The prevalence and preventability of medication-related readmissions after bariatric surgery: an interim analysis

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ABSTRACT

Aim: The anatomical changes to the gastrointestinal tract that result from bariatric surgery, are not merely associated with changes in food intake, but could also affect the pharmacokinetics of oral medication. This study aims to establish the influence of bariatric surgery on the prevalence and preventability of medication-related readmissions (MRRs), a topic yet unexplored.

Methods: In this single centre, retrospective, observational study, unplanned hospital readmissions of patients who underwent primary bariatric surgery between January 1, 2018 and August 31, 2020 in the St. Antonius hospital, The Netherlands were included. Readmissions had to have taken place within the two year follow-up period. Admission records were screened for potential adverse drug events, which were then assessed for causality and preventability. Readmissions were classified as medication-related or medication-unrelated, the former further categorised as preventable or non-preventable. Comparisons between the two types of admissions (medication-related or unrelated) were performed using the appropriate statistical tests.

Results: This interim analysis included 89 unplanned readmissions of which 10.1% (n= 9) were identified as medication-related. Of these MRRs, 33.3% (n= 3) were considered potentially preventable. There were no statistically significant differences when comparing surgery years (p = .362), surgical procedures (p= .056) and time to readmission (p= .830) between the two types of readmissions.

Conclusion: This study demonstrated that 10.1% of the unplanned hospital readmissions after primary bariatric surgery were medication-related, of which 33.3% potentially preventable. To reduce the number of preventable MRRs in the future, additional interventions such as pharmacist-led medication reviews could be considered in patients who are at higher risk for preventable MRRs.

INTRODUCTION

It is estimated that 17.5% of the global population will be obese by 2030 (1). Consequently, the need for adequate weight loss management will continue to rise. The World Health Organisation defines obesity as a body mass index (BMI) 30 kg/m2 or higher (2). Obesity can be further classified according to its severity, with class III being the highest (BMI ≥ 40). Class III obesity is also known as severe or morbid obesity (3). Obesity is associated with an increased risk of cardiovascular diseases, diabetes and several types of cancer (4). Current available methods for weight loss are conventional (diet, exercise, mental health), pharmaceutical and/or surgical. Bariatric surgery remains the most effective treatment for morbid obesity. It is effective in establishing long-term weight loss, improvements of comorbidities, quality of life and survival rate (5).

At present, Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are two of the most performed bariatric procedures.(6) With RYGB, a small pouch is created from the stomach and connected to the small intestines, thus partially bypassing the gastro-intestinal tract. With SG, a large portion of the stomach is vertically resected, thus producing a tube shaped stomach (7). It has been recognized that these gastrointestinal changes induced by bariatric surgery may have an influence on the absorption, distribution, metabolism and/or elimination of orally administered medication (8).

Earlier studies have shown overall 180-day readmission rates of 7.8% and 13.2% after SG and RYGB, respectively, while one study even suggested that one out of four bariatric patients will be readmitted within two years of surgery (9,10). Furthermore, a systematic review by El Morabet et al. regarding medication-related hospital readmissions has reported a median prevalence of 21%, with the interquartile range (IQR) between 14-23%. (11). When limiting the readmission window to 30 days after discharge, Uitvlugt et al. found a prevalence of 16% (12). Both El Morabet et al. and Uitvlugt et al. investigated medication-related readmissions without focusing on a specific medical conditions.

Despite these earlier findings, little is known about the prevalence of medication-related readmissions (MRRs) after bariatric surgery. This is especially relevant given the prior knowledge that the pharmacokinetics of oral medication changes after surgery (8). As a result, bariatric surgery may lead to an increased risk of MRRs due to causes such as therapy failure or overdosing.

This study aims to provide a clear overview on the prevalence and preventability of MRRs within two years following primary bariatric surgery. Through this study, we aim to identify areas for improvement in bariatric patient care.

METHODS

Setting and sample population

This was a single centre, retrospective observational study carried out in St. Antonius hospital, The Netherlands over a period of five months.

Readmissions were eligible for inclusion if the readmitted patient had undergone a primary procedure of RYGB or SG in the St. Antonius hospital, The Netherlands between January 1, 2018 and August 31, 2020. The surgery date was also registered as the index date. Additionally, the readmissions had to be unplanned and had to have taken place after primary bariatric surgery. Unplanned readmissions included unplanned hospital visits (e.g. emergency room) and unplanned hospitalisations. The unplanned readmission had to have taken place within the follow-up period, which was two years post-index date. In case of repeated readmissions within the follow-up period, only the first readmission was included.

Readmissions were excluded if the readmission was due to attempted suicide; if the readmission was to the obstetrics department; or if the readmission took place after revisional bariatric surgery. Lastly, readmissions of patients who have objected to sharing data for scientific research have been omitted from the study.

This study was reviewed and approved by the regional Medical Research Ethics Committee 'MEC-U', as well as the local review committee within the St. Antonius hospital. The study was registered under R&D/Z22.069.

Data collection

Identification of readmissions was performed by the Business Intelligence department of the St. Antonius hospital. Patients were identified by the procedural codes for RYGB or SG linked to their medical record.

Baseline characteristics were collected from the patient's medical record. Characteristics at index consisted of sex, age, BMI, type of surgery, surgery date, preoperative comorbidities, Charlson Comorbidity Index (CCI) score, number of medications before and after surgery and whether medication reconciliation had taken place at discharge. Characteristics at readmission included age, BMI, readmission and discharge date, medical department (surgical/non-surgical or visit), length of stay and number of medications before readmission.

To establish the number of medications in use, the medication overview, after medication reconciliation by the hospital pharmacy, was reviewed. If medication reconciliation did not take place, the medication overview established by the physician was adopted. When neither options were available, the number of medications in use was estimated using the expected medication list, generated by the hospital information system. We recognised a substance as medication if it was present in the national medicine register. Different dosages of the same active pharmaceutical ingredient counted towards one. Moreover, due to the nature of the study, vitamin and mineral supplements also contributed to the number of medications in use.

