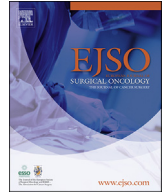




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Postponing surgery to optimise patients with acute right-sided obstructing colon cancer - A pilot study

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ABSTRACT

Background: Right-sided obstructing colon cancer is most often treated with acute resection. Recent studies on right-sided obstructing colon cancer report higher mortality and morbidity rates than those in patients without obstruction. The aim of this study is to retrospectively analyse whether it is possible to optimise the health condition of patients with acute right-sided obstructing colon cancer, prior to surgery, and whether this improves postoperative outcomes.

Method: All consecutive patients with high suspicion of, or histologically proven, right-sided obstructing colon cancer, treated with curative intent between March 2013 and December 2019, were analysed retrospectively. Patients were divided into two groups: optimised group and non-optimised group. Pre-operative optimisation included additional nutrition, physiotherapy, and, if needed, bowel decompression.

Results: In total, 54 patients were analysed in this study. Twenty-four patients received optimisation before elective surgery, and thirty patients received emergency surgery, without optimisation. Scheduled surgery was performed after a median of eight days (IQR 7–12). Postoperative complications were found in twelve (50%) patients in the optimised group, compared to twenty-three (77%) patients in the non-optimised group ($p = 0.051$). Major complications were diagnosed in three (13%) patients with optimisation, compared to ten (33%) patients without optimisation ($p = 0.111$). Postoperative in-hospital stay, 30-day mortality, as well as primary anastomosis were comparable in both groups.

Conclusion: This pilot study suggests that pre-operative optimisation of patients with obstructing right sided colonic cancer may be feasible and safe but is associated with longer in-patient stay.

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1. Introduction

The management of obstructing colon cancer is diverse. Patients treated with emergency surgery have a higher postoperative morbidity rates than patients with non-obstructing colon cancer [1–5]. In particular, elderly patients with (multiple) comorbidities are vulnerable to complications after emergency surgery [5–7]. The

reasons for high postoperative morbidity after emergency surgery have been widely discussed [6–11].

Different treatment options to optimise the preoperative health status of patients suffering from obstructing colon cancer have been investigated over the years [12–23]. Multiple treatment options to postpone emergency surgery for left-sided obstructing colon cancer have been evaluated [12,13,15,22,24], while literature on different treatment options for right-sided obstructing colon cancer is far less extensive [16,17,25,26]. The majority of patients with right-sided obstructing colon cancer are still treated with emergency resection [27,28]. Varying rates in postoperative mortality after emergency surgery for right-sided obstructing colon cancer have been reported [7,8,11,27,29]; postoperative mortality and morbidity rates found in patients with right-sided obstructing colon cancer are higher compared to patients treated electively for colon cancer [8,11,27,30,31].

Abbreviations: CRC, colorectal cancer; CT - scan, computed tomography scan; ERAS, enhanced recovery after surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; IQR, interquartile range; MEC-U, Medical Research Ethics Committees United; SEMS, self-expandable metallic stenting; TPN, total parenteral nutrition.

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Over the years, short-term postoperative morbidity and mortality in patients with colorectal cancer (CRC) have decreased, due to efforts such as improved preoperative care and enhanced recovery after surgery (ERAS) programs [32–34]. Novel insights suggest that, in addition to improvements in postoperative care, the preoperative health condition influences the postoperative outcome in patients with CRC [35–40]. Recent evidence suggests that prehabilitation (preoperative training and nutritional programmes) improves the health condition and postoperative outcome in elective surgery patients [41–44]. Prehabilitation has promising results in the outcomes of spinal surgery, thoracic surgery, coronary artery bypass graft surgery, oesophagogastric surgery, major abdominal surgery and elective colorectal surgery [42,43,45–50]. It is unknown whether prehabilitation is beneficial in patients who are diagnosed with an acute obstruction caused by CRC, due to the limited time frame for prehabilitation.

In patients with obstructing colon cancer, postponing surgery grants additional time to complete a preoperative screening of the patient's health condition, in order to examine possible comorbidities, and to evaluate the possibility of treating and optimising the patient's medical condition. This study aims to retrospectively analyse whether postponing surgery, to optimise the patients' medical condition, is feasible and safe in patients with acute right-sided obstructing colon cancer.

