatment and an indicator of the patient's health condition. This bias is referred to as *confounding by indication*. Based on the knowledge of a poorer outcome of surgery in smokers and those with high BMI, indication for *elective* surgery could have differed between these individuals and those with no such risk factors. However, it seems that these two risk factors do not alter the indication for surgery [187, 188].

The type of prosthesis or the surgical approach could be affected by the preferences of the surgeon and/or hospital traditions. In a large dataset as in studies I and II it is unlikely that a different case-mix of patient's characteristics between hospitals would have confounded the effects of high BMI and smoking on the outcome after THR. Furthermore, if the choice of the surgically-related factors such as the type of prosthesis is secondary to patients' characteristics such as a high BMI, they will no longer be confounders but instead will act as an intermediate step in the causal pathway. Thus, there is no reason to believe that the results of studies II and III were biased due to the lack of information about factors related to joint arthroplasty procedure.

11.1.4 Bias related to randomized clinical trials

A randomised clinical trial is an experiment to investigate the effect of medical treatments on human subjects. By randomization, subjects are by chance assigned to separate groups to compare different types of treatments. The purpose of randomization is to create homogenous groups with as low variability as possible in the baseline characteristics. Several factors in the study design could bias the results of study IV. Post-entry exclusion of study participants and the lack of compliance with allocation status are two factors that could strongly bias the results of an RCT. Post-entry exclusion could lead to selection bias and prohibited [189]. In the published paper there was post-entry exclusion but in this thesis this recommendation was followed.

Non-adherence to the randomized allocated treatment would dilute the results of the intention to treat analysis. In addition to intention to treat analysis, a per-protocol

analysis of the actual smoking status of patients was performed. This result showed that the complication reducing impact of smoking cessation persisted. The lack of masking may reduce objectivity in assessing the outcome variables. There was a possibility that the allocation status would have become un-blinded if the participants revealed their allocation status or the level of exhaled CO could have exposed them. The resulting *observer bias* could have influenced the validity of data recording. As discussed before, this issue was handled by pre-definition of outcome and panel review of the outcomes without prior knowledge of allocation status.

The proportion of patients declining participation was quite high. Unwillingness to quit smoking and being stressed by the forthcoming surgery were the two main reasons for declining participation. Recruitment to an RCT includes more or less always self-selection of individuals from a population. There is a possibility that the resulting cohort in study IV consisted of highly motivated individuals who were amenable to smoking cessation. This may have contributed to the high resulting rates of smoking cessation.

Premature termination of a trial before the estimated numbers of individuals are recruited may lead to imbalance in the distribution of the known and unknown confounders between the intervention and control groups. As previously noted, study IV was terminated due to slow recruitment of patients. The important known risk factors for a poor postoperative outcome such as the level of alcohol consumption or BMI were documented in this trial. None of these affected the association between abstinence and the risk of developing postoperative complications in a significant manner. There could be a possible residual confounding by the unknown confounders but given the fact that the study had access to the important acknowledged risk factors for development of postoperative complications, such possible confounding would be small.

11.1.5 Random error

Random error or chance is in contrast to systematic error an uncontrollable phenomenon that is always present in epidemiological studies. There are three ways to reduce random errors a) to increase the sample size b) to repeat a study c) to improve the quality of the exposure and outcome information. Although being based on large study samples, the results of study I-III were based on relatively few numbers of events. Furthermore, due to slow recruitment and premature termination of the trial in study IV, there was a limitation of statistical power in that study. Although the role of chance should be kept in mind when interpreting the results of especially study IV, many of our findings were in agreement with previous studies.

12. INTERPRETATION OF FINDINGS

12.1 Smoking, obesity and the short-term risk of postoperative complications

In this thesis, both smoking and obesity were found to increase the risk of postoperative complications considerably in two different surgical procedures. Due to few numbers of events, the effect of obesity and smoking on specific complications was not evaluated.

In study III, those with PA showed a higher baseline risk of complications. This reduced the risk difference between the subgroups. Therefore, the magnitude of the impact by smoking and high BMI was weaker compared to those with NPA. Furthermore, in study I, overweight and obesity were significantly associated with increased risk of local complications when adjusted for confounders. However, given the lack of a trend towards an increased risk of complications in heavier individuals, this increased risk was not convincing and was likely to be a chance finding.

Interestingly, in study III, current smokers had a dose-dependent increased risk of being discharged from hospital with a diagnosis code of PA. If causal, this finding might reflect a more rapid progression of appendicitis to perforation in smokers. Factors associated with altered pain physiology [190, 191] or modulation of the immune system [192, 193] may be involved.

Using a male construction worker population may theoretically affect the applicability of the results on females. Moreover, it is known that those employed are healthier than the general population. This phenomenon is known as the *healthy worker effect* [194]. Although there is no reason to believe that smoking or high BMI would have physiologically different effects on the health of women or other occupational groups in comparison to male construction workers, extrapolation of these results on the general population should be done with caution.

