Doctoral theses at NTNU, 2021:108

Magnus Strømmen

Towards individualized management of bariatric surgery patients

Doctoral thesis

NTNU
Norwegian University of Science and Technology
Thesis for the Degree of
Philosophiae Doctor
Faculty of Medicine and Health Sciences
Department of Mental Health

NTNU
Norwegian University of
Science and Technology

Magnus Strømmen

Towards individualized management of bariatric surgery patients

Thesis for the Degree of Philosophiae Doctor

Trondheim, April 2021

Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Mental Health

NTNU
Norwegian University of
Science and Technology

NTNU
Norwegian University of Science and Technology

Thesis for the Degree of Philosophiae Doctor

Faculty of Medicine and Health Sciences
Department of Mental Health

ISBN 978-82-326-6109-1 (printed ver.)
ISBN 978-82-326-6236-4 (electronic ver.)
ISSN 1503-8181 (printed ver.)
ISSN 2703-8084 (online ver.)

Doctoral theses at NTNU, 2021:108

Printed by NTNU Grafisk senter

TABLE OF CONTENT

Innhold

ACKNOWLEDGEMENTS

Thanks to the Norwegian University of Science and Technology (NTNU)

At the outset, I want to thank the Dept. of Neuroscience and Dept. of Mental Health at the Faculty of Medicine and Health Science, NTNU, for accepting me as a Ph.D.-student. The courses provided me with an understanding of scientific methods, the very foundation of critical thinking in research. I am also grateful for the supervision I have received over the years, and finally, for the opportunity to defend my thesis publicly.

My main supervisor

Professor Are Holen has been imperative for me to put the thesis' 160,000 letters in a meaningful order. Thanks to him, the readers were spared for approximately the same number of letters. These were sections and paragraphs, words and repetitions I convinced myself were of great importance, and that I reluctantly agreed to delete. Although frustrating at times, today I am happy for this!

I am indebted to him for agreeing to be my supervisor even though he was well aware of the fact that I spent too much time on my Master's Degree, and also that I would do the Ph.D. without a stipend and I would have two regular jobs at the university hospital. As my supervisor, he demonstrated endurance far beyond what I could expect, and he walked the full distance with me. Moreover, during the time I have been working on this thesis, two great children materialized, and a lot of life happened.

Undoubtedly, I have benefitted from his rich experience in supervising doctoral students. A bonus has been his godsent linguistic strengths. Even so, I regret to admit that after numerous corrections of my manuscripts I realize that I may hardly ever master fully conjunctions, adverbs and prepositions in English. However, there is more to the scientific genre than those small words making sentences flow. In that respect, his red pen has been invaluable for enhancing the precision of the drafts. Reluctantly, I am realising what loss this will be for my future writings now when our paths diverge.

My co-supervisors

I want to express my deep gratitude to our *Grand Old Man of Obesity*, my boss Professor Bård Kulseng. He has generously provided me with opportunities that I hardly

could dream of, and he has kept on nurturing my professional growth all these years. With his innate positive attitude, he has always been listening and supportive.

Special thanks also go to Senior Adviser Inger Johanne Bakken and Professor Christian Klöckner. I have greatly benefited from their contributions. Inger Johanne opened an entire new universe of registry data to me while also pointing out some of the boundaries of this field. And Christian, who was responsible for the PhD-course in statistics became my rescue line, and later on, a cherished active partner in several of my papers. And Ellen Andenæs, pure serendipity brought us together.

My employer

I want to thank the Clinic of Surgery for the wonderful opportunity to be a part of a rather unique environment that integrates research and clinical practice. The clinic first facilitated the Regional Centre for Obesity Research at which I have been affiliated from the start. The clinic also promoted the establishment of the Outpatient Obesity Clinic at which I was engaged the first years after its inception in 2008.

Colleagues and friends

I am particularly grateful to the bariatric surgeons, Ronald Mårvik and Gjermund Johnsen. They have been supportive all the way, but more importantly, they have acted with determination in establishing a culture of research at the Obesity Clinic. Without Ronald's generous invitation to do my Master's Degree at the start of bariatric surgery in Trondheim, I would not have been here today.

Furthermore, I greatly appreciate the many supportive remarks and fondness of my colleagues at the Centre for Obesity Research, the Obesity Clinic, and the Clinical Research Ward. Special thanks go to the eminent study nurses, Sissel Salater and Hege Bjøru, the backbone of our clinical research. Thanks to the retired secretary, Unni Lehn, for demonstrating how many hours a working day actually can have. Thanks also to surgeon Jorunn Sandvik for fruitful discussions. Thanks to my former and present office mates, Kjersti Hognes Berg and Ingrid Følling for many openhearted conversations. And thanks to the former Chief Nurse at the university hospital, Grete Samstad, for her persistence in convincing the hospital administration about the need for formal research competency also among the nurses.

My family

Although I do not think the work on this theses ever made me neglect my two, very dear and fine sons, Aleksander and Teodor, but definitely, the work has influenced my parenting. I am grateful to both of them for occasionally climbing up on my lap and forcing my hands off the keyboard. They helped me calibrate my existence.

And many great thanks to my dear Kristian for being both a carrot and stick during these years. He inspired me into doing this and his numerous encouragements have been valuable for me.

Thanks also go to my mum and dad for always being my devoted and enthusiastic fans. Although I struggle to make them understand the concept of a PhD, they have been instrumental and supportive ever since my first days at school. And thanks to Pat and Stig for a lot of support during these years.

And also thanks to…

… the engineers of Bose Corporation for their innovations in noise cancellation technology

… Merriam-Webster Inc. for their spelling guidance

… Nespresso – for their aluminium capsules, which made this work possible

… the optician for correcting my astigmatism which made the whole thesis seem less blurry, especially those many days that made this PhD-project appear never-ending and foggy.

Trondheim, the 1st of December 2020

Magnus Strømmen

LIST OF PAPERS

Paper I — Magnus Strømmen, Inger Johanne Bakken, Ellen Andenæs, Christian A Klöckner, Ronald Mårvik, Bård Kulseng, Are Holen. ***Fet, feit eller bare overvektig?*** Tidsskrift for den norske legeforening (2015) 135, 1732-1736
DOI: 10.4045/tidsskr.14.0828

Paper II — Magnus Strømmen, Bård Kulseng, Einar Vedul-Kjelsås, Harald Johnsen, Gjermund Johnsen, Ronald Mårvik. ***Bariatric surgery or lifestyle intervention? An exploratory study of severely obese patients' motivation for two different treatments.*** Obesity Research & Clinical Practice (2009) 3, 193-201
DOI: 10.1016/j.orcp.2009.04.004

Paper III — Magnus Strømmen, Arne Helland, Bård Kulseng, Olav Spigset. ***Bioavailability of methadone after sleeve gastrectomy: A planned case observation.*** Clinical Therapeutics (2016) 38, 1532-1536
DOI: 10.1016/j.clinthera.2016.04.033

Paper IV — Magnus Strømmen, Inger Johanne Bakken, Christian A Klöckner, Jorunn Sandvik, Bård Kulseng, Are Holen. ***Diagnoses related to abuse of alcohol and addictive substances after gastric bypass and sleeve gastrectomy – A Nation-Wide Registry Study from Norway.*** Surgery for Obesity and Related Diseases (2020) 16, 464-470
DOI: 10.1016/j.soard.2019.12.011

ACRONYMS AND ABBREVIATIONS

ANOVA	Analysis of variance
AUC	Area under curve
AUD	Alcohol use disorder
AUDIT	Alcohol use disorder identification test
BMI	Body mass index
BS	Bariatric surgery
CI	Confidence interval
C_{max}	Maximum concentration
GHS-R1A	Growth Hormone Secretagougue Receptor 1A
GP	General practioner, primary care physician
HADS	Hospital Anxiety and Depression Scale
ICD	International Classification of Diseases and Related Health Problems
NHANES	National Health and Nutrition Examination Survey
PK	Pharmacokinetic
REC	Regional Committee for Medical and Health Research Ethics
RYGB	Roux-en-Y gastric bypass
SF-36	Short Form 36
SG	Sleeve Gastrectomy
SOS-study	Swedish Obese Subjects Study
T_{max}	Time to reach maximum concentration
VTA	Ventral Tegmental Area
WHO	World Health Organization

CENTRAL DEFINITIONS

Anthropometric concepts

- *Anorexigenic peptides* are appetite-depressing gastro-intestinal signaling molecules.
- *BMI* or body mass index is an index for weight for height used to classify underweight, overweight and obesity in adults. BMI is body weight (kg) divided with the body height (m) squared. Although different cutoffs have been proposed, BMI is normally classified as (1):
    - Underweight: BMI < 18,5
    - Normal range: 18,5 ≤ BMI 18,5 < 25,0
    - Overweight: 25,0 ≤ BMI < 30,0
    - Obesity: BMI ≥ 30,0
- *Obesity* is a condition of abnormal or excessive fat accumulation in adipose tissue, to the extent that health may be impaired. This definition has been used by the World Health Organization (1).

Pharmacological concepts

- *AUC* is the area under the concentration time curve. This quantifies the systemic exposure of a drug.
- C_{max} signifies the maximum concentration.
- *First-pass metabolism* refers to the initial absorption of a drug in the intestines that is filtered through the liver and the fraction of a drug that is metabolized and removed from the blood before it continues through vena cava inferior and reaches systemic circulation. Depending on the drug properties, a fraction of some drugs will never reach the systemic circulation (2).
- *Oral drug bioavailability (F_{oral})* is the fraction of a drug that is absorbed in the intestinal wall (f_a), which escapes gut metabolism (F_G), while also escaping the hepatic metabolism (F_H). It can be expressed as the product of the three fractions, $F_{oral} = f_a \times F_G \times F_H$ (3).

- *Pharmacokinetic* (PK) processes encompass the absorption, distribution and elimination of drugs in the body (2).
- T_{max} is the time to reach maximum concentration of a drug.

ENGLISH SUMMARY

Background

Bariatric surgery has become an area of priority in specialist medicine. With an accelerating number of operations, surgeons are continuously developing the quality of their procedures. However, the complexity of bariatric services exceeds the challenges of the operating room.