2. Material and methods

2.1. Database and definitions

This is a retrospective single-centred observational cohort study. Data was collected from all patients treated surgically, between March 2013 and December 2019, in our hospital, with a high suspicion of, or histologically proven, CRC. Patients presenting symptoms of obstruction due to right-sided OCC were included. (Near) obstruction is defined as patients presented with severe reduced oral intake with symptoms of nausea, vomiting, difficulty bowel movement, and/or weight loss. No specific considerations were made for the determination whether or not the ileocecal valve was competent. Right-sided colon cancer was defined as a tumour primarily located in the caecum, ascending colon, hepatic flexure, or transverse colon proximal to the splenic flexure. A clinically suspected obstruction could be confirmed by a dilated colon and/or ileum with a computed tomography scan (CT scan). Excluded from the study, were all patients with obstructions caused by other reasons than colon cancer, patients with metastatic disease receiving palliative treatment at the time of diagnosis, patients without description of the location of the primary tumour, as well as patients younger than 18 years of age. Demographic, clinical, tumour-related, and surgery-related data were collected from medical records. The urgency of the surgery was classified into four categories: emergency surgery, semi-acute surgery, postponed elective surgery and other surgical procedures. In the case of an emergency operation, surgery was performed within 24 h after the diagnosis of obstructing colon cancer, or within 24 h after surgical consultation. Semi-acute surgery was performed within 72 h of diagnosis, and postponed elective surgery was performed after optimisation of the patients' medical condition. If no optimisation was performed, and surgery was performed more than 72 h after diagnosis, the patients were classified as treatment 'other'.

In patients who did receive optimisation, surgery was postponed in order to improve their preoperative health condition. The decision for optimisation was made by the patients' treating physician. Optimisation of health condition included supplementary nutrition (total parenteral nutrition (TPN) or tube feeding), physiotherapy before surgery, and, if needed, bowel

decompression. Bowel decompression was performed using a decompressing nasogastric tube or by means of self-expandable metallic stenting (SEMS). Surgery-related mortality was defined as death within 30 days after surgery, or in-hospital death during hospital admission. Pathological classification of the tumour was based on the TNM classification. All complications surrounding the surgical treatment were collected from patients' medical records. Complications were divided into two categories: preoperative complications (complications diagnosed before the surgery was performed, when admitted at the hospital) and postoperative complications (complications diagnosed after surgery), which were reported until 90 days after presentation in the surgical department. All complications were scored according to the Clavien-Dindo classification [51].

2.2. Ethical standards

The Medical Research Ethics Committees United (MEC-U) was consulted for ethical approval. They confirmed that the Medical Research Involving Human Subjects Act (WMO) does not apply to this study (reference number W19.099).

2.3. Statistics

The normal distribution of the data was tested. In the case of a normal distribution, the mean and standard deviation were delineated. If data were non-normally distributed, the median and interquartile range (IQR) were reported. The Mann-Whitney *U* test was performed to determine significant differences between groups on continuous variables. χ^2 -tests and Fisher exact tests were utilized to compare categorical variables. All data analyses were performed with IBM SPSS Statistics Program version 25.

3. Results

Between March 2013 and December 2019, a total of 74 patients with right-sided obstructing colon cancer were treated in the surgical department of our hospital. Twenty patients were excluded from the study for the following reasons: either, patients were treated with palliative intent for right-sided colon cancer ($n = 16$), or a bowel perforation was identified at the time of diagnosis ($n = 4$) (Fig. 1).

The remaining 54 patients that received surgical treatment for right-sided obstructing colon cancer were included for analyses. The median age of the complete group was 72 years (IQR 66–79), and sex was equally divided (male: $n = 29$, 54%). The primary tumour was located in the caecum in most patients ($n = 25$, 46%), followed by the ascending colon ($n = 14$, 26%) (Table 1). Preoperative American Society of Anaesthesiologists (ASA) classification between both groups showed no significant difference between ASA I t/m IV (Table 1).

3.1. Optimisation versus non optimisation

Optimisation was performed in 24 patients (44%), whereas 30 patients (56%) received surgery without optimisation. The median age of patients in both groups was comparable, i.e., 72 and 71.5 years. The optimised group consisted of more women (71%, $n = 17$) compared to the non-optimised group (27%, $n = 8$; $p < 0.01$). Primary tumour locations were comparable in both groups (Table 1).

