Outliers Matter

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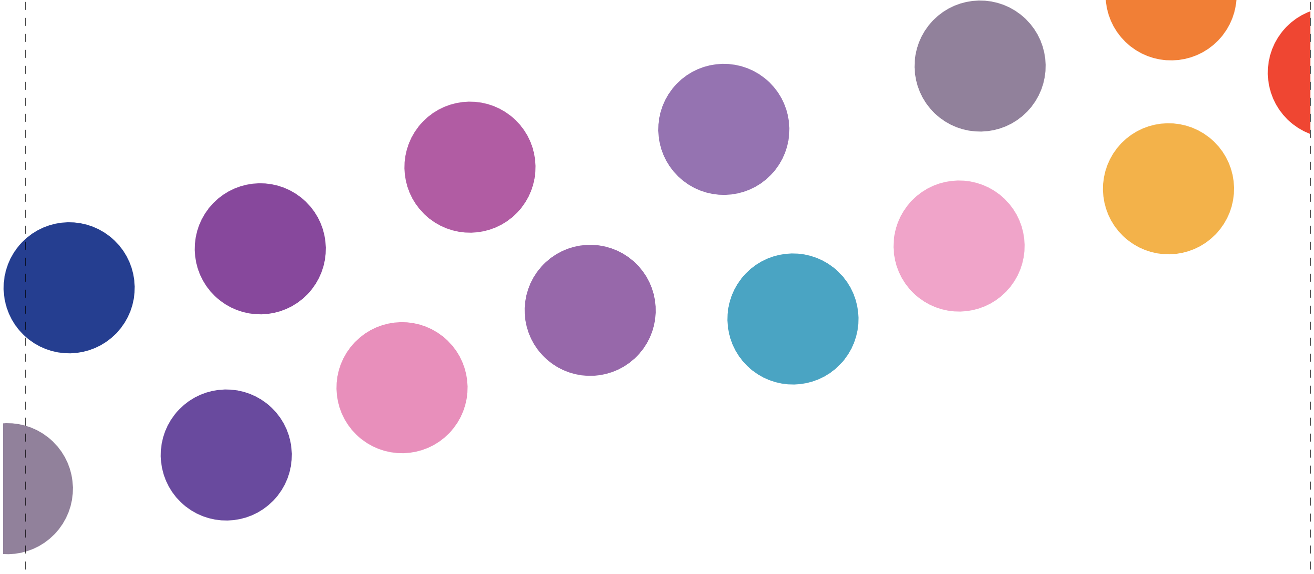
CONTENTS



Introduction

INTRODUCTION

Surgery is a substantial component of healthcare and it is performed in patients of all ages. It can contribute to the prevention or treatment of a broad spectrum of diseases, alleviation of symptoms, or diagnosis and supportive care. Each year, more than 300 million major surgical procedures are performed worldwide and this number continues to grow. [1-3]

Surgical outcome is influenced by the patient's preoperative status, severity of disease, the risk estimate according to the type of surgery and quality of care.[4] In the Netherlands, the occurrence of all-cause death after elective and non-day case surgery is estimated around 1,8% [5,6] and approximately 37% of patients experience postoperative complications.[7] Perioperative myocardial infarction occurs in 3% of patients undergoing major non-cardiac surgery.[8] An important step in optimizing care seems the recognition of patients at risk of adverse outcome. Surgeons of all specialties should keep this in mind when a patient is referred for surgery, whereas anesthesiologists play a more specific role, considering patients' general health condition. In high-risk patients, a multidisciplinary consultation meeting can be useful, as healthcare professionals of different specialties together can make decisions that will ensure best possible patient management.

The purpose of this thesis is to evaluate outcome after non-cardiac surgery and thereby identify the "outliers", meaning patients with risks beyond the conventional risk factors. Our research question is to compare perioperative risks in "outliers" (i.e. obese or underweight patients, older patients, frail patients, patients experiencing postoperative complications, or patients with a low socioeconomic status) with the "normal" population. This knowledge can guide the clinician and the patient in deciding whether the patient benefits from surgery or not.

The body mass index as a predictor of postoperative outcome

According to the World Health Organization, the worldwide prevalence of obesity has nearly tripled since 1975. Obesity, defined as a body mass index (BMI) > 30 kg/m² is associated with an array of comorbidities and necessitates careful clinical counseling.[9] Although obesity is generally believed to be a risk factor for postoperative complications, clinicians seldom discuss it with their patients, or document it.[10] The first chapter evaluates the influence of body mass index on postoperative complications and long-term survival after surgery. Obese patients are compared to patients with overweight (BMI 25-30 kg/m²), normal weight (BMI 20-25 kg/m²) and patients who are underweight (BMI < 18,5 kg/m²).

Although patients at extremes of the BMI seem to have the highest morbidity and mortality hazard, a paradox between the BMI and survival is described in the general population, as well as in several specific populations.[11-13] Chapter 2 provides a review of the obesity paradox in the surgical setting. Recent literature concerned with the obesity paradox in the surgical population is summarized, together with the theories explaining its causation. In general, the body mass index is the preferred formula to assess different weight categories. The easy, safe and inexpensive acquirement of weight and stature might explain its popularity and several studies have validated the BMI as a reasonable marker of adiposity.[14,15] Chapter 3 evaluates the predictive value of an alternative BMI formula, designed to provide a more accurate estimation of weight categories, not limited in a two-dimensional manner.

Advanced age and frailty as risk factors of adverse postoperative outcome

As the average human life expectancy has increased, so too has the demand for surgical care of the elderly.[16,17] In the Netherlands life expectancy has been rising as well, reflecting an upward age trend in the hospital population. Currently, the life expectancy of an average Dutch 80-year old is more than seven years.[18] Most elderly patients will present themselves with more risk factors prior to surgery than their younger counterparts and their higher age is associated with a decline in physiological reserve.[19,20] In chapter 4 we present the characteristics and outcomes of a large cohort of patients aged 80-years and older, undergoing non-cardiac surgery. The secondary objective of this study is to evaluate time trends from 2004-2017 within this cohort. Recently the concept of frailty has been coined. Frailty can be defined as a clinically recognizable state of increased vulnerability resulting from ageing-associated lack of physiological reserve and decline in function across multiple physiologic systems.[21] Frailty is increasingly recognized as a better predictor of adverse postoperative events than chronological age alone. In chapter 5 we present a systematic review and meta-analysis evaluating the predictive role of frailty on postoperative outcomes after non-cardiac surgery.

Long-term prognosis after general surgery

At this time, life expectancy at birth in The Netherlands is 81.6 years and well above the European average. The increase in life expectancy, observed in Dutch citizens, is mainly the result of reduction of premature deaths from cardiovascular diseases (CVD). The Dutch cardiovascular disease rate is now one of the lowest in Europe[22]. However, the overall time spent in good health has been declining. Cancer (in particular lung cancer), dementia and cardiovascular diseases are currently the leading causes of death.[22] The wide implementation of modern perioperative programmes such as fast-track surgery or goal-directed therapy seems to contribute to a reduced postoperative morbidity in the surgical population.[23,24] Further reduction in postoperative morbidity is important, because evidence increasingly suggests that patients experiencing postoperative complications have a reduced quality of life and life expectancy itself.[25,26] It is unclear if the cause of death is also affected. Chapter 6 describes long-term mortality rates and causes of death in a general surgical population. Also, the effect of postoperative complications on long-term mortality is explored. In chapter 7 we aim to look beyond the conventionally considered risk factors and evaluate the association between socioeconomic status (SES) and survival after general surgery. As a result of governmental regulation, medical care in the Netherlands is equal among all layers of society, and has even been credited the most equally accessible healthcare system in the world. This equal access to and provision of health care provides an opportunity to evaluate the impact of socioeconomic disparities on outcome. Additionally, we aim to establish whether socioeconomic status is associated with cause-specific survival and major 30-day complications.

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Part I

The body mass index as a predictor of postoperative outcome

Chapter 1

Obesity – A risk factor for postoperative complications in general surgery?

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ABSTRACT

Background

Obesity is generally believed to be a risk factor for the development of postoperative complications. Although being obese is associated with medical hazards, recent literature shows no convincing data to support this assumption. Moreover a paradox between body mass index and survival is described. This study was designed to determine influence of body mass index on postoperative complications and long-term survival after surgery.

Methods

A single-center prospective analysis of postoperative complications in 4293 patients undergoing general surgery was conducted, with a median follow-up time of 6.3 years. We analyzed the impact of bodyweight on postoperative morbidity and mortality, using univariable and multivariable regression models.

Results

The obese had more concomitant diseases, increased risk of wound infection, greater intraoperative blood loss and a longer operation time. Being underweight was associated with a higher risk of complications, although not significant in adjusted analysis. Multivariate regression analysis demonstrated that underweight patients had worse outcome (HR 2.1; 95% CI 1.4-3.0), whereas being overweight (HR 0.6; 95% CI 0.5-0.8) or obese (HR 0.7; 95% CI 0.6-0.9) was associated with improved survival.

Conclusion

Obesity alone is a significant risk factor for wound infection, more surgical blood loss and a longer operation time. Being obese is associated with improved long-term survival, validating the obesity paradox. We also found that complication and mortality rates are significantly worse for underweight patients. Our findings suggest that a tendency to regard obesity as a major risk factor in general surgery is not justified. It is the underweight patient who is most at risk of major postoperative complications, including long-term mortality.

BACKGROUND

According to the World Health Organization, obesity has doubled since 1980, with a prevalence that is continuing to rise. In the United States, more than one-third of the adult population is currently obese.[1] As in Europe, obesity has also reached epidemic proportions, although with considerable geographic variation.[2]

Being obese is associated with increased risk of a number of medical conditions, including diabetes, coronary artery disease, hypertension, hyperlipidemia and certain types of cancer.[3] Obesity reduces quality of life[4] and life expectancy itself.[5-7] However, recent studies show that, except for wound infections, complication rates are not increased in this group of patients.[8-10] Despite considerable investigation, the effect of different weight categories on all other types of postoperative complications and long-term survival remains controversial.

More recently a paradox between body mass index and survival is described in both cardiac and non-cardiac surgical population.[11-13] This paradox shows an inverse relationship between body mass index and mortality, with lower mortality rates among the overweight and mild obese and increased mortality rates in the underweight population.

We hypothesized that a tendency to consider obesity as a major risk factor in general surgery, is not justified. Therefore, this study was designed to determine influence of body mass index on postoperative complications and long-term survival after surgery.

METHODS

Study Sample

This study is a single-center prospective analysis of postoperative complications in patients undergoing general surgery. We obtained data from all consecutive patients undergoing general surgery at our institution from March 2005 to December 2006. Since the beginning of 2005 this general teaching hospital contains a highly modern degree of automation and a reliable registration of the electronic medical record. All patients undergoing elective or urgent surgery within the mentioned study period were included. Exclusion criteria were procedures performed under local anesthesia, patients younger than 14 years old and assisting surgery for a specialism other than the surgery department (for example: a member of the surgical staff assisting in a gynecologic procedure). Bariatric surgery was not performed in this medical center. The study cohort consisted of 5030 procedures in 4479 patients. Because one of our primary endpoints is long-term survival, we decided to restrict our analyses to the patient's first operation only. When a patient needed repeated surgery during the same hospital stay, we did include the need for a reoperation as a separate outcome measure. Patients (n=186) of whom height or weight were not available were excluded. Therefore, the study population consisted of 4293 patients. The study complies with the Helsinki statement on research ethics and due to the non-interventional character of this study; approval by the medical ethical committee at time of enrolment was not necessary according to Dutch law. Even though, the local medical ethical committee granted a formal statement of approval retrospectively.

Baseline Characteristics

Before surgery all patients were seen by a surgeon or a surgical resident who collected the patient characteristics. Information was gathered about the patient's medical history such as pulmonary, cardiac or cerebrovascular disease, American Society of Anesthesiologists (ASA) classification, diabetes, hypertension, any malignancy, medication, intoxications and height and bodyweight. Pulmonary disease was defined as any illness of the lungs or respiratory system, such as asthma, lung cancer, chronic infections, previous pulmonary embolisms, or chronic obstructive pulmonary disease (COPD). Cardiac disease refers to coronary artery disease with or without previous intervention, heart failure, arrhythmias, valvular heart disease or cardiomyopathy.

The Body Mass Index (BMI; kg/m^2) was used, according to the recommendation of the World Health Organization, as the measure to classify underweight, overweight and obesity in adults.

Patients with a body mass index (BMI) > 30kg/m^2 were defined as obese and were compared to patients with underweight (BMI < 18.5kg/m^2), normal weight (BMI 18.5-25kg/m^2), and patients with overweight (BMI 25-30kg/m^2).[1] Furthermore, we collected surgery related characteristics. Surgical risk was divided into low, intermediate and high-risk procedures as proposed by Boersma et al in their surgical risk classification system.[14] Secondly, we collected the type of anesthesia, divided into loco regional (i.e. neuraxial or peripheral nerve blocks) or general anesthesia. Finally we determined whether the patient was treated in an inpatient or outpatient surgical setting.

Postoperative and long-term outcome

Primary endpoints were complications within 30 days from surgery and long-term mortality. Patients were followed during hospital stay and during their visits to the outpatient clinic up to one year. To analyze the outcome we obtained the following data: length of hospital stay (LOS), blood loss, operating time and the presence of postoperative complications, e.g. wound infections, pneumonia, thromboembolic events, cardiovascular and cerebrovascular events, ICU-admission, readmission, the need for repeated surgery, as well as in-hospital mortality. For an objective interpretation of complications, we used a modified classification system proposed earlier by Clavien and Dindo, in order to increase uniformity in reporting outcome measures.[15,16] Concisely, the grade of complications is based upon five grades, according to severity of the problem. Grade I is a minor and self-limiting complication, not needing any specific treatment. A grade II complication needs specific drug therapy (such as antibiotics), or a minor treatment such as opening the wound at the patient's bedside, whereas a grade III complication needs invasive procedures such as percutaneous drainage of an abscess or repeated surgery. Grade IV are these complications with residual disability, including organ failure or resection. Finally grade V means the patient died due to his complications. Any event that deviated from a normal postoperative course was registered as a complication. Long-term survival was based on information from the national public register. All complications were independently graded by a surgical resident as well as a member of the surgical staff.

Statistical Analysis

We presented categorical variables as numbers and percentages. Continuous variables were presented as mean ± standard deviation (SD) when normally distributed, or as median and interquartile range (IQR) when data was skewed. A chi-square test was used for all categorical variables. Continuous variables were compared by using analysis of variance or the Kruskal Wallis test. In order to study the association between different BMI categories and postoperative complications, univariable and multivariable logistic regression models were used. Kaplan-Meier survival curves were calculated to assess the relation between the BMI categories and 5-year survival and compared with a log-rank test. The relation between BMI categories and long-term mortality was evaluated using multivariable Cox proportional hazard regression analysis. All potential confounders (age, gender, surgical risk, type of anesthesia, ASA classification, diabetes, hypertension, pulmonary -, cardiac -, or cerebrovascular disease and the presence of a malignancy) were entered in the multivariable model to ensure giving an unbiased as possible estimate in the regression models. Patients in different BMI categories were compared to those of normal weight. Results are reported as odds ratios (OR) or hazard ratios (HR) with a 95% confidence interval. For all tests, significance was set at a two-sided P-value < 0.05. The statistical analyses were performed using SPSS, version 20.0.0 statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

Patient population

A total of 4293 patients were suitable for analysis, of which 1815 (42.3%) were of normal weight, 100 (2.3%) were underweight, 1635 patients (38.1%) were overweight and 743 patients (17.3%) were obese. Table 1 shows the baseline and surgery related characteristics of the study population.

When categorized by BMI, obese patients had more comorbidities, such as diabetes (P < .001), hypertension (P < .001), cardiovascular disease (P =.006) and pulmonary disease (P =.010) than patients of normal weight. High-risk surgery was more often performed in the group of underweight patients (n=15, 15.0%), while in the obese group; the surgical risk was predominantly low or intermediate (n=725, 96.2%). Table 2 shows the use of cardiovascular and pulmonary medication at time of surgery.

Postoperative complications

Obesity resulted in a longer operation time (P<0.001), more intraoperative blood loss (P<0.001) and higher rates of surgical site infections (P < 0.001) (Table 3). Underweight patients also had higher rates of complications than normal weight patients (Table 3). The overall mortality rate within 30 days was 1.2% (52 patients), with a disadvantage for underweight patients (n=4, 4.0%). Complication grades were different between groups, with more non self-limiting (>grade 1) complications in the underweight (n=25, 25%), overweight (n=277, 16.9%) and the obese (n=154, 20.7%), compared to 14.2% (n=258) in normal weight patients (overall P-value P<0.001) (Figure 1). A multivariate regression analysis, adjusting for confounders, demonstrated that obesity was associated with a higher risk of postoperative complications (OR 1.3; 95% CI 1.1-1.7) (Table 4).

Long-term survival

Long-term survival was based on information from the national public register, available in 4218 patients (98.3%), with a median follow-up time of 6.3 (interquartile range 5.8-6.8) years. Last available follow-up information was used for 93 patients (2.2%) who lived abroad or had emigrated. A total of 687 patients (16.3%) died during a follow-up of 6.3 (IQR 5.8-6.8) years, including the 52 patients who died within 30 days of first hospital admission. Figure 2 shows a Kaplan-Meier estimate of overall long-term survival. Six-year survival estimates varied significantly among the different BMI-categories: 64.2% in the underweight group, 82.1% in the normal weight group, 87.1% in the overweight group and 86.6% in the obese group. Multivariate regression analysis, adjusting for confounders, demonstrated that underweight patients undergoing general surgery again had the worst outcome (HR 2.1; 95% CI 1.4-3.0), whereas being overweight (HR 0.6; 95% CI 0.5-0.8) or obese (HR 0.7; 95% CI 0.6-0.9) is associated with improved survival (Table 4).

Table 1. Baseline Characteristics

	Normal weight BMI 18.5-25(kg/m²) (N=1815)	**Underweight BMI < 18.5(kg/m²)** (N=100)	**Overweight BMI 25-30(kg/m²)** (N=1635)	**Obese BMI>30(kg/m²)** (N=743)	**p value**
Demographics					
Age, years (mean ± SD)	53.7 (±18.9)	51.6 (±21.6)	57.0 (±15.5)#	55.5 (±14.9)#	<0.001
BMI (mean ± SD)	22.6 (±1.7)	17.3 (±1.1)	27.2 (±1.4)	33.5 (±3.4)	<0.001
Male sex (%)	893 (49.2%)	39 (39.0%)#	970 (59.3%)#	315 (42.5%)#	<0.001
ASA classification (%)		#	#	#	<0.001
I	727 (40.1%)	31 (31.3%)	535 (32.8%)	135 (18.2%)	
II	553 (30.5%)	20 (20.2%)	636 (39.0%)	362 (48.8%)	
III	460 (25.4%)	39 (39.4%)	412 (25.3%)	223 (30.1%)	
IV	72 (4.0%)	8 (8.1%)	47 (2.9%)	21 (2.8%)	
V	1 (<1%)	1 (<1%)	0 (0.0%)	1 (<1%)	
Medical history (%)					
Diabetes mellitus	86 (4.7%)	6 (6.1%)	162 (9.9%)#	134 (18.1%)#	<0.001
Hypertension	257 (14.2%)	14 (14.1%)	360 (22.1%)#	225 (30.3%)#	<0.001
Cerebrovascular disease	123 (6.8%)	8 (8.1%)	118 (7.2%)	54 (7.3%)	0.919
Malignant disease	451 (24.9%)	25 (25.3%)	362 (22.2%)#	172 (23.2%)	0.308
Pathological cardiac history	302 (16.7%)	18 (18.2%)	316 (19.4%)#	158 (21.3%)#	0.033
Pathological pulmonary history	261 (14.4%)	15 (15.2%)	205 (12.6%)	138 (18.6%)#	0.002
Current smoking *	490 (35.4%)	39 (48.8%)#	374 (30.4%)#	163 (26.9%)#	<0.001
Surgery risk (%)		#		#	<0.001
Low	1078 (59.4%)	33 (33.0%)	969 (59.3%)	365 (49.1%)	
Intermediate	643 (34.4%)	52 (52.0%)	577 (35.3%)	350 (47.1%)	
High	94 (5.2%)	15 (15.0%)	89 (5.4%)	28 (3.8%)	
Type of anesthesia (%)					
General	1499 (82.8%)	93 (93.9%)#	1376 (84.3%)	684 (92.2%)#	<0.001
Surgical setting (%)					
Outpatient surgery	690 (38.0%)	22 (22.0%)#	607 (37.1%)	216 (29.1%)#	<0.001

#Significantly different (p<.05) compared to normal weight
*Data was available in 76.9% of patients

Table 2. Baseline Characteristics; Medication

	Normal weight BMI 18.5-25(kg/m²) (N=1815)	Underweight BMI < 18.5(kg/m²) (N=100)	Overweight BMI 25-30(kg/m²) (N=1635)	Obese BMI>30(kg/m²) (N=743)	p value
Medication groups					
Antiplatelet therapy	214 (11.8%)	12 (12.0%)	247 (15.1%)#	122 (16.4%)#	0.005
Anticoagulant therapy	59 (3.3%)	5 (5.0%)	62 (3.8%)	35 (4.7%)	0.31
ßblockers	165 (9.1%)	13 (13.0%)	225 (13.8%)#	116 (15.6%)#	<0.001
Calcium channel blockers	66 (3.6%)	2 (2.0%)	80 (4.9%)#	58 (7.8%)#	<0.001
Angiotensin-converting enzyme inhibitors	103 (5.7%)	4 (4.0%)	123 (7.5%)#	78 (10.5%)#	<0.001
Angiotensin-II receptor antagonists	58 (3.2%)	1 (1.0%)	118 (7.2%)#	72 (9.7%)#	<0.001
Statins	195 (10.7%)	10 (10.0%)	238 (14.6%)#	141 (19.0%)#	<0.001
Diuretics	199 (11.0%)	13 (13.0%)	252 (15.4%)#	147 (19.8%)#	<0.001
Nitrates	90 (5.0%)	3 (3.0%)	119 (7.3%)#	42 (5.7%)	0.018
Pulmonary medication	86 (4.7%)	4 (4.0%)	71 (4.3%)	48 (6.5%)	0.153

#Significantly different (p<.05) compared to normal weight

Table 3. Postoperative Outcome within 30 Days

	Normal weight BMI 18.5-25(kg/m²) (N=1815)	Underweight BMI < 18.5(kg/m²) (N=100)	Overweight BMI 25-30(kg/m²) (N=1635)	Obese BMI>30(kg/m²) (N=743)	p value
Wound infection	87 (4.8%)	11 (11.0%)#	127 (7.8%)#	81 (10.9%)#	P < 0.001
Pneumonia	31 (1.7%)	4 (4.0%)	41 (2.5%)	16 (2.2%)	P = 0.231
Deep vein thrombosis and/or pulmonary embolism	7 (0.4%)	1 (1.0%)	5 (0.3%)	5 (0.7%)	P = 0.474
ICU admission	232 (12.8%)	27 (27.0%)#	198 (12.1%)	95 (12.8%)	P < 0.001
Reoperation	87 (4.8%)	11 (11.0%)#	72 (4.4%)	39 (5.2%)	P = 0.028
Readmission	57 (3.1%)	5 (5.0%)	67 (4.1%)	34 (4.6%)	P = 0.246
Length of hospital stay (days) (median + IQR)	3 (1-8)	7 (3-16)#	2 (1-7)#	2 (1-7)	P < 0.001
Operation time (minutes) (median + IQR)	39 (24-65)	41 (27-90)	41 (26-66)	50 (27-80)#	P < 0.001
Blood loss (mL)* (median + IQR)	10 (5-50)	25 (5-138)#	15 (5-50)	20 (10-100)#	P < 0.001
30 days mortality	27 (1.5%)	4 (4.0%)	11 (0.7%)#	10 (1.3%)	P = 0.008
Cardiovascular complication	67 (3.7%)	4 (4.0%)	53 (3.2%)	26 (3.5%)	P = 0.897
Any complication	339 (18.7%)	28 (28.0%)	345 (21.1%)	185 (24.9%)	P = 0.001

#Significantly different (p<.05) compared to normal weight
*Data was available in 84.3% of patients

Figure 1. Bar chart of Different Complication Grades

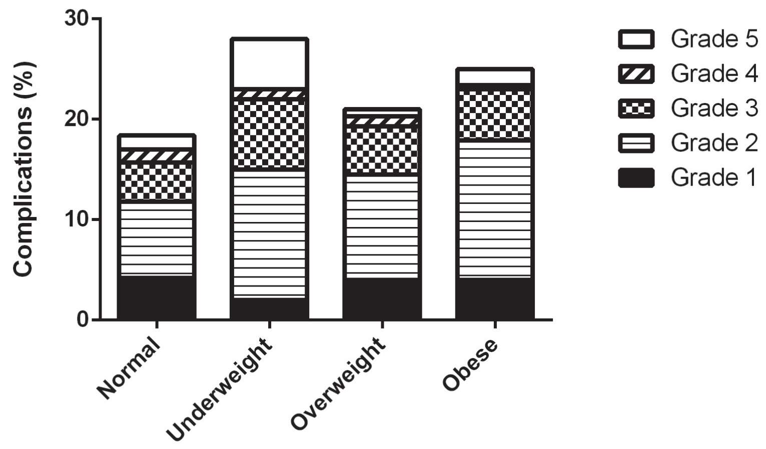


Table 4. Univariable and Multivariate Associations of BMI-categories and Complications/Mortality

BMI-categories	30 days Complications N (%)	OR (95% CI)	Adjusted* OR (95% CI)	Long-term Mortality N (%)	HR (95% CI)	Adjusted* HR (95% CI)
Normal weight BMI 18.5-25(kg/m²)	334 (18.4)	1	1	331 (18.6)	1	1
Underweight BMI < 18.5(kg/m²)	28 (28.0)	1.67 (1.05-2.63)	1.20 (0.73-1.97)	35 (35.4)	2.14 (1.51-3.05)	2.07 (1.44-2.96)
Overweight BMI 25-30(kg/m²)	343 (21.0)	1.17 (0.99-1.38)	1.14 (0.95-1.36)	212 (13.2)	0.68 (0.58-0.81)	0.63 (0.53-0.75)
Obese BMI>30(kg/m²)	186 (25.0)	1.46 (1.19-1.79)	1.31 (1.05-1.65)	109 (14.8)	0.77 (0.62-0.96)	0.71 (0.56-0.89)

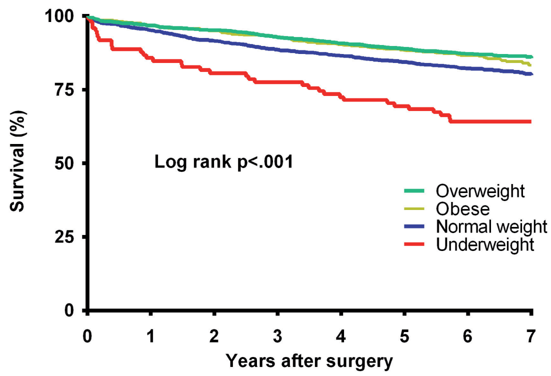
*Potential confounders: age, gender, surgical risk, type of anesthesia, ASA classification, diabetes, hypertension, pulmonary -, cardiac - or cerebrovascular disease and the presence of malignancy

DISCUSSION

In this large sample of patients we found that obesity is a significant risk factor for surgical site infection, more surgical blood loss and a longer operation time, however these complications did not affect long-term survival.

Our finding that the incidence of surgical site infection increases with an increase of BMI confirms previous studies.[8,17-19] A couple of explanations can be given for this association. First of all, excessive subcutaneous fat tissue predisposes these patients to impaired healing due to low regional perfusion and oxygen tension.[20] Secondly, in our study there was an increase in operation time for the obese and a longer operation time has been described as a significant predictor of postoperative wound infections.[17,18] Furthermore impaired immunity, elevated blood glucose levels and too much tension on the surgical incision are also contributory factors to impaired wound healing.[21,22] Thus, with exception of the complications described earlier, there was no difference in risk of any major postoperative adverse event between the obese and patients of normal weight. Being overweight or obese was actually associated with improved 30-day and long-term survival, also known as the obesity paradox. Increased awareness of both the surgeon and the anesthesiologist of obesity related health hazards might have contributed to improved perioperative care.[23,24] Another explanation could be that obese patients are less often referred for major surgery, leading to selection bias.

Figure 2. Kaplan Meier Estimate of Overall Long-term Survival



N at risk, % with clinical success

1763 (-)	98 (-)	1594 (-)	726 (-)
1603 (91.5%)	80 (80.6%)	1505 (95.2%)	686 (94.9%)
1509 (86.5%)	72 (72.5%)	1432 (90.7%)	643 (90.3%)
1107 (82.1%)	46 (64.2%)	1069 (87.1%)	486 (86.6%)

When compared to patients of normal weight, the underweight patients had a higher ASA classification and a higher risk of postoperative complications. It should be noted however that the underweight patients represent a rather small number of the total study population and results, especially short-term complications, should be interpreted with caution. In the present study, a bigger proportion of patients who underwent high-risk surgery were underweight, although not statistically significant. The underweight group contained more smokers, a potential confounder, since smoking is associated with wound infection, weight loss and chronic diseases.[25,26] Also recent weight loss of more then 10% or low serum albumin levels are known predictors of postoperative morbidity and mortality.[27-29] With the hypothesis that cachexia might be related to an unhealthy lifestyle or non-compliance, we compared the use of medication between the different BMI groups. We conclude that there was no undertreatment of pulmonary or cardiovascular medication in the underweight group. Unlike we expected, the incidence of malignant disease was not different between underweight and normal weight patients, which might again be explained by a relatively small sample size of the underweight group.

Besides complications, we focused on postoperative mortality and long-term prognosis. Our study supports recent data and shows a significantly higher mortality rate for the lowest of BMI rankings.[30]

This study has a few potential limitations that must be addressed. First, the recorded data on height and weight were partially self-reported, although this can be considered as a reliable estimate of BMI.[31] There might be a bias in referral pattern, since patients with major comorbidities and the super obese are usually seen in a tertiary hospital. With the prevalence of obesity in our study population being almost twice as high as in the Dutch population, this might not be an important bias.[2] Furthermore, we restricted analyses to patient's first operation. Repeated surgery within the study period was often performed because of the same illness; for example a sentinel node procedure, followed by a mastectomy in the next hospital stay. A sensitivity analysis showed no difference in crude or adjusted estimates when including all duplicate cases. We did not have a direct measurement of central (or visceral) adiposity. Instead we used BMI as an indicator of adiposity, but the BMI is unable to distinguish between different kinds of body mass.[32,33]

The surgical procedures in this study have been performed eight up to nine years ago. Advances in clinical medicine can alter current practice. Finally, due to the observational character, this study is inherent to unmeasured confounding.

In conclusion, our findings suggest that a tendency to consider obesity as a major risk factor in general surgery is not justified. It is the underweight patient who is most at risk of major postoperative complications, including long-term mortality.

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Appendix 1. Resume table with complications divided in different complication groups

	No complications %	Self-limiting complications (Grade 1) %	Non self-limiting complications (Grade 2+3) %	Major complications (Grade 4+5) %
Normal weight	1480 (81.5%)	77 (4.2)	209 (11.5)	49 (2.7)
Underweight	73 (73.0%)	2 (2.0)	20 (20.0)	5 (5.0)
Overweight	1293 (79.1%)	65 (4.0)	249 (15.2)	28 (1.7)
Obese	559 (75.2%)	30 (4.0)	141 (19.0)	13 (1.7)

Chapter 2

The obesity paradox in the surgical population

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ABSTRACT

Background

Despite the medical hazards of obesity, recent reports examining body mass index (BMI) show an inverse relationship with morbidity and mortality in the surgical patient. This phenomenon is known as the 'obesity paradox'. The aim of this review is to summarize both the literature concerned with the obesity paradox in the surgical setting, as well as the theories explaining its causation.