Missing data

If BMI was not registered in the relevant record, we accepted a previous or future BMI up to four weeks of difference. Missing data (n= 10, 11.2%) was substituted by the median BMI of the sample (13). Missing data existed largely in hospital visits rather than hospitalisations. A probable cause is due to the relatively

short amount of time patients spent at the hospital during a visit, thereby standard procedures such as medication reconciliation or the registration of body weight and height might be neglected.

Study procedures

A two-step approach was carried out to identify and review possible MRRs. This method consisted of identification of potential adverse drug events (pADEs) and assessments of causality and preventability. The identification was performed by a pharmacy student, under supervision of experienced researchers, while the assessments were conducted by a clinical pharmacist.

Identification of pADEs

Admission records were first screened to establish the main or contributory reason(s) for readmission. To determine whether medication contributed to the readmission, an adjusted version of the drug-related hospital admissions (DRA) adjudication guide was used (see *Appendix A*) (14). This is a validated trigger tool for identifying medication-related hospital admissions in older people. When used by trained pharmacy students, Coppes et al. have demonstrated a moderate agreement (81%, κ=0.62 (CI:0.54-0.70)) between students and expert panel (15). The guide was tailored to the bariatric population by two clinical pharmacists and a physician, the former specialised in pharmacotherapy after bariatric surgery and the latter in internal medicine. If the reason for readmission matches a trigger or event in the trigger tool, the medication overview of the patient at readmission was reviewed, alongside the entire admission record, lab results and discharge letter for the presence of suspected causative medication. In case of a match between reason for readmission, trigger or event and suspected causative medication, the case was considered a pADE.

Assessment of causality and preventability

After identifying a pADE, an adjusted version of the algorithm of Kramer et al. was utilised (see *Appendix B*) (16). This adjusted algorithm was used in earlier studies investigating the prevalence medication-related (re)admissions (12,17). The algorithm lay emphasis on previous experiences, alternative etiologic candidates and the timing when assessing the causal relationship between medication and event. Depending on the score, the causal relationship was then categorised as unlikely, possible and probable. Readmissions were labelled medication-unrelated if the causal relationship had been deemed unlikely. The remaining readmissions were grouped as medication-related.

Subsequently, the algorithm of Schumock & Thornton and adapted by Lghoul was applied to determine whether the medication-related readmission was preventable (see *Appendix C)* (18,19). This algorithm consisted of ten questions regarding preventable events, otherwise known as medication errors (20), which could be answered with either ‘yes’, ‘no’ or ‘too little information to assess the admission’. To be labelled potentially preventable, at least one question had to be applicable to the readmission and answered with ‘yes’.

Outcomes

The primary findings of this study were the prevalence of MRRs after primary bariatric surgery (defined as the number of MRRs divided by the total number of unplanned readmissions) and the percentage of preventable MRRs (defined as the number of potentially preventable MRRs divided by the total number of MRRs). Secondary findings included the influence of surgery year and surgical procedure on the prevalence of MRRs. Additionally, we wanted to know which types of medications and medication errors contribute

to potentially preventable MRRs. Lastly, the relationship between time to readmission and type of readmission (medication-related and unrelated) was investigated.

Data analysis

Collected data was exported to IBM SPSS Statistics for Windows Version 26.0 for analysis. Comparisons of baseline characteristics between medication-related and medication-unrelated readmissions were made using the appropriate statistical tests. The Mann-Whitney U test was used for non-normally distributed numerical variables. For categorical variables, the chi-square ($\chi 2$) test was used or substituted with the Fisher's exact test or the Fisher-Freeman-Halton exact test when assumptions for the $\chi 2$ test were not met.

Furthermore, a survival analysis was performed using the Kaplan-Meier procedure to demonstrate the relationship between time to readmission and type of readmission. Comparisons of both curves were made using the log rank test.

RESULTS

A total of 1564 hospital readmissions have been identified, of which 956 were unplanned, as is portrayed in Figure 1. After application of the exclusion criteria, 356 readmissions remained eligible to be included, screened for pADEs and potentially assessed for causality and preventability. Thus far, a total of 89 readmissions have been included in this interim analysis. Table 1 describes the baseline characteristics of the included sample at index and at readmission.