Patients in the optimised group received a decompressing nasogastric tube in 67% ($n = 16$) of the cases. One patient received self-expandable metallic stenting (SEMS) as a bridge to surgery in the transverse colon. Nutrition was optimised using TPN in 96% of the patients ($n = 23$), with a median time of 8 days (IQR 7–11)

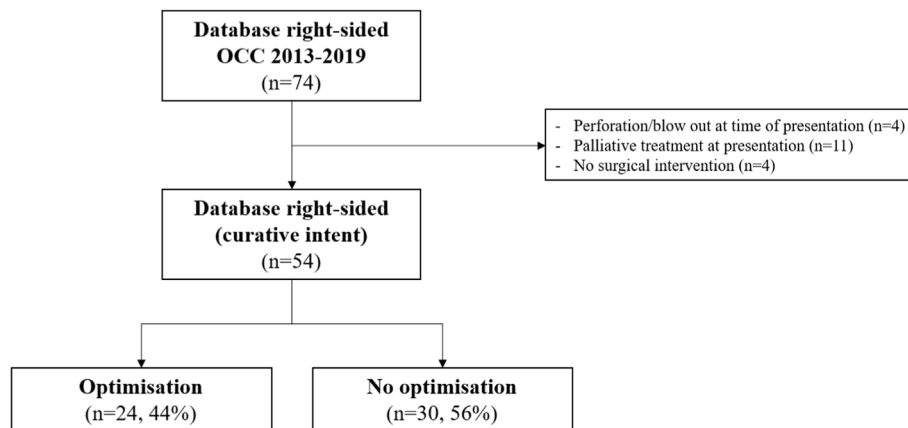


Fig. 1. Flow-chart of inclusion.

Table 1

Treatment characteristics per group (optimisation versus no optimisation).

	Optimised group (n = 24)	Non-optimised group (n = 30)	p-value
Urgency of operation			
Acute surgery (<24 h)	0	18 (60)	<0.01*
Semi-acute surgery (<72 h)	0	11 (37)	<0.01*
Other (>72 h)	0	1 (10)	1.000
Electively	24 (100)	0	<0.01*
Pre-operative nutrition			
TPN	23 (96)	-	NA
Probe feeding	3 (13)	-	NA
Preoperative complication	5 (21)	1 (3)	0.078
Optimisation (days)	8 (IQR 7–12)	-	NA
ASA classification			
ASA I	1 (4)	1 (3)	1.000
ASA II	9 (38)	12 (40)	1.000
ASA III	12 (50)	7 (23)	0.051
ASA IV	2 (8)	1 (3)	0.578
Missing	0	9 (30)	<0.01*
Surgical approach			
Laparoscopic	6 (25)	5 (17)	0.510
Conversion to laparotomy	7 (29)	0	<0.01*
Laparotomy	11 (46)	24 (80)	0.012*
Surgical treatment			
Resection + anastomosis	17 (71)	21 (70)	1.000
Resection + -ostomy	4 (17)	4 (13)	1.000
Decompressing -ostomy	2 (8)	3 (10)	1.000
Intestinal internal bypass	1 (4)	2 (7)	1.000
Synchronous metastases	8 (33)	10 (33)	1.000
During surgery	5 (21)	8 (26)	0.753
< 6mnd after OCC diagnosis	3 (13)	2 (7)	0.646
Per-operative metastases			
Peritoneum	4 (17)	6 (20)	1.000
Liver	0	1 (3)	1.000
Distant lymph nodes	1 (4)	1 (3)	1.000
Postoperative complication	12 (50)	23 (77)	0.051
Major complication	3 (13)	10 (33)	0.111
Re-operation	2 (8)	5 (17)	0.443
In hospital stay (postop)	8.0 (5–10)	10 (7–16)	0.133
In hospital stay**	17 (12–23)	10 (7–16)	<0.01*
Mortality			
30-day/in hospital	1 (4)	1 (3)	1.000
90-day (surgical consultation)	1 (4)	4 (13)	0.367

*Significant value, ** Optimisation duration + postoperative stay (days).

(Table 1). Two of the patients (8%), who had started with enteral tube feeding, switched to TPN, due to nausea and/or vomiting caused by the obstruction. Surgery was postponed for a median of eight days (IQR 7–12 days) for all patients in the optimised group. One patient received surgery earlier than initially planned, after seven days of optimisation, while no further improvement of decompression was achieved. The patient was treated in elective

setting and emergency interference was not needed. In the non-optimised group, patients were most often operated on within 24 h (n = 18, 60%) or 72 h (n = 11, 37%) after diagnosis. Surgery was postponed for more than 72 h in one patient within the non-optimised group, for whom analysis for chronic lymphocytic leukaemia was required prior to surgery.