Methods

PubMed was searched to identify available literature. Search criteria included obesity paradox and BMI paradox, and studies in which BMI was used as a measure of body fat were potentially eligible for inclusion in this review.

Results

The obesity paradox has been demonstrated in cardiac and in non-cardiac surgery patients. Underweight and morbidly obese patients displayed the worse outcomes, both postoperatively as well as at long-term follow-up. Hypotheses to explain the obesity paradox include increased lean body mass, (protective) peripheral body fat, reduced inflammatory response, genetics and a decline in cardiovascular disease risk factors, but probably unknown factors contribute too.

Conclusions

Patients at the extremes of BMI, both the underweight and the morbid obese, seem to have the highest postoperative morbidity and mortality hazard, which even persists at long-term. The cause of the obesity paradox is probably multi-factorial. This offers potential for future research in order to improve outcomes for persons on both sides of the 'optimum BMI'.

INTRODUCTION

With advancement of medical care in modern societies, two distinct growing phenomena are observed, which pose new challenges to the surgeon. These are the overweight and obesity epidemic on the one hand, and the growing elderly population on the other hand.[1-3] These two categories of patients share a number of risk factors and associated comorbidities that predispose them to cardiovascular and other life-threatening complications.[4,5]

Body mass index (BMI), formerly known as Quetelet's index, has been introduced to public health science as a proxy of overall body fat content. It is calculated by dividing weight in kilograms by the square of height in meters. In late and even in upcoming years, much attention has been paid to this index and to other measures of total or abdominal fat, due to the increasing prevalence of overweight and obesity. Because of its simplicity, BMI has gained widespread acceptance and application in daily clinical practice. The World Health Organization (WHO) has defined different BMI categories (Table 1).[6,7]

Clinical research in the surgical population frequently focused on the prognostic value of certain clinical variables obtained from the preoperative assessment and the perioperative course.[8-11] Some of these variables are incorporated in guidelines regarding preoperative cardiovascular management in non-cardiac surgery,[12] which have been shown to reduce postoperative cardiac events and improve long-term outcomes. Furthermore, recognition and optimization of other, non-cardiac, chronic ailment conditions prior to surgery can also be beneficial, both in the perioperative stage as well as for the long-term.[13] Although several preoperative risk-scoring systems exist,[14] BMI has not been included, since it was not considered as an independent (preoperative) risk factor or predictor for postoperative and long-term outcomes.

The purpose of this article is to give an overview of the relationship between BMI and outcome in the surgical population, reporting both postoperative and long-term outcomes. Furthermore, the literature regarding the inverse relationship between BMI and outcome, known as the obesity paradox, as well as the theories explaining its causation, are reviewed.

Table 1. BMI classification according to the WHO[6]

	BMI (kg/m²)
Underweight	< 18.5
Normal	18.5 – 24.9
Overweight (pre-obese)	25.0 – 29.9
Obese	≥ 30.0
Obese class I (mild obese)	30.0 – 34.9
Obese class II (moderate obese)	35.0 – 39.9
Obese class III (morbid obese)	≥ 40.0

METHODS

We performed a PubMed search to identify available literature up to January 1, 2012. Search criteria included obesity paradox and BMI paradox, each of which was subsequently combined with additional search criteria including surgery, general surgery, cardiac surgery, outcome, and survival to narrow search results. Search criteria were restricted to English language, humans, and adults (age > 19 years). Original articles (observational, cohort, case-control, cross-sectional, longitudinal and experimental), systematic reviews and meta-analyses were considered for inclusion in the review. Eligible studies were first identified by title, and abstracts in which BMI was used as a measure of body fat were retrieved as full-text papers. Additional studies were identified after reviewing related PubMed citations and references of the included papers.

The risks of obesity in the surgical patient

The worldwide broadening of the obesity epidemic has also affected surgery, not only because more surgical patients are obese, but also because of an increase in obesity related diseases that require surgery.[1,4] Substantial data from literature showed the preponderance of cardiovascular risk factors in the overweight and obese population.[1,4,15] Moreover, increased body mass was found to be a predictor of increased cardiac risk, independent of cardiovascular risk factors.[16] Obesity is also known to be related to left-ventricular morphological changes and impaired diastolic function.[17] Therefore, the observation of a strong association between obesity and long-term mortality in several studies was not unexpected.[18,19]

However, the perioperative risks associated with obesity might have been overestimated. Increased anesthetic and surgical interest in obesity, particularly in bariatric surgery, might have led to better care of obese patients and lower perioperative complication rates.[20,21] Several prospective cohort studies with strict definitions of postoperative morbidity, demonstrated that in general (non-bariatric) surgery, postoperative complications like surgical site infections are related to obesity,[22-27] with the highest rates in morbid (class III) obese patients.[22,24,26,27] In addition, morbidly obese patients had the highest postoperative mortality rates.[23,24,26,27] On the other hand, the lowest postoperative mortality risk was reported in the overweight and obese class I and class II patients.[23,24,27] In several surgical oncology populations the postoperative mortality rates did not differ between normal weight and overweight and obese patients.[25,28-30] However, most data regarding the risks of obesity in the (non-bariatric) surgical population are obtained from large-scale studies in cardiac surgery patients. Since overweight and obesity are known to promote the progression of coronary heart disease,[7] it is not surprising that around two thirds of all coronary artery bypass grafting (CABG) surgery is performed in overweight and obese patients.[31,32] Similar to non-cardiac surgery, several prospective studies in CABG surgery demonstrated that obesity was shown to be related to postoperative morbidity, with the highest rates of deep sternal wound infection and prolonged ventilation and hospitalization in moderate (class II) and morbid (class III) obese patients.[33-35] However, the majority of cardiac surgery studies, including CABG studies, did not report adverse associations with postoperative morbidity[31,32,36] or mortality in obese patients.[31,32,35-38] It is important to notice that current studies in various surgical populations do not make a distinction between obese surgical patients with normal metabolic profiles and those with diabetes, although it is widely known that diabetes adversely affects postoperative outcomes.

Despite the large body of evidence showing that postoperative mortality is not increased in the majority of obese patients undergoing surgery, much attention has been paid to the association with postoperative morbidity, which might have led to a negative attitude towards obesity as a comorbid condition in patients requiring surgery.

The obesity paradox

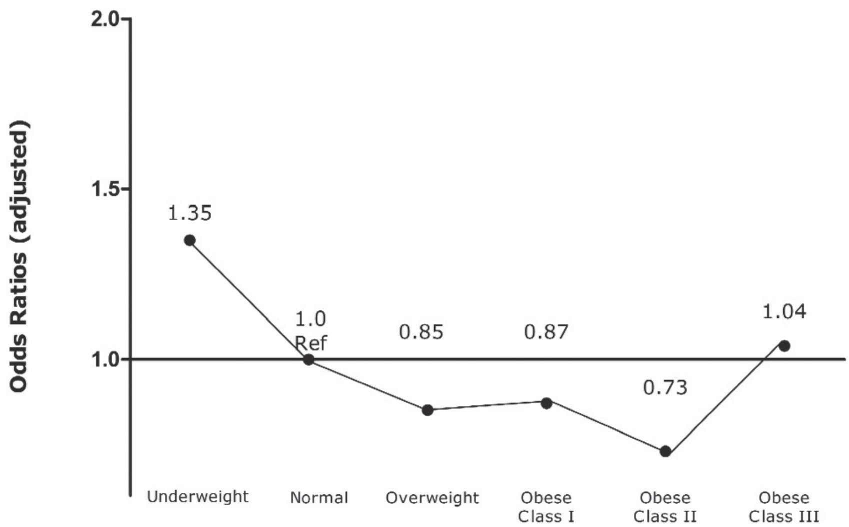
Recent epidemiological studies in the general population have shown a longer life expectancy in modern societies with prevalent overweight and obesity, compared to those that did not join the obesity epidemic.[39,40] The inverse relationship between body fat composition, particularly defined by the BMI, and all-cause mortality, is frequently referred to as the *obesity paradox*. The more comprehensive term *reverse epidemiology* also comprises the obesity paradox. It represents the unexplained counterintuitive relationship of traditional cardiovascular risk factors and mortality in various (patient) populations.[41-44]

Many studies in surgical populations have demonstrated a similar paradoxical relationship between BMI and postoperative mortality, with the highest postoperative mortality risks in the underweight and morbid (class III) obese patients (Figure 1). The obesity paradox has been shown in various surgical populations, both in cardiac[31,32,34,36-38] and in non-cardiac surgery.[23,24,26,27]

The majority of studies examining the effects of BMI on surgical outcome merely studied short-term (i.e. postoperative) mortality; however some also reported long-term survival.[25,29,30,33,37,45-48] Underweight patients displayed the worse long-term survival, both in non-cardiac[45] and in cardiac surgery.[33,46,48] Overweight and obese patients showed conflicting results regarding long-term survival. Studies in vascular surgery,[45] oncology surgery[29,30] and cardiac surgery[37] reported survival benefit for overweight and obese patients, whereas other studies in oncology surgery[25] and cardiac surgery[47] did not demonstrate any association with long-term survival.

Table 2 gives an overview of different patient populations in which an inverse relationship between BMI and mortality was demonstrated. Most of these studies were conducted in Western populations; however, the obesity paradox has recently been described in East Asians as well.[59]

Figure 1. Odds ratios (adjusted) for 30-day mortality after (non-bariatric) general surgery displayed by obesity class, with normal BMI class used as reference (adapted with permission from Mullen et al., Ann Surg 2009[22]).



The paradox theories

Since the first observation of the obesity paradox, several suggestions were made to overcome the unexpected survival benefit of the overweight and obese. One suggestion was that the values of BMI cut-offs representing the categories defined by the WHO should be revised, so that overweight patients showing survival improvement should merge into the control group i.e. the normal BMI population.[60] However, it is important to consider that BMI does not discriminate between fat mass and lean mass, and as a result, BMI does not adequately reflect adiposity.[61,62] Therefore, it might be that overweight and (mild) obese persons do not have more fat, but instead have a preserved or increased lean body mass, which would offer a possible explanation for the survival benefit in these groups. Consequently, it has been suggested to omit the BMI completely as an index of body fat and replace it with more accurate indices such as waist circumference, waist-to-hip ratio and waist-to-height ratio, and with computed tomographic measurement of intra-abdominal fat content.[63-65]

2

Table 2. Populations showing the obesity paradox

Non-surgical Populations	Surgical Populations
Cardiac Disease	**Vascular surgery**
Acute coronary syndromes[50,51]	Peripheral arterial disease[23,45]
Percutaneous coronary interventions (PCI)[37]	Abdominal aortic aneurysm[24]
Coronary artery disease[55]	
Chronic atrial fibrillation[49]	**Cancer surgery**
Chronic heart failure[44,54]	Pancreaticoduodenectomy[30]
	Gastrectomy[29]
Chronic obstructive pulmonary disease[44,52]	
	Orthopedic surgery
Renal disease	Arthroplasty[58]
Chronic kidney disease[43]	
Maintenance dialysis[57]	**Cardiac surgery**
	Coronary artery bypass grafting[31,32,34,36-38]
Rheumatoid arthritis[44]	Left-ventricular assist device placement[46]
Acquired immunodeficiency[44]	
Intensive care unit patients[56]	
Hospitalized patients[53]	
Advanced age[44]	

Conversely, others have tried to find explanations for the occurrence of the obesity paradox, which was first recognized in chronic disease populations. Moreover, the obesity paradox has also been described in the general population.[19,60] Studies of BMI and cause-specific mortality in the general population, excluding persons with prior cardiovascular disease, cancer and chronic obstructive pulmonary disease (COPD), revealed that overweight was not associated with an increased risk of cancer or cardiovascular disease, and appeared to be relatively protective for survival.[66] However, excess mortality in the obese population was mainly attributable to cardiovascular disease and obesity-related cancers, including colon cancer, breast cancer, esophageal cancer, pancreatic cancer, uterine cancer, ovarian cancer and kidney cancer.[66,67] In contrast, upper aerodigestive cancers, COPD and other respiratory diseases could explain excess mortality in the underweight population.[66,67] Chronic diseases, including cardiovascular disease, cancer and COPD, are characterized by wasting and increased inflammatory responses, thereby offering possible explanations for the obesity paradox, which causation is probably multi-factorial.

The benefits of obesity

Adipose tissue is a potential endocrine organ capable of secreting a variety of cytokines with opposing actions.[4] Tumor necrosis factor-α (TNF-α) is a pro-inflammatory and atherogenic macrophage-derived cytokine, and is known to promote cardiac and endothelial injury through its apoptotic and negative inotropic effects.[68] Adipocytes release soluble TNF-α receptors, which can neutralize TNF-α in various inflammatory wasting states.[69] Moreover, adipocytes secrete adipokines, of which adiponectin plays a key role in regulating inflammation and endovascular homeostasis and increasing insulin sensitivity in peripheral tissues.[70] Particularly visceral (abdominal) adiposity is associated with chronic inflammation, insulin resistance and enhanced progression of atherosclerosis.[4] On the other hand, peripheral (lower-body) fat has a protective effect.[71] These differences between visceral and peripheral adiposity are irrespective of gender.[71] However, since BMI cannot distinguish between visceral and peripheral adiposity, this might offer an explanation for the observed survival benefit in the obese population.

Inflammatory responses in obesity can also be reduced by the toxin-scavenging ability of adiposity. Lipopolysaccharides (LPS) are potent endotoxins that induce the release of pro-inflammatory cytokines.[72] Plasma concentrations of LPS are higher in chronic debilitating disorders.[73-75] In overweight and obesity the negative effects of lipopolysaccharides are neutralized by the toxin-scavenging effect of adiposity, in which lipophilic end products of increased catabolism are sequestrated.[57] Furthermore, increased levels of lipoproteins, which are often observed in overweight and obesity, may offer a survival advantage in chronic diseases, because lipoproteins can actively bind to and neutralize circulating endotoxins, the so-called endotoxin-lipoprotein hypothesis.[76]

In addition, the prevalence of cardiovascular risk factors among the overweight and obese has declined in the past decades.[77] Although cardiovascular disease remains the leading cause of death among the obese, this decline in cardiovascular risk factors might have led to a decrease in cardiovascular related mortality, and therefore to a decrease in total mortality.[19] These findings are consistent with declining mortality rates from ischemic heart disease.[78,79] However, it may take several years to decades for obesity and its related cardiovascular disease to have its full impact on mortality.[80] Consequently, in studies without long-term (e.g. more than 15 years) follow-up, the effects of obesity on mortality might have been underestimated, suggesting survival benefit for the obese.

Finally, genetics might offer a different explanation for the survival advantage of the overweight and obese. The thrifty genotype theory is an old theory explaining obesity. This genotype emerged as an adaptive and selective gene-environment interaction in times of famine, and led to obesity when famines no longer occurred in the modern era.[81] This theory would explain the survival advantage of the overweight and obese, however, it is not supported by any substantial scientific evidence.[82] On the other hand, genetic polymorphism in systems related to food intake, energy expenditure and BMI definition can result in variable effects on body composition, which might lead to differential effects on survival among the obese population.[83-85] Figure 2 gives an overview of the multi-factorial causation of the obesity paradox. In addition to the various aforementioned explanations, there might be currently unknown factors that also contribute to its causation, as presented in the figure.

The hazards of underweight

The association of increased mortality in the underweight population might, at least in part, be attributable to *reverse causation*, which means that lower weight is not a cause but a result of chronic diseases that are related to poor outcome.[86] Chronic diseases that cause weight loss may remain unnoticed for months or even years, for example, in the case of cancer, chronic respiratory or cardiac diseases.

Smoking is another potential confounding factor, because it is associated with both a decreased weight and an increased mortality risk.[86] In order to minimize the effects of reverse causation and smoking on mortality rates, deaths occurring in the initial follow-up period should be disregarded, and analyses should be restricted to patients without preexisting disease and to persons who had never smoked. However, studies that addressed these potential confounders still show increased mortality rates in the underweight population.[18,19,67]

Figure 2. Schematic representation of possible causes of the obesity paradox, showing its multi-factorial origin with several (overlapping) hypotheses. CVD, cardiovascular disease.

COPD and other respiratory diseases are responsible for the vast majority of mortality in the underweight population.[66,67] This may be due to weight loss associated with COPD (reverse causation). However, low BMI in COPD has also been shown to be a risk factor for mortality, irrespective of disease severity.[87] In addition, skeletal muscle dysfunction is a common feature in COPD, and can be caused by muscle loss due to wasting and by intrinsic muscular alterations, in which the proportions of skeletal muscle fiber types change.[88] Skeletal muscle dysfunction is recognized to be an independent predictor of mortality in patients with COPD.[89] In underweight patients with COPD the intrinsic muscular alterations are aggravated,[90] and this could also explain the increased mortality risk in this group.

Wasting and inflammation could offer additional explanations for the mortality hazard of the underweight population. Improper nutrition and wasting in chronic illness can result in catabolic changes in skeletal muscle in lean subjects having minimal stores of fat, leading to cachexia.[91] Oxidative stress may be an important underlying cause for both wasting and inflammation.[92] Accumulation of oxidants results from a reduction in anti-oxidant capacity in the face of elevated metabolic requirements. These oxidants have pro-inflammatory effects, which eventually will lead to fatal complications. This cascade is called the "*malnutrition-inflammatory-cachexia complex*".[93] The deleterious effects of the malnutrition-inflammatory-cachexia complex occur rapidly, and the short-term risks of underweight outweigh the long-term (cardiovascular) risks associated with obesity.[93] The malnutrition-inflammatory-cachexia complex clearly explains the increased mortality risk in the underweight population.

Implications for the surgical population

As previously described, the obesity paradox has also been shown in the surgical population. The mechanisms explaining the survival benefit of the obese in the general population might also be applicable to the obese surgical patient. Moreover, it is speculated that overweight and mild obese patients have a more appropriate inflammatory and immune response to the stress of surgery than their leaner and morbid obese counterparts.[26,27] There is a close relationship between the immune and metabolic response systems, and proper function of each is dependent on the other.[94] Compared to normal weight patients, overweight and obese patients have a more sufficient nutritional reserve and might be functioning in a more efficient metabolic state, and as a result, the inflammatory and immune response to surgery might be more adequate. In contrast, both underweight and morbid obese patients are inefficient in energy expenditure, due to underlying malnutrition and metabolic excess. The inflammatory response to the stress of surgery is aggravated, which leads to further metabolic dysfunction and immunosuppression. Consequently, these patients suffer from adverse outcomes following surgery.[26,27]

In addition, recent weight loss of more than 10% of body weight and lower mean albumin levels, due to protein-energy malnutrition, are common in underweight patients and are indicators of malnourishment. Both conditions are well-known risk factors for adverse outcomes following surgery.[95-98] Several nutrition-screening tools can adequately assess malnourishment, and are able to identify patients who should benefit from nutritional support.[99] Peri- and postoperative nutritional support in malnourished underweight patients can improve outcomes following major surgery.[100-103] On the other hand, preoperative nutritional support in obese patients is not recommended,[101,102] although in obese patients nutritional deficiencies like iron deficiency, resulting in a higher prevalence of anaemia, are common.[21] Weight loss in obese patients prior to surgery is not recommended as well, because studies that evaluated this strategy showed conflicting evidence regarding postoperative outcomes.[21] In obese patients undergoing surgery, the highest priority should be on the recognition and adequate treatment of underlying cardiopulmonary comorbidities that negatively influence postoperative outcomes, including obstructive sleep apnea syndrome, in order to reduce postoperative complications.[21]

Conclusion

Despite the feeling that obese patients requiring surgery are at increased risk for adverse postoperative outcomes, surgery can be relatively safely performed in the higher BMI categories. However, patients at the extremes of BMI, both the underweight and the obese class III, seem to have the highest postoperative morbidity and mortality hazard, which even persists at long-term. The inverse relationship between BMI and mortality is referred to as the obesity paradox, and has been observed both in the general population as well as in several disease specific populations. Cancer and respiratory diseases, including COPD, are responsible for excess mortality in the underweight population, exerting its effects at relatively ‘short’ long-term, i.e. within years. On the other hand, cardiovascular disease accounts for the majority of deaths among the obese, particularly at longer follow-up. Cancer, COPD and cardiovascular disease are characterized by wasting and inflammation, thereby offering possible explanations for the obesity paradox. Moreover, it is important to consider that BMI is not a measure of body fat distribution. Likely, the cause of the obesity paradox is multi-factorial. It is suggested that future research should be directed at more accurate indices of body fat, such as waist circumference or computed tomographic measurement of intra-abdominal fat content and its relation with inflammation, in order to examine the association with survival and to evaluate whether the obesity paradox remains valid, not only in the general population, but also in disease specific populations. This provides more insight into the hazards of both underweight and (morbid) obesity and might lead to a more tailored approach, including dietary and drug strategies, in order to improve outcomes for patients at the extremes of BMI.

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Chapter 3

The new body mass index formula; not validated as a predictor of outcome in a large cohort study of patients undergoing general surgery

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ABSTRACT

Background & Aims
A new and interesting body mass index (BMI) formula has been proposed. This formula was designed to provide a more accurate estimation of weight categories, not limited in a two-dimensional manner. The objective of this study was to evaluate the predictive value of the new BMI formula on postoperative complications and long-term survival in a large cohort of patients undergoing general surgery.

Methods
4293 consecutive patients undergoing general surgery in a general teaching hospital were included. Data on comorbidity and demographics were gathered prior to surgery. We also collected data on surgery related characteristics. BMI was calculated using the conventional as well as the new BMI formula. Patients were then divided into four weight categories (BMI < 18.5, 18.5-25, 25-30 and > 30 kg/m^2) as recommended by the World Health Organization.

Results
The study population consisted of 4293 patients. Multivariate regression analyses and the area under the ROC-curve (0.531 ± .011 and 0.539 ± .011) showed comparable results in predicting outcome between the two formulas. A demographic shift was noticed after complementing the new BMI formula. Male patients were the subjects of this shift, usually towards a lower BMI. According to the conventional BMI formula, 58% of men were overweight BMI > 25 kg/m^2, compared to 51.4% according to the new formula.

Conclusions
This study showed no difference in prediction of outcome after general surgery when comparing the current BMI formula to the new BMI formula. Thus, despite the fact that the new mathematical proposition seemed more logical and interesting, both calculations can be used in clinical practice. Moreover, our results do not support a change from the conventional BMI formula, currently used and accepted worldwide.

INTRODUCTION

Most often the body mass index (BMI) is the preferred formula to assess different weight categories. The body mass index was developed in the 1840's and is defined as weight divided by height squared. It was known for years as the Quetelet Index, until it was renamed and popularized by an American scientist as the body mass index.[1] The easy, safe and inexpensive acquirement of weight and stature might explain its popularity. Ever since, many studies have validated the BMI formula as a reasonable marker of adiposity in children and adults.[2-4] Recently, professor Trefethen from the department of numerical analysis at the University of Oxford proposed a new and interesting BMI formula.[5] The reason for this new formula, he claims, is that weight categories should not be limited in a two-dimensional manner. According to Trefethen, the current BMI formula seems to underestimate obesity in shorter people and overestimate obesity in taller people. His suggested new formula is $BMI = 1.3*weight(kg)/height(m)^{2.5}$.

It is well known that body weight is associated with outcome after surgery. Obesity increases the risk of wound infection, results in a longer operation time and more intraoperative blood loss.[6-10] As for long-term outcome, a non-expected inverse and thereby paradoxical relationship between body mass index and survival is described in both cardiac and non-cardiac surgical populations.[11-13] This paradox shows an inverse relationship between body mass index and mortality, with a lower mortality rate in the overweight and mild obese population and an increased mortality rate in the underweight population. Since professor Trefethen emphasizes he is an applied mathematician, it seems interesting to subject his formula to a clinical study population. According to our knowledge, there are two studies describing this new formula in clinical practice, both limited by small groups of patients.[14,15] Therefore, the objective of this study was to evaluate the predictive value of the new BMI formula, compared to the current BMI formula, on postoperative complications and long-term survival in a large cohort of patients undergoing general surgery.

MATERIALS AND METHODS

We included consecutive patients undergoing general surgery in the Orbis Medical Center (now part of the Zuyderland Medical Center) from March 2005 to December 2006. The study complies with the Helsinki statement on research ethics and the local medical ethical committee gave formal review and approval. Patients younger than 14 years old were excluded. Other exclusion criteria were procedures performed under local anesthesia and assisting procedures for a specialism other than the general surgery department. When a patient underwent more than one procedure during the study period, only the first operation was included. A surgeon or a surgical resident in the outpatient clinic gathered information on comorbidity and demographics prior to surgery. We also collected data on surgery related characteristics. Validation of the database using a random sampling audit procedure confirmed a high level of accuracy and completeness of data.

The original Body Mass Index formula (BMI = weight (kg)/height (m)^2) was used to calculate BMI. Subsequently, as recommended by the World Health Organization (WHO), patients with a BMI < 18.5kg/m^2 were defined as underweight, BMI 18.5-25kg/m^2 as normal weight, BMI 25-30kg/m^2 as overweight and patients with a BMI > 30kg/m^2 were defined as obese.[16] We then calculated patients' BMI with the new formula, after which they were divided into the same WHO recommended weight-categories.

Patients were followed during hospital stay and visits to the outpatient clinic up to one year after surgery. Any event within 30 days after surgery deviating from a normal postoperative course was defined as a complication. The following complications were separately documented: wound infections, pneumonia, cardiovascular and cerebrovascular events, deep vein thrombosis and or pulmonary embolisms, ICU-admission, readmission and need for complication surgery. Information on long-term survival was gathered from the national public register, available in 98.3% of patients, with a median follow-up time of 6.3 (interquartile range 5.8-6.8) years.

We used a chi-square test for comparison of categorical variables and analysis of variance for continuous variables. Univariable and multivariable regression models were used to evaluate which of the two BMI formulas was better in predicting outcome. We entered all potential confounders, such as age, gender, surgical risk, type of anesthesia, ASA classification (Table 1), diabetes, hypertension, pulmonary -, cardiac - or cerebrovascular disease, and the presence of a malignancy in the multivariable regression model. Finally, we used the receiver operating characteristic (ROC) curves to determine which of the two formulas was a better predictor of outcome. Results were reported as odds ratios (OR) or hazard ratios (HR) with a 95% confidence interval. Significance was defined as a two-sided P-value < 0.05. Primary endpoints of this study were 30-day complications and long-term mortality. Statistical analyses were performed with SPSS, version 22.0.0 statistical software (SPSS Inc., Chicago, Illinois).

Table 1. The American Society of Anesthesiologists (ASA) Classification (21).

ASA I	A normal healthy patient
ASA II	A patient with mild systemic disease
ASA III	A patient with severe systemic disease
ASA IV	A patient with severe systemic disease that is a constant threat to life
ASA V	A moribund patient who is not expected to survive without the operation

RESULTS

A total of 4479 patients underwent surgery during the study period and were found suitable for analyses. Information on height or weight was not available in 186 patients (4,2%), whom were subsequently excluded. Therefore, our study population consisted of 4293 patients. There was an equal percentage of men and women in the cohort and the mean height was 1.77 ± 0.79 m and 1.65 ± 0.69 m respectively. For each patient we calculated BMI and the new BMI, after which they were categorized into the four different weight groups. Table 2a shows the baseline characteristics for both BMI formulas. The mean BMI for male patients was 26.1 ± 4.0 kg/m^2 when using the current BMI formula and 25.5 ± 4.0 kg/m^2 when calculated with the new formula. For female patients these numbers were 26.2 ± 5.1 kg/m^2 and 26.5 ± 5.3 kg/m^2 respectively. Table 2b shows demographic shifts after complementing the new formula. Especially male patients seemed the subject of this shift, usually towards the better end. 58% of all men were overweight BMI > 25 kg/m^2 according to the conventional BMI calculation, compared to 51.4% according to the new formula.

Table 2a. BMI values according to current and new BMI formula for different baseline characteristics.

	Current BMI (mean)	New BMI (mean)
Demographics		
Age		
Age > 60 years	26.2 ± 4.3	26.2 ± 4.4
Age < 60 years	26.1 ± 4.7	25.8 ± 4.8[#]
Sex		
Male sex	26.1 ± 4.0	25.5 ± 4.0
Female sex	26.2 ± 5.1	26.5 ± 5.3[##]
ASA classification**		
I	25.1 ± 3.8	24.8 ± 3.9
II	27.0 ± 4.7	27.0 ± 4.8
III	26.2 ± 4.9	26.2 ± 5.0
IV	25.3 ± 4.7	25.3 ± 4.8
V	24.8 ± 8.0	24.7 ± 7.9
Medical history		
Diabetes mellitus	28.6 ± 5.4	28.6 ± 5.6
Hypertension	27.5 ± 4.9	27.6 ± 5.0
Cerebrovascular disease	26.1 ± 4.5	26.1 ± 4.6
Malignant disease	26.0 ± 4.5	26.1 ± 4.7
Pathological cardiac history	26.5 ± 4.6	26.5 ± 4.7
Pathological pulmonary history	26.5 ± 5.1	26.5 ± 5.3
Current smoking *	25.6 ± 4.7	25.4 ± 4.7

[#] Significantly different ($p<.05$) when compared to age > 60 years, within the new BMI-group
[##] Significantly different ($p<.05$) when compared to male sex, within the new BMI-group
* Data available in 75.7% of patients
** American Society of Anesthesiologists

Tables 3 shows the 30-day complications and long-term mortality rates, as well as the regression analysis of each weight-category for both BMI formulas. Multivariate regression analyses, using the normal weight group as reference showed comparable results between the two BMI formulas.

Table 2b. BMI categories according to current and new BMI formula stratified for different baseline characteristics.

		Normal weight N (%)	**Underweight N (%)**	**Overweight N (%)**	**Obese N (%)**
Overall	*Current BMI*	1815 (42.3)	100 (2.3)	1635 (38.1)	743 (17.3)
	New BMI	1901 (44.3)	110 (2.6)	1572 (36.6)	710 (16.5)
Male	*Current BMI*	893 (40.3)	39 (1.8)	970 (43.8)	315 (14.2)
	New BMI	1022 (46.1)	57 (2.6)	886 (40.0)	252 (11.4)
Female	*Current BMI*	922 (44.4)	61 (2.9)	665 (32.0)	428 (20.6)
	New BMI	879 (42.3)	53 (2.6)	686 (33.0)	458 (22.1)
Age > 60	*Current BMI*	741 (40.7)	36 (2.0)	743 (40.8)	302 (16.6)
	New BMI	755 (41.3)	35 (1.9)	723 (39.7)	309 (17.0)
Age < 60	*Current BMI*	1074 (43.5)	64 (2.6)	892 (36.1)	441 (17.8)
	New BMI	1146 (46.4)	75 (3.0)	849 (34.4)	401 (16.2)

When comparing different weight categories, obese patients had an increased risk of 30-day complications (OR 1.29; 95% CI 1.03 - 1.62). Underweight patients had an increased risk of long-term mortality (HR 2.17; 95% CI 1.52 - 3.10), whereas the overweight (HR 0.66; 95% CI 0.55 – 0.79) and obese (HR 0.70; 95% CI 0.56 – 0.89) patients had a lower risk of long-term mortality. When using the current BMI formula, the area under the ROC-curve for predicting 30-day complications is 0.531 ± 0.011 and 0.539 ± 0.011 when using the new calculation (table 4).

3

Table 3. Association between 30-day complications and long-term mortality rates and BMI-categories.