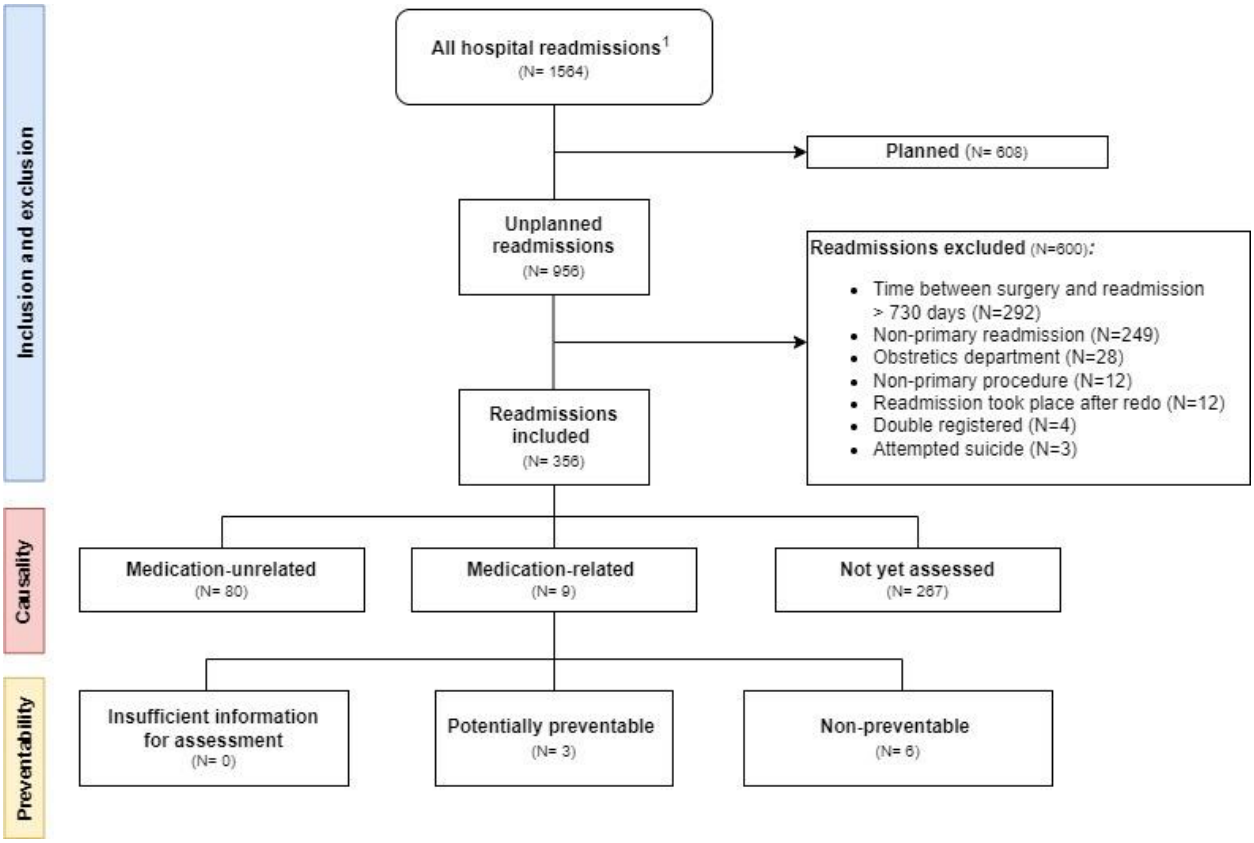

Figure 1 Flow diagram of performed study procedures. [1]All hospital readmissions between 2018 and 2022 of patients who have undergone primary bariatric surgery between January 2018 and August 2020 in the St. Antonius hospital.

Prevalence and preventability of MRRs

Figure 1 illustrates that of the 89 included readmissions, 10.1% (n= 9) were considered medication-related, of which 33.3% (n= 3) of the MRRs were believed to be potentially preventable.

Surgery year and surgical procedures on the prevalence of MRRs

With MRRs, 66.7% of the primary bariatric procedures took place in 2018 and 33.3% in 2019, as is described in Table 1. No patients readmitted due to medication-related causes had undergone surgery in 2020. In contrast, 42.5%, 40.0% and 17.5% of the surgeries took place in 2018, 2019 and 2020, respectively, within the medication-unrelated readmissions. Statistical testing demonstrated no significant difference between the groups (p = .362)

When comparing the surgical procedures, it was found that 66.7% of the MRRs eventuated after SG and 33.3% after RYGB, opposed to 30% after SG and 70% after RYGB within the medication-unrelated readmissions. Likewise, no statistically significant differences were observed (*p = .056).*

Table 1 Baseline characteristics of the sample at readmission and at index

	Medication-unrelated (n=80)	**Medication-related (n=9)**	***p*-value**
At readmission			
Age in years, median (IQR)	46.0 (35.3-50.8)	42.0 (30.5-58.0)	.984
BMI in kg/m2, median (IQR)	36.9 (29.1-40.4)	36.9 (33.3-43.6)	.310
Department, n (%)			1.000
- Non-surgical	6 (7.5)	0	
- Surgical	29 (36.3)	3 (33.3)	
- Hospital visit	45 (56.3)	6 (66.7)	
Length of stay in days, median (IQR)	1.0 (1.0-2.0)	1.0 (1.0-3.5)	.830
Number of medications before readmission, median (IQR)	4.0 (3.0-6.0)	5.0 (3.5-6.5)	.591
At index			
Female sex, n (%)	67 (83.8)	7 (77.8)	.664
Age in years, median (IQR)	46.0 (35.0-49.8)	42.0 (29.5-57.0)	.989
BMI in kg/m2, median (IQR)	42.2 (39.6-44.8)	41.3 (40.1-48.6)	.995
Preoperative comorbidities, n (%):			
• Asthma	9 (11.3)	0	.590
• Hypertension	19 (23.8)	3 (33.3)	.684
• Hypothyroidism	8 (10.0)	2 (22.2)	.266
• Musculoskeletal complaints	27 (33.8)	3 (33.3)	1.000
• Obstructive sleep apnoea	50 (62.5)	5 (55.6)	.727
Charlson Comorbidity Index (CCI) score, n (%):			.555
- 0 (none)	56 (70.0)	6 (66.7)	
- 1-2 (mild)	20 (25.0)	2 (22.2)	
- 3-4 (moderate)	4 (5.0)	1 (11.1)	
Number of medications before bariatric surgery, median (IQR)	2.0 (1.0-5.0)	3.0 (1.5-5.5)	.625
Number of medications after bariatric surgery, median (IQR)	5.0 (3.0-7.0)	4.0 (3.5-7.5)	.962
Medication reconciliation at discharge, n (%)	61 (76.3)	5 (55.6)	.229
Type of bariatric surgery, n (%):			.056
- RYGB	56 (70.0)	3 (33.3)	
- SG	24 (30.0)	6 (66.7)	
Surgery year, n (%)			.362
- 2018	34 (42.5)	6 (66.7)	
- 2019	32 (40.0)	3 (33.3)	
- 2020	14 (17.5)	0	

IQR = Interquartile range, BMI = Body Mass Index

Types of medications and medication errors in potentially preventable MRRs

Four types of medication were associated with the potentially preventable MRRs, namely opioids, antibiotics and the combination of beta blocking agents with antidepressants.

66.7% (n= 2) of the cases were identified as resulting from required additional measures not taken, hence, leading to a preventable readmission. 33.3% (n= 1) of the cases was deemed preventable, because the readmission was caused by an adverse interaction between medications, which was a repeat of a previous adverse reaction associated with the same type of medication combination.

Relationship between time to readmission and type of readmission

Figure 2 shows a Kaplan Meier curve, representing the fraction of patients who are readmitted within the two-year follow-up period. The median survival is 7.0 months (95% CI: 0.0-15.8) and 4.0 months (95% CI: 1.3-6.6), for medication-related and medication-unrelated readmissions, respectively. Within the first month, 40% (n= 32) of the medication-unrelated readmissions had occurred, compared to the 11.1% (n= 1) in the opposite group. When comparing both curves, the log rank test presented a *p*-value of .830, showing no statistically significant differences between the distributions of time to readmission in both groups.