St. Olavs Hospital has offered bariatric surgery several years before establishing a specialised team, the Obesity Clinic, devoted to patient screening, treatment and follow-up. A dedicated team carried out systematic explorations of a broad range of relevant issues in these patients. Aligned with these endeavours, I wanted in this thesis to address some research questions related to the phases patients undergo before surgery as well as in follow-up phases after surgery.

The thesis contains four papers; they reflect questions that originate from my patient interaction over several years at the Obesity Clinic, and later, at the Centre for Obesity Research. The first two papers focus on issues before the decision is made about letting the patient get bariatric surgery. The last two explore potential problems in the aftermath of bariatric surgery.

Brief summary of Paper I:

Magnus Strømmen, Inger Johanne Bakken, Ellen Andenæs, Christian A Klöckner, Ronald Mårvik, Bård Kulseng, Are Holen. ***Obese, fat, or just overweight?*** *Tidsskrift for den norske legeforening (2015) 135, 1732-1736*

The first paper explores an aspect of the patient-doctor communication. More precisely, the paper investigates the Norwegian patients' preferences and dislikes in relation to words describing overweight or obesity. Some guidance is being offered to health personnel about what words Norwegian patients tend to find acceptable; their use may improve the communication with the patients and thereby ease the referral and preparatory processes related to bariatric surgery.

The research questions of Paper I were:

- To what extent had patients undergoing treatment for morbid obesity experienced that their general practioners initiated discussions about their excess weight?
- What words describing excess weight were regarded as desirable by the obese patients?
- Is the rating of "word desirability" by the obese associated to possible covariates such as gender, age, education, marital status, mental health, happiness with weight, and/or age at obesity onset?

This was a cross-sectional, descriptive study using a questionnaire approach. Patients rated different Norwegian words or expressions used to describe obesity according to "word desirability" as seen by the obese patients. Possible covariates related to background factors were also tested.

The study showed that among the fourteen words or expressions tested, 'weight' was considered the most appropriate for use in clinical consultations, while 'fat' was rated as the most inappropriate. Women were more sensitive to the use of such words than men. The same applies to patients with an early-life obesity onset, those with higher education, and those least satisfied with their own weight. One third of the patients reported that their physician had initiated a discussion about their obesity, and nine out of ten patients meant it would be appropriate for a physician to do that. Most patients reported that their physician's choice of words influenced their doctor-patient relationship.

Brief summary of Paper II:

Magnus Strømmen, Bård Kulseng, Einar Vedul-Kjelsås, Harald Johnsen, Gjermund Johnsen, Ronald Mårvik. ***Bariatric surgery or lifestyle intervention? An exploratory study of severely obese patients' motivation for two different treatments.*** *Obesity Research & Clinical Practice (2009) 3, 193-201*

The second paper is an inquiry into the subcategories of motivation that may lie behind patients' preferences for either surgical or conservative obesity treatment. Often patients have a strong motivation for just one of the two treatment modalities. For clinicians to

understand what lies behind the patient's treatment choice or motivation may aid in clarifying and recommending an optimal personalized treatment.

The research questions of Paper II were:

- Do patients having chosen the same obesity treatment share the same motivation?
- Do patients differ in outcomes on psychopathological measures according to motivation differences?

This paper was a cross-sectional study. In addition, it utilized a mixed methods approach. Written free texts were used to analyse the patients' motives for their choice of one of the two obesity treatments, while another part of the questionnaire collected data about their mental health.

The qualitative part unveiled different motivational subgroups among the patients opting for the same treatment. Of interest was that anxiety seemed to be an important factor for two motivational subgroups. For these patients, the treatment choice seemed to be driven by fearful avoidance of the alternative treatment. I have labelled this phenomenon of avoidance 'negative motivation'.

The psychometric part of the data also indicated that psychopathology may influence the treatment choice. Statistical tests indicated that patients reporting fearful reluctance to social exposure in therapy groups related to conservative treatment preferred instead to undergo bariatric surgery. They had significantly higher psychopathological symptom scores than all the other pro-surgery subgroups. Patients reporting fear of dying during surgery as their primary drive towards conservative treatment displayed significantly higher symptom scores than the other motivational subgroups wanting non-surgical treatment.

Brief summary of Paper III:

Magnus Strømmen, Arne Helland, Bård Kulseng, Olav Spigset. ***Bioavailability of methadone after sleeve gastrectomy: A planned case observation.*** *Clinical Therapeutics (2016) 38, 1532-1536*

The third paper documents the altered absorption of methadone in a woman in her forties after sleeve gastrectomy. So far, there is limited research providing insights into how bariatric surgery can alter the pharmacokinetics of drugs. This knowledge gap may lead to reluctance in approving certain patients for surgery. After surgery, adequate dosing of medication may be of importance for long-term maintenance of good health.

The aim of this study was to look for and describe alterations in key pharmacokinetic properties of methadone before and after sleeve gastrectomy. Other drugs may likewise display altered pharmacokinetic processes post-surgery.

Although based on the results of a single patient, the study was structured as a prospective clinical trial with pre- and post-analyses of time-concentration curves as a basis for exploring key pharmacokinetic parameters of methadone.

The analyses showed significantly higher serum concentrations of methadone after sleeve gastrectomy when compared to preoperative serum levels. Furthermore, the serum concentrations kept on increasing in the subsequent measurements, after 5 days, 1 month, 7 months and 12 months. At the 7 months check, the area under curve of the active enantiomer *R*-methadone had reached +163%; the maximum serum concentration had increased from 616 to 1379 nmol/L. In addition; the time for reaching the peak concentration was reduced from 2.5 to 1.0 hour.

The magnitude of these changes could not be explained only by a reduction in the patient's distribution volume due to the weight loss. Genotyping of the patient revealed the presence of the CYP3A5 *1/*3 mutation. This mutation is associated with increased metabolism of the CYP3A5 substrates, which may explain the low drug concentrations prior to surgery. For the dramatic increase in the serum concentrations after surgery, the hypothesis was that the reduced gastric transit time may have lowered the gut metabolism of methadone, resulting in increased absorption.

Brief summary of Paper IV:

Magnus Strømmen, Inger Johanne Bakken, Christian A Klöckner, Jorunn Sandvik, Bård Kulseng, Are Holen. ***Diagnoses related to abuse of alcohol and addictive substances after gastric bypass and sleeve gastrectomy – A Nation-Wide Registry Study from Norway.*** *Surgery for Obesity and Related Diseases (2020) 16, 464-470*

The last paper of the thesis compares sleeve gastrectomy and gastric bypass with regard to the postoperative risks for developing diagnoses related to alcohol or other addictive substances. While there are several reports suggesting an association between gastric bypass and alcohol problems, the research is not conclusive about sleeve gastrectomy. If the two surgical procedures carry different risks for later addiction, more knowledge would be vital when recommending a particular surgery to addiction prone patients.

The aim of the study was to compare the incidence rates of diagnoses related to alcohol and other addiction related substances after sleeve gastrectomy and gastric bypass.

Paper IV uses a retrospective cohort to calculate the incidence rates of the diagnoses related to alcohol abuse or other substances among patients having undergone either gastric sleeve or gastric bypass. The paper summarizes 33,352 years of postoperative observation time for 10,208 patients who underwent either sleeve gastrectomy or gastric bypass in any public hospital in Norway. The average postoperative observation time varied between SG (2.7 years) and RYGB (3.4 years).

The postoperative incidence rate (IR) for the diagnoses related to alcohol was 6.06 (95% CI 5.45-7.36) per 1000 person-years after RYGB, and 4.54 (2.94-6.70) after SG. The hazard ratio (HR) for the alcohol diagnoses was .75 (.49-1.14) for SG compared with RYGB when controlling for age and sex. For diagnoses related to substances other than alcohol, the IR was 3.48 (2.82-4.25) after RYGB compared with 3.27 (1.94-5.17) per 1000 person-years after SG. The corresponding HR was .99 (.60-1.64) for SG compared with RYGB. The wide confidence intervals of the HRs give no support for arguing that SG and RYGB involves significantly different risks for subsequent diagnoses related to alcohol or other substances.

Minor discussion of all papers

When putting these four papers together, one interpretation is that the surgical procedure *per se* constitutes a major, but still a part in the totality of what surgical treatment of obesity may encompass. Many regular surgical procedures are obvious solutions to some anomaly, e.g., appendectomy in the case of appendicitis. Although severe obesity as a phenotype is even more easily identified than an inflammation of the appendix, Paper I addresses verbal obstacles in the patient-doctor communication; they may limit the prospects of reaching adequate referral for treatment. Paper II follows up on this by indicating that rather diverse and perhaps irrational motives may steer the patient's choice of obesity treatment. Furthermore, the study underscores that psychological screening may identify some patients' needs of more thorough considerations before deciding what treatment to choose.

The needs for personalized approaches in bariatric surgery are also parts of the focus in Paper III and Paper IV. Most patients undergoing surgery will at some later point need medical treatment. Paper III demonstrates that the absorption of medication may be altered after surgery, and that the postoperative pharmacokinetics is determined by an interplay between the particular drug, the choice of surgical procedure, and patients' genetics etc. The incidence rates reported in Paper IV did not suggest that sleeve gastrectomy and gastric bypass involves different risks for developing diagnoses related to alcohol or other substances. The systematic collections of comprehensive registry data may contribute to better algorithms for research and personalizing patients' treatments in the future.

The last decades' research has widened our understanding of the heterogeneity of obese patients, both in terms of etiology and treatment outcome. This has paved the way for the term *obesities,* which stands in contrast to regarding obesity as merely one condition. Good screening of patients is a precondition to uncover the kind of obesity that the patient represents, and perhaps also, it may be the starting point for providing higher levels of personalized obesity treatment both before and after surgery.

NORSK SAMMENDRAG

Bakgrunn

Fedmekirurgi er i dag en etablert behandlingsform i spesialisthelsetjenesten. Det høye antallet inngrep legger stadig grunnlag for bedret kvalitet i den kirurgiske inngrepet, men fedmekirurgi omfatter også kompetanse ut over det rent kirurgiske.