	30 day complications				Long-term Mortality			
	Current BMI		New BMI		Current BMI		New BMI	
	N (%)	Adjusted* OR (95% CI)	N (%)	Adjusted* OR (95% CI)	N (%)	Adjusted* HR (95% CI)	N (%)	Adjusted* HR (95% CI)
Normal weight	335 (18.5%)	1	345 (18.1%)	1	331 (18.6%)	1	328 (17.6%)	1
Underweight	27 (27.0%)	1.20 (0.73-1.97)	28 (25.5%)	1.17 (0.72-1.91)	35 (35.4%)	2.07 (1.44-2.96)	36 (33.0%)	2.17 (1.52-3.10)
Overweight	342 (20.9%)	1.14 (0.95-1.36)	336 (21.4%)	1.16 (0.96-1.38)	212 (13.2%)	0.63 (0.53-0.75)	213 (13.8%)	0.66 (0.55-0.79)
Obese	184 (24.8%)	1.31 (1.05-1.65)	179 (25.2%)	1.29 (1.03- 1.62)	109 (14.8%)	0.71 (0.56-0.89)	110 (15.6%)	0.70 (0.56-0.89)

OR: Odds ratio; HR: Hazard ratio
* Potential confounders: age, gender, surgical risk, type of anaesthesia, ASA classification, diabetes, hypertension, pulmonary -, cardiac - or cerebrovascular disease and the presence of malignancy.

Table 4. Receiver operating characteristics (ROC) current and new BMI formula for the prediction of 30-day complications.

	30-day complications	
	Area	Standard Error
Current BMI	0.531	.011
New BMI	0.539	.011

DISCUSSION

We found no difference in the prediction of outcome after general surgery when comparing the current BMI formula to the Trefethen BMI formula. The conventional calculation is widely used and has been proven to be a reasonable marker of adiposity in children and adults.[2-4]

However, since it is only a surrogate measure of body fatness, it has been the topic of debate for mathematicians, epidemiologists and clinical practitioners for as long as it exists. Evolution beyond the BMI formula has been suggested. The use of sitting height is proposed to be a better predictor of total body mass than total height.[17] Of more clinical importance, standards based on actual measurements of body fat[18], or newer techniques such as computerized tomography-based body composition analysis seem promising.[19] However, conventional BMI continues to serve well as a marker, probably because of its practicality. Professor Trefethen claims that the current BMI formula seems to underestimate obesity in shorter people and overestimate obesity in taller people. With the suggestion of his new BMI formula he brought the discussion back to life. According to our knowledge, there are two studies describing the new formula in clinical practice, both limited by small groups of patients.[14,15] These studies found no statistical significant differences in predicting outcome when comparing the two BMI calculations. In order to overcome the limitations of a small study population we validated the Trefethen formula in this large group of patients undergoing general surgery. The new BMI formula was designed to provide a more accurate estimation of different weight categories.

This study shows a shift for male patients towards a lower BMI-category, which can be explained by their greater height when compared to women. Indeed obesity might be overestimated in the taller patients.[5] For women there was no significant shift among the four BMI-categories. When comparing the four BMI categories, the obese patient has a significantly increased risk of postoperative complications. We also found an inverse relationship between body mass index (BMI) and long-term mortality, with a lower mortality rate in the overweight and obese population and a higher mortality rate in the underweight population, validating the obesity paradox with the old as well as the new BMI-formula. A few potential limitations must be addressed. First, our study is conducted in a single center with a potential bias in referral pattern. However, at the time of enrollment, only patients needing total pelvic exenteration or patients with severe comorbidity were referred to tertiary centers. All other major abdominal surgery was performed in this regional hospital. Our data contains quite a large number of intermediate and high risk procedures and procedures with a long operation time. Second, the recorded data on height and weight were partially self-reported. The difference between self-reported and measured values however, is of minor importance and these data can be considered a reliable estimate of actual BMI[20]. So, where the mathematical proposition was interesting and seemed logical, also in this large population it does not alter the prediction of outcome when compared to the standard BMI formula as proposed by Quetelet, making this in the meantime almost 2 centuries old observation still valid.

In conclusion, there is no difference in the prediction of outcome after general surgery when comparing the current BMI formula to the Trefethen BMI formula. Results from our study do not support a change in the current practice where the BMI formula is accepted worldwide. Both calculations can be used in clinical practice, but Quetelet's formula in its simplicity and ease of use still seems to be preferred.

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Part II

Advanced age and frailty as risk factors of adverse postoperative outcome

Chapter 4

Perioperative and long-term outcomes in patients aged eighty years and older undergoing non-cardiac surgery

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ABSTRACT

Background
Decision-making whether older patients benefit from surgery can be a difficult task and information on outcomes in these patients is limited. This retrospective observational study investigates characteristics and outcomes of a large cohort of inpatients, aged 80 years and over, undergoing non-cardiac surgery.

Methods
Perioperative data of 8251 patients, undergoing 19027 surgical interventions between 2004 and 2017, were collected. Patients aged 80 years or older, undergoing elective or urgent non-cardiac surgery, were included. Procedures were classified into low-, intermediate- or high-risk. Primary outcomes were length of stay, discharge destination, 30-day and long-term mortality. Secondary outcomes were time trends.

Results
A total of 7032 primary procedures were found suitable for analyses. Median LOS was three days in the low-risk group, compared to six in the intermediate- and ten days in the high-risk group. Median LOS of the total cohort decreased from 5.8 days (IQR 1.9-14.5) in 2004-2007 to 4.6 days (IQR 1.9-9.0) in 2016-2017. Three quarters of patients were discharged to their own home. Postoperative 30-day mortality in the low-risk group was 2.3%, but overall 30-day mortality was high and remained constant during the study period (6.7%, ranging from 4.2-8.4%).

Conclusion
In this large cohort of surgical patients aged 80 years and older, overall 30-day mortality was 6.7%. Although 30-day mortality risk in the low-risk surgery group was relatively low, patients undergoing intermediate and high-risk surgery, had worse prognosis. Time trend analysis didn’t show a remarkable variation in volume of procedures performed over the years, neither in postoperative mortality risk.

INTRODUCTION

In the Netherlands, life expectancy has been rising continuously for both women and men[1,2] and the average 80-year old has a life expectancy of more than seven years[3,4]. This upward age trend is also reflected in the hospital population; in 1995, 24% of all surgical procedures were performed in patients of 65 years or older and this percentage has increased progressively ever since (32% in 2010).[5]

Old age is related with a decline in physiological reserve, such as cardiac and vascular dysfunction, advanced atherosclerosis, decreased lung function, decreased (respiratory) muscle strength, renal insufficiency, and altered immunological state[6,7]. Due to this decreased physiological reserve, comprehensive perioperative care for the older patients is warranted. Furthermore, most older patients will present themselves with more risk factors than their younger counterparts[8]. There is limited information on surgical outcomes in patients of 80 years or more[9]. Identification of health deficits associated with increased age can guide the clinician in the decision whether or not a patient benefits from surgical treatment.

The primary objective of this study is to investigate the characteristics and outcomes of a large cohort of inpatients aged 80-years and older, undergoing non-cardiac surgery. Our secondary objective is to evaluate time trends from 2004 until 2017.

METHODS

Study design

This is a retrospective observational study, analysing perioperative data of older patients undergoing non-cardiac surgery at a tertiary university medical centre in the Netherlands. The Medical Ethical Committee (METC) of the Erasmus University Medical Centre granted a formal statement and approved the non-interventional character of this study on September 25th, 2018.

Patient selection

Data were obtained from all consecutive older patients undergoing elective or urgent surgical interventions from January 2004 to June 2017. All patients of 80 years or older undergoing surgery within the mentioned study period were included. Exclusion criteria were outpatient, or short-stay procedures and cardiac surgery. Data on surgical procedures were extracted from the electronic patient registration system by procedure codes. Surgical interventions frequently consisted of multiple procedure codes. Purely administrative codes, or anaesthesia-related codes, such as placement of an intra-arterial or intravenous catheter were excluded. When multiple procedure codes were linked to one intervention, the primary code was identified for further analysis. If a patient underwent different interventions during the study period, this resulted in multiple primary interventions, each included for analysis. However, for long-term survival, one of the primary endpoints, we restricted our analysis to the patient's procedure with the highest surgical risk. The final study population consisted of 19027 surgical procedures in 8251 patients.

Baseline characteristics

Perioperative data were extracted from the electronic patient registration system. Baseline characteristics included age, sex, height and bodyweight. The body mass index (BMI) was calculated using height and bodyweight: kg/m^2 following the classification system recommended by the World Health Organization[10]. The American Society of Anesthesiologists (ASA) classification and patients' following laboratory-findings were also collected: haemoglobin (Hb), estimated glomerular filtration rate (eGFR), albumin and C-reactive protein (CRP). The laboratory values recorded on the closest preceding date of the intervention were used. In more than 97% this date was within the year prior to surgery. Furthermore, type of surgery, dates of surgery, hospitalisation and discharge, as well as discharge location were recorded. Surgical procedures were categorised according to the ESC/ESA Guidelines into 29 surgery types and subsequently divided into low-, intermediate- and high-risk procedures (Table 1)[11]. The anaesthetic technique was documented and divided into general anaesthesia, sedation analgesia, neuraxial techniques, regional anaesthesia and local anaesthesia. Finally, the postoperative ward receiving the patient after the interventions was documented. This gave an insight into whether the patients went to a general ward, an intensive care, high care, medium care or post anaesthesia care unit (PACU). In this hospital, the PACU is a ward where anaesthetists provide clinical care during the first 24 hours after surgery. This care may include invasive, or non-invasive ventilation, goal-directed haemodynamic management, invasive monitoring and optimal pain management.

Table 1. Surgical risk estimate according to type of surgery or intervention[a,b]

Low-risk: < 1%	Intermediate-risk: 1-5%	High-risk: > 5%
• **Superficial surgery** • **Breast** • **Dental** • **Endocrine: thyroid** • **Eye** • **Reconstructive** • **Carotid asymptomatic (CEA or CAS)** • **Gynaecology: minor** • **Orthopaedic: minor (meniscectomy)** • **Urological: minor (transurethral resection of the prostate)**	• Intraperitoneal: splenectomy, hiatal hernia repair, cholecystectomy • Carotid symptomatic (CEA or CAS) • Peripheral arterial angioplasty • Endovascular aneurysm repair • Head and neck surgery • Neurological or orthopaedic: major (hip and spine surgery) • Urological or gynaecological: major • Renal transplant • Intra-thoracic: non-major	• Aortic and major vascular surgery • Open lower limb revascularization or amputation or thromboembolectomy • Duodeno-pancreatic surgery • Liver resection, bile duct surgery • Oesophagectomy • Repair of perforated bowel • Adrenal resection • Total cystectomy • Pneumonectomy • Pulmonary or liver transplant

CAS: carotid artery stenting; CEA: carotid endarterectomy.
[a] Surgical risk estimate is a broad approximation of 30-day risk of cardiovascular death and myocardial infarction that takes into account only the specific surgical intervention, without considering the patient's comorbidities. [b] ESC/ESA Guidelines (11)

Postoperative and long-term outcome

Primary outcomes were LOS, destination after hospital discharge and 30-day and long-term mortality. Discharge destination was defined as home versus non-home. Non-home consisted of: nursing home, rehabilitation, deceased during hospital stay, other hospital, and other or unknown. Information on mortality was assessed through the institution's medical records and long-term mortality was based on information from the national public register. Secondary outcomes were time trend analysis for these primary outcomes.

Data analysis

Continuous variables were presented as mean ± standard deviation (SD) when normally distributed, or as median and interquartile range (IQR) when data were skewed. Categorical variables were described with frequencies and percentages. Differences in baseline characteristics were determined using Pearson's chi-squared test and Kruskal-Wallis test. Univariate and multivariate logistic regression were used to assess predictive factors for discharge destination and 30-day mortality. Potential associated variables (sex, age, ASA classification, and BMI) were entered in the multivariable model. Results are reported as odds ratio's (OR) with a 95% confidence interval. Due to missing data in ASA classification and BMI, multivariate regression was performed in a two-step approach: without ASA and BMI (aORI) and with both variables included (aORII). Long-term survival estimates were performed using Kaplan Meier analysis in individual patient cohort.

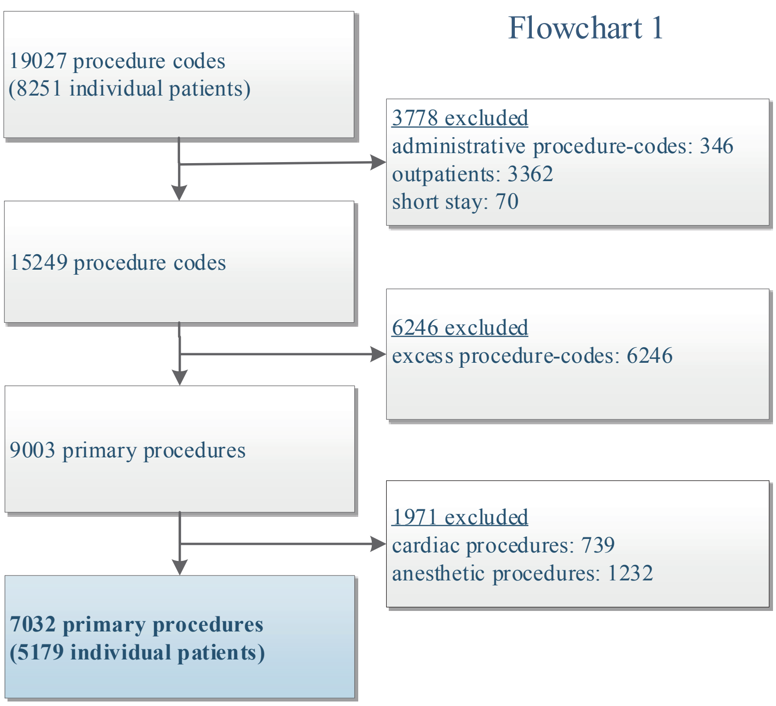
For time trend analyses, patients were divided into four consecutive 3-year periods and one 2-year period (2004 to 2015, and 2016 to 2017 respectively). For absolute counts within time trends we analysed year 2004 up to and including 2016, as only part of year 2017 was assessed due to start of a new electronic health registration system.

Differences in time trends were assessed with the Mantel-Haenszel chi-square test of linear association for categorical variables. The data were provided in Excel-sheets (Microsoft Excel 2010), statistical analyses were carried out using SPSS (version 24, SPSS Inc., Chicago, Illinois). Graphs were made using R software version 3.51 (The R foundation for Statistical Computing, Vienna, Austria (2018)).

RESULTS

The database search resulted in 19027 procedure code cases representing 8251 individual patients aged 80 years or older. After exclusion of administrative, cardiac and anaesthetic procedure codes, outpatients and short stay patients; the final study population consisted of 5179 individual patients who underwent 7032 primary procedures. Of these, 1225 (23.6%) patients underwent more than one intervention during the inclusion period. The selection process is visualized in the flowchart in Figure 1.

Figure 1. Flowchart procedure codes selection



Of the 7032 primary procedures, 3137 (44.6%) were categorized as low-risk, 3365 (47.9%) as intermediate-risk and 530 (7.5%) as high-risk. The large majority of patients undergoing surgery had an ASA classification II (47.7%) or III (45.3%). The frequency of patients with ASA classification I and II decreased with each higher risk group (P<0.001) (Table 2).

Table 2. Baseline characteristics and outcome

	Total (n=7032)	**Low-risk < 1% (n=3137; 44.6%)**	**Intermediate-risk 1-5% (n=3365; 47.9%)**	**High-risk > 5% (n= 530; 7.5%)**	**P-value**	**Missings n (%)**
Female n (%)	3750 (53.3)	1785 (56.9)	1785 (53.0)	180 (34.0)	<0.001	-
Age (median(IQR))	83.0 (81.0-86.0)	83.0 (81.0-86.0)	83.0 (81.0-85.0)	82.0 (81.0-85.0)	<0.001	-
80-84 n (%)	4665 (66.3)	1995 (63.6)	2263 (67.3)	407 (76.8)		
85-89 n (%)	1826 (26.0)	889 (28.3)	833 (24.8)	104 (19.6)		
90+ n (%)	541 (7.7)	253 (8.1)	269 (8.0)	19 (3.6)		
BMI * (median(IQR))	25.0 (22.8-27.9)	25.3 (22.9-27.9)	24.8 (22.7-28.0)	24.7 (22.7-27.3)	0.036	41428 (58.7%)
ASA n (%)					<0.001	3702 (52.6)
I	112 (3.4)	54 (3.6)	51 (3.3)	7 (2.4)		
II	1590 (47.7)	810 (54.3)	666 (42.9)	114 (39.9)		
III	1510 (45.3)	595 (39.9)	770 (49.6)	145 (50.7)		
IV&IV	118 (3.5)	32 (2.1)	66 (4.2)	20 (7.0)		
Anesthesia n (%)					<0.001	326 (4.6)
General	5437 (81.1)	2138 (70.3)	2868 (90.0)	431 (90.0)		
Sedation Analgesia	56 (0.8)	40 (1.3)	14 (0.4)	2 (0.4)		
Neuraxial	411 (6.1)	197 (6.3)	194 (6.1)	20 (4.2)		
Regional	131 (2.0)	94 (3.1)	32 (1.0)	5 (1.0)		
Local	647 (9.6)	548 (18.0)	78 (2.4)	21 (4.4)		
Analgesia	24 (0.4)	24 (0.8)	0	0		
Post Operation n (%)					<0.001	527 (7.5)
General ward	4509 (69.3)	2514 (85.7)	1953 (63.3)	42 (8.6)		
PACU	1090 (16.8)	287 (9.8)	619 (18.4)	184 (37.8)		
Medium/High Care	390 (6.0)	87 (3.0)	160 (4.8)	143 (29.4)		
Intensive Care	516 (7.9)	44 (1.5)	354 (10.5)	118 (24.2)		
Length of stay (days) (median(IQR))	5.1 (2.0-11.3)	3.0 (1.4-6.9)	6.2 (3.2-10.8)	10.3 (6.0- 17.8)	<0.001	-
Destination n (%)					<0.001	-
Home	5246 (74.6)	2805 (89.4)	2062 (61.3)	379 (71.5)		
Non-Home	1786 (25.4)	332 (10.6)	1303 (38.7)	151 (28.5)		
Nursing home / Rehabilitation*	840 (11.9)	225 (7.2)	547 (16.3)	68 (12.8)		
Deceased	370 (5.3)	45 (1.4)	262 (7.8)	63 (11.9)		
Other hospital	494 (7.0)	27 (0.9)	453 (13.5)	14 (2.6)		
Other/Unknown	82(1.2)	35 (1.1)	41 (1.2)	6 (1.1)		
Mortality 30 days n (%)	469 (6.7)	72 (2.3)	336 (10.0)	61 (11.5)	<0.001	-
Long term survival estimate (standard error)						-
1 year	0.768 (0.007)	0.845 (0.009)	0.711 (0.010)	0.708 (0.023)		
5 years	0.445 (0.010)	0.525 (0.016)	0.390 (0.015)	0.358 (0.032)		
10 years	0.152 (0.013)	0.214 (0.024)	0.108 (0.016)	0.117 (0.039)		

BMI: body mass index; ASA: American Society of Anesthesiologists; PACU: post anesthesia care unit
* Nursing home, Rehabilitation centre, Psychiatric centre.
Missing data in bodyweight and height measurements resulted in 58.7% of missing BMI in the study-cohort. Other missing data were of ASA classification (52.6%), type of anesthesia (4.6%), and post-operation destination (7.5%).

Most patients undergoing low- and intermediate-risk surgery were admitted to a surgical ward postoperatively (85.7% and 63.3%, respectively). Thirty-eight percent of high-risk patients were admitted to the post anaesthesia care unit. LOS increased by increasing surgical risk level; three days in low-risk patients, six days in intermediate-risk patients and ten days in the high-risk group (P <0.001).

Overall, 5246 (74.6%) patients went home after hospital discharge. When categorized by risk, the highest percentage of patients went home in the low-risk category (89.4%), compared to 61.3% in the intermediate-risk group and 71.5% in the high-risk group (P<0.001). Increasing age, surgical risk and ASA classification were all independent predictors of non-home discharge destination (Table 3).

The overall 30-day mortality rate was 6.7% increasing from 2.3% in the low-risk to 11.5% in the high-risk patients. Independent predictors for 30-day mortality were male sex, surgical risk, ASA classification and BMI <18.5 kg/m^2. A BMI 25-30 kg/m^2 was associated with low 30-day mortality (Table 3).

The median survival time of the study population (N=5179, without duplicate cases) was 4.1 years (CI 3.87-4.28) and differed across surgical risk categories, with highest survival rate in patients undergoing low-risk surgery (P<0.001), Figure 2. The survival curves for intermediate-risk and high-risk surgery were comparable (P=0.43). The 5-year survival estimate for the low-risk group was 0.525 ± 0.016, for the intermediate-risk group 0.390 ± 0.015, and 0.358 ± 0.032 for the high-risk group, respectively. The 10-year estimates were 0.214 ± 0.024, 0.108 ± 0.016, and 0.117 ± 0.039 respectively.

Time trends for the total count of primary procedures showed little variation (Figure 3). Importantly, while the intermediate-risk and low-risk procedures showed a minimal down sloping trend, the high-risk procedures showed an increase in absolute numbers (Figure 3). Age distribution was also relatively constant over time with little variation between the proportions: 80-84 years varying from 65.4% to 67.5%; 85-89 years varying from 24.3% to 27.2%; and 90 years or older varying from 6.3% to 9.4% (P= 0.22).

Table 3. Univariate and multivariate logistic regression for 30-day mortality and discharge destination.

	Predictors for 30-day mortality			Predictors for non-home discharge		
	Univariable (95% CI)	Multivariable (95% CI)		Univariable (95% CI)	Multivariable (95% CI)	
	OR	aOR I ***	aOR II ****	OR	aOR I ***	aOR II ****
Gender						
Male	1.4 (1.1-1.7)	1.3 (1.1-1.6)	0.9 (0.6-1.4)	0.9 (0.8-1.0)	0.9 (0.8-1.0)	0.6 (0.5-0.8)
Age	1.01 (0.99-1.04)	1.04 (0.99-1.08)	1.06 (1.01-1.12)	1.05 (1.03-1.07)	1.05 (1.03-1.07)	1.10 (1.07-1.13)
Surgical risk						
Low	1	1	1	1	1	1
Intermediate	4.7 (3.6-6.1)	4.7 (3.6-6.1)	2.9 (1.8-4.5)	5.4 (4.7-6.1)	5.5 (4.8-6.3)	4.4 (3.6-5.5)
High	5.5 (3.9-7.9)	5.3 (3.7-7.6)	1.6 (0.8-3.5)	3.4 (2.7-4.2)	3.7 (2.9-4.6)	1.7 (1.1-2.4)
ASA	*			*		
I	1		1	1		1
II	1.2 (0.4-3.8)		1.2 (0.3-4.9)	1.5 (0.9-2.5)		2.0 (1.0-4.1)
III	2.9 (0.9-9.2)		2.2 (0.5-9.2)	3.0 (1.8-5.1)		3.9 (1.9-7.9)
IV&V	13.5 (4.0-45.6)	-	7.9 (1.7-36.3)	10.9 (5.7-20.7)	-	11.0 (4.8-25.3)
BMI	**			**		
<18.5	3.6 (1.9-6.7)		3.2 (1.6-6.2)	1.1 (0.7-1.8)		0.8 (0.4-1.4)
18.5-25	1		1	1		1
25-30	0.6 (0.4-0.9)		0.6 (0.4-1.0)	0.8 (0.6-0.9)		0.8 (0.6-1.0)
≥ 30	7.2 (0.4-1.3)	-	0.8 (0.4-1.4)	0.8 (0.7-1.1)	-	0.9 (0.7-1.2)

OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval.
* Variables were ASA categories and analyses were based on 3330 patients
** Variables were BMI categories and analyses were based on 2904 patients
*** aORI: Variables included in the model: gender, age, surgical risk, and analyses were based on 7032 patients
****aOR II: Variables included in the model: gender, age, surgical risk, ASA, BMI, and analyses were based on 2528 patient

Figure 2. Kaplan-Meier estimate of long-term survival

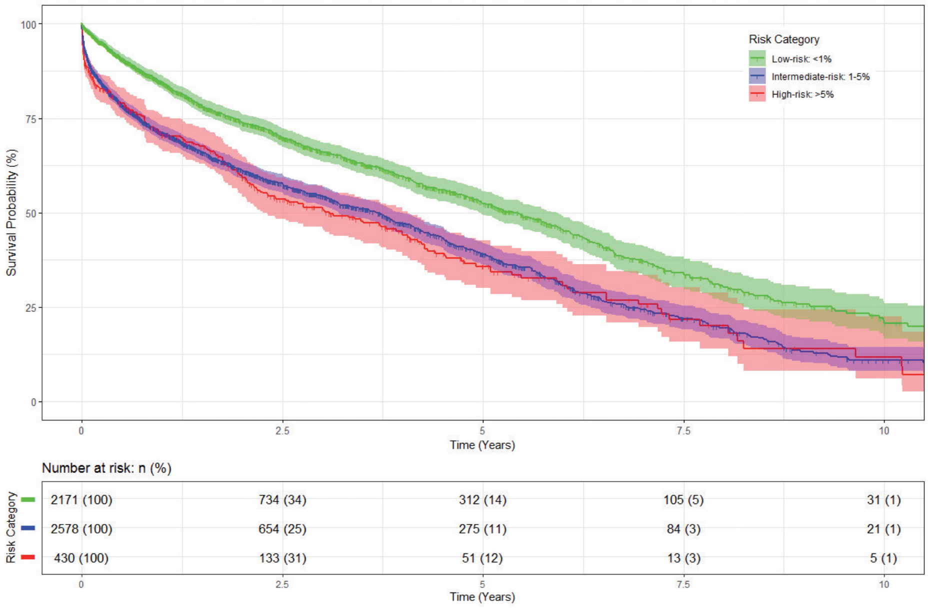
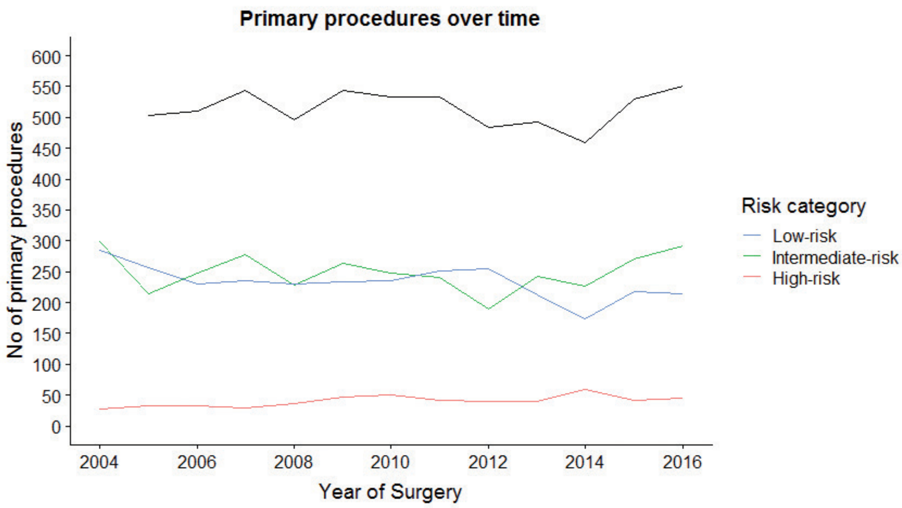
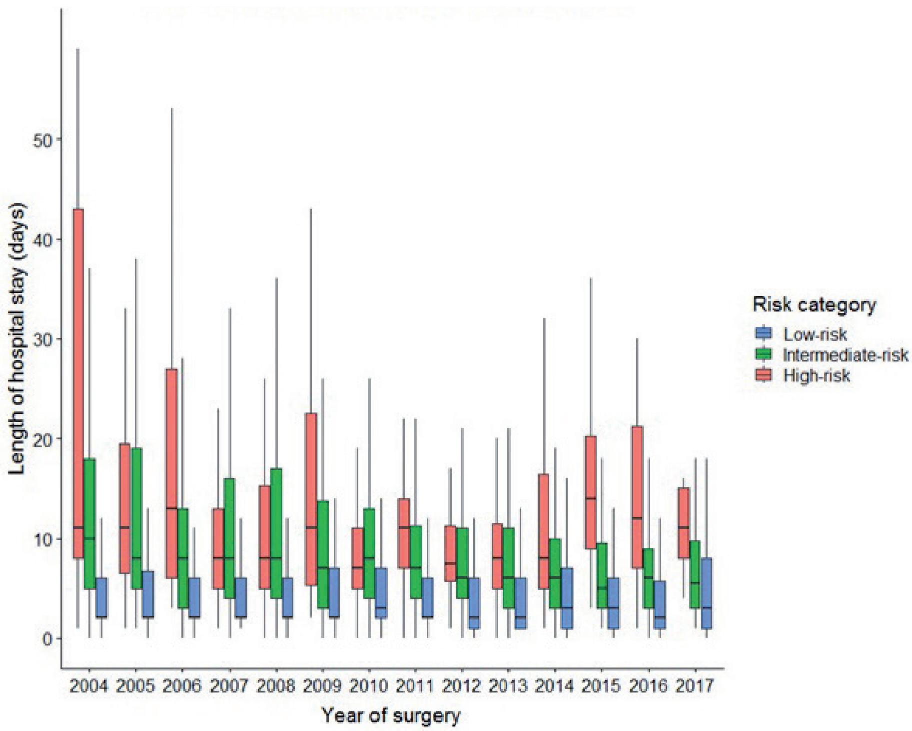


Figure 3. Primary procedures over time



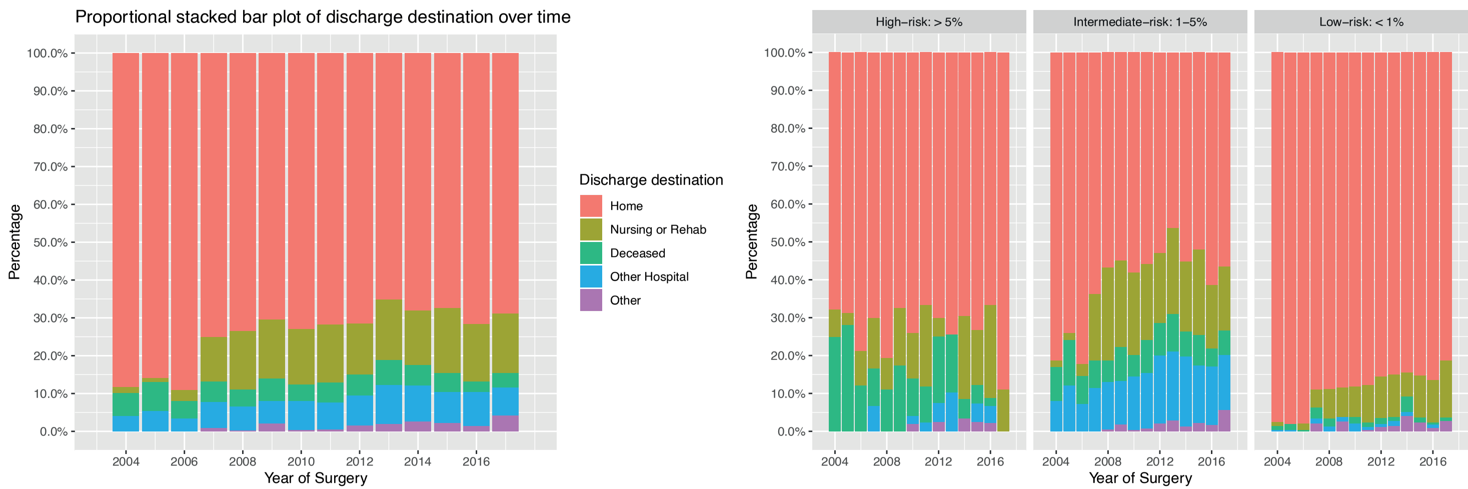
The LOS showed a slightly declining trend over the years. In the earliest time-group (2004-2006) the median was 5.8 days (IQR 1.9-14.5), which decreased in the most recent years (2016-2017) to 4.6 days (IQR 1.9-9.0). When stratified according to surgical risk, the median LOS increased for the low-risk interventions and decreased strongly in the intermediate-risk group (P=0.04, P<0.001, respectively) (Figure 4).