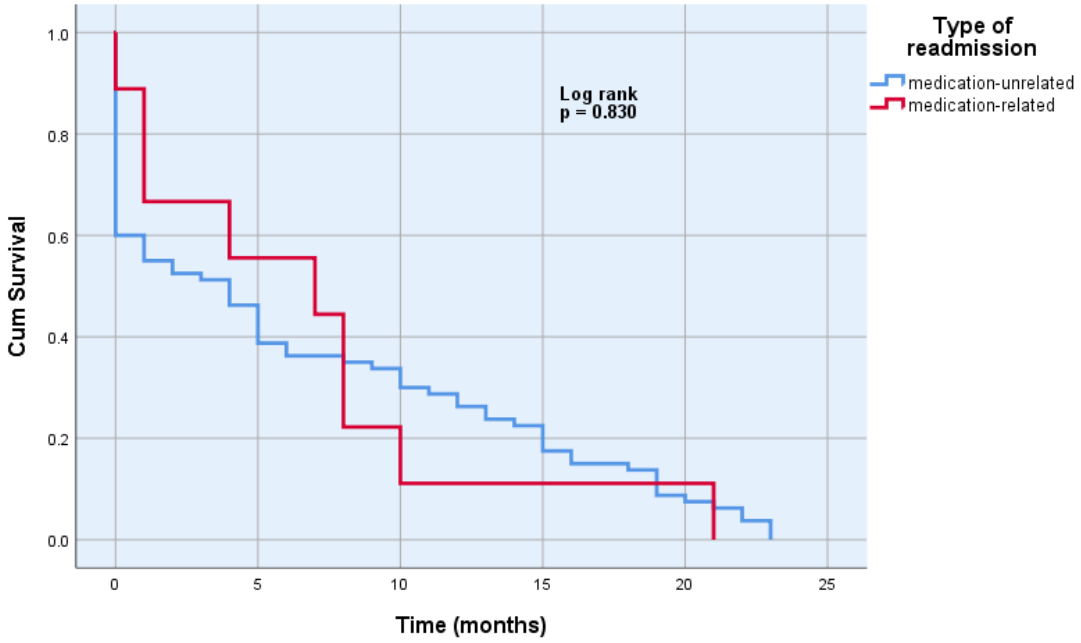

Figure 2 Kaplan-Meier survival curves over 24 months in medication-related and medication-unrelated readmissions.

DISCUSSION

The findings of this interim analysis depict that 10.1% of unplanned hospital readmissions after primary bariatric surgery were medication-related, of which 33.3% potentially preventable. This study demonstrated no correlations between surgical procedures, surgical years and the prevalence of MRRs. Likewise, the data suggested no associations between time to readmission and the type of readmission. Medication errors associated with preventable MRRs were due to the required additional measures not, or inadequately, taken (66.7%) or due to a known history of a previous reaction or allergy (33.3%).

To our knowledge, this study is the first to establish the prevalence of MRRs and the percentage of preventable readmissions after bariatric surgery. The discovery that 33.3% of MRRs were potentially preventable, suggests that at least a fraction of the bariatric patients could benefit from additional interventions to reduce MRRs. Furthermore, the results suggest that the risk of MRRs is not significantly influenced by the surgery year, type of bariatric procedure, or the time passed since the surgery. However, when observing these results, a considerably lower prevalence of unplanned readmissions was found in 2020 compared to prior years, which could be due to the COVID-19 pandemic. Another plausible explanation exists within our inclusion criteria, in which we only included readmissions up to August 31, 2020, rather than the entire year. Both explanations are not mutually exclusive. Interestingly, and just shy from significance (p= .056), there appears to be a trend towards a higher prevalence of MRRs in patients who underwent SG compared to RYGB. Moreover, the median survival of medication-unrelated readmissions (4.0 months (95% CI: 1.3-6.6)) vs. MRRs (7.0 months (95% CI: 0.0-15.8)) seems to suggest that it takes less time for 50% of the medication-unrelated readmissions to occur, compared to 50% of the MRRs. However, due to the wide range of the confidence interval in the median survival of MRRs, the result must be considered with some uncertainty. Lastly, medication errors could have been prevented if more attention was invested in the medical history of the patient and the adequate measures that had to be taken. It would be interesting to see if future research could reproduce our current findings.

A prevalence of 10.1% is relatively low compared to frequencies of 16% reported by Uitvlugt et al. or the median of 21% (IQR 14-23%) in a systematic review by El Morabet et al. (11,12). These studies explored the prevalence of MRRs in generally older populations. In our study, the median age at readmission was 42.0 years (IQR 30.5-58.0) in the MRR-group and 46.0 years (IQR 35.3-50.8) in the medication-unrelated group. This is quite a difference compared to the mean of 69.5 years (SD 13.7) or the median of 76 years (IQR 57–82) as reported by Uitvlugt et al. and El Morabet et al., respectively (11,12). This could explain the differences in prevalence rates, as we know from earlier reports that higher age is a risk factor for medication-related hospital admissions (19). Besides the sample demographics, the two-fold difference between our study and El Morabet et al. could be explained by other differences in methodology. To illustrate, the majority (33.0%) of included studies in El Morabet et al. have reported to use the Naranjo algorithm, with no mentions of the adjusted version of the Kramer algorithm. The former is believed to have a lower positive agreement between experts when assessing for causality, albeit investigated in a geriatric population, making these studies more prone to unreliable results (21). Furthermore, the review did not discriminate between planned or unplanned readmissions, while in our study, the former was removed from the sample population. Uitvlugt et al., on the contrary, utilised the same algorithm to assess for causality in unplanned readmissions. The main differences lay in the in- and exclusion criteria, namely the follow-up duration of two years vs. 30 days, exclusion vs. inclusion of repeated readmissions and inclusion vs. exclusion of hospital visits in our study compared to Uitvlugt et al., respectively.

Our reported preventability rate of 33.3% is comparable to the 40% of Uitvlugt et al., but nowhere near the median of 69% (IQR 19-84%), established by El Morabet et al. (11,12). A striking feature is the high variability in which the rates are expressed in the review. This is likely due to a diversity of methods used to assess for preventability, for which the algorithm of Schumock and Thornton only accounted 22%.