Med etableringen av Fedmepoliklinikken fikk St. Olavs hospital et team av helsepersonell dedikert til utredning, behandling og oppfølging av fedmepasienter. Min tilknytning har vært som sykepleier i Fedmepoliklinikken de første årene etter etableringen og siden i Senter for fedmeforskning. Denne avhandlingen er basert på fire artikler. De tar for seg forskningsspørsmål med utgangspunkt i møter jeg har hatt med pasienter. De to første artiklene fokuserer på prosesser i forkant av behandling, mens de to siste tar for seg potensielle utfordringer etter kirurgi.

Kort sammendrag av artikkel I:

Magnus Strømmen, Inger Johanne Bakken, Ellen Andenæs, Christian A Klöckner, Ronald Mårvik, Bård Kulseng, Are Holen. ***Fet, feit eller bare overvektig?*** *Tidsskrift for den norske legeforening (2015) 135, 1732-1736*

Fedme er et sensitivt område å tematisere for både pasienter og klinikere. I den første studien er pasientenes preferanser undersøkt for ulike ord som de foretrekker brukt til å beskrive deres fedme. På fastlegens kontor har evnen til å kommunisere og derfor ordvalget betydning for pasientens innstilling til det videre behandlingsforløpet.

Dette var en deskriptiv studie. Pasientene ble bedt om å rangere fjorten ulike ord eller uttrykk for overvekt og fedme for å vise hva de helst foretrakk at legen brukte. Hva som særlig kjennetegner pasienter som er mest sensitive for ordbruken ble deretter undersøkt.

Det mest foretrukne ordet blant pasientene var 'vekt'. Det skiller seg fra andre ord ved at det oppfattes som nøytralt og ved at det i utgangspunktet ikke formidler en kritikk om at man veier *for mye*. Kvinner, pasienter som utviklet fedme tidlig i livet, de som hadde høyere utdannelse eller var misfornøyde med egen vekt rangerte ordene på måter som

tilsier at de er mer sensitive for hvordan fedme omtales og tematiseres av helsepersonell.

Kort sammendrag av artikkel II:

Magnus Strømmen, Bård Kulseng, Einar Vedul-Kjelsås, Harald Johnsen, Gjermund Johnsen, Ronald Mårvik. ***Bariatric surgery or lifestyle intervention? An exploratory study of severely obese patients' motivation for two different treatments.*** *Obesity Research & Clinical Practice (2009) 3, 193-201*

Vi har erfart at pasienter i klinikken ofte uttrykker sterk motivasjon for én spesiell behandling. I denne studien undersøkes hvilke motiver som kan ligge bak et slikt bestemt behandlingsønske i forhold til kirurgisk eller konservativ fedmebehandling.

Dette har ikke vært undersøkt tidligere. Ulike metoder og datakilder ble brukt for å utforske problemstillingen. Pasientene beskrev i fritekst deres viktigste motiv for sitt behandlingsvalg. Dette genererte en hypotese om at stilt overfor to svært ulike behandlingsvalg, kan frykt og unngåelse for en av behandlingene være en vesentlig del av motivasjonen for valget. Når fryktsom unngåelse står sentralt for valget, betegnes dette som 'negativ motivasjon'.

Tekstmaterialet om motiver for behandlingsvalget ble kategorisert. Dermed ble det tilgjengelig for statistiske analyser hvor man på grunnlag av supplerende symptomscorer undersøkte om psykisk helse var med og påvirket valget av behandlingstype. Denne del av studien viste at pasientene med negativ motivasjon også hadde vesentlig høyere psykopatologiske symptomscorer, noe som dermed støtter hypotesen om at psykisk helse kan påvirke behandlingsvalget.

Kort sammendrag av artikkel III:

Magnus Strømmen, Arne Helland, Bård Kulseng, Olav Spigset. ***Bioavailability of methadone after sleeve gastrectomy: A planned case observation.*** *Clinical Therapeutics (2016) 38, 1532-1536*

Lite er ennå kjent om hvorvidt og hvordan fedmekirurgi endrer kroppens opptak, omsetning og eliminasjon av legemidler. Denne mangelen på kunnskap kan gjøre at

man ikke fanger opp uheldige virkninger av et medikament hos pasienter etter operasjonen. Det kan også føre til at man ut fra usikkerhet avslår pasienter fedmekirurgisk behandling fordi pasienten står fast på annen medikamentell behandling.

Den tredje artikkelen er en kasuistikk. Her undersøkte man farmakokinetiske endringer av metadon hos en pasient behandlet for opiatavhengighet og som gjennomgikk gastric sleeve. Mens kasuistikker ofte beskriver tilfeldige funn, var dette en planlagt studie; monitorering av legemiddelrespons var en forutsetning for å innvilge kirurgi for pasienten.

I analysene fant man mye høyere serumkonsentrasjoner av metadon etter operasjonen enn tidligere. Gjentatte målinger i månedene etter operasjonen viste at økningene tiltok frem til siste fullstendige måling, 7 måneder etter operasjonen. Pasientens vekttap kan ikke alene forklare en så stor økning i serumkonsentrasjoner.

Genotyping viste at pasienten hadde en mutasjon for CYP3A5. Det, innebærer økt metabolisering av metadon i tarm, altså økt nedbrytning før opptak i blodet. Årsak til absorpsjonsøkningen antas å være at metadon etter operasjonen glir raskere gjennom tarmen og passerer hurtigere de tarmsegmentene hvor virkningen av CYP3A5 er mest uttalt. Dette kan gi økt absorpsjon distalt i tarmen.

Kort sammendrag av artikkel IV:

Magnus Strømmen, Inger Johanne Bakken, Christian A Klöckner, Jorunn Sandvik, Bård Kulseng, Are Holen. ***Diagnoses related to abuse of alcohol and addictive substances after gastric bypass and sleeve gastrectomy – A Nation-Wide Registry Study from Norway.*** *Surgery for Obesity and Related Diseases (2020) 16, 464-470*

Bakgrunnen for den siste artikkelen er at noen observasjoner kan tyde på at pasienter som har gjennomgått fedmekirurgi har økt risiko for å utvikle alkoholmisbruk, noe som kan henge sammen med økt absorpsjon av etanol i tarmen etter operasjonen. Datamaterialet er et uttrekk fra Norsk Pasientregister fra mer enn 10.000 fedmeopererte nordmenn. I studien sammenlignes insidensratene for diagnoser relatert enten til alkohol eller andre rusmidler hos pasienter som har gjennomgått gastric sleeve og gastric

bypass. Mer kunnskap om prosedyrespesifikk risiko kan eventuelt gi grunnlag for bedre seleksjon av pasienter til de ulike operasjonsmetodene.

Selv om insidensratene virket noe lavere for alkoholdiagnoser etter gastric sleeve sammenlignet med gastric bypass, var hazard ratio på 0,75 ikke signfikant (95 % konfidensintervall 0,49-1,14). For andre rusdiagnoser var det heller ikke signifikante forskjeller mellom de to operasjonsmetodene. Med den observasjonstiden våre data omfattet, er det ikke grunnlag for å anbefale en av de to operasjonsmetodene fremfor den andre til pasienter som antas ha høyere sannsynlighet for å utvikle avhengighet.

Kort diskusjon av artiklene

Avhandlingens fire studier gjelder behandlingsforløpet for fedmepasienter behandlet med kirurgi. Studiene tar opp spørsmål av klinisk betydning på områder der vi bør vite mer både i forkant og etterkant av selve operasjonen. Et optimalt pasientforløp avhenger av flere faktorer enn selve det kirurgiske inngrepet.

To av artiklene dreide seg om forhold i forkant av operasjonen. Artikkel I illustrerer noen av utfordringene ved å tematisere fedme som er grunnlaget for videre henvisning til kirurgi. Artikkel II følger opp utfordringene som kan ligge i forkant av spesialistbehandling og avdekket at pasienter kan ha svært ulike, og i noen tilfeller nokså irrasjonelle motiver for å søke seg til enten kirurgi eller konservativ behandling. Begge artiklene viser behov for en mer individuell tilnærming til pasienten.

Viktigheten av en persontilpasset behandling kommer enda sterkere frem i artikkel III og IV. Artikkel III viste hvordan gastric sleeve kan påvirke absorpsjonen av legemidler, noe som med nåværende standard oppfølging ikke er lett å fange opp. Forklaringen på de høye serum konsentrasjonene av pasientens legemiddel lå trolig i samspillet mellom operasjonsmetode, legemiddelet og pasientens genotype. Selv om man på bakgrunn av artikkel IV ikke kan konkludere med at gastric bypass og gastric sleeve innebærer ulik risiko for rusproblemer, illustrerer artikkelen at registerdata kan gi grunnlag for innføring av mer persontilpassede behandlingsalgoritmer. Dette er i tråd med moderne tenkning om fedme som en kompleks og sammensatt tilstand.

1 INTRODUCTION

1.1 About obesity

1.1.1 Definition, classification and disease recognition

The World Health Organization (WHO) defines obesity as "a condition of abnormal or excessive fat accumulation in adipose tissue, to the extent that health may be impaired" (1). Notably, 'body weight' is left out of the definition. For classification purposes, however, body weight is required for calculating the body mass index (BMI), a crude population level measure (1). BMI is extensively used also on the individual level by both clinicians and people in general.

Even though obesity was described as a health problem already in the earliest written sources of medical science (4), it is only recently that modern medicine has recognized this condition as a disease (5). Outside the field of clinical obesity, this may seem odd. However, there have been great controversies about the disease label. The choice has implications for how to approach obesity. While some claim obesity fails to fit the philosophical concept of disease (6), others argue that the clinical reality should determine the concept (7). In his paper with the title "*Obesity is a chronic, relapsing neurochemical disease*" (8), Bray argues how obesity fulfils the criteria of aetiology, pathogenesis, pathology and pathophysiology. In 2017, the descriptor *progressive* was added as one of the key features of obesity (9). The chronic and progressive nature of obesity have implications for how this condition needs to be approached clinically. Both the World Obesity Federation and the Obesity Society states that obesity is a disease (9, 10). The public, however, is split in their views. Among Americans, particularly those holding that personal behaviour rather than biology is the strongest aetiological factor, do not endorse the idea of obesity as a disease (11).