Figure 4. Boxplot length of stay over time, stratified per risk category



Furthermore, a clear time trend regarding discharge location during the inclusion period was observed, with more patients being discharged to a specialized facility over the years (Figure 5). Thirty-day mortality remained rather constant over time varying from 4.2 to 8.4% (P=0.36).

Figure 5. Discharge destination over time



Left: total study cohort. Right: stratified into surgical risk categories.

DISCUSSION

In this large observational study including 8251 patients aged 80 years and older undergoing elective or urgent non-cardiac surgery, the overall 30-day mortality was high (6.7%). 30-day mortality risk in the low-risk surgery group seems relatively low (2.3%). However, patients undergoing intermediate and high-risk surgery had worse prognosis. Surgical risk and patients' ASA-classification were independent predictors of postoperative death and discharge to specialized facilities.

The overall LOS in this study was 5.1 days in a cohort of older surgical patients. The LOS increased for the low-risk category and declined strongly for the intermediate-risk category. With the evolution of surgical techniques and medical care, there is a shift of procedures towards outpatient surgical care that previously required hospital admission[12]. Lagergren et al. investigated outcomes after endovascular aneurysm repair in octogenarians. With comparable patient characteristics they found a similar LOS of 5.3 days[13]. Our low-risk group spent a median of 3.0 days in hospital. Polanczyk et al. found age to be a risk factor for LOS in the hospital, noticing that patients over 80 on average stayed one day longer in hospital[14]. Further determinants of LOS were sex, surgical risk and ASA classification[15].

After hospital discharge, 75% of the patients in this study went home. The highest percentage of patients returning to their homes were in the low-risk category: 89.4%. Unexpectedly, in the intermediate-risk group, the percentage of patients going home was the lowest. In this category more patients went to another hospital after discharge than in the other two groups (24% versus 0.9% and 2.6 %). Since the hospital in this study is a tertiary academic centre, patients were referred to our hospital and sent back after surgery when considered fit enough; in the high-risk group this might not have been appropriate. Similar discharge characteristics were presented by Lagergren et al.[13]. McDonald et al. described lower rates: 62% of patients went home after hospital-stay. Since their patients mainly underwent intermediate-risk surgery, this is comparable with the 61.3% in the intermediate group of our research[16]. Age was a predictive factor, older age made it less likely that a patient could be discharged home[13,14].

The European Surgical Outcomes Study of more than 46000 inpatients undergoing non-cardiac surgery, aged 16 years and older, showed a 4% in-hospital mortality in Europe and a 2% in-hospital mortality in the Netherlands[15]. In the Dutch population a 1.8% risk of 30-day mortality after clinical surgery has been described[17]. In the present study of patients aged 80 years or older, we observed an in-hospital mortality of 5.3%.

When looking at other studies investigating the outcome of older surgical patients, Hamel et al. found a 30-day mortality of 8.2%[9] in a population of 26648 patients, undergoing non-cardiac surgery in a veteran hospital. Patients included were predominantly classified as intermediate or high-risk, nearly all patients were men and the prevalence of ASA classification 4 was 20%, which may explain the higher mortality rate when compared to the findings of this study. Other studies which included octogenarians and patients aged over 75[18], described a 30-day mortality varying from 0.8%[19] to 8.3%[13,18,20,21]. These differences can probably be attributed to the surgical risk, which varied within each of these studies from low- to high-risk. In line with previous research, age, surgical risk and ASA classification were independent predictors of 30-day mortality[9,19-21]. Another independent predictor of adverse outcome found in this study was being underweight (BMI <18.5). These patients had a threefold higher risk of postoperative mortality. These results are comparable to findings in a general non-elderly surgical population[22].

When looking at time trends, Breugom et al. described a decrease in 30-day mortality from 8.3% to 6.2% in the period 2009-2013, whereas no decline in 30-day mortality was found in our study[18]. From 2014 to 2018 the number of inpatients aged 70 years or older increased in our hospital with 14% to 5798 in 2018. This upward trend was not reflected in the number of clinical surgical procedures, as the total number of procedures remained constant during the study-period. This can possibly be explained by the exclusion of outpatients and short stay patients, which is the patient-category that seems to increase the most over the years. In the Netherlands, the total number of operations on 80-year olds and older increased from 63866 (6.1%) in 1995 to 119273 (8.4%) in the year 2010[12]. In that timespan the number of inpatients remained virtually constant with an increase of 10%. The outpatients however, undergoing mostly low-risk surgery, increased with a staggering 600%: from 8336 to 58389[12].

The present study has some limitations and concerns. First, this was a single centre study with data collected in an academic tertiary referral centre, with a peculiar patient population. Therefore, our results cannot be extrapolated to a general hospital population. Second, only inpatients were included, leaving out many low-risk interventions.

The scope of this manuscript was to provide characteristics and outcomes of 80 year olds and over, as well as time trend analysis. Due to the retrospective design on this study, we were dependent on the data registered in the hospital registration system with the related missing data and limited number of variables. Possible predictors as comorbidities or complications could have been important. Since routine standardized assessment of frailty was not available, the presence of this comorbid condition was not taken into account.

Laboratory data were recorded up to one year prior to the intervention, which is a broad time range in the life of an 80 year-old. However, the laboratory values recorded on the closest preceding date of the intervention were used, in more than 97% of cases this date was well within the year prior to surgery.

Strengths of the present study are the large number of older patients, undergoing a wide variety of surgical procedures with different risk-profiles and the long follow-up time.

McDonald et al. demonstrated that despite older age, the odds can be turned with perioperative optimization of senior health, and that an older patient can have better outcomes in LOS, complications and discharge location[23]. Literature is concordant that geriatric assessment plays a key role, covering multiple domains such as medical, mental health, functional capacity, social circumstances and environment; making it a multidisciplinary effort[16,24,25]. This enables the health care professionals to provide a patient-centred plan; optimizing the patient preoperatively where necessary, and creating an optimal postoperative management strategy[16,24-27]. Chow et al described the importance to assess the patient's decision-making capacity; to determine their ability to provide informed consent[26]. This touches another important aspect of the preoperative assessment: advance care planning. Considering the patient's short- and long-term (health) goals, and what treatment is appropriate in those cases. Multiple studies show that it is important for patients to maintain their functional independence.[25-27]. For this reason, future research should probably reconsider outcome measures such as survival and length of stay as justifications for operating, since these outcomes do not provide contextual information about whether survival fulfils the patient's goal of care, nor is it aligned with meaningful postoperative survival.

Older patients present with specific health care challenges; they have physiological, pharmacological, psychological, and social attributes different than younger patients. Better outcomes are beneficial for the patients, but they can also relieve the burden of a large and growing percentage of older patients on the hospital system[28]. In accordance with recent literature, this large observational study, including patients aged 80 years and older, suggests that patients should not be withheld surgery solely based on their age[21,29-31]. However, making the decision whether an older patient benefits from surgery will often be a difficult task. Understanding individual potential risks, being aware of the older patients' wishes and providing patient-centred plans are key principles of good perioperative care.

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Chapter 5

Influence of frailty on outcome in older patients undergoing non-cardiac surgery – a systematic review and meta-analysis

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ABSTRACT

Background
Frailty is increasingly recognized as a better predictor of adverse postoperative events than chronological age. The objective of this review was to systematically evaluate the effect of frailty on postoperative morbidity and mortality.

Methods
Studies were included if patients underwent non-cardiac surgery and if frailty was measured by a validated instrument using physical, cognitive and functional domains. A systematic search was performed using EMBASE, MEDLINE, Web of Science, CENTRAL and PubMed from 1990 – 2017. Methodological quality was assessed using an assessment tool for prognosis studies. Outcomes were 30-day mortality and complications, one-year mortality, postoperative delirium and discharge location. Meta-analyses using random effect models were performed and presented as pooled risk ratios with confidence intervals and prediction intervals.

Results
We included 56 studies involving 1.106.653 patients. Eleven frailty assessment tools were used. Frailty increases risk of 30-day mortality (31 studies, 673.387 patients, risk ratio 3.71 [95% CI 2.89-4.77] (PI 1.38-9.97; I2=95%) and 30-day complications (37 studies, 627.991 patients, RR 2.39 [95% CI 2.02-2.83). Risk of 1-year mortality was threefold higher (six studies, 341.769 patients, RR 3.40 [95% CI 2.42-4.77]). Four studies (N=438) reported on postoperative delirium. Meta-analysis showed a significant increased risk (RR 2.13 [95% CI 1.23-3.67). Finally, frail patients had a higher risk of institutionalization (10 studies, RR 2.30 [95% CI 1.81- 2.92]).

Conclusion
Frailty is strongly associated with risk of postoperative complications, delirium, institutionalization and mortality. Preoperative assessment of frailty can be used as a tool for patients and doctors to decide who benefits from surgery and who doesn't.

INTRODUCTION

Life expectancy has increased with the focus on the quality of added life-years[1]. This prolonged life expectancy has created an increased demand for surgical care of the elderly[2,3].

Several studies have described age as an independent risk factor for postoperative morbidity and mortality in both cardiac and non-cardiac surgery[4-7]. Advantages in operative techniques and perioperative management seem to improve outcome and multiple studies have even demonstrated an improved quality of life and enhancement of functional status after cardiac surgery in octogenarians[8-10]. Despite these improvements in perioperative care, postoperative adverse effects still remain more common in older patients when compared to the younger ones[5,11].

Adequate risk assessment integrates surgical factors and factors that describe the biological status of the patient, rather than age alone, as age per se seems to be responsible for only a small increase in adverse events[3,12].

Recently the concept of frailty has come into view[2]. Frailty can be defined as a clinically recognizable state of increased vulnerability resulting from aging-associated lack of physiological reserve and decline in function across multiple physiologic systems[13]. Focus on and optimization of frail patients can contribute to a reduced postoperative morbidity and thereby to better outcome in the older surgical population[2]. Globally, the World Health Organisation has recently developed recommendations on integrated care for older patients in order to maintain their physical and cognitive functions[14].

In order to adequately inform our patients of significant perioperative risks, additional information on frailty as a risk factor influencing postoperative outcome is essential. During the preoperative assessment, this information can guide the clinician in shared decision making on whether the older patient benefits from surgery or not. The aim of this study was to evaluate the predictive role of frailty on postoperative outcomes after non-cardiac surgery by conducting a systematic review and meta-analysis of literature.

METHODS

Search Strategy

A search of literature was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement and MOOSE criteria[15]. The objective was to find all studies on frail patients undergoing non-cardiac surgery, correlating their age and its subsequent risk factors to postoperative morbidity and mortality. The systematic Internet based search was performed using EMBASE, MEDLINE, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL) and PubMed. Full electronic searches can be found in **appendix A**. In addition, we screened the reference section of all articles included in this review. The search was limited to original articles, human subjects and articles published from January 1990 – December 2017.

Publication selection

Two reviewers independently (EKMT and JMKvF) screened potentially relevant articles from the initial search, first by title and abstract and later on by full text. Any disagreements between the two reviewers were resolved by discussion and consensus with a third reviewer (SH). Studies were found eligible for inclusion if their subjects underwent non-cardiac surgery and if frailty was measured by a frailty instrument using at least physical, cognitive and functional domains. Also, the relationship between frailty and primary outcomes of 30-day mortality, or 30-day complications should be evaluated, with stratification of the outcome (frail versus non-frail). Studies were excluded if they were review articles, case reports, editorials or comments, or if full text was not available. Duplicate articles were removed during the initial search.

Data Extraction

The following data were gathered from eligible publications: publication date, study design, sample size, type of surgery, proportion of females, mean age, the frailty score and outcome. Outcome was measured by the following adverse events: 30-day mortality, 30-day complications, one-year mortality, manifestation of postoperative delirium (POD) and discharge to a specialized facility. 30-day complications are generally defined as suggested by the Clavien-Dindo classification system[16]; otherwise the authors should have predefined this outcome. Postoperative delirium was defined as a temporary state of confusion and diagnosis made with validated delirium screening tools or by a geriatric expert team[17]. Discharge destination was defined as "home", or "not able to return home". Furthermore, surgical procedures were categorised according to the ESC/ESA Guidelines[18] and divided into low-, intermediate- and high-risk procedures. Occasionally, the surgical risk category was documented as "mixed surgical population". A subanalysis per surgery type was performed to better understand the effect of frailty according to the surgical risk category. Where absolute data were not presented in table or text and authors could not be reached, when possible, data were extracted from figures using WebPlotDigitizer (version, 2.6.8).

Assessment of quality and possible biases

Two reviewers performed assessment of quality. In case of disagreement a third reviewer was consulted. The quality assessment tool for prognosis studies as proposed by Hayden et al. was used for the appraisal of all included studies[19]. This tool focuses on six areas of potential bias; first *study participation* (i.e. the study sample represents the population of interest on key characteristics), second *study attrition* (i.e. whether the study was able to obtain a complete follow up), third *prognostic factor measurement* (i.e. a clear definition or description of the prognostic factor measured is provided), fourth *outcome measurement* (i.e. a clear definition of the outcome of interest), fifth *confounding measurement and account* (i.e. important potential confounders are appropriately accounted for) and sixth *analysis* (i.e. the statistical analysis is appropriate for the design of the study). After the evaluation of these six areas of potential bias, all studies were subsequently divided according to the Quality in Prognosis Studies tool into good (11 or 12 points), fair (9 or 10 points) and poor (< 9 points) quality.

Statistical methods

Numerical values reported by the studies were used for analysis. In some cases further calculation was required for ascertaining outcomes. In the studies using the modified frailty index (mFI) patients were categorized into two groups: "not frail" (mFI < 0.27), or "frail" (mFI ≥ 0.27). The decision to divide patients into those categories was based on thresholds most commonly used to indicate the presence of frailty and was made before analysis. In the remaining studies, using ten different frailty instruments, outcome was also dichotomized according to predefined criteria as "not frail" or "frail". Random effects models for meta-analysis were used because of the large expected heterogeneity in determinant and other study characteristics. The primary outcome measures 30-day mortality and 30-day complications were stratified by frailty score. Furthermore, a subanalysis per surgery type was performed to better understand the effect of frailty according to the surgical risk category. Effect estimates are presented as pooled risk ratios (RR) with 95% confidence intervals (CI's). Robust meta-analytic conclusions of prognosis studies will be more appropriately signaled when prediction intervals are provided[20]. Thus, to further account for between-study heterogeneity, 95% prediction interval (PI) were also estimated, which evaluates the uncertainty of the effect that would be expected in a new study addressing the same association[21]. I^2 statistic was calculated, which is the percentage of variation across studies due to heterogeneity rather than random error. Since all reported outcomes were adverse events, a positive relative risk indicates that frailty is associated with worse patient outcome. A meta-regression analysis was carried out to assess the influence of the patient's mean age (using mean or median age of the study populations as a proxy) on 30-day mortality. Finally, an additional sensitivity analysis was performed (excluding studies using ACS-NSQIP database) to circumvent the issue of possible duplicate cases and demonstrate the effect of frailty on postoperative outcome.

Data gathering and data analysis was performed using Excel (version 14.7.2) and Rstudio (version 1.1.463) respectively.

RESULTS

Initial literature search identified 2117 manuscripts as potentially relevant. Of these, 1904 were excluded due to unrelated research questions or study type. Full text was not available in one study; therefore 212 full text articles were thoroughly screened for eligibility. A total of 56 studies were found suitable for this systematic review. **Figure 1** shows the search strategy flow chart.

Frailty assessment tools

A total of eleven different frailty assessment tools were used. The majority of studies (twenty-four) used the Modified Frailty Index (mFI), created by Saxton and Velanovich[22]. The mFI consists of eleven variables present in the Canadian Study on Health and Aging Frailty Index, as well as in the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) dataset[23,24]. Variations on the Fried Frailty Criteria[25] were used in eleven studies, where frailty was defined by identifying unintentional weight loss, exhaustion, low energy expenditure, low grip strength and slow walking speed. Frailty assessment tools were often based on comprehensive geriatric assessments, which can be derived from questionnaires or patient files, including the Frailty Index and the Groningen Frailty Indicator. **Appendix B** provides a detailed description of all frailty assessment tools used in this review.

Quality assessment

The quality assessment of the included studies is provided in **appendix C** and **table 1** provides a summary of our appraisal. Study participation was adequately described in 37 studies. The study attrition - referring to the response rate and attempts to collect information on patients who were lost to follow up - was adequately defined in 40 studies. Prognostic factors were clearly defined or described in most studies (86%). Ninety-one percent of studies provided a clear definition of the outcome of interest. When summarizing, 95% of all studies included were of at least fair quality, with more than half assessed as good quality.

Figure 1. PRISMA flowchart for study selection

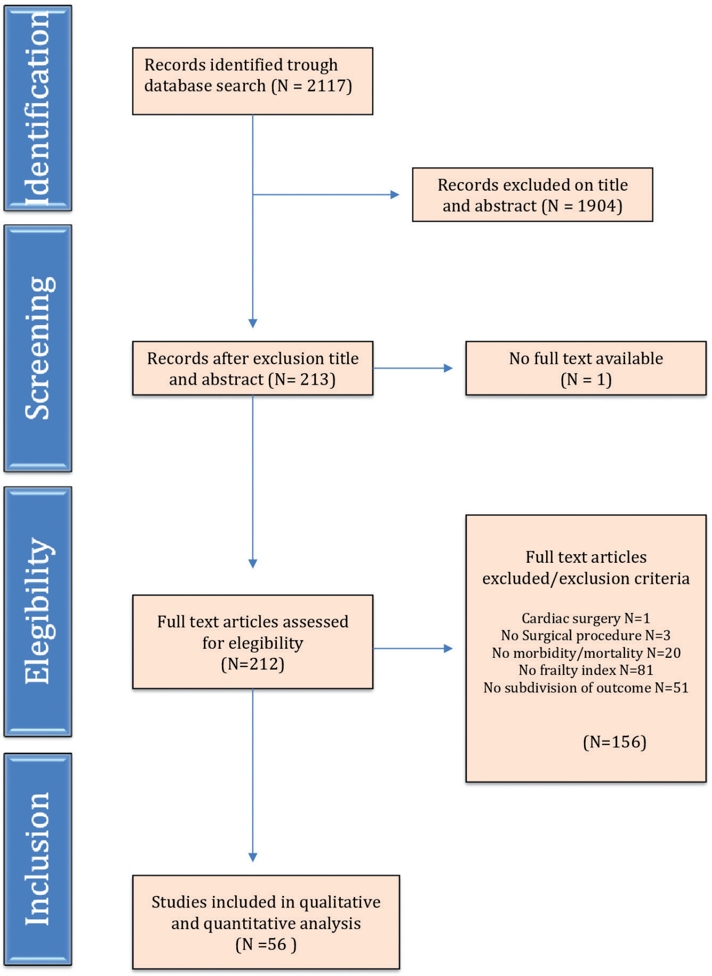


Table 1. Study demographics and method of determining frailty

Author	Year	N	Setting	Period	Study design	Type of surgery	Frailty score	Definition of complication	Quality of study
Abt	2016	1193	Multicenter cohort study (NSQIP)	2006-2013	Prospective	Head and neck cancer surgery	Modified frailty index	CD 4	Good
Adams	2013	6727	Multicenter cohort study (NSQIP)	2005-2010	Prospective	Head and neck cancer surgery	Modified frailty index	CD 4 or 5	Good
Arya	2015	23027	Multicenter cohort study (NSQIP)	2005-2012	Prospective	Vascular surgery (Open or EVAR)	Modified frailty index	CD 4	Good
Augustin	2016	13020	Multicenter cohort study (NSQIP)	2005-2010	Prospective	Pancreatic resections	Modified frailty index	CD 4	Good
Brahmbhatt	2016	24645	Multicenter cohort study (NSQIP)	2005-2012	Prospective	Infrainguinal vascular surgery	Modified frailty index	CD 4	Good
Bras	2015	90	Single-center cohort study	2008-2013	Retrospective	Surgery for head and neck cancer	Groningen frailty indicator	CD ≥ 2	Fair
Chappidi	2016	2679	Multicenter cohort study (NSQIP)	2011-2013	Prospective	Radical cystectomy	Modified frailty index	CD 4 or 5	Good
Chimukangara	2016	885	Multicenter cohort study (NSQIP)	2011-2013	Prospective	Paraesofageal hernia repair	Modified frailty index	CD ≥ 3	Fair
Cloney	2016	243	Multicenter cohort study (NSQIP)	2000-2012	Prospective	Glioblastoma surgery	Modified frailty index	Complications (Glioma Outcomes Project System)	Fair
Cooper	2016	415	Multicenter cohort study	2010-2013	Prospective	General and orthopedic surgery	Frailty phenotype; frailty index	Major complications	Fair
Courtney-Brooks	2012	37	Single-center cohort study	2011	Prospective	Surgery for gynecologic cancer	Fried frailty criteria	Surgical complications (NSQIP)	Fair
Dale	2014	76	Single-center cohort study	2007-2011	Prospective	Pancreaticoduodenectomy	4 (of 5) components of Fried frailty criteria; VES-13	CD ≥ 3	Fair
Dasgupta	2009	125	Single-center cohort study	2002-2003	Prospective	Elective noncardiac surgery (82%) orthopedic)	Edmonton frail scale	Cardiac - / pulmonary comlications, POD	Fair
Farhat	2012	35334	Multicenter cohort study (NSQIP)	2005-2009	Prospective	Emergency general surgery	Modified frailty index	Any complication (not mortality)	Fair

Table 1. (Continued)

Author	Year	N	Setting	Period	Study design	Type of surgery	Frailty score	Definition of complication	Quality of study
Flexman	2016	52671	Multicenter cohort study (NSQIP)	2006-2012	Prospective	Spine surgery	Modified frailty index	Major complications	Good
Hewitt	2015	102	Multicenter cohort study	2013	Prospective	Emergency general surgery	Rockwood clinical frailty scale	Not reported	Fair
Huisman	2015	328	Multicenter cohort study	2008-2012	Prospective	Surgery for solid tumors	Groningen frailty indicator; VES-13	CD ≥ 3	Good
Joseph	2016	220	Single-center cohort study	2012-2014	Prospective	Emergency general surgery	Rockwood clinical frailty scale	Surgical complications (NSQIP)	Fair
Kenig	2015	184	Single-center cohort study	2013-2014	Prospective	Emergency abdominal surgery	VES-13, GFI; Rockwood; Balducci; TRST; Geriatric-8	Any complication (CD)	Fair
Kim	2016	197	Single-center cohort study	2012-2014	Prospective	Elective noncardiac surgery	Fried frailty criteria	Surgical complications (NSQIP)	Good
Kim	2014	275	Single-center cohort study	2011-2012	Prospective	Elective intermediate-risk or high-risk surgery	Multidimensional frailty score	Surgical complications (NSQIP)	Good
Krishnan	2014	178	Single-center cohort study	2011	Prospective	Low trauma hip fracture surgery	Frailty index	Not reported	Poor
Kristjansson	2010	178	Multicenter cohort study	2008-2011	Prospective	Elective surgery for colorectal cancer	Comprehensive geriatric assessment	CD ≥ 2	Good
Kua	2016	82	Single-center cohort study	2013	Prospective	Hip fracture surgery	Edmonton frail scale; (modified) Fried frailty criteria	Any complication	Fair
Lascano	2015	41681	Multicenter cohort study (NSQIP)	2005-2013	Prospective	Surgery for urologic cancer	Modified frailty index	CD 4	Good
Lasithiotakis	2013	57	Single-center cohort study	2008-2011	Prospective	Elective laparoscopic cholecystectomy	Comprehensive geriatric assessment	Any complication	Poor
Leung	2011	63	Single-center cohort study	2007	Prospective	Noncardiac surgery	Fried frailty criteria	Not reported	Fair
Levy	2017	23104	Multicenter cohort study (NSQIP)	2008 to 2014	Prospective	Robot-assisted radical prostatectomy	Modified frailty index	CD 4	Good
Li	2016	189	Single-center cohort study	Not reported	Prospective	Major intra-abdominal surgery	Fried frailty criteria	CD	Fair

Table 1. (Continued)

Author	Year	N	Setting	Period	Study design	Type of surgery	Frailty score	Definition of complication	Quality of study
Louwers	2016	10300	Multicenter cohort study (NSQIP)	2005-2011	Prospective	Hepatectomy	Modified frailty index	CD 4	Good
Makary	2010	594	Single-center cohort study	2005-2006	Prospective	Elective surgery	Fried frailty criteria	Surgical complications (NSQIP)	Good
McAdams-DeMarco	2015	537	Single-center cohort study	2008-2013	Prospective	Kidney transplant surgery	Fried frailty criteria	Not reported	Fair
McIsaac	2016	202811	Single-center cohort study	2002-2012	Retrospective	Major elective noncardiac surgery	ACG frailty-defining diagnoses indicator	Not reported	Good
McIsaac	2016	125163	Single-center cohort study	2003-2012	Retrospective	Total joint arthroplasty	ACG frailty-defining diagnoses indicator	ICU-admission	Good
Melin	2015	44832	Multicenter cohort study (NSQIP)	2005-2011	Prospective	Carotid endarterectomy	Frailty-based bedside Risk Analysis Index	Not reported	Fair
Mogal	2017	9986	Multicenter cohort study (NSQIP)	2005–2012	Prospective	Pancreaticoduodenectomy	Modified frailty index	CD 3 or 4	Good
Mosquera	2016	232352	Multicenter cohort study (NSQIP)	2005-2012	Prospective	elective high-risk surgery	Modified frailty index	Major and minor complications	Fair
Neuman	2013	12979	Single-center cohort study	1992–2005	Retrospective	Elective colorectal cancer surgery	ACG frailty-defining diagnoses indicator	Readmission within 30 days	Fair
Obeid	2012	58448	Multicenter cohort study (NSQIP)	2005–2009	Prospective	Laparoscopic and open colectomy	Modified frailty index	CD 4 or 5	Fair
Partridge	2015	125	Single-center cohort study	2011	Prospective	Arterial vascular surgery	Edmonton frail scale	Composite postoperative complications	Fair
Pearl	2017	4330	Multicenter cohort study (NSQIP)	2011-2014	Prospective	Radical cystectomy	Modified frailty index	Major in-hospital complications	Good
Phan	2017	3920	Multicenter cohort study (NSQIP)	2010-2014	Prospective	Elective anterior lumbar interbody fusion (ALIF) surgery	Modified frailty index	Any complication	Good
Reisinger	2015	159	Single-center cohort study	2010-2012	Prospective	Colorectal surgery	Groningen frailty indicator	Sepsis	Good

Table 1. (Continued)

Author	Year	N	Setting	Period	Study design	Type of surgery	Frailty score	Definition of complication	Quality of study
Revenig	2015	351	Single-center cohort study	Not reported	Prospective	Major intra-abdominal surgery	Fried frailty criteria	CD 1-4	Fair
Revenig	2014	80	Single-center cohort study	Not reported	Prospective	Intra-abdominal minimally invasive surgery	Fried frailty criteria	CD 1-4	Fair
Revenig	2013	189	Single-center cohort study	Not reported	Prospective	Major intra-abdominal surgery	Fried frailty criteria	Any complication	Good
Robinson	2013	72	Single-center cohort study	2007-2010	Prospective	Colorectal surgery	Rockwood clinical frailty scale	Any postoperative complication (VASQIP)	Fair
Shin	2017	6148 ACDF; 817 PCF	Multicenter cohort study (NSQIP)	2005-2012	Prospective	Cervical spine fusion; anterior cervical discectomy and fusion or posterior cervical fusion	Modified frailty index	CD 4	Good
Shin	2016	14583 THA; 25223 TKA	Multicenter cohort study (NSQIP)	2005-2012	Prospective	Total hip and knee arthroplasty	Modified frailty index	CD 4	Good
Suskind	2016	95108	Multicenter cohort study (NSQIP)	2007-2013	Prospective	Common urological surgery	Modified frailty index	Major and minor complications	Good
Suskind	2016	20794	Multicenter cohort study (NSQIP)	2011-2013	Prospective	Inpatient urological surgery	Modified frailty index	Not reported	Good
Tan	2012	83	Multicenter cohort study	2008-2010	Prospective	Colorectal surgery	Fried frailty criteria	CD ≥ 2	Fair
Tegels	2014	127	Single-center cohort study	2005-2012	Retrospective	Surgery for gastric cancer	Groningen frailty indicator	CD ≥ 3	Fair
Tsiouris	2013	1940	Multicenter cohort study (NSQIP)	2005-2010	Prospective	Open lobectomy	Modified frailty index	CD 4	Good
Ugolini	2015	46	Single-center cohort study	2009-2012	Prospective	Elective colorectal cancer surgery	Groningen frailty indicator; VES-13	Not reported	Poor
Uppal	2015	6551	Multicenter cohort study (NSQIP)	2008-2011	Prospective	Surgery for gynecologic cancer	Modified frailty index	CD 4 and 5	Good

Abbreviations: CD = Cavien-Dindo classification of surgical complications; NSQIP = National Surgical Quality Improvement Program

Postoperative outcome predicted by frailty

Table 1 shows the details of study demographics and methods of frailty measurement. In the selected studies, fifty-one were of prospective design and sample size ranged from 37 – 232 352 patients. Gender distribution was reported in 93% of the studies with a proportion of females ranging from 0% in the study of Levy et al, describing a male population undergoing robot assisted radical prostatectomies, until 100% in the study of Courtney-Brooks et al, describing complications in elderly women undergoing gynecologic oncology surgery. Twenty-seven studies investigated the effect of frailty in oncological surgery (predominantly abdominal cancer surgery), four studies in vascular surgery, nine in orthopedic surgery, eleven in elective general surgery (predominantly intermediate - and high-risk surgery), four in emergency surgery and one study in transplant surgery.

Thirty-one studies investigated the influence of frailty on 30-day mortality. **Figure 2** shows a forest plot of this primary outcome with a pooled RR of 3.71 [95% CI 2.89-4.77] (PI 1.38-9.97; I2=95%) for frail patients compared to those who were not frail. The 95% prediction interval also showed exclusion of the null value.

Stratified for frailty assessment tool, the association of frailty and 30-day mortality was observed according to the ACG frailty-defining diagnosis indicator, Fried frailty criteria, Frailty-based Risk Analysis Index and the Modified Frailty Index.

Figure 3 shows the relationship between frailty and the occurrence of postoperative complications, stratified for frailty assessment tool. This adverse outcome was evaluated in 37 papers. **Table 1** shows the predefined 30-day complications reported by the authors, in most cases defined as suggested by the Clavien-Dindo classification system. Overall, a positive relationship between frailty and 30-day complications with a pooled RR of 2.39 [95% CI 2.02-3.07] was observed (PI 0.96-5.69; I2=98%), regardless of the frailty score used.

Stratified per surgical risk category, pooled RR's for 30-day mortality were 2.75 [95% CI 2.48-3.05] for high-risk surgery (4 studies), RR 4.79 [95% CI 3.42-6.70] for intermediate-risk surgery (18 studies) and RR 3.06 [95% CI 2.35-3.97] for mixed surgical population (8 studies). The association of frailty and the primary outcome 30-day complications was also stratified per surgical risk category and again a positive relationship was observed with pooled RR's of 1.62 [95% CI 1.43 -1.82] for high-risk surgery (3 studies) and RR 2.94 [95% CI 2.44-3.54] for intermediate-risk surgery (24 studies).