To prevent MRRs in the future, a possible course of action could be the implementation of medication reviews led by clinical pharmacists. Unlike medication reconciliations, medication reviews are not part of the standard procedure after bariatric surgery or in general in The Netherlands (22). Medication reviews can lead to the identification of medication-related problems (23). Depending on when the review is performed, it has the potential to resolve these problems before a patient experiences harm, thereby preventing medication errors. A study by Hellström et al. demonstrated that medication reconciliation and reviews performed by clinical pharmacists lead to significant reductions of unplanned MRRs among elderly patients (24). This claim is further supported by a meta-analysis in which pharmacist-led medication reviews were reported to significantly lower the prevalence of MRRs (25). However, this conclusion was based on two included studies. Although our study population does not completely match the description of the geriatric population, it could be argued that bariatric patients who are at high risk for preventable MRRs may benefit from this added intervention. Future research should focus on characterising this at-risk population and establish the time frame in which medication reviews should be conducted to be beneficial.

Strengths and limitations

As mentioned before, and to the best of our understanding, this study is the first to provide data on MRRs after primary bariatric surgery. Given the growing need for weight loss surgery, it is essential to gain new insights into this topic. New insights may establish foundations for future research, which can eventually lead to improved outcomes for patients after bariatric surgery.

Another strength of our study lies within the prolonged follow-up period of two years, which allowed us to study long-term outcomes of bariatric surgery. Within this period, delayed effects of bariatric surgery on the prevalence of MRRs could be captured, that would otherwise be missed in shorter follow-up studies.

However, the findings of this study must be seen in light of some potential limitations. The foremost being the small sample size (n= 89) included within this interim analysis. The presumable small power and precision of the study limit the generalisability of our findings. Therefore, caution is advised when interpreting current results, as they should be considered alongside other available literature.

The second limitation is the inclusion of only first-time readmissions after bariatric surgery, which excluded 26% (n= 249) of all unplanned readmissions. It could be challenged that every readmission is unique, which would mean that time should be irrelevant when investigating the prevalence of medication-related readmissions. However, previous studies show that within 30 and 180-day readmissions, ‘complication of the procedure’ was the most common reason for readmission (10,26). One could hypothesise that in case of repeated readmissions, the first readmission is more likely to be surgery-related, while subsequent readmissions are more likely to be medication related. Our established prevalence of MRRs could therefore be inaccurate, when considering the neglected repeated readmissions.

The third limitation is that this was a single centre study. The dataset we obtained does not necessarily contain all readmissions of the patients included but is limited to the readmissions to the St. Antonius hospital. It is conceivable that patients who do not associate their medication-related complaints with the

bariatric procedure might visit another hospital, one more convenient, thus possibly leading to an underestimation of the prevalence of MRRs.

The last limitations lie within the performed study procedures, in which a pharmacy student was the researcher screening all unplanned readmissions using the DRA-adjudication guide, before presenting pADEs for assessments. Despite the documented agreement of 81% between trained pharmacy students and expert panel, MRRs can still be missed when pADEs go unnoticed (15). Moreover, the assessments of causality and preventability were performed by one clinical pharmacist, rather than by a multidisciplinary panel consisting of a clinical pharmacist and physician. Although originally planned, this panel could not be realised due to time constraints on the researchers. We acknowledge that these limitations could introduce misclassification and observer bias, potentially leading to unreliable data.

Recommendations

We invite future studies to investigate the prevalence of medication-related readmissions after bariatric surgery using an improved study design, including repeated readmissions and a bigger sample size. Additionally, the identification of potential adverse drug events should be executed by a medical expert, with two independent assessors evaluating the causality and preventability. Furthermore, it would be interesting to examine risk factors for preventable medication-related readmissions after bariatric surgery, to provide targeted care for at-risk patients.

CONCLUSION

Our study suggests that 10.1% of the unplanned readmissions after primary bariatric surgery were medication-related, of which 33.3% considered potentially preventable. To reduce the number of preventable medication-related readmissions in the future, additional interventions such as medication reviews could be considered for high-risk patients. Further research on medication-related readmissions after bariatric surgery, with bigger sample sizes, are needed to support our findings and to establish what subset of bariatric patients may benefit from additional preventative measures.

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Appendix A. Adjusted trigger tool for medication-related readmissions after bariatric surgery [14]