The ICD-code *obesity* (International Classification of Diseases and Related Health Problems) came with its sixth revision in 1948, and *morbid obesity* was included in ICD-9 (1995) (7). Sobal, a sociologist, describes how obesity over several decades has been medicalized: From the moral model (*fatness* as *badness*), to a medical model (*obesity* as *sickness*) (12). Different medical societies, including the American Medical

Association in 2013 (13), have made explicit statements that recognizes obesity as a disease (14). Such statements can be seen as parts of a societal negotiation.

The recognition of obesity as a disease may have implications for treatment and cost reimbursements (8). Moreover, the disease label can ease the moral burden that many patients feel; they are exempted from blame regarding their condition (15).

1.1.2 Obesity in numbers

The National Health and Nutrition Examination Surveys (NHANES) have documented the Americans' health status and its changes over time. The BMI trajectories have increased by each survey. However, in the 2015 US Health-report, the category overweight (but not obese) declined among adult men while remained stable for women. Nevertheless, the proportion of the population with obesity is still increasing. By 2014, the U.S. prevalence of overweight (including obesity) were 70.7% (16).

From the Nord-Trøndelag Health Survey (HUNT), a dramatic increase was observed in both overweight and obesity in the 22-year survey period until 2012. The prevalence of overweight (including obesity) in this representative survey for Norway is 60.8% and 74.5% for women and men over 20 years, respectively (17). Although numbers from the U.S. and Norway are relatively similar when merging overweight and obesity into one category, the proportion of the population with severe obesity is relatively larger in the U.S.

On the global level, obesity and its related chronic disorders closely follow the economic growth and urbanisation; this has made overweight and obesity a worldwide problem (18). From 1980 to 2013, the global prevalence of overweight, including obesity, in adults rose by 27.5% and by 47.1% in children. The prevalence data from 183 countries estimate that 2.1 billion people are overweight or obese (19).

The BMI-distribution among adults is becoming more and more right-skewed, indicating that there are more people with severe obesity. That upper weight brackets of the population run a high risk of serious diseases and shorter life spans. Although overweight, excluding obesity, seems to be leveling off in the U.S., some reports

estimate that severe obesity (BMI > 40) may rise 133% by 2030. This would generate tremendous future healthcare costs (20).

1.1.3 Bariatric surgery

Since the first weight loss surgery was carried out in the 1950s, three surgical procedures have recently been dominating: The Roux-en-Y gastric bypass (RYGB), the adjustable gastric banding, and the sleeve gastrectomy (SG) (21). Since banding is uncommon in Norway, only the RYGB and SG (see Figure 1) will be dealt with in this thesis.

In the RYGB, the surgeon creates a small pouch of the cardia; this is detached from the rest of the stomach. The jejunum is divided approximately 50-100 cm from the ligament of Treitz, and the distal limb is connected to the gastric pouch. This creates an alimentary Roux limb. The bilio-pancreatic limb and the alimentary limb are anastomosed 100-150 cm distally to the gastrojejunostomy (22). Technically, the RYGB can be reversed.

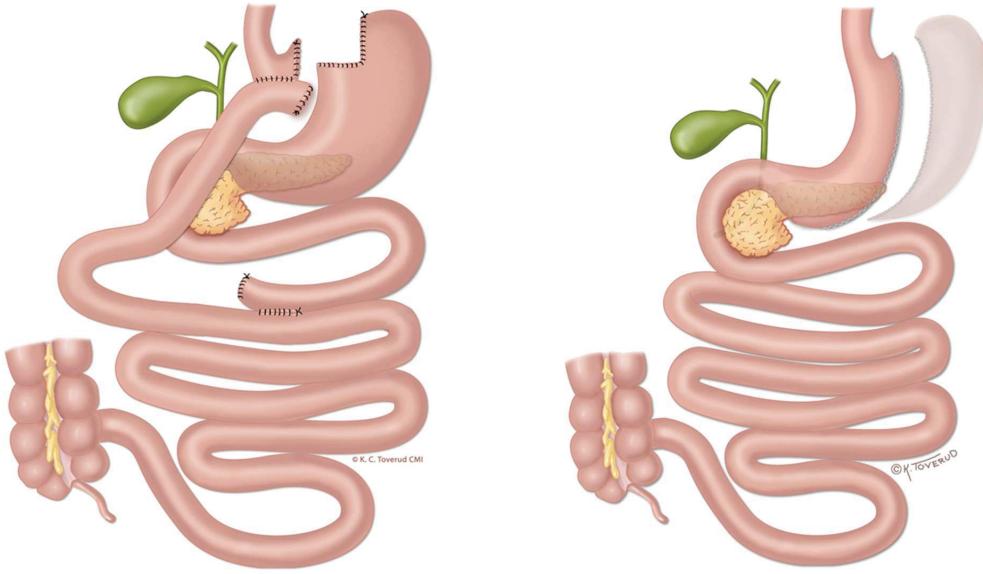


Figure 1: Illustrations of the Roux-en-Y gastric bypass (left) and the Sleeve gastrectomy. (Illustrations: Kari C. Toverud, certified medical illustrator.)

The SG is a relatively new surgical procedure, introduced in 2001 (23). It is less invasive compared to the RYGB. However, it is irreversible as it involves the removal of the greater curvature. The stomach is transformed into a gastric tube. The lumen of the gastric tube is guided per-operatively by the insertion of a naso-gastric tube of 34 to 46 French. No anastomoses are made (22).

Despite the anatomical differences, the RYGB and the SG involve several similar physiological mechanisms. Although the pyloric sphincter remains after SG, the gastrointestinal transit time increases (21). Regarding the hormonal appetite regulation, both procedures induce reductions in leptin and ghrelin while they also stimulate increased post-prandial secretion of GLP-1 (glucagon-like peptide) and PYY (peptide YY) (21, 24). However, for the remission of type 2 diabetes, there may be hormonal differences between the procedures. The recently published one-year data from the Oseberg study, which is a blinded randomised trial, found significantly better remission rates after RYGB compared to SG (25).

BS seems superior to non-surgical obesity treatment with regard to the degree of weight loss, its maintenance over time, associated improvements in comorbid conditions (26, 27), and life expectancy (28). In addition, RYGB is considered most cost-effective, although the economic models show considerable variability in the cost estimates (27). A Cochrane-review states the need for long-term assessments; they suggest at least five years observations of the outcomes related to BS (26). Most studies on BS only include short-term data of the outcome. Patients lost to follow-up are another major problem in these studies (29).

In 2016, nearly 630,000 surgical procedures were carried out in the 62 IFSO-nations (International Federation for the Surgery of Obesity and Metabolic Disorders) (30). As most patients live several decades after surgery, the accumulated number of operated patients will grow. This has implications for the volume of expected complications that may follow. In Norway, about 3,000 surgical procedures are carried out annually (31).

By way of concluding this general introduction about obesity and BS, I will briefly indicate the structure of the following parts of this chapter. The introductions will be presented to each of the four papers of this thesis, and the introduction will be rounded

off with a brief summary of the main findings of each paper. The design of the studies' and details about the participants will be covered in the chapter on Methods. The comprehensive chapter, Discussion, contains separate discussions for each of the four papers.

1.2 Paper I – Language in a clinical setting

Strømmen M, Bakken IJ, Andenæs E, Klöckner CA, Mårvik R, Kulseng B, Holen A. Fat, obese, or just overweight? Tidsskrift for den norske legeforening (2015) 135, 1732-1736

Considering that many patients have been stigmatised due to their obesity, words or expressions used with the best intention by health personnel may, nevertheless, be perceived as negative by the patient. Using words or expressions to describe obesity that are felt by most patients as offensive or demeaning may jeopardize the doctor-patient climate. Paper I was an effort to facilitate the professional communication with obese patients.

Stigmatization may lead to mental health problems. People with obesity are not exempted from weight stigma even in clinical settings. Providers of care may carry both implicit and explicit attitudes. Implicit attitudes are sometimes automated and beyond awareness. Attitudes towards obese patients can impair the patient interaction even though positive attitudes are also displayed towards the individual. Related to obesity, less patient-centred communication has been demonstrated to be associated with non-adherence and less weight loss in the patients (32).

It is a common idea that moderate stigma and shaming can motivate weight loss. However, the evidence suggests the opposite; stigma may lead to binge eating, reduced physical activity, and social isolation (33). Even 'well-intended' stigmatization is likely to reduce the chances of weight loss. The patient's fear of weighing and of having gained weight since the last appointment, dissuades the obese, women in particular, from adequately utilizing the health services. There is a positive correlation between BMI and appointment delay in the health services (34). Accordingly, communication patterns that reinforces stigma or shame may become an obstacle to continued appointments.

Studies indicate that overweight respondents who felt judged by their primary care providers, reported less trust in them than those who did not feel judged (35). Patients who feel stigmatized by their physicians are less willing to comply with the recommendations, and they are less willing to see the physician again (36). In general, physicians tend to build significantly less emotional rapport with overweight and obese patients (37). Although obesity may not influence the length of the consultation, it may impact what happens during the visits. Physicians spend less time on health education with overweight patients (38). This is a paradox considering how prevalent multimorbidity and polypharmacy are among obese patients (39, 40). A good doctor-patient relationship is likely to be a good and necessary start for reducing weight and pathological conditions.

A precondition for a good doctor-patient climate is the awareness of the patients' *language sensitivity* in the communication; the concept was defined by Aycock et al. and the preferred version of it includes the 'use of respectful, supportive, and caring words' (41). A common view is that the words and phrases should not be offensive or demeaning. At least seven studies have focused on what type of words the care providers preferably should chose together with patients who are heavy. Four studies, all from the US, involved patients' ratings of a list of words in regard to their *desirability* as seen by the obese patient (42-45). One study (US) also included ratings of words' *stigmatizing*, *blaming* and *motivating* effects (46). Another study (US) looked into what is called *people-first language* (47). If referred to as an 'obese person' rather than a 'person with obesity', the first version may leave the person feeling as if obesity is inherent in his/her personality. The last of the seven studies (UK) explored qualitatively the participants' reflections about word desirability (48).

Most of these studies included treatment-seeking patients (42, 44, 45, 47). Except for one based on a representative national sample (46), the studies encompassed solely overweight or obese participants. Gender, age, education level, BMI, binge eating, and race occurred as covariates in the analyses. I have not looked into studies exploring relevant words in relation to children's and adolescents' weight.