12.2 Obesity and the risk of implant dislocation

In study III, overweight and obesity were found to be strong risk factors for implant dislocation after primary THR. Recently, Lubekke et al reported that obesity doubled the risk of implant dislocation after primary THR compared to those who were non-obese [195]. In that study, no differences in implant- or surgically-related factors between the obese and non-obese were observed. After performing sensitivity analysis, the results in study II were more in agreement with the results of Lubekke et al. Two other reports, studying the risk of implant dislocation in patients undergoing revision hip replacement (repeated surgery due to implant failure) showed significant associations between implant dislocation and obesity [196, 197].

Malposition of the prosthesis components seemed not to be associated with obesity and is not likely to explain the increased risk of implant dislocation [196, 198]. The high load exerted on the prosthesis could be a factor that in extreme joint positions leads to implant dislocation.

Obesity and smoking are risk behaviours. Whereas non-smokers with normal weight practically did not develop implant dislocation, smokers with overweight had a substantially increased risk of this complication (Table 6). Therefore, non-compliance to postoperative recommendations such as avoiding certain joint positions could also be a factor that increases the risk of implant dislocation.

Since THR improves mobility and results in relieved of joint pain in those with osteoarthritis, the results should be used to further improve the safety and quality of THR for those with high BMI.

12.3 Smoking cessation and postoperative complications

Preoperative smoking cessation initiated as late as four weeks before surgery was shown to successfully reduce the risk of postoperative complications. The importance of this finding lies in the fact that many surgical conditions do not allow as much as six to eight weeks of preoperative planning. This longer period of time was used by Moller et al for preoperative cessation to reduce the risk of postoperative complications in those undergoing elective hip- and knee joint replacements [157]. As discussed earlier, smoking cessation has positive effects on wound healing and cardiopulmonary health. This physiological adaptation can explain the reduced risk of postoperative complications.

The high rate of smoking cessation in the current study was consistent with other comparable studies [157, 159, 161, 162]. Thus, a forthcoming surgical procedure could act as a “teachable moment” to modify the patient’s life-style into a healthier one. Still, the life-style modifying effect of surgery fades with time and abstained smokers tend to relapse. Knowing that only 3 - 5 percent of all smokers quit smoking spontaneously and remain abstinent 6 to 12 months after a given quitting attempt [74], it appears that a highly intensive intervention, as performed in the current study, is necessary to increase the probability of long-term abstinence.

13. CONCLUSIONS

- Smoking and obesity are important risk factors for the development of short-term complications after orthopaedic and general surgery. Furthermore, current smoking increased the risk of perforated appendicitis.
- Overweight and obesity were highly associated with an increased risk of implant dislocation after elective total hip replacement. Smoking was not found to be a predictor for the risk of implant dislocation.
- Preoperative smoking cessation initiated four weeks prior to elective orthopaedic and general surgery procedures was found to substantially reduce the development of postoperative complications.

14. IMPLICATIONS OF FINDINGS

14.1 Obesity and the long-term survival of hip implant

More than 10,000 THRs are performed annually in Sweden and since 1979 over 270,000 primary hip replacements have been registered in the Swedish Hip Register [199]. Other countries' hip registers are either much smaller in size or do not have the same high reporting rates as the Swedish Hip Register. Therefore, by introducing BMI in this register, new possibilities for studying the effect of overweight and obesity on the outcome after THR could be created.

14.2 Preoperative smoking cessation and surgery

Given the short- and long-term benefits of preoperative abstinence, smoking cessation intervention should be provided to all patients scheduled to undergo elective minor or moderately major orthopaedic and general surgery. It is likely that patients in other surgical disciplines, such as gynaecology and ear, nose and throat, could also benefit from preoperative smoking cessation interventions. To maximize the beneficial effects of this intervention, preoperative smoking cessation could be included in standardized clinical care protocols such as enhanced recovery after surgery (EARS) clinical care protocol [200]. This could improve postoperative outcomes and recovery.

14.3 Obesity and surgery

A great challenge in the field of surgery worldwide will be to perform surgery on obese individuals. To substantially reduce weight a few weeks before surgery will be impossible. However, improving the metabolic control of obese individuals is a possible target for intervention. This field of research will unavoidingly occupy the efforts of many researchers in the forthcoming years.

15. FUTURE STUDIES

- There is a lack of well-designed studies that investigate how biomechanical factors related to patient BMI might affect the risk of hip implant dislocation. The risk of high BMI on the development of implant failure and revision arthroplasty is another important area for further studies.
- The beneficial effect of smoking cessation on the outcome after surgery has been shown for patients undergoing minor or moderately major surgery. Thus, the effect of preoperative smoking cessation in patients undergoing more complicated surgical procedures, such as upper gastrointestinal cancer surgery, needs to be further investigated.
- There is need a for interventional studies to test different weight reducing approaches on the outcome after surgery. The main focus should be to improve metabolic control rather than reduce weight.

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