TRIGGER TOOL TO SCREEN FOR DRUG-RELATED HOSPITAL ADMISSIONS IN OLDER PERSONS	
Trigger on admission up to 48h of admission	**Suspected causative drugs or causes for underuse**
Diagnoses	
Fall and/or fracture	**Use** of any of the following drugs? ☐ Benzodiazepines ☐ Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem ☐ Antipsychotics ☐ Antidepressants ☐ Sedating antihistamines ☐ Opioids ☐ Anticholinergic drugs[a] ☐ Other (*Please specify*):
	Use of any drugs causing orthostatic hypotension? ☐ Calcium channel blockers ☐ Diuretics ☐ α1-receptor blockers ☐ Nitrates ☐ β-blockers ☐ ACE-inhibitors ☐ Angiotensin receptor blockers ☐ Direct renin inhibitors (e.g. aliskiren) ☐ Anti-Parkinson drugs ☐ Antidepressants (mainly tricyclic) ☐ Antipsychotics ☐ Gliflozines (SGLT2-inhibitors) ☐ Other (*Please specify*):
	If a fall is caused by hypoglycaemia, look for **use** of drugs contributing to hypoglycaemia (check trigger hypoglycaemia)
	Underuse of any of the following drugs in patients with known osteoporosis and/or history of fragility fracture(s) and/or Bone Mineral Density T-scores of -2.5 or lower in multiple sites? ☐ 800 IU Vitamin D/day (+ 1000-1200 mg calcium/day if dietary intake is <1200-1000mg/day) ☐ Bone anti-resorptive therapy (e.g. bisphosphonates, strontiumranelate,teriparatide, denosumab)
	Underuse of any of the following drugs in patients on corticosteroid therapy ≥ 3 months? ☐ 800 IU Vitamin D/day (+ 1000-1200 mg calcium/day if dietary intake is <1200-1000mg/day) ☐ Bisphosphonates
	Underuse of vitamin D in patients who are housebound and/or experiencing falls or with osteopenia with Bone Mineral Density T-score between -1 and -2.5 in multiple sites?
Confusion/delirium[b]	**Use** of any of the following drugs? ☐ Benzodiazepines ☐ Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem ☐ Antipsychotics ☐ Anti-epileptics ☐ Antihistamines (H1- and H2-receptor blockers) ☐ Antidepressants ☐ Opioids ☐ Dopaminergic agonists ☐ Digoxin ☐ Fluoroquinolones *(dose adjustment in renal impairment required)* ☐ Acetylcholinesterase-inhibitors (new onset confusion in patients with dementia) ☐ Other anticholinergic drugs[a] (*Please specify*):
	Abrupt discontinuation/rapid dose reduction of any of the following drugs? ☐ Benzodiazepines ☐ Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem ☐ Corticosteroids ☐ Dopaminergic agonists ☐ Antidepressants ☐ Opioids ☐ Lithium ☐ Antipsychotics ☐ Other (*Please specify*):
Acute renal impairment[b]	**Use** of any of the following drugs? ☐ Non-steroidal anti-inflammatory drugs ☐ ACE-inhibitors ☐ Angiotensin receptor blockers ☐ Diuretics ☐ Sulphonamides ☐ Cephalosporins ☐ Quinolones (ciprofloxacin) ☐ Aminoglycosides ☐ Vancomycin ☐ Pentamidine ☐ SGLT2-inhibitors ☐ Rifampicin ☐ Acyclovir, valacyclovir, gancyclovir, valgancyclovir, foscarnet, cidofovir ☐ Lithium ☐ Calcineurin Inhibitors (e.g. cyclosporine, tacrolimus) ☐ Cisplatin ☐ Radiology contrast medium ☐ Amphotericin ☐ Bisphosphonates ☐ Other nephrotoxic drugs (*Please specify*):
Dehydration	Use of any of the following drugs? ☐ Diuretics ☐ Gliflozines (SGLT2-inhibitors) ☐ Laxatives ☐ Any drugs causing vomiting ☐ Any drugs causing diarrhoea ☐ Other (*Please specify*):

(Continued)

Bleeding[b]	**Use** of any of the following drugs? ☐ Antiplatelets ☐ Vitamin K antagonists ☐ Direct oral anticoagulants ☐ Unfractionated heparin ☐ Low molecular weight heparins ☐ Selective serotonin reuptake inhibitors ☐ Non-steroidal anti-inflammatory drugs ☐ Other (*Please specify*): ☐ **Underuse** of proton pump inhibitors prophylaxis while - NSAIDs monotherapy (≥ 70 years old) or on concurrent NSAIDs and/or antiplatelets and/or corticosteroids - NSAIDs or antiplatelet or corticosteroids monotherapy with a history of peptic ulcer disease/gastrointestinal bleeding while on these drugs
Stroke	**Underuse** of any of the following drugs in patients with known chronic atrial fibrillation? ☐ Vitamin K antagonists ☐ Direct oral anticoagulants (except valvular atrial fibrillation) **Underuse** of adequate antihypertensive therapy? * *Note*: Adequate antihypertensive therapy is defined according to the recommendations for older patients in the 2013 European ESH/ESC guidelines for the management of arterial hypertension. **Underuse** of any of the following drugs in patients with history of coronary, cerebral or peripheral vascular disease? ☐ Antiplatelets ☐ Statins** (unless end-of-life or > 85 years old) ***Note*: Evidence for statin treatment above the age of 80-85 years is limited and clinical judgement should guide decisions in the very old, taking into account life expectancy, serious adverse events, possible drug interactions. Low to moderate intensity statin regimens are recommended. (**low**: simvastatin 10mg, pravastatin 10-20mg, fluvastatin 20-40 **moderate**: atorvastatin 10-20mg, Rosuvastatin 5-10mg, Simvastatin 20-40mg, pravastatin 40-80 mg, Fluvastatin 80 mg, Fluvastatin 40 mg BID)
Thromboembolic event (DVT or PE)	**Underuse** of adequate anticoagulation? ☐ Unfractionated heparin ☐ Low molecular weight heparins ☐ Direct oral anticoagulants ☐ Vitamin K antagonists
(Recurrent) myocardial infarction or ischaemic disease	**Underuse** of cardiovascular secondary prevention? ☐ Antiplatelets (unless already anticoagulated) ☐ Statins** (unless end-of-life or > 85 years old) ☐ β-blocker/ACE-inhibitor or angiotensin receptor blocker /adequate anti-anginal therapy in case of ischaemic disease **Underuse** of adequate antihypertensive therapy? *
Heart failure exacerbation	**Use** of any drugs that could precipitate heart failure exacerbation? ☐ Thiazolidinediones (glitazones) ☐ Non-steroidal anti-inflammatory drugs ☐ Corticosteroids ☐ Non-dihydropyridine calcium channel blockers (verapamil, diltiazem) ☐ Sodium-containing formulations (effervescent, dispersible and soluble medications) ☐ Other (*Please specify*): **Underuse** of any of the following drugs? ☐ β-blockers[¥] ☐ ACE-inhibitors[¥] ☐ Diuretics *Note*: [¥] β-blocker and ACE-inhibitors in heart failure due to left ventricular dysfunction
COPD exacerbation	**Use** of any drugs that could precipitate COPD exacerbation? ☐ Benzodiazepines with acute or chronic respiratory failure ☐ Opioids ☐ Other (*Please specify*): **Underuse** of any of the following drugs? ☐ Single or dual inhaled bronchodilator therapy i.e. a β2 agonist and/or anticholinergic bronchodilator according to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) grade
Uncontrolled (non-neuropathic) pain	**Underuse** of adequate pain treatment (according to the WHO analgesic ladder)? ☐ A strong opioid in moderate to severe pain if paracetamol, NSAIDs or weak opioids are not appropriate (e.g. because of insufficient pain relief) ☐ Short-acting opioids for break-through pain during treatment with long acting opioids ☐ Other (*Please specify*):
Gastrointestinal disorders (severe diarrhoea, vomiting)	**Use** of any of the following drugs? ☐ Antibiotics ☐ Laxatives ☐ Selective serotonin reuptake inhibitors ☐ Digoxin ☐ Cholinesterase-inhibitors ☐ Opioids ☐ Non-steroidal anti-inflammatory drugs ☐ Chemotherapy (*Please specify*): ☐ Other (*Please specify*):