In different languages and cultures, words describing excess weight may carry different connotations. Accordingly, the mere translation of words or expressions from English to Norwegian could lose some of the nuances and connotations. So far, there has been no inquiry about obesity-related words in any of the Scandinavian language. This constituted the reason for carrying out a study in the Norwegian context.

In a sample of patients undergoing treatment for morbid obesity, we sought answers to these questions:

- To what extent had their general practioners (GPs) initiated discussions about excess weight?
- What words describing excess weight in the GP-context would be regarded as desirable by the obese patients?
- Is word desirability among the morbid obese related to possible covariates such as gender, age, education, marital status, mental health, happiness with their weight, and/or age at the obesity onset?

1.2.1 Summary – Main findings from Paper I

This was the first investigation of obese patients' word desirability in Norwegian when their excess weight was to be addressed. 'Weight' was considered the most appropriate word for use in clinical consultations, while 'fat' was reported to be most inappropriate of the 14 words that were tested. Most sensitive to such words were women, patients with an early-life obesity onset, those with higher education, and those least satisfied with their own weight. One third of the patients reported that their physician had initiated a discussion about their obesity, and nine out of ten patients meant it would be appropriate for a physician to initiate such discussions. Most patients reported that the physician's choice of words influenced the quality of their doctor-patient relationship.

1.3 Paper II – Motivation and choice of treatment

Strømmen M, Kulseng B, Vedul-Kjelsås E, Johnsen H, Johnsen G, Mårvik R. Bariatric surgery or lifestyle intervention? An exploratory study of severely obese patients' motivation for two different treatments. Obesity Research & Clinical Practice (2009) 3, 193-201

Why is it that patients strongly are motivated for BS while others exclusively want non-surgical treatment? In this study, we explored subcategories of the motivation behind the patient's choice of treatment, and also, if the choice was somehow related to psychopathology. Understanding the patients' motivation and its underpinnings may enable health personnel to obtain better understanding of the patient and thereby lead to more adequate recommendations and personalization of their treatment. In research, it may also be relevant to control for the motivational subcategories when evaluating the outcome of treatment.

The costs of the health services in Norway are mostly covered by the governmental National Insurance Scheme. Compared to nations with private insurance-based health care, Norwegian citizens are freer to choose their treatments; this also applies to the treatment of obesity. Moreover, in countries with a protestant value orientation like Norway, an operation due to what many consider to be the result of a flawed character seems harder to accept (49).

In Central Norway, obese patients seeking treatment are informed about the various available options. The regional obesity specialist centre receives referrals both for BS and non-surgical alternatives. The ideal would be that the choice of treatment is a shared decision between the doctor and the patient. However, some patients are right from the outset rather opinionated about what treatment they want. The motives for their choice, however, are not always obvious.

Several studies have focused on the under-utilization of treatment among the obese. In particular, men tend not to not seek treatment (50). Patients with a history of adverse childhood experiences or food addictions are less likely to undergo BS than those with no such history (51). Many patients withdraw from treatment during the screening process (52-55). Another issue of clinical significance is whether the patient's motivation can predict the treatment outcome. Maintaining a lower weight after surgery

or conservative treatment, necessitates persistent behavioural changes. It seems intuitive that the patient's motivation may play a part in the patient's long-term ability to self-regulate life style issues. Our assumption is that motivation and adherence to the required post-treatment behavioural changes are partially linked.

1.3.1 What may influence treatment choice

A number of studies have looked at the prognostic role of motivation in relation to the patient outcomes of BS (56-59). There have also been studies focusing on the predictive value of the patients' expectations towards weight loss (60, 61); could disappointments with the initial outcome of surgery jeopardize the patient's continued efforts to uphold the required behavioural changes? Studies of the patients risk willingness indicate that both safety issues and the invasiveness of the operation are taken into consideration when they decide which surgical procedure they want (62, 63).

BS represents a rather different approach than non-surgical treatments. Surgery is invasive, and a step with rather absolute consequences. From patient education, it is my impression that many patients seem to be more focused on technical aspects and specific nutritional consequences of surgery rather than what is required of them with regard to behavioural changes. In contrast, non-surgical treatments' primary focus is empowering the patients to change and maintain their necessary dietary behaviour. Despite the fundamental differences between surgery and non-surgical treatments, I will refer to them as *treatment modalities*. Patients seeking surgical treatment will be referred to as SurgP below, while ConsP refers to patients wanting conservative treatment.

1.3.2 Brief literature review

In 2017, Fischer et al. claimed to be the first to investigate the reasons for why some patients choose non-surgical alternatives over surgery. SurgP had more often depression (self-reported, but no standardized psychometrical instrument), more painful joints,

and/or they viewed surgery as the last resort to lose weight. Several ConsP, however, reported fear of surgery (64).

Bancheri et al. identified no overt psychopathology neither among SurgP or ConsP, although ConsP scored higher on the bulimia and ineffectiveness scales (Eating Disorder Inventory-2) (65). No observed differences were found in the levels of depression gauged by Beck Depression Inventory-II when comparing ConsP and SurgP in a study by Matthews-Ewald et al. However, SurgP reported more hunger and food cravings, poorer quality of life related to sex and public distress (IWQOL-lite). Moreover, they reported higher numbers of weight loss attempts (66).

When using the Hospital Anxiety and Depression Scale (HADS) as a measure of psycho-pathology, Miras et al. found no difference in eating behaviour and mental health between patients choosing any of the two treatment modalities (67). However, SurgP scored higher on impulsivity and reward responsivity as well as poorer quality of life (IWQOL-lite) in the public distress domain. No differences in the quality of life in any domain were observed with the instrument SF-36 (Short-Form 36).

Stout et al. found more emotional eating (Binge Eating Scale) and poorer quality of life in all domains (IWQOL-lite) among SurgP compared to ConsP. There were no differences found on the Beck Depression Scale (68).

In a large number of patients, Castellini et al. combined a comprehensive battery of psychometrical tests and DSM-IV clinical interviews for Axis I diagnoses (69). Their findings showed a high rate of unipolar depression and binge eating disorder among SurgP. ConsP scored higher on eating and body concerns when using the Eating Disorder Examination Questionnaire (69).

Finally, Gradaschi et al. observed no differences in eating behaviour or psychopathological status among patients choosing any of the two treatment modalities (70). However, the presence of metabolic derangement, e.g., type 2 diabetes and dyslipidaemia, predicted a desire for surgery. This suggests that the patients' physical condition may be a strong motivator in the choice of treatment.

Regarding depression, the research has come up with rather diverse conclusions. Two of the studies found more depression among SurgP (64, 69), while the other five did not observe any significant differences. Three studies found disturbed eating behaviour among SurgP (66, 68, 69), while two studies did not observe any such patterns (67, 70). All three studies using IWQOL-lite for the quality of life, found SurgP to have poorer quality of life (66-68). However, the instrument SF-36 uncovered no such difference (67). These conflicting findings raise questions about the adequacy of using specific psychometric instruments in this context. A more fundamental question is whether group level analyses based on patients' choice of treatment provide useful clinical information? Group averages may mask differences among subgroups of patients.

In this study, we took a naïve, explorative perspective. The aim was to detect potential subgroups of patients based on their motivation related to the choice of treatment modality. Instead of gauging psychometrics at the group level, we used HADS to screen for psychopathological differences on a subgroup level.

The research questions for Paper II were:

- Do patients who choose the same treatment also share a similar motivation?
- Do patients differ in outcomes on psychological measures according to the rationale for their motivation?

1.3.3 Summary – Main findings from Paper II

About a quarter of the patients (N=36/138) referred for BS to a university hospital in Norway preferred a comprehensive 18-week lifestyle programme instead of gastric bypass. The qualitative part of the study unveiled different motivational subgroups. Among the patients seeking surgery (N=102/138), the four reported motives were:

A) avoidance of social exposure in group therapy (n=4);
B) surgery was believed to be a permanent solution to their eating problem (n=65);
C) caring responsibilities for family members (n=28);
D) matters related to their work (n=5).

The motives reported by the patients who opted for conservative treatment were:

E) fear of dying during the surgery (n=4);
F) concerns about surgical complications (n=11);
G) preference for a natural weight loss (n=14); and
H) long-term support and follow-up provided by the conservative programme (n=7).

As listed, the motivational subgroups A-D (surgery) and E-H (conservative treatment) represent decreasing HADS total-scores.

For the two subgroups with the highest HADS total-scores (A and E), fear or anxiety seemed to be an important factor swaying their choice of treatment. These patients appeared to prefer one of the treatment primarily to avoid the other. We labelled such phenomena characterized by fearful avoidance as 'negative motivation'.

Based on these findings, we generated a hypothesis that psychopathology may influence the treatment choice in some cases. This was tested statistically using Dunnett's test for multiple comparisons. The HADS-scores of those reporting reluctance to the social exposure (subgroup A) were significantly higher than all the other pro-surgery subgroups (subgroups B-D). Among the patients opting for conservative, i.e., lifestyle treatment, those with fear of dying during surgery (E) had significantly higher HADS scores than those who preferred a more "natural" way of losing weight (G) and those favouring the longer follow-up (H).

1.4 Paper III – Sleeve gastrectomy and methadone absorption

Strømmen M, Helland A, Kulseng K, Spigset O. Bioavailability of methadone after sleeve gastrectomy: A planned case observation. Clinical Therapeutics (2016) 38, 1532-1536

Polypharmacy is common among treatment-seeking obese patients. Health personnel have worried that BS may influence the intestinal absorption of drugs and render adequate postoperative dosing difficult. The case study in Paper III documents the drug responses in one patient on opiate maintenance therapy; the drug responses were explored both before and several times after the operation.

Prior to the referral of this patient, she had already been denied BS at another hospital due to the uncertainty about the possible pharmacokinetic effects of such operations.