Figure 2. Forest plot 30-day mortality per frailty score

Study	Frail Events	Frail Total	Non-frail Events	Non-frail Total	RR	95%-CI	Weight
ACG frailty-defining diagnoses indicator							
McIsaac 2016	39	3023	548	122140	2.88	[2.08; 3.97]	6.7%
Random effects model		3023		122140	2.88	[2.08; 3.97]	6.7%
Heterogeneity: not applicable							
Rockwood clinical frailty scale							
Hewitt 2015	0	27	1	75	0.92	[0.04; 21.80]	0.6%
Joseph 2016	7	82	0	138	25.18	[1.46; 435.21]	0.7%
Random effects model		109		213	5.06	[0.11; 241.44]	1.3%
Heterogeneity: $I^2 = 70\%$, $\tau^2 = 5.42$, $p = 0.07$							
Edmonton frail scale							
Dasgupta 2009	1	16	0	109	19.91	[0.85; 468.56]	0.6%
Random effects model		16		109	19.91	[0.85; 468.56]	0.6%
Heterogeneity: not applicable							
Frailty index							
Krishnan 2014	13	122	0	56	12.45	[0.75; 205.82]	0.7%
Random effects model		122		56	12.45	[0.75; 205.82]	0.7%
Heterogeneity: not applicable							
Fried frailty criteria							
Li 2016	3	50	0	139	19.34	[1.02; 367.84]	0.7%
Revenig 2015	5	96	1	255	13.28	[1.57; 112.23]	1.2%
Tan 2012	0	23	0	60	2.57	[0.05; 126.03]	0.4%
Random effects model		169		454	11.29	[2.33; 54.79]	2.2%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.51$							
Frailty-based bedside Risk Analysis Index							
Melin 2015	144	5187	317	39645	3.47	[2.86; 4.22]	7.2%
Random effects model		5187		39645	3.47	[2.86; 4.22]	7.2%
Heterogeneity: not applicable							
Groningen frailty Indicator							
Bras 2015	0	36	0	54	1.49	[0.03; 73.58]	0.4%
Reisinger 2015	3	39	8	114	1.10	[0.31; 3.93]	2.5%
Tegels 2014	7	30	5	97	4.53	[1.55; 13.22]	3.1%
Random effects model		105		265	2.31	[0.80; 6.68]	6.1%
Heterogeneity: $I^2 = 30\%$, $\tau^2 = 0.27$, $p = 0.24$							
VES-13							
Ugolini 2015	1	24	0	22	2.76	[0.12; 64.23]	0.6%
Random effects model		24		22	2.76	[0.12; 64.23]	0.6%
Heterogeneity: not applicable							
Modified frailty index							
Abt 2016	2	66	12	1128	2.85	[0.65; 12.47]	2.1%
Adams 2013	17	354	33	6307	9.18	[5.16; 16.31]	5.4%
Augustin 2016	65	1040	253	11976	2.96	[2.27; 3.86]	6.9%
Brahmbhatt 2016	433	14738	98	9886	2.96	[2.38; 3.68]	7.1%
Chimukangara 2016	1	43	7	842	2.80	[0.35; 22.23]	1.2%
Cloney 2016	10	47	4	196	10.43	[3.42; 31.79]	3.0%
Farhat 2012	2040	10318	2068	25158	2.41	[2.27; 2.55]	7.5%
Levy 2017	0	212	19	22892	2.76	[0.17; 45.60]	0.7%
Louwers 2016	34	600	238	9050	2.15	[1.52; 3.06]	6.5%
Mogal 2017	40	637	249	9349	2.36	[1.71; 3.26]	6.6%
Mosquera 2016	1324	34853	2634	197399	2.85	[2.67; 3.04]	7.4%
Obeid 2012	1190	6801	1345	50947	6.63	[6.16; 7.14]	7.4%
Phan 2017	1	49	6	3871	13.17	[1.62; 107.32]	1.2%
Shin 2016	10	714	33	13883	5.89	[2.92; 11.91]	4.7%
Shin (2) 2016	8	1488	31	23735	4.12	[1.90; 8.94]	4.3%
Shin 2017	2	65	13	1128	2.67	[0.62; 11.58]	2.1%
Random effects model		72025		387747	3.71	[2.75; 5.00]	74.1%
Heterogeneity: $I^2 = 97\%$, $\tau^2 = 0.24$, $p < 0.01$							
Multidimensional frailty score							
Kim 2014	3	98	0	177	12.61	[0.66; 241.72]	0.7%
Random effects model		98		177	12.61	[0.66; 241.72]	0.7%
Heterogeneity: not applicable							
Random effects model		**80878**		**550828**	**3.71**	**[2.89; 4.77]**	**100.0%**
Prediction interval						**[1.38; 9.97]**	
Heterogeneity: $I^2 = 95\%$, $\tau^2 = 0.22$, $p < 0.01$							
Residual heterogeneity: $I^2 = 96\%$, $p < 0.01$							

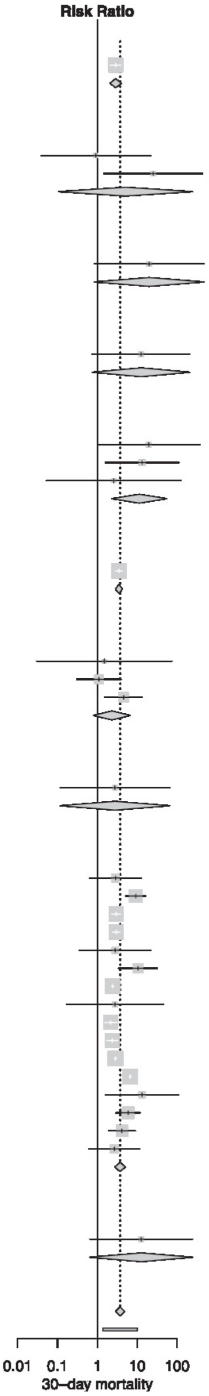
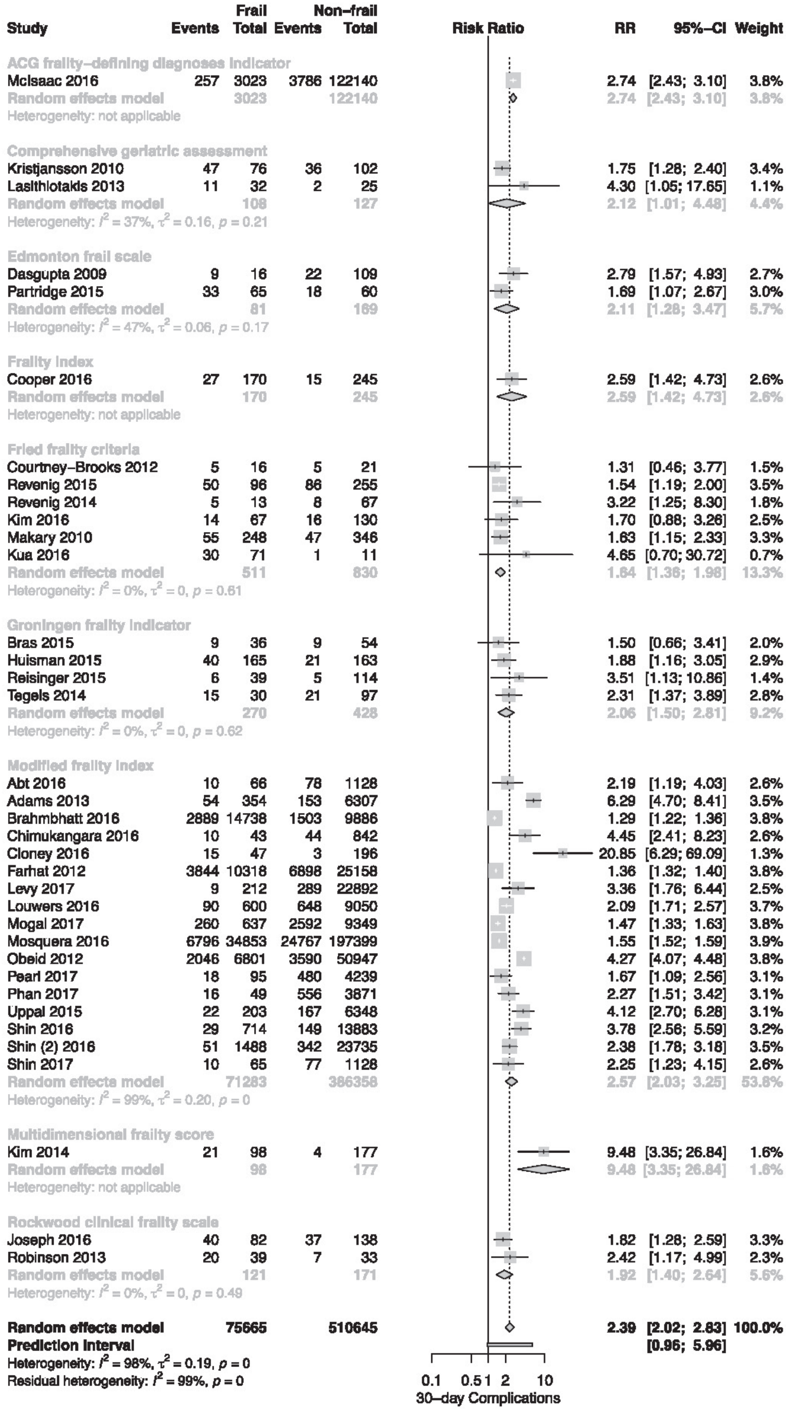


Figure 3. Forest plot postoperative complications per frailty score



Six studies investigated the association between frailty and one-year mortality (**figure 4**). In most of these studies, frailty increases the risk of one-year mortality with a pooled consequent risk ratio of 3.40 [95% CI 2.42-4.77], (PI 1.19- 9.68; I2=96%).

Figure 5 shows a forest plot**,** which summarizes the relationship between frailty and postoperative delirium. Four studies (438 patients) describe a positive relationship between frailty and POD with a pooled RR of 2.13 [95% CI 1.23-3.67], (PI 0.64- 7.05; I2=0%).

Figure 6 shows that frail patients seem to struggle to return to their own home, as these patients, described in ten studies (149 752 patients), have a twofold higher risk of being discharged to a specialized facility after surgery (RR 2.30 [95% CI 1.81-2.92]), (PI 1.06- 4.96; I2=92%). Just like in 30-day mortality and one-year mortality, the 95% prediction interval for postoperative discharge location showed exclusion of the null value.

A meta-regression analysis showed no influence of age on primary outcome. Finally, to circumvent the issue of possible duplicate cases, the additional sensitivity analysis excluding studies using ACS-NSQIP database, showed an overall pooled RR of 3.62 [CI 95% 2.21-5.92] (PI 1.46-8.98; I2=14%) for 30-day mortality.

Figure 4. Forest plot 1-year mortality

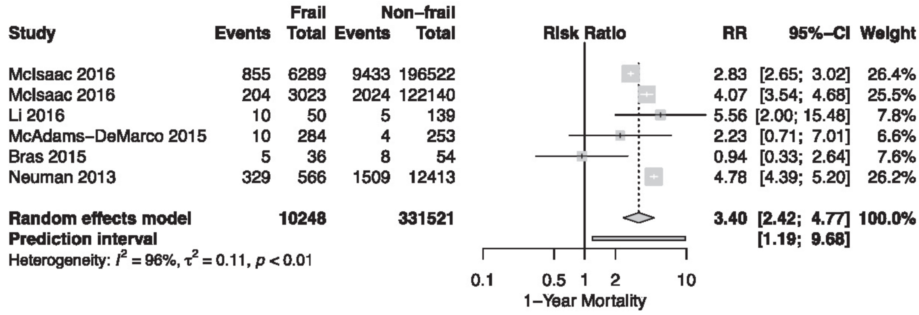


Figure 5. Forest plot postoperative delirium

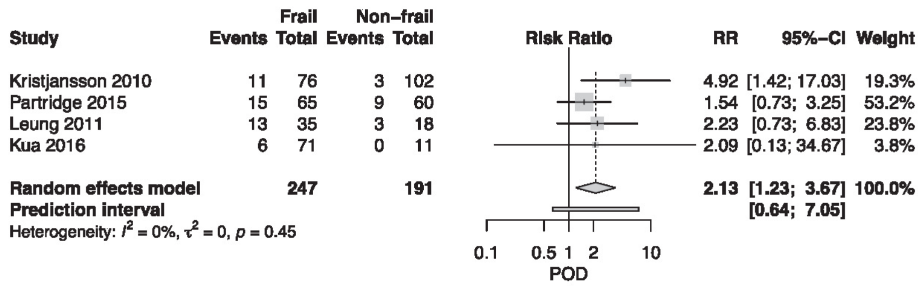
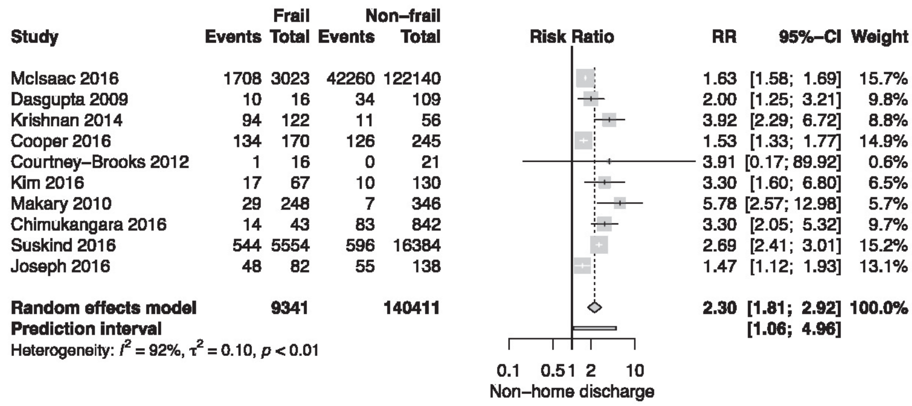


Figure 6. Forest plot discharge to specialized facility



5

DISCUSSION

Since life expectancy keeps rising, the amount of frail patients being offered for surgical treatment will dramatically increase. Frail patients are vulnerable and may excessively decompensate after stressors such as surgery, because of their lack of physiological reserve[13].

In this systematic review and meta-analysis we found frailty to be a strong predictor of post surgical complications, delirium, institutionalization and all-cause mortality. After reviewing fifty-six articles, 30-day mortality shows the strongest association with preoperative frailty with almost 4 times increased risk.

Our results are congruent with several other reviews investigating the effect of frailty on postoperative outcome.[26-30] However, most of the previous studies focused on specific age groups, specific types of surgery, or specific frailty assessment tool. Therefore, extrapolations to a heterogeneous group of elderly and multimorbid patients should be limited.

The strength of the present study is the extensiveness of the search, the inclusion of different validated frailty scores and the inclusion of different types of non-cardiac surgery, both elective and acute. The quality of this meta-analysis is dependent on the quality of the studies reviewed. Of all studies included 95% were of at least fair quality, with more than half assessed as good quality. Ninety-one percent of all studies were prospectively designed.

Recently, relevant developments have been made towards methodological frameworks, in order to improve the reliability and applicability of prediction studies[31]. Although the authors found improved reporting standards in the last decade, poor reporting and poor methods are still a topic of concern and likely to limit the reliability in this type of clinical research.

The studies in this review and meta-analysis describe eleven different frailty assessment tools. Moreover, the surgical procedures included could basically be divided into six different groups, which will have contributed to the heterogeneity. Heterogeneity, as assessed with I2, t2, Cochran's Q and prediction intervals, was estimated as a high degree of statistical heterogeneity. Importantly, the association between frailty and outcome seems robust throughout the reviewed articles regardless of the frailty assessment tool used. Furthermore, prediction intervals of 30-day mortality, one-year mortality and postoperative discharge location showed exclusion of the null value, which strengthens our findings. A plausible explanation may be the fact that frailty was consistently measured by instruments using physical, cognitive and functional domains. Studies using only measurements of body composition or patients' phenotype, such as sarcopenia, hypoalbuminemia or cachexia were not included, as these studies did not use an established frailty assessment tool. The frailty instrument used in most studies was the modified frailty index (mFI), which has been validated as a reliable assessment tool in several studies[32-36]. It should be recommended that future studies focus on using a standardized, robust and validated frailty assessment tool, which is time-efficient and suitable for the medical staff to be conducted at patient's bedside.

Limitations of this study are those commonly seen with systematic reviews and meta-analysis. Hence, the results of this review and meta-analysis should be interpreted with caution. Besides the heterogeneity, another possible limitation is a variation among studies in the definition of discharge location. Despite these small differences, ten studies confirm that frail patients, when compared to healthier counterparts, struggle to return to their own home. Unfortunately, in many countries, availability of beds and nursing staff in specialized facilities are a topic of current concern. To overcome this limitation the need for rehabilitation or nursing home placement was defined as "not able to return home". Comparable heterogeneity was found within the definition of postoperative complications. Although most authors defined 30-day complications as suggested by the Clavien-Dindo classification system, others used the American College of Surgery National Surgical Quality Improvement Program definition, or other standardized complication definitions. It should be recommended that future studies in the area of frailty use a standardized postoperative complication definition as this might create a more accurate comparison. The International Consortium for Health Outcomes Measurement (ICHOM) recently developed the first global standard set of outcome measures in older persons. Their effort towards standardization of outcome measures can possibly improve care pathways and quality of care[37].

Although we have performed an exhaustive literature search, the broad scope of our research question could have resulted in the omission of some studies.

Many studies in this systematic review and meta-analysis are observational registry studies, but several studies have derived their outcomes from clinical trials. Since many studies have used the ACS NSQIP database, there may be studies, which are double counted from the same cohort of patients. However, **table 1** shows that most of these studies observed different subgroups of patients, as well as different timeframes and kinds of surgical specialisms. Additionally, the sensitivity analysis we have performed, excluding studies using ACS-NSQIP database, demonstrated a positive relationship between frailty and primary outcomes. Finally, subgroup analyses gave insight in the heterogeneity among the types of surgery and different frailty assessment tools, but this stratification has the drawback of small groups.

In a previous study we have found that the occurrence of postoperative complications is an important prognostic factor of late mortality[38]. Efforts to improve postoperative outcome have predominantly focused on enhanced recovery protocols and the improvement of surgical and anesthetic techniques[39,40]. The concept of prehabilitation is a modern and proactive approach, based on the principle that structured exercise over a period of weeks leads to a better cardiovascular, respiratory and muscular condition. Optimization of patients' functional capacity may provide a physiological buffer and enables the patient to better withstand the stress of surgery[39,41,42].

Preoperative identification of frail patients provides an opportunity for prehabilitation, which subsequently may lead to reduced postoperative morbidity. Besides prehabilitation, regionalization in health care might improve surgical outcome in complex oncological surgery. Regionalization is about enabling appropriate allocation and integration of health resources, focusing on the local populations needs. Frail patients may benefit from high-volume hospitals with high-volume surgeons in so called centers of excellence[43].

This study demonstrates that the presence of preoperative frailty increases the risk of adverse outcome after non-cardiac surgery. It should be noted that heterogeneity of the frailty scores is high, but associations with postoperative outcome are robust. Frailty status should be considered to be part of the preoperative screening, at least in patients who seem to have a lack of physiological reserve. Identification of potentially reversible health deficits is important, as may provide an opportunity to optimize the patient's clinical condition prior to surgery. Conversely, irreversible frailty should be taken most seriously, as it can guide both clinician and patient in their decision making on whether the patient benefits from surgery or not.

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Appendix A. Full literature search

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('frail elderly'/de OR ((frail* NEAR/6 (elderl* OR centenarian* OR nonagenarian* OR octogenarian* OR septagenarian* OR '65 year*' OR aging OR ageing OR aged OR senior* OR geriatric* OR old OR older))):ab,ti OR ((frail*):ab,ti AND (aged/exp OR aging/de OR 'geriatrics'/de OR 'geriatric care'/de OR 'geriatric assessment'/de))) AND ('abdominal surgery'/exp OR 'breast surgery'/exp OR 'cancer surgery'/exp OR 'ear nose throat surgery'/exp OR 'endocrine surgery'/exp OR 'eye surgery'/exp OR 'head and neck surgery'/exp OR 'major surgery'/exp OR 'neurosurgery'/exp OR 'orthopedic surgery'/exp OR 'plastic surgery'/exp OR 'esophagus surgery'/exp OR 'lung surgery'/exp OR 'transplantation'/de OR 'organ transplantation'/de OR 'kidney transplantation'/de OR 'liver transplantation'/de OR 'lung transplantation'/de OR 'urologic surgery'/exp OR 'vascular surgery'/de OR 'aneurysm surgery'/exp OR 'aorta surgery'/de OR 'artery surgery'/de OR 'carotid artery surgery'/exp OR Endarterectomy/exp OR ('artery surgery'/exp NOT 'coronary artery surgery'/exp) OR 'carotid angioplasty'/exp OR 'carotid artery stenting'/exp OR 'blood vessel shunt'/de OR 'leg revascularization'/exp OR 'embolectomy'/exp OR 'endovascular surgery'/exp OR 'limb salvage'/exp OR 'microvascular surgery'/exp OR 'vein surgery'/exp OR ((('non cardiac' OR noncardiac OR abdominal* OR breast* OR cancer* OR ear* OR nose* OR throat* OR endocrine* OR eye* OR head* OR neck* OR orthopedic* OR plastic* OR urologic* OR esophag* OR oesophag* OR lung* OR pulmonar* OR gastrointestin* OR intestin* OR gastric OR vascul* OR joint* OR renal OR kidney OR hepatic OR liver OR pancrea* OR urologic* OR aneurysm* OR aort* OR carotid* OR colorect* OR orthognat* OR breast* OR neoplasm* OR otorhinolar* OR endocrin* OR ophtalmol* OR orthoped* OR plastic* OR urolog*) NEAR/3 (surg* OR operat* OR perioperat*)) OR neurosurg* OR 'general surgery' OR ((organ* OR kidney* OR liver* OR hepatic* OR renal Or pulmonar*) NEAR/3 transplantat*)):ab,ti)

Medline Ovid
("Frail Elderly"/ OR ((frail* ADJ6 (elderl* OR centenarian* OR nonagenarian* OR octogenarian* OR septagenarian* OR "65 year*" OR aging OR ageing OR aged OR senior* OR geriatric* OR old OR older))).ab,ti. OR ((frail*).ab,ti. AND (exp aged/ OR exp aging/ OR "Geriatrics"/ OR "Geriatric Assessment"/))) AND (Surgical Procedures, Operative/ OR Specialties, Surgical/ OR Colorectal Surgery/ OR General Surgery/ OR Orthognathic Surgery/ OR breast/su OR exp neoplasms/su OR exp Otorhinolaryngologic Diseases/su OR Endocrine Surgical Procedures/ OR exp Ophthalmologic Surgical Procedures/ OR exp neurosurgery/ OR exp Neurosurgical Procedures/ OR Orthopedics/su OR Surgery, Plastic/ OR exp Pulmonary Surgical Procedures/ OR transplantation/ OR organ transplantation/ OR kidney transplantation/ OR liver transplantation/ OR lung transplantation/ OR exp Urologic Surgical Procedures/ OR Vascular Surgical Procedures/ OR Endarterectomy/ OR embolectomy/ OR limb salvage/ OR Microvascular Decompression Surgery/ OR Neurosurgical Procedures/ OR (((non cardiac OR noncardiac OR abdominal* OR breast* OR cancer* OR ear* OR nose* OR throat* OR endocrine* OR eye* OR head* OR neck* OR orthopedic* OR plastic* OR thora* OR urologic* OR esophag* OR oesophag* OR lung* OR pulmonar* OR gastrointestin* OR intestin* OR gastric OR vascul* OR joint* OR renal OR kidney OR hepatic OR liver OR pancrea* OR urologic* OR aneurysm* OR aort* OR carotid* OR colorect* OR general* OR orthognat* OR breast* OR neoplasm* OR otorhinolar* OR endocrin* OR ophtalmol* OR orthoped* OR plastic* OR urolog*) ADJ3 (surg* OR operat* OR perioperat*)) OR neurosurg* OR ((organ* OR kidney* OR liver* OR hepatic* OR renal Or pulmonar*) ADJ3 transplantat*)).ab,ti.)

Cochrane
(((frail* NEAR/6 (elderl* OR centenarian* OR nonagenarian* OR octogenarian* OR septagenarian* OR '65 year*' OR aging OR ageing OR aged OR senior* OR geriatric* OR old OR older))):ab,ti) AND (((('non cardiac' OR noncardiac OR abdominal* OR breast* OR cancer* OR ear* OR nose* OR throat* OR endocrine* OR eye* OR head* OR neck* OR orthopedic* OR plastic* OR urologic* OR esophag* OR oesophag* OR lung* OR pulmonar* OR gastrointestin* OR intestin* OR gastric OR vascul* OR joint* OR renal OR kidney OR hepatic OR liver OR pancrea* OR urologic* OR aneurysm* OR aort* OR carotid* OR colorect* OR orthognat* OR breast* OR neoplasm* OR otorhinolar* OR endocrin* OR ophtalmol*

OR orthoped* OR plastic* OR urolog*) NEAR/3 (surg* OR operat* OR perioperat*)) OR neurosurg* OR 'general surgery' OR ((organ* OR kidney* OR liver* OR hepatic* OR renal Or pulmonar*) NEAR/3 transplantat*)):ab,ti)

Web of science
TS=((((frail* NEAR/5 (elderl* OR centenarian* OR nonagenarian* OR octogenarian* OR septagenarian* OR "65 year*" OR aging OR ageing OR aged OR senior* OR geriatric* OR old OR older)))) AND (((("non cardiac" OR noncardiac OR abdominal* OR breast* OR cancer* OR ear* OR nose* OR throat* OR endocrine* OR eye* OR head* OR neck* OR orthopedic* OR plastic* OR urologic* OR esophag* OR oesophag* OR lung* OR pulmonar* OR gastrointestin* OR intestin* OR gastric OR vascul* OR joint* OR renal OR kidney OR hepatic OR liver OR pancrea* OR urologic* OR aneurysm* OR aort* OR carotid* OR colorect* OR orthognat* OR breast* OR neoplasm* OR otorhinolar* OR endocrin* OR ophtalmol* OR orthoped* OR plastic* OR urolog*) NEAR/2 (surg* OR operat* OR perioperat*)) OR neurosurg* OR "general surgery" OR ((organ* OR kidney* OR liver* OR hepatic* OR renal Or pulmonar*) NEAR/2 transplantat*))))

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("Frail Elderly"[mh] OR ((frail*[tiab] AND (elderl*[tiab] OR centenarian*[tiab] OR nonagenarian*[tiab] OR octogenarian*[tiab] OR septagenarian*[tiab] OR 65 year*[tiab] OR aging OR ageing OR aged OR senior*[tiab] OR geriatric*[tiab] OR old OR older))) OR ((frail*[tiab]) AND (aged[mh] OR aging[mh] OR "Geriatrics"[mh] OR "Geriatric Assessment"[mh]))) AND (Surgical Procedures, Operative[mh] OR Specialties, Surgical[mh] OR Colorectal Surgery[mh] OR General Surgery[mh] OR Orthognathic Surgery[mh] OR breast/su[mh] OR neoplasms/su[mh] OR Otorhinolaryngologic Diseases/su[mh] OR Endocrine Surgical Procedures[mh] OR Ophthalmologic Surgical Procedures[mh] OR neurosurgery[mh] OR Neurosurgical Procedures[mh] OR Orthopedics/su[mh] OR Surgery, Plastic[mh] OR Pulmonary Surgical Procedures[mh] OR transplantation[mh] OR organ transplantation[mh] OR kidney transplantation[mh] OR liver transplantation[mh] OR lung transplantation[mh] OR Urologic Surgical Procedures[mh] OR Vascular Surgical Procedures[mh] OR Endarterectomy[mh] OR embolectomy[mh] OR limb salvage[mh] OR Microvascular Decompression Surgery[mh] OR Neurosurgical Procedures[mh] OR (((non cardiac OR noncardiac OR abdominal*[tiab] OR breast*[tiab] OR cancer*[tiab] OR ear[tiab] OR ears[tiab] OR nose*[tiab] OR throat*[tiab] OR endocrine*[tiab] OR eye*[tiab] OR head*[tiab] OR neck*[tiab] OR orthopedic*[tiab] OR plastic*[tiab] OR thoracic[tiab] OR thorax[tiab] OR urologic*[tiab] OR esophag*[tiab] OR oesophag*[tiab] OR lung*[tiab] OR pulmonar*[tiab] OR gastrointestin*[tiab] OR intestin*[tiab] OR gastric OR vascul*[tiab] OR joint*[tiab] OR renal OR kidney OR hepatic OR liver OR pancreatic*[tiab] OR pancreas*[tiab] OR urologic*[tiab] OR aneurysm*[tiab] OR aort*[tiab] OR carotid*[tiab] OR colorect*[tiab] OR general*[tiab] OR orthognat*[tiab] OR breast*[tiab] OR neoplasm*[tiab] OR otorhinolar*[tiab] OR endocrin*[tiab] OR ophtalmol*[tiab] OR orthoped*[tiab] OR plastic*[tiab] OR urolog*[tiab]) AND (surg*[tiab] OR operation[tiab] OR operative[tiab] OR perioperat*[tiab])) OR neurosurg*[tiab] OR ((organ[tiab] OR organs[tiab] OR kidney*[tiab] OR liver*[tiab] OR hepatic*[tiab] OR renal Or pulmonar*[tiab]) AND transplantat*[tiab]))) AND publisher[sb]

Google scholar
200 first results: Frail|frailty elderly|older|seniors "non cardiac surgery"|"noncardiac surgery"
All results: allintitle:Frail|frailty elderly|older|seniors surgery|operative -cardiac

Appendix B. Frailty assessment tools in detail

Instrument	Description	Items	Range	Suggested Cut-off	Studies
Frailty Index (FI) / Canadian Study of Health and aging frailty index (CSHA-FI) / Frailty index of accumulated deficits (FI-CD)[23]	Index of accumulated health deficits in the physical, cognitive, functional and social realms (symptoms, signs, disabilities, laboratory, radiographic) out of a list of 70 deficits	70	0-1	Not frail ≤ 0.25 Frail > 0.25	[44, 45]
Groningen Frailty Index/indicator (GFI) [46]	(Self-reporting) questionnaire in 4 domains: physical, cognitive, social and psychological	15	0-15	Not frail < 4 Frail ≥ 4	[47-52]
Hopkins Frailty Score / Fried Frailty criteria /(Fried's) Frailty phenotype (FP) [25]	Defining phenotype of frailty by identifying criteria: unintentional weight loss, exhaustion, low energy expenditure, low grip strength, and slowed waking speed	5	0-5	Not frail: 0 (-1) Pre-frail: (1-) 2 Frail ≥ 3	[53-63]
Modified Frailty Index (mFI) [22]	Modification of the CSHA-FI, 11 variables: diabetes mellitus, functional status index of ≥ 2, COPD or pneumonia, congestive heart failure, myocardial infarction, percutaneous coronary intervention and/or stenting or angina, hypertension requiring medication, peripheral vascular disease or ischemic rest pain, impaired sensorium, TIA or CVA, and CVA with deficit	11	0-1	Not frail: 0 Intermediate frail: 0.09-0.18 Frail ≥ 0.27	[33, 35, 36, 64-84]
(Reported) Edmonton Frail Scale ((R)EFS) [85]	Questionnaire/test on 9 domains (mood, functional independence, medication use, social support, nutrition, general health status, continence); two performance-based test: Clock test for cognitive impairment and 'Timed Get Up and Go' for functional performance	11	0-17	Not frail: 0-5 Vulnerable: 6-7 Frail, mildly: 8-9 Frail, moderately: 10-11 Frail, severely: 12-17	[53, 86, 87]
Rockwood 7-point Cical Frailty Scale [88]	7- point clinical frailty score derived from the Canadian Study of Health and Ageing (CSHA)	7	0-7	fit 1; Well 2; Well, treated comorbid disease 3; Apparently vulnerable 4; Mildly frail 5; Moderately frail 6; Severely frail 7	[52, 89-91]
VES-13; Vulnerable Elderly Survey [92]	Self-administrated questionnaire concerning perception of health status, example of everyday activity, difficulty performing activities related to health or physical condition	13	0-15	Not frail < 3 Frail ≥ 3	[48, 51, 52, 93]