(continues)

(Continued)

Major constipation or faecal impaction	**Use** of any of the following drugs? ☐ Chronic (stimulant) laxative use ☐ Opioids (look for **underuse of laxatives** with regular opioid use) ☐ Calcium antagonists (Mainly verapamil) ☐ Calcium ☐ Oral iron ☐ Aluminium antacids ☐ Atypical antipsychotics ☐ Tricyclic antidepressants ☐ Bladder antimuscarinics ☐ Other anticholinergic drugs[a] ☐ Other (*Please specify*):
Laboratory values	
INR > 5	Look for evidence of bleeding (see trigger) to determine if an adverse drug event (ADE) has occurred. A raised INR in itself is not an ADE.
Digoxin level > 2ng/ml	Look for signs or symptoms of digoxin toxicity (bradycardia, nausea, diarrhoea, confusion) to determine if a potential ADE has occurred. Not all levels above normal will result in an ADE.
Hypoglycaemia (blood glucose < 4 mmol/L or 72 mg/dl)	Look for symptoms such as lethargy, tremor, confusion, faintness or administration of intravenous or oral glucose. **Use** of any of the following drugs? ☐ Insulin ☐ Oral hypoglycaemic agents (except metformin in monotherapy) ☐ ☐ MAO – inhibitors β-blockers (masking symptoms of hypoglycaemia)
Hyperglycaemia (blood glucose > 11 mmol/L or 198 mg/dl)	**Use** of any drugs that may cause or worsen hyperglycaemia? ☐ Corticosteroids ☐ Atypical antipsychotics (mainly olanzapine & clozapine) ☐ Thiazide diuretics *less frequent* ☐ β-blockers (except carvedilol and nebivolol) *less frequent* ☐ Protease-inhibitors ☐ Calcineurin Inhibitors (cyclosporine, sirolimus, tacrolimus) ☐ Other (*Please specify*): In case hyperglycaemia is part of diabetic ketoacidosis or hyperosmolar hyperglycaemic state in a patient, review for **underuse** of insulin or oral hypoglycaemic agents.
Hyperkalaemia (K^+ > 5.5 mmol/L)	**Use** of any the following drugs? ☐ Intravenous or oral potassium ☐ Potassium-sparing diuretics ☐ ACE-inhibitors ☐ Angiotensin receptor blockers ☐ Direct renin inhibitors (e.g. aliskiren) ☐ Non-steroidal anti-inflammatory drugs ☐ Heparins (seldom, mainly when treated > 7days and concomitant other risk factors) ☐ Trimethoprim-sulfamethoxazole ☐ Cyclosporine ☐ Tacrolimus ☐ Other (*Please specify*):
Hypokalaemia (K^+ < 3 mmol/L)	**Use** of any of the following drugs? ☐ Loop diuretics ☐ Thiazide and thiazide-like diuretics ☐ Corticosteroids ☐ Laxatives ☐ Salbutamol (IV or aerosol) ☐ Theophylline ☐ Other (*Please specify*):
Hyponatraemia (Na^+ < 130 mmol/L)	**Use** of any of the following drugs? ☐ Diuretics ☐ Selective serotonin reuptake inhibitors ☐ Tricyclic antidepressants ☐ ACE-inhibitors ☐ Angiotensin receptor blockers ☐ Carbamazepine & oxcarbazepine ☐ High dose cyclophosphamide ☐ Other (*Please specify*):
White blood cells < 3000 /mm^3 or < 3 x 10^3/µL	**Use** of any of the following drugs? ☐ Carbamazepine & oxcarbazepine ☐ Antipsychotics (mainly clozapine) ☐ Thyreostatics ☐ Ganciclovir ☐ Immunosuppressants ☐ Chemotherapy (*Please specify):* ☐ Mirtazapine (first 6 weeks of treatment) ☐ Voriconazole ☐ Other (*Please specify*):
Platelet count < 50000 /mm^3 or < 50 x 10^3/µL	**Use** of any of the following drugs? ☐ Carbamazepine & oxcarbazepine ☐ Ganciclovir ☐ Unfractionated heparin ☐ Low molecular weight heparins ☐ Immunosuppressants ☐ Thienopyridines (mainly ticlopidine) ☐ Quinine sulfate ☐ Sulfamides *Less frequent* ☐ Chemotherapy (*Please specify):* ☐ Other (*Please specify*):
Neutrophils < 1400/mm^3 or < 1.4 x 10^3/µL	**Use** of any of the following drugs? ☐ Antipsychotics (mainly clozapine) ☐ Ganciclovir ☐ Thyreostatics ☐ Thienopyridines (mainly ticlopidine) ☐ Chemotherapy (*Please specify):* ☐ Other (*Please specify*):

Hypothyroidism (TSH < 0.35 mU/L or T3 < 1.1 nmol/L or Free T4 < 9.0 pmol/L)	**Underuse** of any of the following drugs? ☐ Levothyroxine ☐ Liothyronine
Hypomagnesemia (Mg < 0.7 mmol/L)	**Use** of any of the following drugs? ☐ Diuretics ☐ Antibiotics: aminoglycosides, amfotericine-B, foscarnet, pentamidine ☐ Immunosuppressants: cyclosporine, tacrolimus, sirolimus ☐ Cisplatin ☐ Proton pump inhibitors
Hypocalcemia (Ca < 2.1 mmol/L)	**Underuse** of any of the following drugs? ☐ Vitamin D suppletion **Use** of any of the following drugs? ☐ Diuretics ☐ Corticosteroids
Anemia (Hb deficiency) (age and sex dependent)	Can be caused by: Iron, vitamin B12 and/or folic acid deficiency
Ferritin < 25 µg/L (m) < 20 µg/L (f)	**Underuse** of any of the following drugs? ☐ Iron suppletion ☐ Multivitamin suppletion
Transferrin < 2.0 g/L	**Underuse** of any of the following drugs? ☐ Iron suppletion ☐ Multivitamin suppletion
Vitamin B12 < 140 pmol/L	**Underuse** of any of the following drugs? ☐ Multivitamin suppletion
Folic acid < 7 nmol/L	**Underuse** of any of the following drugs? ☐ Multivitamin suppletion **Use** of any of the following drugs? ☐ Anti-epileptics: phenytoin, carbamazepine or barbiturates
Vitamin B1 > 227 nmol/L	**Use** of any of the following drugs? ☐ Multivitamin suppletion
Vitamin B6 > 131 nmol/L	**Use** of any of the following drugs? ☐ Multivitamin suppletion
Vitamin-D deficiency < 50 nmol/L	**Underuse** of any of the follow drugs? ☐ Vitamin D/calcium suppletion ☐ Multivitamin suppletion