The simplistic explanation for weight loss after BS has been the restriction of food intake, malabsorption in the intestines, or the combination of the two (71). Many clinicians tend to believe that an operation like the RYGB interferes with the absorption of drugs (72). However, there is limited knowledge about the effects of BS on the absorption of drugs (73). Moreover, much of the existing research on the matter has methodical limitations. Examples: the use of different pre- and post-surgery samples (↑variability); no genotyping (↑variability); small samples (↓statistical power); and, the lack of repeated postoperative measurements to explore the possible long-term physiological changes in the gut. Furthermore, it is difficult to generalize from studies of a small number of drugs to compounds that have not yet been tested. Lastly, observations based on one bariatric procedure cannot be generalized to another; the different types of surgery modify different anatomical structures. The work by Darwich et al. tries to overcome some of these obstacles by using a mechanistic model to assess how the different surgical procedures influence bioavailability of model drugs (3).

Two recent reviews sum up much of this literature (74, 75). The one by McLachlan et al. defined a standard for the quality in such inquiries. Studies with small samples, or the lack of prospective pre-post design were excluded (75). To minimize the risk of bias, they recommended the exclusion of patients with maladaptive disorders and to control for concomitant medications. In the test situation, they standardized the food and water intake. Their review listed 21 cohort studies covering 29 different drugs. Only five studied the pharmacokinetics (PK) of patients undergoing SG. The sample sizes ranged from five to 34 participants, and the postsurgical measurements took place between three days up to 41 months after surgery (75).

The other recent review by Angeles et al., focused on the physiological mechanisms that may be used for modeling the bioavailability of drugs when clinical data are lacking. By controlled tests on probe drugs, i.e., substances that are selective substrates for specific drug metabolizing enzymes, the results were extrapolated and made to resemble drugs

with similar PK properties (74). Most of the reports listed in their review were based on RYGB (18 reports compared to six on SG). The majority of the studies indicated faster absorption of oral drugs. The shorter time to reach maximum concentration (T_{max}) may be a direct effect of surgery as the altered postoperative anatomy reduces the gastric volume and stimulates more rapid emptying of the stomach. Quicker absorption may not be the only reason for increased maximum concentration (C_{max}), but also the reduced distribution volume due to the weight loss. Despite changes in T_{max} and C_{max}, the systemic exposure (AUC, area under curve) of the drugs remained unaltered in several studies (74).

Polypharmacy is common among patients referred to BS. A US-study reported that these patients regularly take on average 4.4 prescribed medications (40). Although many patients experience partial or complete remission from their diseases after surgery, there is still a need for more knowledge about both the short- and long-term effects of surgery on bioavailability. In the review by Bland et al. there are speculations about the altered drug absorption as the key to understand what some studies have reported, i.e., exacerbations of depressive symptoms and more frequent suicide events after BS (76). These reviews demonstrate that BS and drug PKs represent an area where more research is needed. At the same time, this gap of knowledge makes it understandable why physicians may be reluctant to operate patients on orally administered medication that is vital for their health.

1.4.1 A case observation

Patients on substitution therapy are uncommon in the Obesity Clinic. However, a female Caucasian in her forties using methadone (120 mg/day, oral mixture) was referred to St. Olavs Hospital for BS. After starting the intake of methadone in the past, she had gained 30 kg. Weight gain is a known side-effect of this substitution therapy (77). The referral was a request for a second opinion after surgery had been declined at another hospital. The unknown effects of surgery on her drug absorption was emphasized as the main reason in the former decline.

The patient underwent a comprehensive multidisciplinary screening that also included a dialogue with her GP as well as the specialist responsible for her methadone treatment. The patient was informed about the lack of evidence and the doctors' concern that the surgical procedure may affect negatively her substitution therapy. The patient was still strongly motivated for surgery and had support from both her GP and the specialist who had prescribed the opioid agonist. As an extra measure, we consulted the Ethics Committee for advice. After approval, we planned a systematic case study of her and prepared for surgery with the intention to publish the results with her consent. As the SG surgically was less invasive than the RYGB, she was prepared for SG.

The research aim was to study key her pharmacokinetic variables (AUC, T_{max}, C_{max}) of methadone before and up to one year after SG.

1.4.2 Summary – Main findings from Paper III

This case observation manifested in the first report about the effect of BS on methadone PK. Compared to the serum concentrations before SG, the methadone concentrations were elevated after the operation, and they kept on rising in the consecutive measurements, i.e., after 5 days, 1 month, 7 months and 12 months. The AUC of the active enantiomer *R*-methadone increased gradually and reached +163% at 7 months postoperatively. *R*-methadone was absorbed quicker; T_{max} was reduced from 2.5 to 1.0 hours, C_{max} increased from 616 to 1379 nmol/L.

There are several possible explanations for the major observed changes in the methadone bioavailability. From the time of referral prior to surgery until one year after surgery, the patient lost 36 kg; the lean body mass was reduced 9.3 % in the first seven months. The weight loss gave a smaller volume for the distribution of the drug, which contributed to a higher drug concentration. Higher drug clearance due to changes in the liver function could not be ruled out, but assuming a reduction in the liver size proportionate to the loss of lean mass, this would only explain a small part of the elevated methadone concentrations found.

Despite being prescribed a rather high methadone dose, the patient had relatively low preoperative serum concentrations. Genotyping for the CYP-isoenzymes which is involved in the metabolism of methadone, revealed the presence of the CYP3A5 *1/*3 mutation. This mutation is associated with increased metabolism of the CYP3A5 substrates, which may explain the low drug concentrations prior to surgery. For the dramatic increase in the concentrations after surgery, the hypothesis was that it may be due to reduced gastric transit time, i.e., when methadone enters the duodenum more rapidly, the intestinal CYP3A enzyme capacity could be overwhelmed. This would reduce the capacity of pre-systemic metabolism and lead to the considerable rise in methadone concentration.

1.5 Paper IV – Bariatric surgery and alcohol abuse

Strømmen M, Bakken IJ, Klöckner CA, Sandvik J, Kulseng J, Holen A. Diagnoses related to abuse of alcohol and addictive substances after gastric bypass and sleeve gastrectomy – A Nation-Wide Registry Study from Norway. Surgery for Obesity and Related Diseases (2020) 16, 464-470

In recent years, there have been reports indicating that alcohol problems may be a long-term complication to BS. If the risks for alcohol problems differ between RYGB and sleeve gastrectomy (SG) patients, it would be relevant when deciding which surgical procedure to recommend for patients presumed to be at higher risk of addiction. As research into the effect of SG on alcohol absorption so far is inconclusive, large registry data may provide some indications about possible links. Paper IV compares the incidence rates of diagnoses related to alcohol or other addictive substances after RYGB and SG.

Until quite recently, reports on alcohol problems after BS were mostly anecdotal (78). The low awareness about a possible association between BS and alcohol use disorders (AUD) may have made these problems overlooked. My interest in alcohol problems after surgery stems from the encounter of one single patient: Five years after surgery, when I asked about her general health, she for the first time opened up about her alcohol problems. The severity of the problems combined with her strong conviction that there

was a causal relationship between BS and her alcohol problems, initiated a new direction in my research.

Since the introduction of BS, the development has partly been driven by the need to avoid adverse complications (79). Different from the commercial development of new pharmaceutical products, there are no similar regulatory agencies surveilling novel surgical procedures. Thus, the chances of detecting rare or long-term adverse effects are much smaller than for pharmaceutical treatments.

1.5.1 Observational studies

Recent research indicates that alcohol problems is a complication to BS. Former operated patients seem to be over-represented in the substance abuse treatment programs; one study found 2-6 % of such patients to have undergone BS. The authors reported that the patients with BS drank heavier than most other patients in treatment for substance abuse (80). A US study found 18% of the patients referred to BS to have a lifetime history of alcohol abuse (81). The corresponding number was smaller (11%) among German BS patients; a history of alcohol abuse was more frequent among those having an additional eating disorders (82).

The prospective, longitudinal SOS-study (Swedish Obese Subjects-study) compared three different surgical procedures; they showed that the mean daily alcohol intake was reduced during the first year after BS. RYGB patients, however, later increased significantly their intake above the preoperative levels. The higher intake was maintained at the ten-year publication. The other two groups, vertical banded gastroplasty and gastric banding, returned to their preoperative levels of alcohol intake (83). Other studies also indicate that alcohol problems surface years after the RYGB (84, 85). A recent prospective study of 1,481 RYGB patients found the 5-year cumulative incidence of AUD to be 20.8% (86). Numbers this high call for concern and more research.

Several studies have found that about 2/3 of the patients who develop alcohol problems after surgery had no prior history of such abuse (85, 87-91). The large proportion of

new onset after BS was not expected. The median age of onset in the general population for substance use disorders is 20 years (92). The average BS patient, however, is in their forties. Thus, most patients had already passed the age at which onset is more likely. This suggests a possible association between BS and later alcohol problems. Patients report increased sensitivity to alcohol after BS (93-96).

1.5.2 Altered ethanol bioavailability

In general, several factors influence the absorption of orally administered drugs such as the acidity of the stomach, the gastric emptying time, the gastrointestinal transit time and the pre-systemic metabolising effects of CYP-enzymes excreted in the mucosa of the duodenum and jejunum (97). In the introduction to Paper III, I have described how BS influences several of these factors that make the drug absorption difficult to predict.

Like several other medications, ethanol is not fully absorbed in the gastrointestinal tract. In contact with the gastric mucosa, a significant proportion of the ethanol is oxidised by alcohol dehydrogenase (ADH). This constitutes a part of the gastric first-pass metabolism (98), which can be influenced by factors such as gastric emptying time, alcohol concentration (99), food intake (100), gender (101), drugs (102), and the stomach morphology (103).

The first-pass metabolism is a natural protection against the toxicity of alcohol. Hence, surgical procedures resulting in either a reduced mucosal surface or speeding up the gastric emptying time may in both cases increase the potential harmful effects of alcohol. After RYGB, the mucosal surface is significantly smaller, and bypassing of the pyloric sphincter makes liquids go almost directly into the small intestine. Here, alcohol is efficiently absorbed. Four studies have confirmed increased bioavailability of ethanol following RYGB (104-107).

In later years, SG has become a common bariatric procedure in Norway. Research on SG and bioavailability of ethanol, however, is less consistent, so far. Two studies have concluded that SG had no significant effect on bioavailability (108, 109), while two

other studies found a major increase in the peak concentration of ethanol (C_{max}) after SG (93, 110).

Table 1: Studies on bariatric surgery and ethanol bioavailability after RYGB and SG.