Appendix B. (Continued)

Instrument	Description	Items	Range	Suggested Cut-off	Studies
John Hopkins' Adjusted Clinical Groups (ACG) case-mix system / ACG frailty diagnoses indicator/Johns Hopkins ACG frailty Indicator [94]	Measure of frailty developed to be used specifically on administrative data Assesses frailty by the presence of 11 conditions (e.g., difficulty walking, weight loss, frequent falls, malnutrition, impaired vision, decubitus ulcer, incontinence and 4 unnamed criteria.)	12	0-12	Not frail 0 Frail ≥ 1	[95-97]
Frailty-based bedside risk analysis index (RAI) [98]	Assessment scoring sex, age, cancer, co-morbidities, residence, cognition, ADL	11	0-75	Not frail < 10 Frail ≥ 10	[99]
Comprehensive geriatric assessment / CGA / Balducci-score [100]	A multidimensional process that identifies medical, psychosocial, and functional limitations of a frail elderly person	4-6	0-4(/6)	Not frail 0 Frail ≥ 1	[52, 101, 102]
Multidimensional Frailty Score [103]	Scoring index based on results of the CGA, patient characteristics and laboratory variables	9	0-15	Not frail ≤ 5 Frail > 5	[103]

Appendix C. Quality assessment of included studies

Study	Study participa-tion	Study attrition	Prognostic factor measurement	Outcome measurement	Confounding measurement and account	Analysis	Overall rating
Abt	+	+	+	+	±	+	11
Adams	+	+	+	+	±	+	11
Arya	+	+	+	+	+	+	12
Augustin	+	+	+	+	+	+	12
Brahmbhatt	+	+	+	+	+	+	12
Bras	±	±	+	+	?	±	8
Chappidi	+	+	+	+	+	+	12
Chimukangara	±	+	+	+	±	±	9
Cloney	+	±	+	+	-	±	8
Cooper	+	+	+	±	-	±	8
Courtney-Brooks	±	+	+	+	-	±	8
Dale	±	+	±	+	±	±	8
Dasgupta	±	±	+	+	+	+	10
Farhat	+	+	±	+	?	+	9
Flexman	+	+	+	+	+	±	11
Hewitt	±	+	+	+	±	±	9
Huisman	+	±	+	+	+	+	11
Joseph	±	±	+	+	±	+	9
Kenig	±	±	+	±	+	+	9
Kim (2016)	+	+	+	±	+	+	11
Kim (2014)	+	±	+	+	+	+	11
Krishnan	±	±	±	±	-	±	6
Kristjansson	+	+	+	+	+	±	11
Kua	±	?	+	+	±	+	8
Lascano	+	+	+	+	+	+	12
Lasithiotakis	±	?	±	+	-	±	5
Leung	-	±	+	±	+	+	8
Levy	+	+	+	+	+	+	12
Li	+	±	±	+	+	±	9
Louwers	+	+	+	+	±	+	11
Makary	+	+	+	+	±	+	11
McAdams-DeMarco	±	+	+	+	+	±	10
McIsaac (JAMA)	+	+	+	+	+	+	12
McIsaac	+	+	+	+	+	+	12
Melin	+	+	+	+	-	-	8
Mogal	+	+	+	+	+	+	12
Mosquera	+	+	±	+	?	+	9
Neuman	+	±	±	+	±	+	9
Obeid	+	+	+	+	±	±	10
Partridge	±	±	+	+	±	+	9
Pearl	+	+	+	+	±	+	11
Phan	+	+	+	+	+	+	12
Reisinger	+	+	+	+	±	+	11
Revenig (2015)	+	+	+	+	±	±	10
Revenig (2014)	±	+	+	+	±	+	10

5

Appendix C. (Continued)

Study	Study participa-tion	Study attrition	Prognostic factor measurement	Outcome measurement	Confounding measurement and account	Analysis	Overall rating
Revenig (2013)	±	+	+	+	+	+	11
Robinson	+	+	±	+	-	±	8
Shin (2017)	+	+	+	+	+	+	12
Shin (2016)	+	+	+	+	+	+	12
Suskind	+	+	+	+	+	+	12
Suskind (Urology)	+	+	+	+	+	+	12
Tan	±	+	+	+	±	+	10
Tegels	±	±	+	+	±	+	9
Tsiouris	+	+	+	+	±	+	11
Ugolini	±	±	+	+	±	-	7
Uppal	+	+	+	+	+	+	12

Study participation: The study correctly defines and describes the study population
Study attrition: The study was able to obtain a complete follow up
Prognostic factor management: The study provides a clear description of the prognostic factor measured
Outcome measurement: The study provides a clear definition of outcome
Confounding measurement and account: Adequately valid and reliable measurement of potential confounders
Analysis: The statistical analysis is appropriate for the design of the study
Description of used symbols:
+ Yes; adequate and complete description
± Partly; incomplete description
? Unsure; doubtful description
- No; not described

Part III

Long-term prognosis after general surgery

Chapter 6

Perioperative complications are associated with adverse long-term prognosis and affect the cause of death after general surgery

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ABSTRACT

Background

It is unclear how mortality and causes of death vary between patients and surgical procedures and how occurrence of postoperative complications is associated with prognosis. This study describes long-term mortality rates and causes of death in a general surgical population. Furthermore, we explore the effect of postoperative complications on mortality.

Methods

A single-centre analysis of postoperative complications, with mortality as primary endpoint, was conducted in 4479 patients undergoing surgery. We applied univariate and multivariable regression models to analyse the effect of risk factors, including surgical risk and postoperative complications, on mortality. Causes of death were also explored.

Results

75 patients (1.7%) died within 30 days after surgery and 730 patients (16.3%) died during a median follow-up of 6.3 years (IQR 5.8-6.8). Significant differences in long-term mortality were observed with worst outcome for patients undergoing high-risk vascular surgery (HR 1.5; 95% CI 1.2-1.9). When looking at causes of death, high-risk surgery was associated with a twofold higher risk of cardiovascular death (HR 1.9; 95% CI 1.2-3.1), whereas the intermediate-risk group had a higher risk of dying from cancer-related causes (HR 1.5; 95% CI 1.1-2.0). Occurrence of complications – particularly of cardiovascular nature – was associated with worse survival (HR 1.9; 95% CI 1.3-2.7).

Conclusion

High-risk vascular surgery and occurrence of postoperative complications are important predictors of late mortality. Further focus on these groups of patients can contribute to reduce morbidity. Improvement in quality of care should be aimed at preventing postoperative complications and thereby a better outcome in a general surgical population.

INTRODUCTION

Each year, more than 230 million major surgical procedures are performed worldwide.[1] Risk of mortality after surgery differs greatly in patients and surgical procedures. Also, evidence increasingly suggests that patients experiencing postoperative complications have a reduced quality of life and life expectancy itself.[2-4] Khuri et al. demonstrated that this adverse effect of complications on late mortality is independent of patients' preoperative risk factors.[2] However, it is unknown if the causes of death are also effected. Recently, a large cohort study described important variations in postoperative mortality rates between European nations.[5] Both findings highlight room for improvement of perioperative care. In order to adequately inform patients of significant surgery risks, information on surgery-related complications and mortality is important.

The objective of our study is to describe long-term mortality rates and cause of death in a general surgical population. Furthermore, in addition to demographic and disease specific factors, we explored the effect of postoperative complications on long-term mortality.

METHODS

Study Sample

This study was performed in the Zuyderland medical centre, a medium-sized regional hospital in the Netherlands. This hospital contains a modern degree of automation and a reliable registration of the electronic medical record. A prospective database is used containing data on all surgical procedures performed[6]. The study complies with the Helsinki statement on research ethics and the local medical ethical committee gave formal review and approval. Data was collected from patients who underwent elective or urgent non-cardiac surgery. We identified 5373 consecutive patients undergoing surgery from March 2005 to December 2006. Patients younger than 14 years old and patients undergoing surgical procedures under local infiltration were excluded. Because one of our primary endpoints was long-term survival, a patient's first operation within the enrolment period was considered the index operation, and survival was determined from that moment onward. However, when a patient needed repeated surgery during the same hospital stay, we included the need for a re-operation as a separate outcome measure. A total of 4479 patients were considered suitable for the final study population.

Baseline Characteristics

Individual data on the patient's medical history were obtained by a surgeon or a surgical resident prior to surgery. Data collected included main diagnosis, history of cardiac, pulmonary or cerebrovascular disease, diabetes mellitus, hypertension, ASA classification[7], any malignancy, as well as intoxications, use of medication and patient's height and bodyweight. Information from the electronic medical record on baseline characteristics could be completed in 96% up to 100%, except for information on smoking habits, which could be obtained in 75% of patients.

Pathological cardiac history was defined as a condition involving coronary artery disease, heart failure, valvular heart disease, arrhythmias or cardiomyopathy. Pulmonary disease was defined as illness of the lungs or respiratory system, such as COPD, asthma, lung cancer, chronic infections or previous embolisms. A previous cerebral thrombosis, embolism or hemorrhage was noted as cerebrovascular disease. Table 1 shows the surgical procedures, classified according to the standardized Dutch classification system[8]. For the purpose of this study we categorized the main surgical procedures into fifteen generally accepted groups, which were then distributed over three risk categories; low, intermediate and high risk procedures[9]. In this general teaching hospital, trauma patients are physiologically stable and patients undergoing highly complex low-volume surgery are being treated in tertiary university hospitals. Information on whether the patient had surgery requiring hospitalization or day-case surgery was also collected. Finally, we documented the type of anesthesia, divided into general and/or regional. Validation of the database using a random sampling audit procedure confirmed a high level of accuracy and completeness of data.

Outcome

All-cause mortality was the primary endpoint of this study. Secondary endpoints were postoperative complications within 30 days after surgery and cause of death. For the evaluation of outcome a surgical resident followed patients during hospitalization and postoperative visits to the outpatient clinic up to 1 year.

We gathered the following data: date of surgery, date of discharge, length of hospital stay, operating time, blood loss and postoperative complications. Complications were defined as any event deviating from a normal postoperative course within 30 days after surgery.

Table 1. Surgical Categories according to the standardized Dutch classification system[8]

Surgical Categories	
Low risk surgery	
	Breast surgery
	Hernia surgery[a]
	Minor surgery of soft tissue
	Minor trauma surgery
	Perianal surgery
	Varicose vein surgery
Intermediate risk surgery	
	Appendectomy
	Carotid artery surgery
	Cholecystectomy
	Head and neck surgery
	Major abdominal surgery[b]
	Major trauma surgery[c]
	Thoracic surgery
High risk surgery	
	Ischemic limb amputation
	Major vascular surgery[d]

[a] Except for incisional hernia repair
[b] I.e. liver, gastric, bowel, spleen, oesophagus and incisional hernia surgery
[c] I.e. multi trauma or trauma involving the femur or the hip
[d] I.e. open aortic repair and peripheral bypass surgery

We separately documented the following postoperative complications: wound infections, pneumonia, cardiovascular and cerebrovascular events, deep vein thrombosis and or pulmonary embolisms, ICU-admission, readmission and need for complication surgery. A surgical resident as well as a member of the surgical staff independently scored complications. For an objective interpretation of outcome we used the earlier proposed Clavien Dindo classification system as guidance.[10] Complications were subsequently divided into 4 categories: no complication, a self-limiting complication (for example a small wound dehiscence not needing specific treatment), a non-self-limiting complication (for example the need for antibiotics in case of pneumonia or wound infection, a re-operation, or a CT-guided drainage of an abscess) and a major complication, which involves complications with residual disability, including organ failure.

Information on long-term mortality and cause of death were obtained by inquiry of the national public register and Dutch Central Bureau of Statistics. Autopsy was not routinely performed, and the expected cause leading to health deterioration prior to death was considered as the underlying cause of death, in parallel to the strategy used for the overall Dutch population. The causes of death were grouped according to the International Classification of Diseases, 10th Revision (ICD-10). For patients who lived abroad, last available follow-up information was used. For better understanding of surgical outcome we compared our study population with a general age and gender matched Dutch population. Information about the general population was extracted from the Electronic Databank of Central Bureau of Statistics Netherlands[11].

Statistical Analysis

Categorical variables are presented as numbers and percentages. Continuous data are presented as mean ± standard deviation (SD) when normally distributed or as median values and corresponding 25th and 75th percentiles when data was skewed. We used chi-square test for comparison of categorical variables and analysis of variance or Kruskal-Wallis test for continuous variables. Univariate and multivariable Cox regression models were used to evaluate association between surgical risk categories and mortality. Low-risk surgery was used as reference category in the regression analyses. To ensure we give a true estimate of mortality risk, we entered all potential confounders (age, gender, type of anaesthesia, ASA classification, diabetes, hypertension, pulmonary -, cardiac - or cerebrovascular disease, BMI, malignancy) in the multivariable regression models.

Kaplan-Meier survival curves were calculated for each type of surgical category. The predictive value of postoperative complications on cause-specific long-term mortality was assessed in 30-day survivors using Cox regression analysis.

Since it seems predictable that patients undergoing high-risk procedures are more at risk of experiencing postoperative complications and death, we performed an additional sensitivity analysis, excluding this high-risk surgery group.

Results are reported as hazard ratios (HR) with a 95% confidence interval. Significance was set at a two-sided P-value < 0.05. Analysis was performed using SPSS software version 20.0.0.

RESULTS

Patient population
4479 patients undergoing general surgery were included in this analysis. There were an equal percentage of men and women in the cohort and mean age was 55.0 ± 17.5 years. Table 2 shows clinical baseline and surgery-related characteristics of the study population. The majority of procedures (85.6%) were performed under general anaesthesia. Most of the procedures (56.4%) could be classified as low-risk surgery according to the surgical risk classification system[9]. Intermediate and high-risk surgery accounted for 38.4% and 5.2%, respectively.

Table 3 shows baseline characteristics according to the main surgical categories. As expected, demographics and proportion of comorbidities varied widely when categorized by different surgical procedures. Patients with trauma of the hip and major vascular patients were of higher age (76.1 ± 17.2 and 69.8 ± 10.7, respectively). In general, patients who underwent vascular surgery had the highest prevalence of comorbid diseases.

Postoperative complications
We evaluated the effect of different surgical categories on postoperative outcome (Table 4). Complications occurred in 949 patients (21.0%). In general, patients who experienced complications were of higher age (62.7 ± 16.8) when compared to all patients and had more comorbidities (Table 2). Amputation of an ischemic limb and major vascular surgery was associated with highest risk of complications (50.0% and 48.5%). As expected, non-self-limiting complications (32.8%), major complications (4.7%) and 30-day mortality (8.6%) were more often seen in the high-risk group.

All-cause mortality
Overall 30-day mortality rate was 1.7% (75 patients), with cardiac and cancer-related death accounting for 26.6% and 19.0%, respectively. Information on long-term mortality and cause of death was available in 96.4% of patients. For patients who lived abroad or had immigrated (N=108, 2.4%), last available follow-up information was used. The primary endpoint of all-cause mortality was observed in 730 patients (16.3%) during median follow up of 6.3 years (IQR 5.8-6.8). When comparing risk of mortality associated with types of surgery, confounding factors such as demographics and comorbidities must be taken into account. Table 5 shows important differences in long-term mortality in relation to surgical risk in a multivariable regression model. Patients who underwent intermediate (HR 1.2; 95% CI 1.0-1.5) or high-risk surgery (HR

1.5; 95% CI 1.2-1.9) had a significant higher relative mortality risk. Figures 1 and 2 show Kaplan-Meier estimates of long-term survival among different surgical procedures and categories. In order to interpret the effect of surgery on long-term survival, figure 2 also shows the survival curve of the age and gender matched general Dutch population.

Late causes of death

When looking at the cause of late mortality, patients in the high-risk group, i.e. vascular patients, had a twofold higher risk of cardiovascular death (HR 1.9; 95% CI 1.2-3.1) compared to low-risk patients (Table 5). Patients in the intermediate group, i.e. the group consisting of most patients undergoing cancer surgery (28.6%), had a higher risk of dying from a cancer-related cause (HR 1.5; 95% CI 1.1-2.0).

Association between postoperative complications and mortality

We found a significant adverse effect between the presence of postoperative complications and long-term mortality (Table 6). Figure 3 shows a Kaplan-Meier estimate of 30-day survivors, calculated for different types of complications. This survival curve illustrates that survival in the patient group with self-limiting complications is already worse compared to those with no complications, whereas the prognosis in the two patient groups with non-self-limiting and major complications is considerably and increasingly worse. After exclusion of high-risk procedures, this association between complications and mortality still remained significant in low and intermediate surgical risk patients (HR 1.2; 95% CI 1.1-1.5).

Table 2. Baseline Characteristics

	All patients (N=4479)	**Any complication** (N=949)	**Overall mortality** (N=730)
Demographics			
Age, years (mean ± SD)	55.0 ± 17.5	62.7 ± 16.8#	71.6 ± 12.3##
Male sex (%)	2307 (51.5%)	495 (52.2%)	402 (55.1%)##
ASA classification (%)		#	##
I	1501 (33.5%)	157 (16.6%)	19 (2.6%)
II	1600 (35.7%)	292 (31.0%)	149 (20.6%)
III	1169 (26.1%)	405 (42.9%)	428 (59.0%)
IV	161 (3.6%)	85 (9.0%)	125 (17.2%)
V	4 (0,1%)	4 (0.4%)	4 (0.6%)
Medical history (%)			
Diabetes mellitus	402 (9.1%)	142 (15.1%)#	160 (22.2%)##
Hypertension	884 (20.0%)	261 (27.8%)#	259 (35.9%)##
Cerebrovascular disease	313 (7.1%)	92 (9.8%)#	132 (18.3%)##
Malignant disease	1028 (23.2%)	296 (31.4%)#	358 (49.4%)##
Pathological cardiac history	825 (18.6%)	294 (31.3%)#	358 (49.7%)##
Pathological pulmonary history	633 (14.3%)	186 (19.8%)#	221 (30.7%)##
Smoking* (%)		#	##
Current smoking	1075 (32.1%)	202 (29.2%)	183 (32.8%)
History	590 (17.6%)	143 (20.7%)	157 (28.1%)
No smoking	1682 (50.3%)	346 (50.1%)	218 (39.1%)
BMI category (%)		#	##
Normal weight (BMI 18,5-25 kg/m²)	1815 (42.3%)	339 (37.8%)	331 (48.2%)
Underweight (BMI < 18,5 kg/m²)	100 (2.3%)	28 (3.1%)	35 (5.1%)
Overweight (BMI 25-30 kg/m²)	1635 (38.1%)	345 (38.5%)	212 (30.9%)
Obese (BMI>30 kg/m²)	743 (16.6%)	185 (20.6%)	109 (15.9%)
Surgical categories (%)		#	##
Low risk surgery	**2527 (56.4%)**	**302 (31.8%)**	**238 (32.6%)**
Breast	382 (8.5%)	49 (5.2%)	63 (8.6%)
Hernia	839 (18.7%)	88 (9.3%)	79 (10.8%)
Minor surgery of soft tissue	408 (9.1%)	66 (7.0%)	58 (7.9%)
Minor trauma	228 (5.1%)	27 (2.8%)	12 (1.6%)
Perianal surgery	278 (6.2%)	19 (2.0%)	14 (1.9%)
Varicose vein surgery	392 (8.8%)	53 (5.6%)	12 (1.6%)
Intermediate risk surgery	**1720 (38.4%)**	**534 (56.3%)**	**367 (50.3%)**
Appendectomy	251 (5.6%)	55 (5.8%)	11 (1.5%)
Carotid artery	74 (1.7%)	12 (1.3%)	15 (2.1%)
Cholecystectomy	495 (11.1%)	100 (10.5%)	30 (4.1%)
Head and neck	102 (2.3%)	30 (3.2%)	8 (1.1%)
Major abdominal	629 (14.0%)	295 (31.1%)	222 (30.4%)
Major trauma	79 (1.8%)	27 (2.8%)	46 (6.3%)
Thoracic	90 (2.0%)	15 (1.6%)	35 (4.8%)

Table 2. (Continued)

	All patients (N=4479)	**Any complication** (N=949)	**Overall mortality** (N=730)
High risk surgery	**232 (5.2%)**	**113 (11.9%)**	**125 (17.1%)**
Amputation	36 (0.8%)	18 (1.9%)	29 (4.0%)
Major vascular	196 (4.4%)	95 (10.0%)	96 (13.2%)
Surgery characteristics (%)			
General anesthesia	3824 (85.6%)	866 (91.7%)[#]	654 (90.0%)[##]
Outpatient surgery	1539 (34.4%)	139 (14.6%)[#]	67 (9.2%)[##]
Length of stay, days (median + IQR)	2 (1-8)	8 (2-16)	7 (2-15)
Blood Loss, mL (median + IQR)	15 (5-50)	50 (20-250)	50 (10-200)
Operation time, minutes (median + IQR)	41 (25-68)	63 (38-110)	61 (35-113)

[#] Significantly different (p<.05) when compared to patients without complications
[##] Significantly different (p<.05) when compared to alive patients
* Data available in 75.7% of patients

6

Table 3. Baseline characteristics according to main surgical categories

	Male (%)	Age, years Mean ± SD	HT (%)	DM (%)	Cerebrovascular disease (%)	Malignant disease (%)	Pathological cardiac history (%)	Pathological pulmonary history (%)	Current smoking (%)
Low surgical risk	1408 (55.7%)	52.2 (±16.4)	380 (15.2%)	152 (6.1%)	94 (3.8%)	511 (20.5%)	339 (13.6%)	287 (11.5%)	604 (32.6%)
Breast	19 (5.0%)	57.3 (±14.8)	80 (20.9%)	33 (8.6%)	14 (3.7%)	333 (87.2%)	52 (13.6%)	41 (10.7%)	91 (28.2%)
Hernia	739 (88.1%)	56.5 (±15.6)	126 (15.1%)	47 (5.6%)	45 (5.4%)	48 (5.8%)	152 (18.2%)	96 (11.5%)	194 (30.1%)
Minor surgery of soft tissue	226 (55.4%)	49.8 (±16.5)	77 (18.9%)	37 (9.1%)	17 (4.2%)	97 (23.8%)	59 (14.5%)	66 (16.2%)	102 (34.8%)
Minor trauma	102 (44.7%)	48.3 (±18.5)	34 (16.3%)	13 (6.2%)	7 (3.3%)	7 (3.3%)	21 (10.0%)	20 (9.6%)	45 (32.8%)
Perianal surgery	207 (74.5%)	40.5 (±15.7)	21 (7.8%)	14 (5.2%)	5 (1.9%)	9 (3.3%)	28 (10.4%)	21 (7.8%)	98 (50.0%)
Varicose vein surgery	115 (29.3%)	50.9 (±13.0)	42 (10.7%)	8 (2.0%)	6 (1.5%)	17 (4.3%)	27 (6.9%)	43 (11.0%)	74 (28.6%)
Intermediate surgical risk	739 (43.0%)	57.0 (±18.4)	394 (23.1%)	181 (10.6%)	174 (10.2%)	489 (28.6%)	347 (20.3%)	288 (16.9%)	388 (29.6%)
Appendectomy	126 (50.2%)	39.6 (±17.9)	24 (9.7%)	8 (3.2%)	4 (1.6%)	12 (4.9%)	14 (5.7%)	8 (3.2%)	51 (27.7%)
Carotid artery	53 (71.6%)	67.4 (±9.3)	31 (41.9%)	18 (24.3%)	60 (81.1%)	7 (9.5%)	32 (43.2%)	10 (13.5%)	28 (41.2%)
Cholecystectomy	152 (30.7%)	54.0 (±15.2)	97 (19.6%)	38 (7.7%)	24 (4.9%)	36 (7.3%)	74 (15.0%)	48 (9.7%)	123 (31.9%)
Head and neck	41 (40.2%)	54.1 (±15.0)	20 (19.8%)	9 (8.9%)	4 (4.0%)	22 (21.8%)	7 (6.9%)	8 (7.8%)	23 (34.3%)
Major abdominal	292 (46.4%)	62.8 (±16.7)	175 (28.0%)	84 (13.4%)	59 (9.4%)	340 (54.2%)	154 (24.6%)	110 (17.6%)	122 (25.8%)
Major trauma	22 (27.8%)	76.1 (±17.2)	27 (35.5%)	19 (25.0%)	14 (18.4%)	16 (20.8%)	38 (50.0%)	23 (30.3)	9 (18.0%)
Thoracic	53 (58.9%)	60.0 (±15.7)	20 (22.2%)	5 (5.6%)	9 (10.0%)	56 (62.2%)	28 (31.1%)	81 (90.0%)	32 (38.1%)
High surgical risk	160 (69.0%)	69.7 (±11.5)	110 (47.8%)	69 (30.0%)	45 (19.6%)	28 (12.2%)	139 (60.4%)	58 (25.2%)	83 (45.4%)
Amputation	18 (50.0%)	68.8 (±15.2)	16 (44.4%)	19 (52.8%)	13 (36.1%)	4 (11.1%)	21 (58.3%)	9 (25.0%)	11 (40.7%)
Major vascular	142 (72.4%)	69.8 (±10.7)	94 (48.5%)	50 (25.8%)	32 (16.5%)	24 (12.4%)	118 (60.8%)	49 (25.3%)	72 (46.2%)

Table 4. Postoperative Outcome within 30 Days

	No complication (%)	Self-limiting complication (Grade 1) (%)	Non-self-limiting complication (Grade 2+3) (%)	Major complication (Grade 4) (%)	Death (Grade 5) (%)
Low risk surgery	2225 (88.0)	77 (3.0)	216 (8.5)	1 (0.0)	8 (0.3)
Breast	333 (87.2)	13 (3.4)	36 (9.4)	0 (0.0)	0 (0.0)
Hernia	751 (89.5)	19 (2.3)	65 (7.7)	1 (0.1)	3 (0.4)
Minor surgery of soft tissue	342 (83.8)	18 (4.4)	44 (10.8)	0 (0.0)	4 (1.0)
Minor trauma	201 (88.2)	8 (3.5)	19 (8.3)	0 (0.0)	0 (0.0)
Perianal surgery	259 (93.2)	5 (1.8)	13 (4.7)	0 (0.0)	1 (0.4)
Varicose vein surgery	339 (86.5)	14 (3.6)	39 (9.9)	0 (0.0)	0 (0.0)
Intermediate risk surgery	1186 (69.0)	99 (5.8)	349 (20.3)	39 (2.3)	47 (2.7)
Appendectomy	196 (78.1)	16 (6.4)	37 (14.7)	1 (0.4)	1 (0.4)
Carotid artery	62 (83.8)	5 (6.8)	2 (2.7)	3 (4.1)	2 (2.7)
Cholecystectomy	395 (79.8)	30 (6.1)	64 (12.9)	3 (0.6)	3 (0.6)
Head and neck	72 (70.6)	11 (10.8)	19 (18.6)	0 (0.0)	0 (0.0)
Major abdominal	334 (53.1)	31 (4.9)	198 (31.5)	29 (4.6)	37 (5.9)
Major trauma	52 (65.8)	2 (2.5)	19 (24.1)	3 (3.8)	3 (3.8)
Thoracic	75 (83.3)	4 (4.4)	10 (11.1)	0 (0.0)	1 (1.0)
High risk surgery	119 (51.3)	6 (2.6)	76 (32.8)	11 (4.7)	20 (8.6)
Amputation	18 (50.0)	2 (5.6)	9 (25.0)	1 (2.8)	6 (16.7)
Major vascular	101 (51.5)	4 (2.0)	67 (34.2)	10 (5.1)	14 (7.1)
All types	3530 (78.8)	182 (4.1)	641 (14.3)	51 (1.1)	75 (1.7)

Table 5. The association between surgery risk and different mortality hazards

	Events	Univariate		Multivariable*	
	N (%)	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Overall mortality					
Low risk surgery	238	**1**	-	**1**	-
Intermediate risk surgery	367	**2.364**	**1.998– 2.796**	**1.216**	**1.017 – 1.455**
High risk surgery	125	**7.512**	**6.014 – 9.382**	**1.507**	**1.166 – 1.946**
Cardiovascular mortality					
Low risk surgery	57	**1**	-	**1**	-
Intermediate risk surgery	58	**1.686**	**1.170 – 2.431**	**0.860**	**0.574 – 1.287**
High risk surgery	46	**12.747**	**8.621 – 18.848**	**1.923**	**1.194 – 3.095**
Cancer-related mortality					
Low risk surgery	93	**1**	-	**1**	-
Intermediate risk surgery	192	**3.301**	**2.574 – 4.233**	**1.503**	**1.143 – 1.977**
High risk surgery	21	**3.615**	**2.270 – 5.758**	**1.281**	**0.762 – 2.152**

*Analyses were adjusted for age, gender, type of anesthesia, ASA classification, diabetes, hypertension, pulmonary -, cardiac - or cerebrovascular disease, BMI, and the presence of a malignancy

Table 6. The association between 30-day complications and different long-term mortality hazards (in 30-day survivors)

	Events	Univariate		Multivariable	
	N (%)	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Overall mortality	627	**2.393**	**2.033 – 2.818**	**1.197**	**1.009 – 1.421**
Cardiovascular mortality	140	**3.527**	**2.526 – 4.924**	**1.890**	**1.312 – 2.721**
Cancer-related mortality	291	**2.230**	**1.748 – 2.845**	**1.101**	**0.850 – 1.426**

*Analyses were adjusted for age, gender, type of anesthesia, ASA classification, diabetes, hypertension, pulmonary -, cardiac - or cerebrovascular disease, BMI, and the presence of a malignancy

DISCUSSION

Late mortality after surgery might be higher than expected (16% at 6 years). The 30-day mortality of 1.7% we found, is much similar to the 1,9% reported in a study performed in the Netherlands in 2010.[12] Previous studies on outcome following surgery are scarce, mostly retrospective in design and based on administrative databases.[12-14] Lee et al demonstrated that clinical chart review had a significantly better accuracy than a comparable administrative database model, probably due to undercoding of comorbidities in the latter. [15]

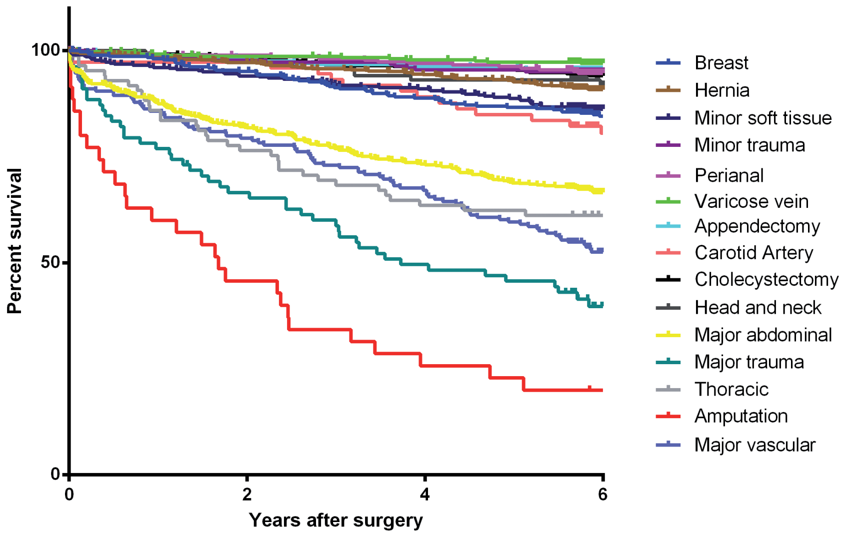
Instead of focussing on demographic and disease specific factors only, we took variables such as postoperative complications into account, which have been reported to be of clinical importance. [2, 3, 16, 17] To our knowledge, this is the first prospective study to combine all these factors in order to analyse long term outcome, including cause of late death.