3.2. Preoperative complications

During the preoperative optimisation period, complications were reported in five patients (21%) (Table 2). The complications diagnosed preoperatively in the optimised group included pneumonia, leakage of the central venous catheter, atrial fibrillation, bladder retention and fever of an unknown origin. One major complication was reported in the optimised group: pneumothorax after placement of a central venous catheter, which was then treated with a chest tube.

3.3. Surgery

The surgical approach was significantly different between both groups. In the non-optimised group, median laparotomy was performed in 24 patients (80%), compared to 11 (46%) patients in the optimised group ($p = 0.012$). Completed laparoscopic surgery showed no difference between both groups, however seven patients (29%) in the optimised group did need a conversion from a laparoscopic procedure to a laparotomy. In the optimised group, resection was performed in 88% of the patients ($n = 21$) (Table 1). In three patients (13%), no resection was performed, due to peritoneal metastases diagnosed during the surgical procedure. The peritoneal depositions were biopsied, and ileostomy ($n = 2$) or intestinal bypass ($n = 1$) were performed. In the patients receiving tumour resection, primary anastomosis was considered unsafe in three of the cases, as a result of a significant dilation of the ileum or colon (Table 1).

In the non-optimised group, a resection was performed in 83% ($n = 25$), and a primary anastomosis after resection was constructed in 84% ($n = 21$, $p = 1.00$) (Table 1). In five of the patients (17%), a resection was not performed, due to one of the following reasons: either a generalised metastatic disease was diagnosed during the surgical procedure, leaving only a palliative treatment option ($n = 2$), a peritoneal disease with the possibility of hyperthermic intraperitoneal chemotherapy (HIPEC) was detected during surgery ($n = 2$), or a resection of the tumour was technically unfeasible ($n = 1$).

3.4. Postoperative course

In the optimised group, patients were discharged from the surgical department after a median of eight days (IQR 5–10 days) after surgery, compared to ten days (IQR 7–16 days) in the non-optimised group ($p = 0.133$). Total length of preoptimisation and postoperative in hospital stay was calculated in 48 of the patients. Two of the patients, who died directly after surgery, were excluded from this analysis. Patients in the optimised group had a significantly longer median hospital stay of 17 days (IQR 12–23), compared to patients in the non-optimised group (median of 10 days, IQR 7–16) ($p < 0.01$) (Table 1). Postoperative complications

were reported in 35 of the patients (65%) (Table 2). Complications were found in twelve (50%) patients within the optimised group, compared to twenty-three (77%) patients in the non-optimised group ($p = 0.051$). Major complications were diagnosed in three (13%) of the patients with optimisation, compared to ten (33%) patients without optimisation ($p = 0.111$) (Table 3).

4. Discussion

The goal of optimisation is ultimately to improve the patients' health condition before surgery. Although the length of postoperative in-hospital stay, the 30-day mortality rate as well as the primary anastomosis rate, were unaffected by optimisation, this pilot study suggests that optimisation in patients with right-sided obstructing colon cancer is safe and feasible. Optimisation in patients may result in fewer complications, compared to patients without optimisation before surgery; especially relevant in this specific patient population.

Postoperative outcome in patients with CRC has improved immensely over the last decade due to an intensified focus on perioperative improvements and enhanced recovery after surgery programmes [32–34]. The preoperative period has gained significant attention as a possible step to improve surgical outcomes, as it grants patients and physicians additional time before a colon cancer surgery. This supplemental time provides an opportunity to improve the patients' health condition and, thus, provides their ability to cope with the metabolic costs of surgical stress [46]. The functional capacity of the patient seems to be an important factor in postoperative mortality and morbidity rates in elective (colorectal) surgery [39,40,44,52–54]. A recent randomized clinical trial showed the importance of exercise prehabilitation in elective colon cancer surgery [55]. Postoperative complications in high-risk patients treated electively for colon cancer were significantly lower in patients receiving prehabilitation exercises compared to patients treated with the usual after care. Prehabilitation exercise was individually correlated with a decreased 30-day risk of postoperative complications, and should therefore be considered as a normative care option in high-risk patients scheduled for elective colon surgery [55]. Prehabilitation and usual care groups in the recent study compared to these studies show similarities in postoperative complication rates, respectively 43% and 72% in the prehabilitation vs. the usual care groups, compared to 50% and 77% in this pilot study.