Bariatric procedure	Study	Sample	Findings[a]
Gastric bypass	Klockhoff et al. (105)	12 operated > 3 years 12 controls (all women)	C_{max} (cases) > C_{max} (controls) T_{max} 10 minutes (cases) and 30 minutes (controls)
	Hagedorn et al. (104)	19 operated ≈ 2 years 17 controls (78% women)	C_{max} (cases) > C_{max} (controls) AUC_{last} 108 minutes (cases) and 78 minutes (controls)
	Steffen et al. (106)	5 operated > 3 years (all women)	T_{max} 5,4 minutes
	Woodard et al. (107)	19 patients pre-post (84% women)	C_{max} (pre) = 0.024% vs C_{max} (post) = 0.088% Longer time to sober postoperatively
Sleeve gastrectomy	Maluenda et al. (110)	12 patients pre-post (33% women)	C_{max} (pre) = 0,87 g/l vs C_{max} (post) = 2,02 g/l AUC_{last} prolonged after surgery
	Changchien et al. (108)	7 patients pre-post (86% women)	No change in C_{max} or AUC_{last}
	Gallo et al. (109)	10 patients pre-post (90% women)	No change in C_{max} or AUC_{last}
	Acevedo et al. (93)	11 operated SG ≈ 2 years, 8 operated RYGB ≈ 2 years, 9 controls (All women)	C_{max}: SG and RYGB > controls

[a] The variation in reported kinetic parameters are due to the lack of a pre-post testing sequence in the gastric bypass trials.
Abbreviations: C_{max}, maximum concentration; T_{max}, time to reach maximum concentration; AUC, area under curve

It is notable that three out of the four studies on SG applied breath analysers to estimate the alcohol content of the blood. Several studies have demonstrated, however, more rapid gastric emptying after SG despite the maintained pylorus sphincter (21). In RYGB-patients, Steffen et al. observed that the T_{max} was reached already after 5 minutes (106). Accordingly, the immediate PK effects may have been missed when the

first measurements were taken after 15 minutes by Changchien et al. (108) or after 20 minutes by Gallo et al. (109) post-dose. These two studies cannot rule out that the true C_{max} actually occurred earlier, which would raise questions about the validity of using breath analysers for estimating C_{max} for research purposes. Recently, a study found that breath analysers missed the true peak blood alcohol content and caused an underestimation of the blood alcohol content (93).

1.5.3 Do RYGB and SG involve similar risks for post-operative alcohol problems?

At St. Olavs Hospital, there has lately been a shift in preference regarding the choice of surgical procedure from RYGB to SG[1]. Even though the SG has become quite common, more time is required for drawing any conclusions about possible differences in the side-effects from to the two surgical procedures.

Currently, the existing health registries are probably the best available sources of information when wanting to shed more light on whether SG and RYGB represent similar risks for later alcohol problems. The Norwegian Patient Registry (NPR) is a database covering somatic and mental health services from all hospitals reimbursed by the government; the registry includes the majority of BS in Norway.

This study aimed to compare the incidence rates of diagnoses related to alcohol and other substances after SG or RYGB based on registry data.

1.5.4 Summary – Main findings from Paper IV

From 2008 to 2014 10,208 patients underwent either SG or RYGB in the public hospitals in Norway. This constituted in total 33,352 person-years for being registered with diagnoses related to alcohol or other substances. While the annual frequency of SG increased almost seven-fold, the RYGB increased only by 44 % within the same

[1] The last three years (2017-2019), the SG accounted for 98, 90 and 81%, respectively, of the surgical procedures for obesity at St. Olavs Hospital.

timeframe. The average postoperative observation time varied between SG (2.7 years) and RYGB (3.4 years).

The postoperative incidence rate (IR) for the diagnoses related to alcohol was 6.06 (95% CI 5.45-7.36) per 1000 person-years after RYGB, and 4.54 (2.94-6.70) after SG. The hazard ratio (HR) for alcohol diagnoses was .75 (.49-1.14) for SG compared with RYGB when controlling for age and sex. For the diagnoses related to substances other than alcohol, the IR was 3.48 (2.82-4.25) after RYGB compared with 3.27 (1.94-5.17) per 1000 person-years after SG. The corresponding HR was .99 (.60-1.64) for SG compared with RYGB. The wide confidence intervals of the HRs leave no basis to conclude that SG and RYGB involve significantly different risks for developing diagnoses related to alcohol or other substances during the post-operative timeframes studied.

Only for women, age was linked to the occurrence of alcohol diagnoses when comparing those <26 years (3.5%, 95% CI 2.3-4.7) to those >40 years (1.4%, .9-1.8)(*P*=.034). For substances other than alcohol, there were no significant differences in risks for women or men.

2 METHOD

This chapter offers an overview of the methodical features of the four papers of this dissertation. At the outset, they are briefly displayed in Table 2.

Table 2: Key methodical features of the four studies of this dissertation.

	Paper I	Paper II	Paper III	Paper IV
Focus	Words used for describing overweight or obesity	Motivation for bariatric surgery vs. conservative treatment	Postoperative bioavailability; absorption of methadone	Postoperative alcohol problems
Main outcome	Word preferences by use of desirability scores	Motivational sub-categories for surgical vs. non-surgical treatment	Increased serum concentrations of methadone after surgery	Diagnoses related to: 1. alcohol 2. other addictive substances
Design	Cross-sectional	Cross-sectional, mixed methods	Clinical trial (case study)	Retrospective cohort
Sample	N=157 Mean age: 43 years Women: 76% Patients from Central Norway referred for bariatric surgery	N=159 Mean age: 41 years Women: 74% Patients from Central Norway referred for bariatric surgery	N=1 Age: Forties Woman Patient from Central Norway referred for bariatric surgery	N=10,208 Mean age: 43 years Women: 72% Norwegian patient population undergoing bariatric surgery in public hospitals, Jan 1st 2008 - Dec 31st 2014
Material	Questionnaires: 1. Word desirability 2. HADS 3. SF-36	Questionnaires: 1. HADS 2. Open ended question about motivation and preferred treatment	Serum: Time series and genotyping	Registry data: Diagnoses and surgical procedures
Analyses	ANOVA, Wilcoxon's signed rank test	Qualitative: Thematic analysis Quantitative: ANOVA, Dunnett's test	Visual inspection of key pharmacokinetic parameters	Incidence rates, Hazard ratios, Cox regression, ANOVA, Games Howell test

Abbreviations: HADS: Hospital anxiety and depression scale; SF-36: Short Form 36; ANOVA: Analysis of variance

2.1 Participants

Common for all four papers are that the participants fulfilled the diagnostic criteria for morbid obesity according to the ICD-10[2] code E66. Prior to treatment, they had BMI >

[2] The 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD), a medical classification list by WHO. Morbid obesity is classified among the endocrine, nutritional and metabolic diseases. Obesity has been a classification code since the ICD-6 (1948), with the term "morbid" since ICD-9 (7).

40 kg/m^2, or BMI > 35 plus one or several comorbid somatic conditions[3]: diabetes type 2, sleep apnoea, severe loss of physical function, treatment resistant hypertension, and/or cardio-vascular disease (112).

The participants in Paper I-III were referred to weight loss treatment at St. Olavs Hospital. Paper IV encompassed comprehensive data from the National Patient Registry (NPR); i.e., all domestic patients who underwent BS at any of the Norwegian public hospitals from January 1st 2008 to December 31st 2014. Patients undergoing surgery before 2008 could not be included for technical reasons; 2008 was the first year that applied the personally identifiable 11-digit national social security number in Norway.

The samples in Paper I-III did not overlap; the studies recruited participants at different times. The population in Paper IV constitutes almost the entire population of patients undergoing BS in public hospitals in Norway (2008-2014). Consequently, the patients in Paper II and III are registered in the national database. In Paper I, some patients eventually did not undergo BS.

Paper I-II indicate that the typical BS patient is a woman in her forties. The registry data in Paper IV provided the actual demographics of the Norwegian population who underwent BS at public hospitals within the timeframe of 2008-2014.

2.2 Design and analyses

The four papers have different research designs. Paper I is a cross-sectional, descriptive study; the patients' preferences for words to be used about their obesity (outcome) was explored in relation to background factors at a single point in time. Analysis of variance (ANOVA) tested the differences in word preferences. The associations between the word preferences and the background factors were tested by multiple linear regression.

[3] Although morbid obesity has systemic health consequences which potentially influence all organ systems, the list of comorbid medical states required for being granted health care within the specialist health service (Nor: "rettighetspasient") is finite and undergoes revisions from time to time. Currently this includes type 2 diabetes, sleep apnoea, arthritis with severe activity limitations, treatment resistant hypertension and/or cardiovascular diseases (111).

Paper II was a cross-sectional study with a mixed methods design. In the qualitative part, thematic analysis was applied in the subcategorization of the patients' motivation for choosing either BS or non-surgical treatment. In contrast to grounded theory and phenomenology, thematic analysis does not rely on a particular epistemology. This makes the method more flexible. However, it has been criticized for not being fully qualitative. Those embracing thematic analysis, however, describe it as a translator enabling communication between researchers who are using different research methods (113). Thus, thematic analysis has been seen as appropriate for mixed methods, which was applied in Paper II.

Furthermore, considering the data source, thematic analysis was also regarded as relevant. An alternative, phenomenological analysis, would typically require interview data. In this study, we analysed written responses. For identifying, organizing and reporting the themes reflecting the patients' motivation for treatment, thematic analysis seemed justified.

Symptom scores for anxiety and depression supplemented the qualitative data. They led to the hypothesis that psychopathology was associated with the patients' choice of surgical vs non-surgical treatment. The sub-categories of treatment motivation derived from the qualitative part and the symptom scores from the quantitative part allowed the exploration of possible links between the two – between motivational subgroups and psychopathology (ANOVA).

Paper III was a case study. According to Sim & Wright, case studies categorised as research must generate data in rigorous and systematic ways (114). At the outset, this was meant to be a larger study with a sample of patients using methadone. However, despite collaboration with three other hospitals, only one patient on methadone emerged with BS. Based on changes in her drug absorption of methadone, we published the results as a single case study. Furthermore, Paper III is the only clinical trial in this thesis that complies with the definition as formulated by the US National Institute of Health (NIH); it involves human participants who prospectively are assigned to an intervention with the purpose of evaluating its health-related biomedical outcomes (115).