According to this study, special focus on two groups of patients is advised in order to improve postoperative care. As can be expected, the first group associated with an adverse outcome is the group of high-risk vascular patients. Although these were only 5% of operated patients, they accounted for 27% of 30-day mortality. The high incidence of postoperative death in this subpopulation is in accordance with previous literature. [9, 12, 18] Taking the surgical procedure itself into account when predicting risk of postoperative complications, rather than patients' comorbidity only, remains very important.

The second group highly and independently associated with late death are patients who experience postoperative complications. In this study, complications occurred in 21% of patients, who were mostly of higher age and had more comorbidities. In order to better understand the relationship between postoperative complications and reduced survival one might ask if a complication is the cause of this reduction, or a sign of a bigger pathological problem. In this study we demonstrated that the relationship between complications and reduced survival remains valid even after adjusting for potential confounders. Moreover, after exclusion of high-risk surgery in a sensitivity analysis, this relationship still remains significant.

Recent literature shows that frailty is associated with higher morbidity and mortality, independent of other risk factors in a surgical population. Preoperative recognition of this multidimensional vulnerability may be an adjunct in assessment of preoperative risk factors. Also, evidence has shown that the surgical procedure itself elicits a stress response, initiated by tissue injury. [19-22] Surgical injury profoundly affects the innate and adaptive immune responses, leading to an increased susceptibility to complications.[22]

Figure 1. Kaplan-Meier estimates of long-term survival among different surgical procedures



Cause-specific mortality analysis showed that the high-risk group had a twofold higher risk of dying from a cardiovascular cause. As expected, patients in the intermediate surgery group were more likely to die from a cancer-related cause. In order to appreciate these numbers, the Dutch registration for cause of death needs clarification. The certificate of death filled in by a medical practitioner is based on guidelines of the World Health Organization. [23] Only one cause can be coded as primary cause of death. Primary cause of death is the cause of the initial health deterioration leading to the end of life. For example, if a patient had surgery because of intestinal cancer and died due to postoperative myocardial infarction, cause of death would be cancer-related and the myocardial event noted as a secondary response to his underlying illness[24].

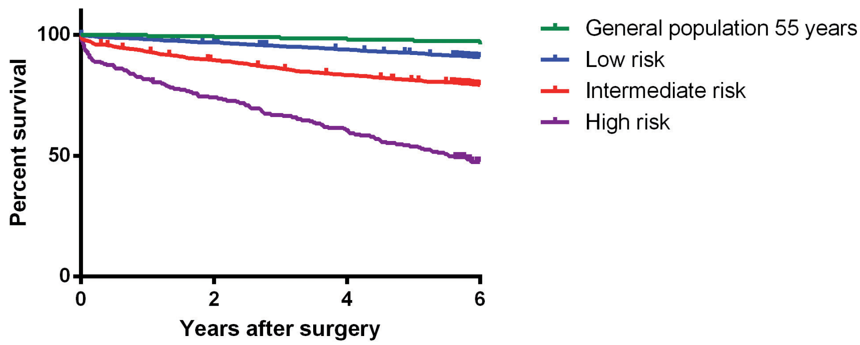
Reliability of cause-of-death coding in the Netherlands turns out to be high (>90%) for major causes of death, such as cancer- and cardiovascular-related causes.[24, 25]

We recognize that our study has potential limitations. It is conducted in a single centre with a potential bias in referral pattern. However, at the time of enrolment, only patients needing total pelvic exenteration or patients with severe comorbidity were referred to tertiary centres. All other major abdominal surgery, such as liver, gastric, bowel, spleen, oesophagus and incisional hernia surgery was performed in this regional hospital. Our data contains quite a large number of intermediate and high risk procedures and procedures with a long operation time.

Second, we only included patients who underwent surgery. There might have been high-risk patients screened for surgery, but denied because of the risk of potential adverse outcome. For patients with malignancy, type and stage of their disease is known to influence life expectancy. We entered presence of a malignancy as a potential confounder in all multivariable models; however, we did not specifically assess severity of malignant disease in this general surgical population.

Finally, due to the observational character, this study is inherent to unmeasured confounding.

Figure 2. Kaplan-Meier estimates of long-term survival among different surgical categories, including a survival curve of the age and gender matched general Dutch population

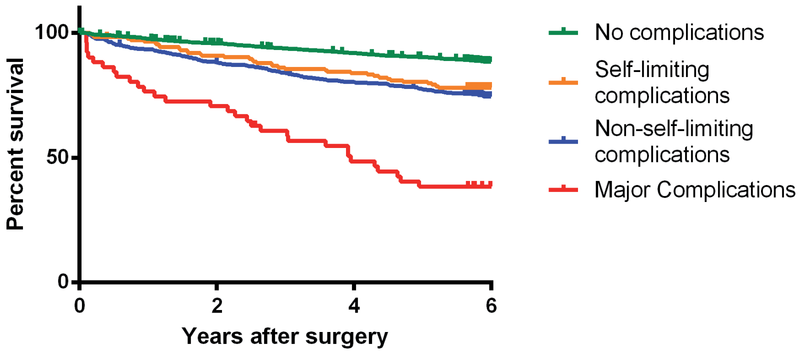


N at risk, % with clinical success

2453 (-)	2353 (96.8%)	2273 (93.9%)	1720 (90.8%)
1678 (-)	1492 (89.5%)	1386 (83.4%)	1029 (79.3%)
274 (-)	166 (74.1%)	136 (60.6%)	88 (47.4%)

Surgical outcome is influenced by the patient's preoperative status, severity of disease or surgical procedure and quality of care.[26] In the Netherlands, a high-resource country, accessibility and quality of care are considered equal for all inhabitants. Also, the wide implementation of modern perioperative programmes such as fast-track surgery or goal directed therapy seems to contribute to a reduced postoperative morbidity.[27, 28]

Figure 3. Kaplan-Meier estimates of 30-day survivors, calculated for different types of complications



N at risk, % with clinical success

3437 (-)	3265 (95.8%)	3124 (91.9%)	2343 (88.4%)
176 (-)	158 (90.8%)	146 (83.8%)	115 (78.0%)
629 (-)	553 (88.1%)	502 (80.2%)	365 (74.5%)
51 (-)	37 (70.6%)	25 (48.6%)	14 (38.5%)

In conclusion, high-risk vascular surgery and the occurrence of postoperative complications are important prognostic factors of late mortality. Further focus on these groups of patients can contribute to a reduced postoperative morbidity. Improvement in quality of surgical care should be aimed at preventing postoperative complications and thereby a better outcome in a general surgical population.

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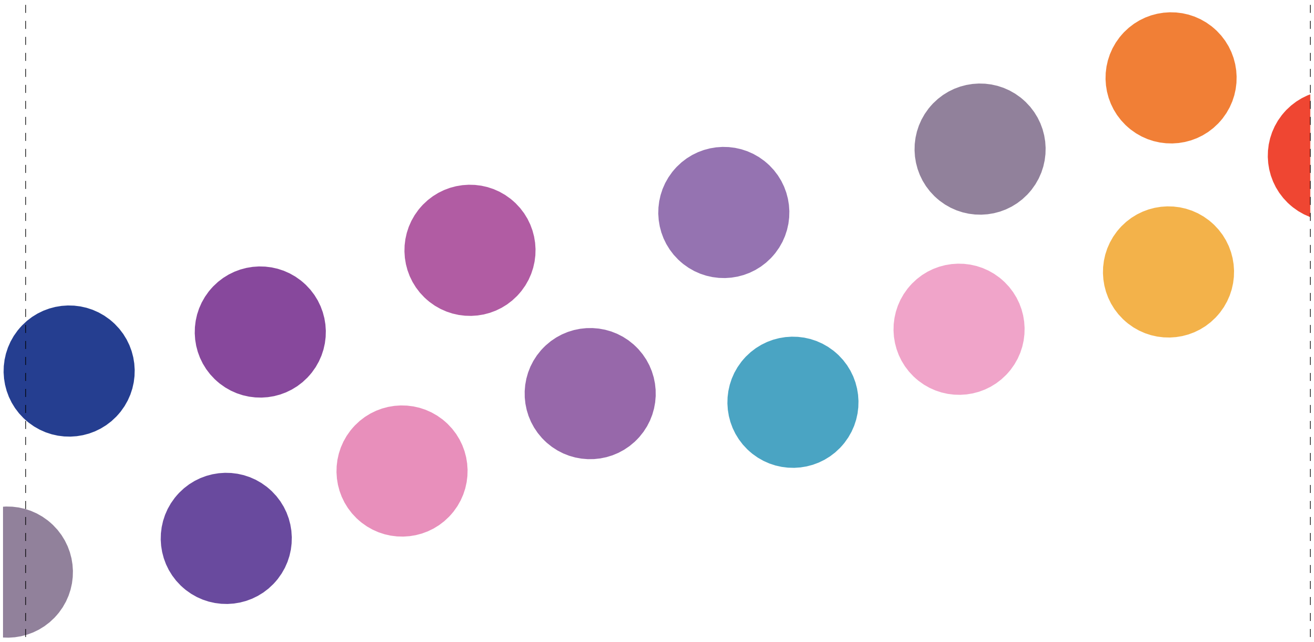

Chapter 7

The relationship between household income and surgical outcome in the Dutch setting of equal access to and provision of healthcare

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ABSTRACT

Background

The impact of socioeconomic disparities on surgical outcome in the absence of healthcare inequality remains unclear. Therefore, we set out to determine the association between socioeconomic status (SES), reflected by household income, and overall survival after surgery in the Dutch setting of equal access and provision of care. Additionally, we aim to assess whether SES is associated with cause-specific survival and major 30-day complications.

Methods

Patients undergoing surgery between March 2005 and December 2006 in a general teaching hospital in the Netherlands were prospectively included. Adjusted logistic and cox regression analyses were used to assess the independent association of SES –quantified by gross household income– with major 30-day complications and long-term postoperative survival.

Results

A total of 3929 patients were included, with a median follow-up of 6.3 years. Low household income was associated with worse survival in continuous analysis (HR: 1.05 per 10.000 euro decrease in income, 95% CI: 1.01 – 1.10) and in income quartile analysis (HR: 1.58, 95% CI: 1.08 – 2.31, first [i.e. lowest] quartile relative to the fourth quartile). Similarly, low-income patients were at higher risk of cardiovascular death (HR: 1.26 per 10.000 decrease in income, 95% CI: 1.07 – 1.48, first income quartile: HR: 3.10, 95% CI: 1.04 – 9.22). Household income was not independently associated with cancer-related mortality and major 30-day complications.

Conclusions

Low SES, quantified by gross household income, is associated with increased overall and cardiovascular mortality risks among surgical patients. Considering the equality of care provided by this study setting, the associated survival hazards can be attributed to patient and provider factors, rather than disparities in healthcare. Increased physician awareness of SES as a risk factor in preoperative decision-making and focus on improving established SES-related risk factors may improve surgical outcome of low SES patients.

INTRODUCTION

The relation between socioeconomic status (SES) and outcome of medical treatment has been the subject of many studies over the past years, and SES-related risks of poor outcome have been demonstrated previously.[1-9] A considerable number of these studies were performed in countries where healthcare is not publicly provided. Although the relation between SES and outcome is multifactorial and complex, differences in outcome between socioeconomic classes were attributed more to differences in accessibility and provision of care in some of these studies, rather than patient factors or healthcare provider factors.[1,6,9-11]

As a result of governmental regulation, medical care in the Netherlands is equal among all layers of society, and has even been credited the most equally accessible healthcare system in the world.[12,13] This characteristic of the present study setting provides a new and unique opportunity to assess the role of SES on outcome of care. Due to the healthcare equality, differences in outcome associated with SES can under these circumstances be attributed to patient and provider factors and their interaction, rather than disparities in healthcare. We have previously demonstrated in a vascular surgery population that SES –quantified by gross household income– implicated significant postoperative survival risks, independent from conventional medical and environmental risk factors.[14] These findings suggest that SES encompasses a wide variety of risk factors and behaviors that are not adequately captured by conventionally considered risk factors.

The association between SES and prognosis in a non-vascular general surgical population remains unexplored. Moreover, it is well known that vascular disease and vascular patients are relatively more susceptive to environmental risk factors, which limits the generalizability of the previous study to non-vascular patients.

The primary objective of this study is to determine the association between SES, reflected by household income, and survival after surgery in a general surgical population. Additionally, we aim to establish whether SES is associated with cause-specific survival and major 30-day complications.

PATIENTS AND METHODS

Study population

Patients undergoing elective or acute surgery between March 2005 and December 2006 in a medium-sized general teaching hospital in the Netherlands were prospectively included.[15] Procedures are detailed in Supplemental Table 1. Since the association between low household income and worse outcome among vascular surgery patients has been established in the previous study,[14] vascular procedures were excluded. Additional exclusion criteria were surgical interventions performed under local anesthesia, and patients younger than 14 years at the time of the procedure. Bariatric surgery was not performed in this hospital. When a patient underwent multiple surgical procedures within the study period, the first operation was included for analysis and survival was assessed from that moment onward. The institutional review board of Zuyderland Medical Center approved this study, and patient consent was waived due to the de-identified nature of the data. The study complies with the Helsinki declaration on research ethics.

Baseline characteristics

Medical characteristics were obtained by a surgeon or a surgical resident during a routine visit prior to surgery. Pulmonary disease was defined as an illness of the lung or respiratory system (i.e. asthma, lung cancer, chronic infections, previous pulmonary embolisms, chronic obstructive pulmonary disease (COPD)). Cardiac disease was considered when the medical history included coronary artery disease (with or without coronary revascularization), heart failure, arrhythmias, valvular heart disease or cardiomyopathy. Cerebrovascular disease was defined as either a Transient Ischemic Attack (TIA) or ischemic stroke in the medical history. A patient was considered diabetic when diabetes mellitus was mentioned in the prior history or medical records show use of insulin or oral anti-diabetics. Hypertension was considered when hypertensive disease was mentioned in the medical history or the patient received anti-hypertensive medication. A history of cancer was defined as malignant neoplastic disease in the prior medical history.

Gathered surgery-related data included the type of anesthesia (locoregional or general) and the surgical setting (inpatient or outpatient). The risk of the performed procedure was defined as low, intermediate or high risk conform the surgical risk classification system by Boersma et al. (Supplemental Table 1).[16] High-risk surgical procedures solely consist of major vascular procedures and were not included in this study for previously mentioned reasons. Finally, all events following surgery were documented.

A surgical resident as well as a member of the surgical staff independently scored all complications. To ensure complications were interpreted objectively and systematically, a classification proposed by Clavien et al. was used as guidance.[17] A major complication was defined as a complication requiring surgical, endoscopic or radiological intervention with or without residual organ dysfunction. Validation of the database using a random sampling audit procedure confirmed a high level of accuracy and completeness of the data.

Endpoints

The primary endpoint was overall mortality. Secondary endpoints were major 30-day complications, cardiovascular and cancer-related mortality.

Socioeconomic status

In this study, gross household income was used as an indicator of SES. Household income is one of the most widely accepted and used methods to quantify SES, and has previously been affirmed to provide an accurate reflection of SES-related health disparities.[18-20] To avoid missing income data due to a patient's death in the year of surgery, gross household income in the year prior to the year of surgery was used to quantify SES. Annual earnings were obtained at the Dutch Central Bureau of Statistics (CBS), and encompassed all types of income of people sharing a household or place of residence combined, including salary, (state) pension, social compensation, and investment revenues. Patients were assigned income percentiles and quartiles in accordance with the national income distribution. To clarify, first income quartile patients included members of a household with an annual salary that corresponds to 0-25% gross household incomes of the Dutch population.

Cause of death

Causes of death obtained through national death registries, which are also maintained by the CBS. The high accuracy of Dutch cause-of-death registration has been demonstrated previously.[21] The cause of death was defined as the cause for the initial health deterioration, which subsequently resulted in death. This approach is similar to the strategy employed for the overall Dutch population death registrations and reports. Autopsy was not routinely performed. The causes of death were coded in accordance with *International Classification of Diseases, 10th Revision* (ICD-10). Cardiovascular death was defined as I10-I79, and cancer-related death as C00-C43, C45-C97.

To obtain information on household income and causes of death, a database consisting of medical data on all study participants was anonymised and matched to the household income and death registry data sets maintained by the CBS. Dutch privacy legislation stipulates that data analysis with national data is only allowed by authorized researchers (KU, FBG) from designated institutions inside a secure environment after approval from the institutional ethical committee. Furthermore, output was checked by the CBS for privacy violations before it was allowed for publication purposes.

Statistical methods

Baseline characteristics are presented as counts and percentages (dichotomous variables), means and standard deviations (continuous variables), or medians and interquartile ranges (IQR). Patients were grouped in quartiles in correspondence with the national gross household income distribution. Differences at baseline between income quartiles were tested using Pearson's chi-square analysis and ANOVA, where appropriate. The predictive value of household income for long-term survival was assessed using Cox-regression analysis. In order to determine both the type (i.e. linear or exponential) and the clinical significance of the relation between income and survival, analyses were performed with income as a continuous variable as well as categorical per income quartile. Exponential properties were tested by including higher-order terms of income in the regression model in continuous analysis. In income quartile analysis, the highest income quartile was designated reference category. Multivariable analyses were performed in a stepwise manner. The step 1 multivariable model adjusted for: surgical risk, age, gender, diabetes, hypertension, cerebrovascular disease, cardiac disease, malignant disease, and pulmonary disease. The step 2 multivariable model additionally adjusted for: smoking and BMI. Cause specific mortality hazards (i.e. cardiovascular and cancer-related) associated with household income were established with the same Cox model. The association between income and major 30-day complications and death following surgery was studied using logistic regression analysis. The multivariable model consisted the same covariates as the long-term survival models. Sensitivity analyses were performed to assess whether the association between income and postoperative survival existed among all patients, including vascular patients. All tests were two-sided and significance was considered when P-value <0.05. Statistical analysis was performed using the IBM SPSS Statistics 20 (IBM Inc., Chicago, IL).

RESULTS

A total of 4153 patients were suitable for analysis. The gross household income could be retrieved for 3929 patients (94.6%).

Table 1. Baseline characteristics

	Quartile 1 (n=708)	Quartile 2 (n=1122)	Quartile 3 (n=1083)	Quartile 4 (n=1016)	P-value
Demographics					
Age – mean (± SD)	61.8 (19.4)	59.3 (16.5)	48.6 (15.6)	46.9 (14.5)	<0.001
Female gender – n (%)	435 (61)	538 (48)	525 (48)	446 (44)	<0.001
Comorbid conditions					
Diabetes mellitus – n (%)	91 (13)	96 (9)	68 (6)	45 (4)	<0.001
Hypertension – n (%)	189 (27)	242 (22)	160 (15)	119 (12)	<0.001
Cerebrovascular disease – n (%)	67 (10)	87 (8)	39 (4)	10 (<1)	<0.001
Cardiac disease – n (%)	184 (26)	239 (21)	131 (12)	76 (8)	<0.001
Malignant disease – n (%)	218 (31)	321 (29)	223 (21)	184 (18)	<0.001
Pulmonary disease – n (%)	128 (18)	197 (18)	124 (12)	79 (8)	<0.001
Surgical risk					
Low – n (%)	363 (51)	653 (58)	681 (63)	671 (66)	<0.001
Intermediate – n (%)	345 (49)	469 (42)	402 (37)	345 (34)	<0.001
Behavioral risk factors					
Smoking [*] *– n (%)*	236 (46)	431 (51)	428 (52)	284 (39)	<0.001
BMI – mean (± SD)	26.1 (4.7)	26.2 (4.4)	26.5 (4.8)	25.7 (4.3)	0.004
Type of anesthesia					
General – n (%)	618 (87)	936 (84)	920 (85)	855 (84)	0.135
Socioeconomic status					
Median income – € (IQR)	16 620.50 (13 914.25 – 19 280.75)	29 375.50 (25 119.50 – 34 474.75)	50 971.00 (44 961.00 – 57 645.00)	83 490.50 (72 924.50 – 101 192.75)	-

Baseline characteristics

Baseline characteristics are detailed in Table 1. Low household income patients were younger (P<0.001) and were more frequently female (P<0.001). All medical conditions were more common among lower income quartile patients (P<0.001 for all medical conditions). Similarly, higher income patients were less often current or former smokers (P<0.001). BMI also significantly differed between the income quartiles (P<0.001).

Major 30-day complications

In the first 30 days following surgery, 206 patients suffered a major complication requiring additional interventions (either surgical, endoscopic or radiological) (Table 2). Within this group, 37 patients (18%) were left with residual organ dysfunction. Income was associated with the occurrence of major complications in univariate continuous analysis (OR: 1.05, 95% CI: 1.004 – 1.11), as well as in income quartile analysis for the first quartile (OR: 1.99, 95% CI: 1.30 – 3.04) compared to the fourth quartile (Table 3). However, no association could be established in adjusted analysis.

Table 2. Survival and short- and long-term event characteristics in accordance with household income quartiles.

	Quartile 1 (n=708)	Quartile 2 (n=1122)	Quartile 3 (n=1083)	Quartile 4 (n=1016)	Total (n=3929)	P-value
5-year survival estimate (± se)	77% (1.6)	84% (1.1)	91% (0.9)	96% (0.6)	88% (0.5)	<0.001
Median follow-up – years (IQR)	6.2 (5.2 – 6.7)	6.3 (5.8 – 6.7)	6.4 (5.9 – 6.8)	6.4 (5.9 – 6.8)	6.3 (5.8 – 6.8)	-
Endpoints						
Severe complications – n (%)	52 (7)	61 (5)	54 (5)	39 (4)	206 (5)	0.014
Overall death – n (%)	189 (27)	222 (20)	107 (10)	52 (5)	570 (15)	<0.001
Cardiovascular death – n (%)	54 (8)	38 (3)	11 (1)	5 (<1)	108 (3)	<0.001
Cancer-related death – n (%)	71 (10)	117 (10)	60 (6)	33 (3)	281 (7)	<0.001

Overall mortality

During a median follow-up of 6.3 years 570 deaths occurred (Table 2). Regarding the relation between income and overall survival, a significant association was found in continuous analysis (Table 4). In multivariable step 1, as well as adjusted for behavioral risk factors in step 2, mortality hazards proved to increase as income diminished (HR: 1.05 per 10.000 euro decrease in household income, 95% CI: 1.01 – 1.10,). A similar relation was found in income quartile analysis. In step 2 multivariable analysis, patients in the first quartile (i.e. the lowest income quartile) had significantly higher mortality risks (HR: 1.58, 95% CI: 1.08 – 2.31). The association lost significance in the second and third quartile, although a trend remained (HR: 1.41, 95% CI: 0.99 – 2.02, HR: 1.32, 95% CI: 0.90 – 1.93, respectively for the second and third quartile).

Table 3. The association between household income and major 30-day complications following surgery.

	Continuous	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Major complications					
Univariate	1.05 (1.004 – 1.11)	1.99 (1.30 – 3.04)	1.44 (0.96 – 2.17)	1.32 (0.86 – 2.00)	-
Multivariate step 1	0.99 (0.95 – 1.03)	1.07 (0.66 – 1.73)	0.89 (0.57 – 1.39)	1.18 (0.76 – 1.81)	-
Multivariate step 2	1.01 (0.95 – 1.06)	1.09 (0.62 – 1.92)	1.02 (0.61 – 1.70)	1.41 (0.86 – 2.31)	-

Odds ratios in continuous analyses are determined per 10.000 euro decrease in household income. In quartile analyses, the fourth quartile serves as reference category. Step 1 multivariable analysis adjusted for: surgical risk, age, gender, diabetes, hypertension, cerebrovascular disease, cardiac disease, malignant disease and pulmonary disease. Step 2 multivariable analysis additionally adjusted for: smoking and BMI.

Cause specific mortality

Of the 570 deaths, 108 (19%) were due to cardiovascular causes. In both step 1 and step 2 continuous analysis, low household income was significantly associated with increased cardiovascular mortality risks (HR: 1.26 per 10.000 euro decrease in household income, 95% CI: 1.07 – 1.48, Table 5). In income quartile analysis, a significant independent income-related cardiovascular survival hazard was observed in the first quartile (HR: 3.10, 95% CI: 1.04 – 9.22). No relation could be established for the higher two quartiles.

Cancer-related death was ascertained in 281 (49%) cases. In continuous analysis, a significant relation was found between income and cancer-related survival in univariate analysis (HR: 1.19, 95% CI: 1.13 – 1.24). The relation was lost after adjusting for conventional risk estimators in multivariable analysis. Similarly, lower quartile patients were not burdened by additional cancer-related mortality in multivariable income quartile analysis.

Table 4. The association between household income and overall mortality.

	Continuous	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Overall mortality					
Univariate	1.25 (1.21 – 1.30)	5.89 (4.33 – 8.00)	4.17 (3.08 – 5.64)	1.97 (1.41 – 2.74)	-
Multivariate step 1	1.06 (1.01 – 1.10)	1.49 (1.06 – 2.09)	1.40 (1.02 – 1.93)	1.30 (0.93 – 1.83)	-
Multivariate step 2	1.05 (1.01 – 1.10)	1.58 (1.08 – 2.31)	1.41 (0.99 – 2.02)	1.32 (0.90 – 1.93)	-

Hazard ratios in continuous analyses are determined per 10.000 euro decrease in household income. In categorical analyses, the fourth quartile serves as reference category. Step 1 multivariable analysis adjusted for: surgical risk, age, gender, diabetes, hypertension, cerebrovascular disease, cardiac disease, malignant disease and pulmonary disease. Step 2 multivariable analysis additionally adjusted for: smoking and BMI.

Sensitivity analyses

Sensitivity analyses with vascular surgery patients included showed that household income was associated with worse overall survival in continuous step 2 multivariable analysis (HR: 1.05 per 10.000 euro decrease in household income, 95% CI: 1.01 – 1.09,), as well as cardiovascular survival (HR: 1.21, 95% CI: 1.02 – 1.41), while no increased risk was found for cancer-related survival (HR: 1.01, 95% CI: 0.96 – 1.07). Income quartile analyses showed similar results for overall and cancer-related mortality as well. For cardiovascular mortality, a non-significant trend towards increased cardiovascular survival hazards was observed among first quartile patients (P=0.055).

Table 5. The association between household income and cause-specific mortality.

	Continuous	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Cardiovascular					
Univariate	1.41 (1.33 – 1.51)	17.99 (7.20 – 44.97)	7.59 (2.99 – 19.29)	2.11 (0.73 – 6.08)	-
Multivariate step 1	1.22 (1.09 – 1.37)	2.84 (1.08 – 7.50)	1.79 (0.69 – 4.65)	1.19 (0.41 – 3.46)	-
Multivariate step 2	1.26 (1.07 – 1.48)	3.10 (1.04 – 9.22)	1.40 (0.47 – 4.20)	1.17 (0.36 – 3.86)	-
Cancer-related					
Univariate	1.19 (1.13 – 1.24)	3.46 (2.29 – 5.23)	3.43 (2.33 – 5.05)	1.74 (1.14 – 2.66)	-
Multivariate step 1	1.04 (0.99 – 1.10)	1.28 (0.81- 2.02)	1.42 (0.95 – 2.14)	1.30 (0.85 – 2.01)	-
Multivariate step 2	1.01 (0.96 – 1.06)	1.04 (0.63 – 1.72)	1.40 (0.90 – 2.18)	1.36 (0.86 – 2.15)	-

Hazard ratios in continuous analyses are determined per 10.000 euro decrease in household income. In categorical analyses, the fourth quartile serves as reference category. Step 1 multivariable analysis adjusted for: surgical risk, age, gender, diabetes, hypertension, cerebrovascular disease, cardiac disease, malignant disease and pulmonary disease. Step 2 multivariable analysis additionally adjusted for: smoking and BMI.

DISCUSSION

The principal finding of this study is that SES, reflected by household income, is a significant predictor of long-term survival in an overall surgical population. Cause specific mortality analysis indicated that the mortality hazards associated with low household income were not caused by increased risks of death due to cancer-related causes, but rather a higher risk of cardiovascular death. Since the association maintained after adjusting for demographics, comorbidities and behavioral risk factors, the mortality risks add to conventionally considered risk estimators. Secondly, this study showed that SES is not related to short-term postoperative outcome, as demonstrated by the lack of association with major 30-day complications.

Differences in outcome after surgery between socioeconomic classes have previously been attributed to disparities in quality and provision of care.[1,6,9,22,23] However, the equality in access to and provision of care provided by this study setting suggests that not healthcare inequalities, but rather patient-related factors that are not adequately captured by conventionally considered risk factors played a dominant causal role in SES-related outcome differences. Hence, even in countries where healthcare is not publicly provided, differences in healthcare utilization are unlikely to fully account for divergences in outcome.[24,25] This is in line with a report by Kilbourne et al., which introduced a model on the determinants of healthcare disparities.[11] Kilbourne et al. propose that healthcare disparities originate from individual, provider, and healthcare system factors. While the impact of disparities in healthcare system factors may be minimal in The Netherlands, individual and provider factors, and their interaction, are likely to be of influence.

With regard to individual patient factors, it has been reported that less than 50% of socioeconomic differences in disease occurrence and prognosis are explained by combined common behavioral risk factors, such as smoking.[19,26-28] What patient-related factors may drive the association of low SES with worse outcome? First, socioeconomic disadvantage is a known risk factor for poor compliance to medication, diet, and lifestyle restrictions.[29-33] Second, psychosocial risk factors implicated in the etiology of cardiovascular disease, such as psychological stress, depression and social isolation, are more often observed in low SES populations.[34-37] Also, material deprivation in individuals from disadvantaged backgrounds is associated with worse dietary quality.[38-41] In addition, SES has been established as an important determinant of physical activity and exercise,[42] which –in turn– is associated with health status and life-expectancy.[42,43] Fifth, low SES patients tend to reside in more disadvantaged neighborhoods with higher concentrations of harmful air pollutants and worse housing conditions, which are associated with worse health outcomes.[44-46] Physical demand, low decision latitude and high job strain, which are more common in lower employment grades, may also explain some of the excess risk among disadvantaged groups.[47]

These factors have been linked to especially increased risks of cardiovascular disease and mortality.[28,46,48-50] Moreover, literature based models suggest that perhaps even epigenetical factors among lower socioeconomic classes may be responsible for the higher prevalence of cardiovascular disease among lower socioeconomic classes.[51] This provides a valid explanation as to why low SES predominantly implied cardiovascular survival hazards in our study.[52,53] Although no relation between SES and cancer-related death was found in the full model, studies have proven such relation to exist.[54,55] Our results showed an association between SES and cancer-related mortality in univariate analysis, but no relation could be established when adjusting for conventional risk factors.[55] This is in line with previous studies showing that that much of the SES-related risk of cancer occurrence and mortality are through conventional risk factors, most importantly smoking.[52,56-58]

Apart from patient-related factors, the previously mentioned provider factors, and their interaction with patient factors, may also influence the relation between SES and poor outcome.[11] Particularly stereotyping of patients with different cultural or ethnic backgrounds and problems in communication between patient and provider play an important role.[59-63] Aside from causing suboptimal care,[60] the discrepancies may result in mistrust and lack of patient engagement in treatment, which only further promote SES-related health disparities.[61,62,64] Although the association between low SES and worse outcome is multifactorial and complex, a better understanding of the relation between low SES and worse outcome may help to attenuate health disparities. In addition to focus on bettering SES-related patient factors, increased physician awareness and improvement of communication between patient and provider may help to improve outcome of low SES surgical patients.[64]

In regards to the association between SES and major complications following surgery, a relation was found in univariate analysis, but point estimates decreased to 1 and significance was lost in the multivariable model. The fact that the relation did not maintain significance after adjusting for commonly considered health hazards suggests that SES is merely a proxy measure in this association and that it provides no additional value over conventional risk factors for the prediction of the short-term postoperative course.