For patients with obstructing colon cancer, prehabilitation or optimisation studies are rare [56]. In obstructing colon cancer, the preoperative timeframe is short, or simply non-existent. This while the benefits of optimisation in patients with obstructing colon cancer might be of significant value while patients often present a poor preoperative health condition. However, postponing surgery in obstructing colon cancer is not yet implemented due to fear of further deterioration. In case of postponing surgery, it is of great

Table 2
Number of pre- and postoperative complications per group (optimisation versus no optimisation).

	Optimised group ($n = 24$)	Non-optimised group ($n = 30$)	p-value
Preoperative complications			
No complications	19 (79)	29 (97)	0.078
One complication	3 (13)	1 (3)	0.312
Two complications	1 (4)	0	0.444
Three or more complications	1 (4)	0	0.444
Postoperative complications			
No complications	12 (50)	7 (23)	0.051
One complication	6 (25)	9 (30)	0.766
Two complications	5 (21)	2 (7)	0.221
Three or more complications	1 (4)	12 (40)	<0.01*

Table 3
Number of postoperative complications per group (optimisation vs. no optimisation).

	Optimised group (n = 24)	Non-optimised group (n = 30)	p-value
Clavien-Dindo grade I			
Abscess operation wound	0	2 (7)	0.497
Bladder retention	1 (4)	4 (13)	0.367
Fever of unknown origin	1 (4)	0	0.444
Pressure-ulcus	0	2 (7)	0.497
Surgical site infection	4 (17)	8 (27)	0.515
Clavien-Dindo grade II			
Atrial fibrillation	1 (4)	0	0.444
Blood transfusion	0	1 (3)	1.000
Cardiac failure	0	2 (7)	0.497
Candida infection	1 (4)	0	0.444
Central venous line infection	1 (4)	0	0.444
Chest pain with ECG changes	0	1 (3)	1.000
Delirium	1 (4)	5 (17)	0.210
Diarrhoea (medication)	0	2 (7)	0.497
Gastroparesis	1 (4)	0	0.444
Haematuria	0	1 (3)	1.000
High-output -ostomy	0	4 (13)	0.120
Ileus	1 (4)	5 (17)	0.210
Intra-abdominal abscess	1 (4)	1 (3)	1.000
Pneumonia	2 (8)	5 (17)	0.443
Pulmonary embolism	0	2 (7)	0.497
Rectal blood loss	1 (4)	0	0.444
Sepsis	0	3 (10)	0.245
Urinary tract infection	0	2 (7)	0.497
Weight loss (tube feeding)	0	1 (3)	1.000
Clavien-Dindo grade III			
Fascia dehiscence ^a	1 (4)	2 (7)	1.000
Infected intra-abdominal hematoma ^a	0	1 (3)	1.000
Infected thrombus ^a	0	1 (3)	1.000
Leakage blind loop ^a	1 (4)	0	0.444
Mechanic ileus ^a	0	1 (3)	1.000
Mycotic aneurysm ^a	0	1 (3)	1.000
Necrosis of the bowel ^a	0	1 (3)	1.000
Necrosis of the -ostomy ^a	0	1 (3)	1.000
Small bowel perforation ^a	1 (4)	2 (7)	1.000
Clavien-Dindo grade IV			
Acute kidney failure	0	1 (3)	1.000
Multi-organ failure	0	1 (3)	1.000
Reanimation	0	2 (7)	0.497
Respiratory distress (ICU)	0	1 (3)	1.000
Clavien-Dindo grade V			
Death (30-day/in hospital)	1 (4)	1 (3)	1.000

^a Re-operation.

importance is to ensure decompression of the small bowel, and if present decompression of the colon. In this retrospective study, special care was given to adequate decompression of the bowel while possible potent ileocecal valve was not specified. In order to achieve adequate decompression during optimisation we believe that next to placement of an NG tube for decompression, clinical evaluation by a physician and monitoring of the NG tube output is mandatory. Alleviation of pain experienced by the patient after decompression indicates adequate management. However, in case of a steep increase in the leukocyte count (L) and/or C-reactive protein (CRP) level, combined with abdominal pain and/or clinical deterioration surgical interference is indicated. Based on the findings from this pilot study, postponing emergency surgery, to generate more time to optimise the patients' preoperative health, seems to be a feasible additional step in the treatment of right-sided obstructing colon cancer.