(Continued)

Other	
Antidote use or treatments that suggest a potential ADE	**Use** of any of the following drugs on the day of admission? ☐ Flumazenil in a patient on benzodiazepines ☐ Naloxone in a patient on opioids ☐ Phytonadione (vitamin K) in a patient on VKA ☐ Protamine sulphate in a patient on heparins ☐ Oral or intravenous glucose or glucagon in a patient taking hypoglycaemic drugs ☐ Potassium supplements in case of hypokalaemia ☐ Sodium polystyrene (Kayexalate) in case of hyperkalaemia ☐ Adrenaline, antihistamines and corticosteroids (general drug allergy) ☐ Acetylcysteine (paracetamol overdose) ☐ Digoxin antibodies in a patient with supratherapeutic digoxin levels ☐ Oral metronidazole or vancomycin in a patient who has recently been treated with an antibiotic that may cause *Clostridium difficile* associated diarrhoea
Mention of a (potential) ADE in the medical record	Assess causality using the WHO-UMC criteria
Abrupt medication stop within 24h of admission	When medications are stopped or withheld as compared to medications taken at home, look for reasons why this was done. Abruptly stopping medications is a trigger requiring further investigation for cause. A sudden change in patient condition requiring adjustment of medications is often related to an ADE.

ADE, adverse drug event; ADR, adverse drug reaction; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; FEV_1, forced expiratory volume in 1 second; ESH/ESC, European Society of Hypertension/European Society of Cardiology; INR, international normalised ratio, NSAIDS, non-steroidal anti-inflammatory drugs; PE, pulmonary embolism; VKA, Vitamin K antagonists
[a]A list of medications with clinically relevant anticholinergic properties is available in the DRA adjudication guide; [b]Detailed definition of trigger available in the DRA adjudication guide

SCREENING QUESTIONS FOR NON-TRIGGERED, SPONTANEOUSLY DETECTED EVENTS

1. Could the main or contributory reason for admission be related to a drug or recent change in medications?

☐ Adverse drug reaction (non-preventable side effect, first allergic reaction)
☐ Overuse of medication(s) (drug without an indication, too long duration of therapy, therapeutic duplication)
☐ Inappropriate discontinuation (removal or dosage decrease) leading to physiological withdrawal signs/symptoms or return of the underlying disease signs/symptoms
☐ Wrong drug
☐ Wrong dose (supratherapeutic or subtherapeutic)
☐ Clinically significant drug-drug or drug-food interactions
☐ Inappropriate monitoring
☐ Other (e.g. drug not correctly dispensed/prepared/administered)

2. Could the main or contributory reason for admission be related to underuse?

☐ Omission of an indicated drug
☐ Too short duration of medication therapy
☐ Suspected adherence concerns

Appendix B. Adjusted version of the algorithm of Kramer [16,17]

Question	Answer	Score
1. Is the clinical manifestation known as an adverse reaction of the suspected drug?	The clinical manifestation is widely known and universally accepted as an adverse reaction of the suspected drug.	+1
	The clinical manifestation has been previously reported, but it is not widely known as an adverse reaction of the suspected drug or it concerns a drug with a new active substance (approved for less than 5 years in the European Union).	0
	The clinical manifestation is not known as an adverse reaction of a drug that has been approved in the European Union for more than 5 years.	-1
2. Are there alternative causes that could explain the clinical manifestation?	There are no alternative etiologies that could explain the relationship between the suspected drug and the clinical manifestation.	+2
	The clinical manifestation is an exacerbation or recurrence of a pre-existing clinical condition.	+1
	There might be alternative etiologies that could explain the relationship between the clinical manifestation and the suspected drug, but these are not likely.	0
	There are alternative etiologies that could explain the relationship between the clinical manifestation and the suspected drug with a high degree of certainty.	-1
3. Is there a plausible temporal relationship between the adverse drug reaction and the onset of drug administration?	The timing of appearance of the clinical manifestation is as expected for an adverse reaction of this drug.	+1
	The temporal relationship is unclear.	0
	The timing of appearance of the clinical manifestation is not as expected for an adverse reaction of this drug.	-2

Score < 0: Causality is unlikely

Score 0-3: Causality is possible

Score ≥ 4: Causality is probable

Appendix C. Adjusted version of the algorithm of Schumock and Thornton and adapted by Lghoul [18,19]

Section A&B

If one or more of the following questions is answered with 'yes' a possible Hospital Admission Related to Medication (HARM) is considered potentially preventable.

In case the following box is checked the admission will be excluded.

□ Too little information available to assess the admission.

1. Was there a history of allergy or previous reaction?
2. Was the drug involved in the HARM not considered appropriate for the patient's clinical condition?
3. Was the dose, route, and frequency of administration not appropriate for the patient's age, weight and disease state?
4. Was an error made in the delivery of the drug?
5. Was an error made in the administration of the drug?
6. Was required therapeutic drug monitoring or other necessary laboratory test not performed?
7. Was a drug interaction involved in the reaction?
8. Was there a duplicated side effect (i.e. sedating or anticholinergic)?
9. Was poor compliance involved in the reaction?
10. Were required additional measures not taken or were they insufficient?

If all questions are answered with 'no', move to section C.

Section C

The admission is considered non-preventable