This study has some limitations that should be considered. First of all, it should be noted that only patients who underwent surgery were included. Patients who were conservatively treated and those with prohibitive surgical risks due to severe comorbidity were consequently excluded. In addition, smoking status was unobtainable for a considerable amount of patients, and resulted in the exclusion of approximately 25% of cases in the full model. Although healthcare in the Netherlands has been established as equal among different layers of society, it would have been valuable to assess the association between socioeconomic status and the various parameters of access to and quality of healthcare. Unfortunately, our data provides insufficient detail to comment on the impact of household income on the different aspects of access and quality of care, and potential interactions. Finally, American studies that have reported on SES-related outcome and healthcare disparities often describe divergences between racial groups as well. Due to Dutch legislation, documentation of ethnicity in patient records is only allowed when medically relevant. Consequently, racial disparities could unfortunately not be investigated.

In conclusion, this study demonstrates that low household income, as an indicator of low SES, is a risk factor for overall and cardiovascular mortality following surgery. Considering the equality in access to and provision of healthcare provided by this study setting, the present results suggest that the observed health hazards accompanying low socioeconomic status are likely to be caused by patient and provider factors, rather than differences in medical care. Although the exact mechanism mediating the postoperative SES-related survival risk remains unclear, increased physician awareness and improvement of known SES-related risk factors and behaviors may help to improve surgical outcome among low SES patients.

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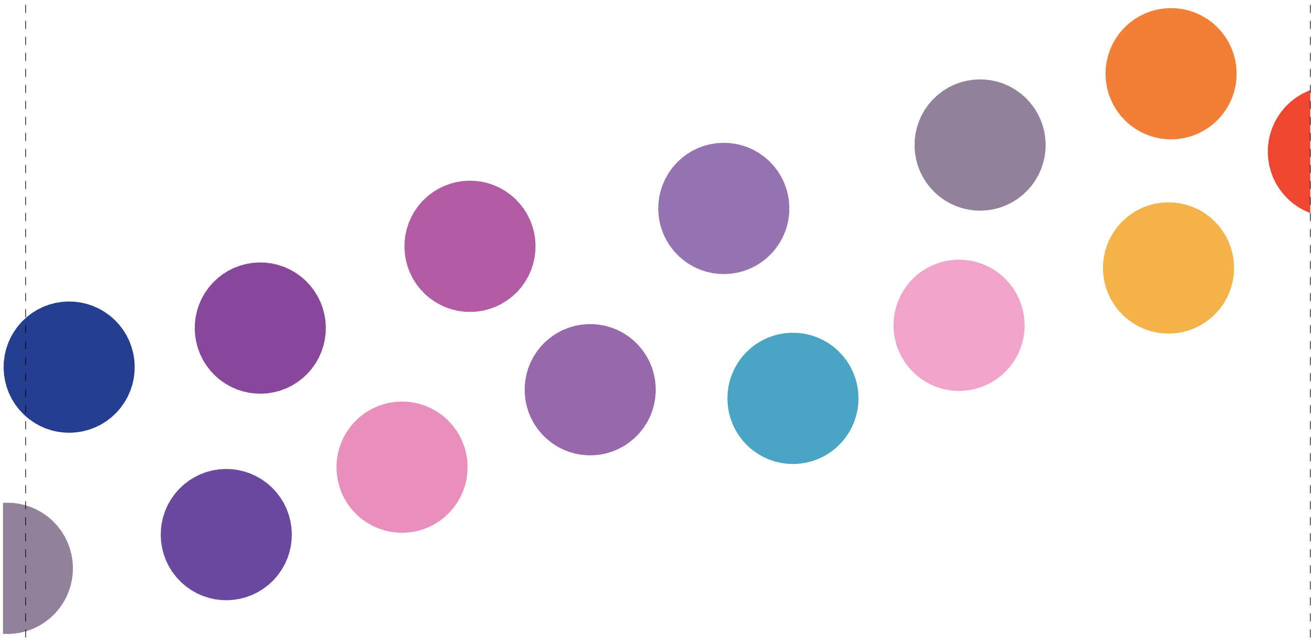
Supplemental Table 1. Risk classification of included surgical procedures.

Low risk surgery	**Procedure**
	Hernia surgery (except incisional hernia surgery)
	Varicose vein surgery
	Perianal surgery
	Minor trauma surgery
	Minor surgery of soft tissue
Intermediate risk surgery	**Procedure**
	Appendectomy
	Cholecystectomy
	Major abdominal surgery (i.e. liver, gastric, bowel, spleen esophagus, incisional hernia surgery)
	Head and neck surgery
	Thoracic surgery
	Major trauma surgery (i.e. multitrauma or trauma involving the femur or hip)



Chapter 8

Summary and discussion

Samenvatting en discussie

Dankwoord

Curriculum vitae

List of publications

PhD portfolio

SUMMARY AND DISCUSSION

The body mass index as a predictor of postoperative outcome

In *part I*, the significance of the body mass index as a predictor of postoperative outcome was assessed. Overweight and obesity are growing public health concerns, particularly in developing countries and this worrying trend is clearly perceptible in health care facilities as well.[1] A growing percentage of patients presenting for surgery is obese, moreover because various obesity-associated diseases require surgery. **Chapter one** described the influence of the body mass index on postoperative complications and long-term survival. Obese patients were compared to patients with overweight, normal weight and underweight. We analysed the impact of bodyweight on postoperative morbidity and mortality, as well as long-term mortality. First, the obese had more concomitant diseases, an increased risk of wound infection, longer operation time and greater intraoperative blood loss. Being underweight was associated with an even higher rate of complications. Second, when looking at long-term mortality, it was again the underweight patient with the highest risk, whereas being overweight or mildly obese was associated with improved survival. This phenomenon of improved survival in the overweight is also known as the obesity paradox. **Chapter two** presented a review of literature regarding this obesity paradox in a surgical population. In this review the obesity paradox has been established in both cardiac and non-cardiac surgical patients. However, patients at the extremes of BMI rankings (the underweight and the super obese) had the highest risk of postoperative morbidity and mortality, which persisted during long-term follow-up. In the underweight population cancer and respiratory diseases were responsible for excess mortality, whereas cardiovascular diseases accounted for the majority of deaths among the obese. Cancer, respiratory – and cardiovascular diseases are associated with malnutrition, wasting and inflammation, which might have explained patients' vulnerability at the extremes of BMI rankings. The cause of improved survival in overweight and mildly obese patients is likely multifactorial and several hypotheses that might account for the obesity paradox were presented in this review. It is important to realize that BMI does not specifically measure adiposity. Therefore overweight and mildly obese patients might just have an increase in lean body mass, instead of body fat.

Other possible explanations included theories on reduced inflammatory response, protective peripheral body fat, and a decline in in cardiovascular risk factors in overweight patients.

Chapter three evaluated the predictive value of an alternative BMI formula on postoperative complication and long-term survival in a large group of patients undergoing general surgery. This formula was mathematically designed to provide a more accurate estimation of weight categories, not limited in a two-dimensional manner. This study however, showed no difference in the prediction of outcome when comparing the new BMI formula to the conventional BMI formula and a change form the currently used and worldwide-accepted BMI formula was not supported. The BMI formula, as proposed by Quetelet almost two centuries ago, is an easy, safe and inexpensive acquirement of weight and stature and ever since, many studies have validated the formula as a reasonable marker of adiposity.[2,3] However, since the BMI formula is only a surrogate marker of body fat, it has been a topic of debate for as long as it exists. Future research, directed at more accurate indices of body fat distribution, such as waist circumference, or actual measurements of body compositions by computed tomography can be of clinical importance.

Advanced age and frailty as risk factors of adverse postoperative outcome

Part II was dedicated to clarify and assess risks associated with advanced age and frailty. The elderly present with unique health-care challenges; they have physiologic, pharmacologic, psychological, and social attributes different than younger counterparts. In **chapter four**, characteristics and outcomes of a large cohort of clinical patients, aged 80-years and older, undergoing non-cardiac surgical procedures were presented. The 30-day mortality risk in elderly patients undergoing low-risk procedures was 2,3%. However, patients undergoing intermediate – or high-risk surgery had much worse prognosis and overall, 30-day mortality was high (6,7%). We also evaluated time trends from 2004-2017 within this cohort. This analysis did not show a remarkable variation in the volume of procedures performed over the years, neither in postoperative mortality risk. In **Chapter five** we have presented a systematic review and meta-analysis, evaluating the predictive role of frailty on postoperative outcomes after non-cardiac surgery. A strong association between frailty and risk of postoperative complications, delirium, institutionalization and mortality was demonstrated. This chapter confirmed the importance of the identification of potentially reversible health deficits, as it may provide an opportunity to optimise patients prior to surgery. Better outcomes are beneficial and can also relieve the burden of the large and growing percentage of elderly on the hospital system. Conversely, irreversible frailty should be taken most seriously and guide both clinician and patient in deciding whether the patient benefits from surgery or not. Future studies should focus on using standardized, robust and validated frailty assessment tools. Preferably, these tools are time-efficient and suitable for the medical staff to be conducted at patient’s bedside. Also, effort towards standardisation of outcome measures can possibly improve study quality and quality of care. Recently members of the Dutch parliament have suggested geriatric consultation in any patient above 70 years old. This policy might be exaggerated, however; the presence of frailty seems a firm indicator for such consultation. Furthermore, it can be questioned whether the amount of geriatricians will be sufficient to provide all these consultations. Finally, the recent development of a surgical risk calculator, specifically designed to predict outcome in geriatric patients seems promising and can be used to capture this population's unique response to risk factors.[4] However, the presence of frailty is not included as an independent risk factor in this risk calculator.

Long-term prognosis after general surgery

Part III was dedicated to evaluate long-term prognosis and causes of death in the surgical population. Risk of mortality differs greatly in patients and surgical procedures and by evaluating outcomes, patients at risk can be identified. In **chapter six** we have described long-term mortality rates and causes of death in a general surgical population. Also, in addition to demographic and disease specific factors, the effect of postoperative complications on long-term mortality was explored. The 30-day mortality in our study population was 1,7% and was found similar to other reported studies performed in the Netherlands.[5] Long-term mortality however, was 16% at median follow-up of 6 years and was higher than expected. High-risk vascular surgery was an important predictor of late mortality and was associated with a twofold higher risk of cardiovascular death. Taking the surgical procedure itself into account when predicting risk of complications, rather than patients' comorbidity alone, remains very important.

The second group highly and independently associated with long-term mortality consisted of patients who experienced postoperative complications. Our data have demonstrated a reduced survival even in patients with self-limiting complications, whereas the prognosis in patients groups with non-self-limiting or major complications was considerably and increasingly worse. After exclusion of high-risk procedures in an additional sensitivity analysis, the association between complications and mortality remained in low and intermediate surgical risk patients. Therefore, focus on the prevention of postoperative complications can improve outcome in the surgical population. In **chapter seven** we have aimed to look beyond conventionally considered risk factors and evaluated the association between socioeconomic status (SES) and survival after general surgery. The relationship between SES and outcome after surgery has been the subject of studies over the past years and the association has been demonstrated previously.[6,7] However, these studies were often performed in countries and at times where SES-related disparity in access to and provision of healthcare existed and was effected by income. Since healthcare in the Netherlands is equally accessible and publicly provided among inhabitants, this study has provided a unique opportunity to evaluate the impact of SES on outcome, regardless of healthcare disparities. The principal finding of our study was that SES was a significant predictor of overall and cardiovascular mortality after surgery. This association maintained after the adjustment of demographics, comorbidities and behavioral risks and low SES could therefore be considered a risk factor on its own. Although the association between SES and outcome remains multifactorial and complex, increased awareness in healthcare providers and the improvement of SES-related risk factors and behaviors could help to improve surgical outcome in low SES patients.

In conclusion, this thesis presents the results of studies evaluating outcome after non-cardiac surgery. Thereby we have identified high-risk patients, or "outliers", high-risk surgical procedures and behavioral risks. Although the studies in this thesis do not include every imaginable "outlier", it is clear that patients at the upper and lower extremes of the BMI, the elderly and frail patients and patients with a low socioeconomic status are more at risk of postoperative morbidity and mortality. It is important to realize that not just patients' comorbidities and demographics are responsible for these risks; surgical risk and the occurrence of postoperative complications play an important role as well. From this perspective, when "outliers" are presented for surgery, we should weigh the potential benefits of an operation against possible perioperative risks even more and discuss this with our patients. Continued research in this medical field remains important, because surgery is a growing and substantial component of healthcare. Adding unconventional risk factors (such as frailty, or low SES) to (artificial intelligence) prediction models, besides the conventional ones, might improve prediction accuracy. Because "outliers" matter, we also recommend against the usual exclusion of these patients in current research and conversely we advise focusing on these groups in future studies. This thesis might have contributed to a better understanding of those at risk, providing an opportunity for clinicians to reduce patients' postoperative morbidity and increase their quality of life.

SAMENVATTING EN DISCUSSIE

De body mass index als voorspeller van postoperatieve uitkomst

In *deel I* werd het belang van de body mass index als een voorspeller van postoperatieve uitkomst onderzocht. Overgewicht en obesitas zijn belangrijke gezondheidsproblemen die, vooral in de westerse wereld, een epidemische omvang hebben bereikt. Deze zorgwekkende trend is ook duidelijk zichtbaar binnen gezondheidsinstellingen.[1] Het aantal obese patiënten dat wordt aangeboden voor een chirurgische ingreep stijgt, temeer omdat verscheidene obesitas gerelateerde aandoeningen chirurgisch ingrijpen vereisen.

In **hoofdstuk één** werd de invloed van de body mass index op postoperatieve complicaties en lange termijn overleving beschreven. Patiënten met obesitas werden vergeleken met patiënten met overgewicht, normaal gewicht en ondergewicht. De invloed van lichaamsgewicht op postoperatieve morbiditeit, mortaliteit en lange termijn overleving werd geanalyseerd. Patiënten met obesitas hadden meer comorbiditeit, een verhoogd risico op postoperatieve wondinfecties, een verlengde operatietijd en meer peroperatief bloedverlies. Ondergewicht werd geassocieerd met een nog hoger risico op postoperatieve complicaties. Wanneer gekeken werd naar lange termijn mortaliteit, liep opnieuw de patiënt met ondergewicht het hoogste risico, terwijl het hebben van overgewicht of milde obesitas juist geassocieerd werd met een betere levensverwachting. Dit fenomeen van een verbeterde overleving voor patiënten met overgewicht wordt ook wel de “obesitas paradox” genoemd.

In **hoofdstuk twee** hebben we een overzicht van de literatuur gepresenteerd met betrekking tot de obesitas paradox in de chirurgische populatie. De obesitas paradox kon zowel na cardiale als na niet-cardiale chirurgie worden aangetoond. Daarentegen hadden patiënten met extreme BMI waardes (ondergewicht en morbide obesitas) het hoogste risico op postoperatieve morbiditeit en mortaliteit, ook op de lange termijn. Pulmonale aandoeningen en maligniteiten waren de voornaamste veroorzakers van het verhoogde sterftecijfer in de populatie met ondergewicht, terwijl de meerderheid van de sterfgevallen in de obesitas populatie kon worden gerelateerd aan cardiovasculaire comorbiditeit.

Maligniteiten, respiratoire en cardiovasculaire aandoeningen worden geassocieerd met malnutritie, inflammatie en een katabole toestand, wat wellicht de toegenomen kwetsbaarheid van patiënten met extreme BMI waardes kan verklaren.

De oorzaak van de obesitas paradox is vermoedelijk multifactorieel en we hebben in dit literatuuroverzicht een aantal hypotheses gepresenteerd die de obesitas paradox zouden kunnen verklaren. Het is belangrijk te realiseren dat de BMI geen exacte afspiegeling is van de hoeveelheid lichaamsvet. Patiënten met overgewicht of milde obesitas kunnen dus een toegenomen vetvrije massa hebben, in plaats van lichaamsvet. Andere mogelijke verklaringen voor de obesitas paradox waren hypotheses over verminderde inflammatoire reactie, beschermend perifeer lichaamsvet en de reductie van cardiovasculaire risicofactoren in patiënten met overgewicht.

In **hoofdstuk drie** werd een alternatieve BMI formule getoetst op de voorspellende waarde voor postoperatieve complicaties en lange termijn overleving in een grote groep chirurgische patiënten. Deze formule werd mathematisch ontworpen met als doel een nauwkeurige schatting te geven van verschillende gewichtsklassen, niet gelimiteerd door een tweedimensionale opzet. Na vergelijking van deze alternatieve BMI-formule met de conventionele BMI formule, toonde deze studie echter geen verschil in het voorspellen van postoperatieve uitkomst en afwijken van de huidige en wereldwijd geaccepteerde BMI formule werd derhalve niet ondersteund. De BMI formule, zoals die bijna twee eeuwen geleden door Quetelet werd voorgesteld, is een makkelijke, veilige en goedkope verwerking van lengte en gewicht, die sindsdien door vele studies werd gevalideerd als een redelijke afspiegeling van adipositas.[2,3] De BMI formule blijft echter een onderwerp van discussie sinds hij gepubliceerd is, omdat deze enkel een schatting geeft van de hoeveelheid lichaamsvet. Toekomstig onderzoek, gericht op feitelijke bepalingen van de verdeling van lichaamsvet, zoals taille omtrek of de lichaamssamenstelling weergegeven door computertomografie, kan klinisch relevant zijn.

Gevorderde leeftijd en frailty als risicofactoren voor nadelige postoperatieve uitkomst

In *deel II* werd aandacht besteed aan opheldering en inschatten van risicofactoren geassocieerd met gevorderde leeftijd en kwetsbaarheid. In navolging van de Angelsaksische literatuur worden kwetsbare ouderen in dit proefschrift aangeduid als “frail”. Ouderen presenteren zich in de gezondheidszorg met unieke uitdagingen, waarbij zij zich op fysiologisch, farmacologisch, psychologisch en sociaal gebied onderscheiden van hun jongere tegenhangers. In **hoofdstuk vier** werden de karakteristieken en uitkomsten van een groot cohort patiënten, ouder dan 80 jaar, gepresenteerd die in een klinische setting niet-cardiale chirurgie ondergingen. Het risico op 30 dagen mortaliteit in deze groep ouderen die een laag-risico ingreep ondergingen bedroeg 2,3%. Echter, patiënten die een chirurgische ingreep ondergingen van hoog of gemiddeld risico, hadden een veel slechtere prognose. De 30-dagen mortaliteit van het gehele cohort was hoog (6,7%). Ontwikkelingen in tijd van dit cohort werden geëvalueerd van 2004-2017. Deze trendanalyse toonde geen opmerkelijke variatie in het aantal klinische ingrepen uitgevoerd over de jaren, noch in postoperatief risico op overlijden. In **hoofdstuk vijf** werd een systematische review en meta-analyse gepresenteerd, die de voorspellende waarde van frailty op postoperatieve uitkomsten evalueerde, na niet-cardiale chirurgie. Er werd een sterke associatie aangetoond tussen frailty en het risico op postoperatieve complicaties, delier, ontslag naar een andere zorginstelling en mortaliteit. Dit hoofdstuk bevestigt het belang van de herkenning van potentieel omkeerbare gezondheidsgebreken, waarmee de mogelijkheid ontstaat om patiënten preoperatief te optimaliseren. Betere postoperatieve uitkomsten zijn gunstig voor de patiënt, maar kunnen ook de toenemende druk van de vergrijzing op de gezondheidszorg verlichten. Daarentegen moet onomkeerbare frailty uiterst serieus genomen worden en meewegen in de gezamenlijke besluitvorming of een patiënt profijt kan hebben van een operatie, of juist niet. Toekomstig onderzoek zou gericht moeten zijn op het gebruik van gestandaardiseerde, robuuste en gevalideerde beoordelingsinstrumenten om frailty te diagnosticeren. Bij voorkeur zijn dergelijke instrumenten tijdbesparend en voor zorgprofessionals geschikt om te worden gebruikt aan het bed van de patiënt. Daarnaast zou de standaardisatie van uitkomstmaten de kwaliteit van studies en de kwaliteit van zorg kunnen verbeteren. Recent werd door leden van het Nederlandse parlement gesuggereerd om bij iedere patiënt boven de 70 jaar in het ziekenhuis een geriater te consulteren. Hoewel dit beleid overdreven lijkt, is de aanwezigheid van frailty een sterke indicator voor een dergelijk consult. Overigens zal het aantal geriaters waarschijnlijk niet toereikend zijn om iedere patiënt boven de 70 jaar te consulteren. Tot slot lijkt de recente ontwikkeling van een preoperatieve risico score, specifiek ontwikkeld om uitkomsten van de geriatrische patiënt te voorspellen, veelbelovend. Deze preoperatieve risico score kan worden gebruikt om de unieke gevoeligheid van deze populatie te voorspellen, hoewel de aanwezigheid van frailty niet als een onafhankelijke risicofactor wordt meegenomen in deze score.[4]

Lange termijn prognose na algemene chirurgie

Deel III was gewijd aan het evalueren van de lange termijn prognose en de oorzaak van overlijden na chirurgie. Het risico op postoperatieve mortaliteit verschilt per patiënt en per chirurgische procedure en door uitkomsten te evalueren kunnen patiënten met verhoogd risico worden geïdentificeerd. In **hoofdstuk zes** werden de mortaliteit op lange termijn en de oorzaak van overlijden in een algemene chirurgische populatie beschreven. Daarnaast werd (naast demografische en ziekte gerelateerde risicofactoren) het effect van doorgemaakte postoperatieve complicaties op lange termijn mortaliteit onderzocht. De 30-dagen mortaliteit in onze studie was 1,7% en was vergelijkbaar met eerder beschreven Nederlandse studies.[5] Echter, de lange termijn mortaliteit was 16% bij 6 jaar mediane follow-up en was hoger dan verwacht. Hoog-risico vaatchirurgie was een belangrijke voorspeller van mortaliteit op de lange termijn en werd geassocieerd met een tweevoudig verhoogd risico op een cardiovasculaire doodsoorzaak. Rekening houden met de chirurgische procedure zelf (en niet alleen met de comorbiditeit van de patiënt) blijft belangrijk wanneer men het risico op complicaties wil inschatten.

De tweede groep die sterk en onafhankelijk geassocieerd werd met lange termijn mortaliteit, bestond uit patiënten die postoperatieve complicaties doormaakten. Ons onderzoek heeft aangetoond dat patiënten met zelflimiterende complicaties al een verminderde levensverwachting hebben en dat de prognose van patiënten met niet-zelflimiterende of ernstige complicaties zelfs sterk was afgenomen. Na exclusie van hoog-risico chirurgie in een additionele sensitiviteitsanalyse, bleef de associatie tussen complicaties en mortaliteit staan in de laag- en gemiddelde chirurgische risicogroepen. Om die reden zal een eventuele verbetering van postoperatieve uitkomsten gericht moeten zijn op de preventie van complicaties.

In **hoofdstuk zeven** hebben we geprobeerd verder te kijken dan de conventionele risicofactoren, door de relatie tussen sociaaleconomische status (SES) en postoperatieve overleving te onderzoeken. De relatie tussen SES en postoperatieve uitkomst werd eerder onderzocht en ook aangetoond in de literatuur. [6,7] Echter, deze studies werden veelal verricht in landen en in tijden waar sociaaleconomische ongelijkheid bestond in de toegankelijkheid tot en de voorzieningen van de gezondheidszorg, die bovendien beïnvloed werd door inkomen. Aangezien de kwaliteit en de toegankelijkheid van de gezondheidszorg in Nederland voor iedereen gelijk is, bood deze studie een unieke mogelijkheid om de impact van SES op uitkomsten te bestuderen, zonder dat er ongelijkheden binnen de gezondheidszorg van invloed waren. De voornaamste uitkomst van onze studie was dat SES een significante voorspeller was voor de totale en de cardiovasculaire mortaliteit. Deze associatie bleef significant na het corrigeren voor demografie, comorbiditeit en gedragsrisico's. Derhalve kan een lage sociaaleconomische status worden beschouwd als een risicofactor op zichzelf. Hoewel de associatie tussen SES en postoperatieve uitkomst multifactorieel en complex blijft, kan de uitkomst mogelijk worden verbeterd voor patiënten met een sociaaleconomische achterstelling. Zeker als de zorgprofessionals aandacht besteden aan de risico's die geassocieerd zijn met lage sociaaleconomische status en bijbehorende gedragsrisico's.

Concluderend: in dit proefschrift werden de resultaten van studies gepresenteerd waarin we de uitkomst na niet-cardiale chirurgie hebben onderzocht. Daarmee hebben wij hoog-risico patiënten (in dit proefschrift aangeduid als “outliers”), hoog-risico procedures en gedragsrisico’s kunnen identificeren. Hoewel niet elk denkbare “outlier” in de studies van dit proefschrift werd onderzocht, is door ons aangetoond dat patiënten met extreem hoge of lage BMI-waardes, ouderen en kwetsbare patiënten en sociaaleconomisch achtergestelden een verhoogd risico hebben op postoperatieve morbiditeit en mortaliteit. Het is belangrijk te realiseren dat niet alleen de comorbiditeit van de patiënt en demografie verantwoordelijk zijn voor deze risico’s, maar ook de risico’s verbonden aan de ingreep zelf en eventueel doorgemaakte postoperatieve complicaties. Vanuit dit gezichtspunt zullen we, wanneer “outliers” zich presenteren voor chirurgie, samen met deze patiënt, de potentiele gezondheidswinst van een operatie nog uitgebreider tegen de mogelijke risico’s moeten afwegen. Verdere studies op dit medisch gebied zijn belangrijk, omdat chirurgie een groeiend en substantieel onderdeel vormt van de gezondheidszorg. Door het toevoegen van onconventionele risicofactoren zoals frailty, of lage sociaaleconomische status aan (artificieel intelligente) predictiemodellen, kan de voorspellingsnauwkeurigheid aanzienlijk worden vergroot. Omdat “outliers” ertoe doen, willen we afraden om deze patiënten standaard uit onderzoeken te excluderen en zelfs aanbevelen om in toekomstig onderzoek de aandacht te richten op deze en andere kwetsbare groepen patiënten. Dit proefschrift heeft mogelijk bijgedragen aan een beter begrip van patiënten met een verhoogd risico en daarmee biedt het zorgprofessionals de kans om de postoperatieve morbiditeit van patiënten te reduceren en hun kwaliteit van leven te verbeteren.

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CURRICULUM VITAE

Elke Kirsten Michelle Tjeertes was born on August 31st, 1982 in Hilversum, the Netherlands. After graduating secondary school in 2000, she applied for Medical school. Since admittance was based on a numerus clausus system, she studied psychology at Maastricht University from 2000-2001 and enrolled in medical school one year later. After obtaining her medical degree in 2007, she worked as a surgical resident in the Orbis Medical Center Sittard (head of the department dr. A.G.M. Hoofwijk). In this period the research presented in the thesis was started. From 2010 to 2015 she followed her specialist training in anesthesiology at the Erasmus Medical Center Rotterdam (head of the department Prof. dr. R.J. Stolker). The continuing and pleasant collaboration between the departments of anesthesiology and surgery has led to this PhD project. In June 2016 she started working as an anesthesiologist in joined partnership in Franciscus Gasthuis & Vlietland, Rotterdam. Elke is married to Joris van Fessem. Together they have two daughters Lauren (2013) and Ava (2015).

LIST OF PUBLICATIONS

1. **Tjeertes EKM***, Simoncelli TFW*, Van den Enden AJM, Mattace Raso FUS, Stolker RJ, Hoeks SE. *These authors contributed equally to this work. Perioperative and long-term outcomes in patients aged eighty years and older undergoing non-cardiac surgery. Submitted

2. **Tjeertes EKM**, van Fessem JMK, Mattace Raso FUS, Hoofwijk AGM, Stolker RJ, Hoeks SE. Influence of frailty on outcome in older patients undergoing non-cardiac surgery – a systematic review and meta-analysis. Aging and Disease 2019; Oct Volume 11 (5).

3. **Tjeertes EKM**, Ultee KHJ, Bastos Gonçalves FM, Rouwet EV, Hoofwijk AGM, Stolker RJ, Verhagen HJM, Hoeks SE. The relationship between household income and surgical outcome in the Dutch setting of equal access to and provision of healthcare. Plos One 2018; Jan 22; 13(1).

4. **Tjeertes EKM**, Hoeks SE, van Vugt JLA, Stolker RJ, Hoofwijk AGM. The new body mass index formula; not validated as a predictor of outcome in a large cohort study of patients undergoing general surgery. Clinical Nutrition ESPEN 2017; Dec 22; 24-27.

5. **Tjeertes EKM***, Ultee KHJ* , Stolker RJ, Verhagen HJM, Bastos Gonçalves FM, Hoofwijk AGM, Hoeks SE. * These authors contributed equally to this work. Perioperative complications are associated with adverse long-term prognosis and affect the cause of death after general surgery. World Journal of Surgery 2016; Nov 40(11); 2581-2590.

6. **Tjeertes EKM**, Hoeks SE, Beks SBJC, Valentijn TM, Hoofwijk AGM, Stolker RJ. Obesity – A Risk factor for Postoperative Complications in General Surgery? BMC Anesthesiology 2015; Jul 31(15); 112.

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8. Vening W, Willigendael EM, **Tjeertes EKM**, Hulsewé KWE, Hoofwijk AGM. Timing and necessity of a sigmoidoscopy in patients with symptoms suggestive of haemorrhoids. Colorectal Dis 2010; Feb 12(2); 109-13.

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1. PhD training

	Year
General Courses	
"Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers" (BROK)	2018
ECG-course	2010
Basic introduction course on SPSS	2001
Presentations	
Interactive lecture, anesthesiologendagen, Maastricht	2017
Interactive lecture, anesthesiologendagen, Maastricht	2016
Research conference, department of anaesthesiology, Rotterdam	2015
Research conference, department of anaesthesiology, Rotterdam	2014
Refereeravond, Franciscus Gasthuis, Rotterdam	2011
Science event, Franciscus Gasthuis, Rotterdam	2011
Conferences	
National conferences Nederlandse Vereniging voor anesthesiologie	2010-2019
Post-ASA meeting	2017
International conference ESA	2014

2. Teaching

	Year
Course "EPA's en bekwaam verklaren", Rotterdam	2018
"Landelijk opleidingsplan anesthesiologie", Utrecht	2018
Teach the teacher III course ("Opleiders"), Rotterdam	2017
Lecture Postoperative delirium	2019
Lecture Patient positioning and potential hazards	2018
Lecture Pulmonary hypertension	2017
Lecture Perioperative mortality	2015
Lecture Perioperative complications	2014
Lecture Perioperative anticoagulation	2014
Trusted person, tutor and supervision of anaesthesiology residents, Rotterdam	2016-2019