Optimisation in patients with right-sided obstructing colon cancer did not alter the postoperative short-term mortality, the postoperative in-hospital stay nor the primary anastomosis rates in the current pilot. However, optimisation did affect the short-term outcomes in terms of the amount of complications. Furthermore, patients with optimisation seemed to have a lessened amount of severe complications, compared to patients treated with

emergency surgery. The feasibility of implementing optimisation was determined by the treating physician and positive results after optimisation led to more confidence in this treatment by treating physicians; therefore, it was utilized more frequently over the years. Over the years, development and improvement of operative skills and perioperative treatment may positively influence the postoperative complication rates for the optimisation group. However, the main goal of this pilot study, investigating the feasibility of optimisation in obstructing colon cancer, has been clearly established.

It must be noted that the study had the well-known limitations of being retrospective. Patients with obstructing colon cancer were treated ultimately determined by the treating physician. This has led to selection bias. The positive results after optimisation led to a more confident approach by the treating physicians to use this protocol; it was therefore applied more frequently over the years. This creates a form of selection bias. The main goal of the study was to examine the feasibility of optimisation in right-sided obstructing colon cancer which has been accomplished, despite the bias in this retrospective series. Second no specific optimisation protocol was available at the start of optimisation, which could have led to suboptimal optimisation. However, all patients received additional nutrition prior to surgery, advised by the hospital dietician using

the SNAQ score. In addition, no specific physical training schedule was detained. However, the hospital policy consisted of individual physiotherapy for all patients at the surgical oncological department. Therefore, all patients treated in the optimised group received individual preoperative physiotherapy adjusted to their performance state. Unfortunately, baseline measurements of the patients physical performance state were neither stated at the start of optimisation nor just before surgery. Which could have shown the influence of physical therapy on the performance state of patients treated with optimisation prior to surgery. Finally, the long-term results of optimisation in patients with right-sided obstructing colon cancer are yet unknown. Postponing emergency surgery, and therefore delaying tumour resection, has not been evaluated for right-sided obstructing colon cancer. Therefore, more long-term (oncological) data needs to be evaluated in the future.

This is the first study that investigated the feasibility of optimisation, prior to surgery, in patients with potentially curable right-sided obstructing colon cancer. Even though optimisation in patients with right-sided obstructing colon cancer did not change the postoperative short-term mortality in this pilot study, a positive trend in the postoperative outcome of the optimisation group was observed. While it has already been shown that mortality and morbidity are related to the patients' preoperative health condition in elective colon cancer surgery, a larger number of patients treated by optimisation are needed to demonstrate its significant positive influence. To further analyse optimisation in patients diagnosed with obstructing colon cancer, a prospective registration study was set up (NL8266). The data collected in this pilot study will be used for the power analysis to estimate the minimum number of patients needed for a more conclusive result.

5. Conclusions

This pilot study showed that optimisation in patients with acute right-sided obstructing colon cancer is safe and feasible, and suggests that optimisation may lead to fewer postoperative complications, compared to patients with no optimisation before surgery. To investigate the potential benefits in the addition of optimisation to the current treatment protocol for patients with obstructing colon cancer, a prospective study was initiated (NL8266).

Credit author statement

Jeske Boeding: Methodology, Data Curation, Formal analysis, Writing - Original Draft, Writing - Review & Editing, Funding acquisition **Iris Cuperus:** Data Curation, Formal analysis.

Arjen Rijken: Conceptualization, Methodology, Writing - Review & Editing **Rogier Crolla:** Conceptualization, Methodology, Writing - Review & Editing **Cornelis Verhoef:** Formal analysis, Writing - Original Draft, Writing - Review & Editing, Supervision **Paul Gobardhan:** Conceptualization, Methodology, Writing - Review & Editing, Funding acquisition **Jennifer Schreinemakers:** Conceptualization, Methodology, Writing - Original Draft, Writing - Review & Editing, Funding acquisition, Supervision.

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Data availability statement

Data can be requested by the corresponding author.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jeske R.E. Boeding reports financial support was provided by Wetenschapsfonds Amphia.

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