Case studies rarely provide enough data for statistical analysis. Instead, the data were analysed visually (114). Time-concentration curves were systematically recorded at four time points; i.e., preoperatively, and at one week, one month and seven months postoperatively. These were ideal for a graphical display of the changes in this patient's methadone levels.

In contrast to the case report of Paper III, Paper IV had an observational, retrospective population design that included an entire cohort of patients having undergone BS at the public hospitals in Norway during the years 2008 to 2014. In the archetype of cohort studies, people exposed to a putative risk are compared to those who were not exposed to anything similar. In our study, however, both groups were exposed, but to two different types of BS.

By focusing on the postoperative diagnoses related to alcohol or other substances (events) and the person-years at risk, incidence rates were calculated as disease occurrence. Hazard ratios were calculated as the measure of the effect of BS on the diagnoses of interest, i.e., the probability that an individual would get any of these diagnoses at a particular point in time. As the time-to-event is essential in the hazard ratio, the results were also illustrated with Kaplan-Meier curves that visually demonstrated the temporal effects of time. In addition, ANOVA was used to analyse any differences related to age and sex.

2.3 Instruments

2.3.1 Word sensitivity captured by questionnaire - Paper I

Appendix 1 shows the questionnaire developed for the quantitative estimates of the patients' perceived word sensitivity or preference for words or expressions describing excess body weight. For comparative purposes, the questionnaire resembles the structure used by Wadden & Didie (45). The actual expressions from the American inventory could not frequently be translated into Norwegian; they would not cover the parochial connotations within our language and culture. The Norwegian Obesity Patients Association as well as a group of patients referred to BS at St. Olavs Hospital

were asked to come up with a list of frequently used Norwegian words or expressions to be included in the Norwegian questionnaire. The list should include expressions which were perceived by the informant to be positive, neutral as well as negative. The most pejorative and shaming suggestions were disregarded as such expressions would not to be applied in professional contexts anyway. Moreover, provocative expressions could potentially introduce some emotional bias in the test situation and put the patient in a state of dismay. The aim of the study was to identify suitable words or expressions for the verbal exchange with obese patients in a professional context in Norway.

In the questionnaire, the patients were asked to imagine the following situation:

> *"You are seeing your GP for a regular check-up. This happened before you were referred to the hospital for treatment of overweight. On his/her initiative, the doctor wants to talk to you about your overweight and its effects on your health. Previously, you have never talked to your GP about your overweight."*

And:

> *"The GP says: -Today I would like to talk to you about your …"*

This was followed by 14 different Norwegian words or expressions for overweight or obesity. Each expression was scored by the patient in terms of its word desirability on a five-point scale; the response alternatives were ranging from *very inappropriate* (-2) to *very appropriate* (+2).

Two procedures were carried out to check the questionnaires' robustness. The same-day test-retest demonstrated high repeatability, the correlations for the words ranged from 0.815 to 0.988 (bootstrapped (1000), $p<0.001$, N=33). Furthermore, when reversed, the order of the words or expressions played no significant role for how they were rated except for 'high BMI'. In this case, the sequence of expressions yielded a score difference of -0.28 (bootstrapped (1000), p=0.028 with 95% CI (confidence interval) [-0.53,0.06], N=32). This suggests that when rating 'BMI' before 'high BMI', any negative response to BMI may be intensified. Changing the sequence of the other expressions did not influence the patients' scoring.

2.3.2 HADS in Paper I and II

Psychopathology was included as a potential covariate both in the study of word desirability (Paper I), and also, in the study of subcategories of motivation in Paper II. The HADS was chosen for several reasons. Axis 1 disorders such as anxiety and mood disorders are relatively common among treatment seeking patients with obesity, in particular among women (116, 117). As anxiety and depression may vary in intensity, the HADS subscale scores give a valid screening measure of the severity of anxiety and depression. The fourteen-item HADS questionnaire was developed for cost-effective screening of psychopathology in somatic hospital settings. Accordingly, the HADS-instrument disregards symptoms that could come from somatic complaints, e.g. insomnia, fatigue and its like. The same applies to symptoms of severe mental disorders that are less common in somatic hospitals (118).

A review by Bjelland et al. supports the questionnaire's two-factor model due to its good psychometric qualities; it has two subscales, HADS-A (anxiety) and HADS-D (depression), with Cronbach's alpha of 0.56 and 0.83 respectively (119). The correlation between the subscales may be somewhat higher than expected; anxiety and depression have overlapping features. The HADS's bi-dimensional factor structure has also been confirmed to work well in a large Norwegian population-based study. A robust factor structure was found across subsamples differing with regard to mental and physical health, age, education and gender (120). The instrument has also demonstrated good psychometric properties in a Norwegian sample of patients from general practice (121). The two Norwegian studies on HADS both found a cut-off of 8+ to reflect the best balance between sensitivity and specificity for the two subscales (120, 121).

BS candidates have been found to respond by social desirability in relation to the HADS (122), i.e., the patients want to portray themselves in ways that may serve their interests. Impression management is not limited to the use of HADS but is likely to occur also in other questionnaires aiming to detect mental symptoms such as Beck Depression Inventory-II (123). Withholding information about their depression to be accepted for BS has previously been documented in a qualitative study of patients at St. Olavs

Hospital (124). Accordingly, the context of the assessment should be taken into consideration. Some mental health professionals have argued that depressive disorders constitute a contraindication to surgery (125). So far, there is no consensus about the relevance of psychopathology for the outcome of BS.

2.3.3 SF-36 Version 2.0 in Paper I

The *Social functioning* subscale from the Short-Form 36 (SF-36) was included as a covariate in relation to the patients' preferences for words used to describe obesity (Paper I). The idea was that patients who do not easily relax in healthcare settings, are more sensitive and conscious about what words are being used about their obesity.

The SF-36 is often referred to as a health related quality of life instrument; it was originally developed to survey the health status in the Medical Outcomes Study (126). In version 2.0, the instructions and layout have been improved, and the scoring precision is higher. The 36 items yield eight subscales; they may also be summarised into a physical health summary score and a mental health summary score. SF-36 is a generic measure; it is useful in the general population, but also for comparing the relative burden of diseases in different patient populations, or when studying the effects of treatments. The instrument has been widely used and translated into a wide range of languages (127) including Norwegian (128).

Two studies report on the construct validity of SF-36 in treatment-seeking samples of obese patients. A principal component analysis suggested a six-component structure would give a better fit compared to the original eight subscales (129, 130). Both publications questioned the discriminatory capacity of the Social functioning subscale in obese populations.

Given the points above, interpreting the score of this particular subscale calls for some caution. A complementary approach would be to add an obesity-specific instrument (129, 130). At the time of this study (Paper I), the quality of life-instrument Impact of Weight on Quality of Life (IWQOL-lite) was not validated in Norwegian. The IWQOL-lite is obesity-specific and has demonstrated robust psychometric properties for this

population (131). In hindsight, it would have been a suitable alternative to the SF-36 in Paper I, however, not feasible for use for practical reasons.

2.3.4 Socio-demography, anthropometry, and health status in Paper I and II

Paper I and II, there were self-reported data on gender, age, family situation, and the level of education.

Moreover, the participants were asked to register their anthropometric measures. This included self-reported weight and height (Paper I and II); age when first developing a weight problem (Paper I and II); the number of diets the patients had tried during the previous five years (Paper II); and their current goal for the weight loss treatment indicated in kgs (Paper II).

For Paper II, participants were given a list of eight diseases that frequently co-occur with obesity, and they were asked to tick of which applied to them.

2.4 Other outcomes

2.4.1 Body composition in Paper III

Bio-electric impedance measurement (InBody 720) was applied for detecting body composition estimates. In particular, the lean mass was relevant when interpreting whether the weight loss could have influenced the drug metabolizing capacity of the liver.

2.4.2 Diagnoses in Paper IV

In Paper IV, the outcome of interest were the diagnoses related to alcohol and/or other addictive substances. The ICD-10 codes F10*, *mental and behavioural disorders related to alcohol* were the main identifiers. In addition, those patients registered with diagnoses that indirectly indicated alcohol problems were also included, e.g., G62.1 alcoholic polyneuropathy. To detect addictive disorders for Paper IV, we used the

diagnoses F11* (opioids), F12* (cannabinoids), F13* (sedatives), F14* (cocaine), F15* (other stimulants), F16* (hallucinogens), F18* (volatile solvents), and F19* (multiple drug use). The exception was F17* as tobacco has significantly less effect on the central nervous system compared to the other substances. There are also reasons to believe that physicians rarely register tobacco diagnoses despite its high prevalence.

2.5 Attrition and missing data

For Paper I, 157 patients responded (response rate 76%) of which 142 participants returned complete datasets. Paper II with a different sample consisted of data from 159 patients (response rate 76%) of which nine were excluded. One reason for the exclusion was that they had already had a bariatric operation in their past. Being referred for re-operation would imply unsatisfactory results from the original surgery which likely would sway their motivation for treatment. Another reason for exclusion was contradictory information; patients opting for one treatment (binary check point) while arguing for the other (open-ended question). As both Paper I and II contained cross-sectional studies, no patients could be lost over time. However, we did not get information about who were the non-responders and whether they systematically differed from the responders.

Paper III depended on 24-hour PK test series consisting of thirteen intermittent blood samples to be taken at every follow-up. Although it was possible to locate peripheral veins in this patient, they had been compromised after years of self-injecting heroin. Blood sampling was particularly a problem at the 12-month follow-up: Despite the assistance of anaesthesiologists, we got only one sample. However, as this was a fasting pre-dose, it added value by indicating that the alterations in PKs after sleeve gastrectomy may happen gradually. Half a year after surgery, the methadone absorption still had not reached a steady state.

Paper IV used a comprehensive national database. At the outset, it consisted of 11,392 patients with procedure codes indicating intestinal bypass operations or bariatric operations. In total, 1,184 patients were excluded due to such as invalid personal identification numbers (n=25), other kinds of surgeries than SG/RYGB (n=284), or they

were registered with two surgical procedures on the very same day (n=35), and finally, when the postoperative observation period was less than six months (n=840). This left 10,208 patients for the analyses.

2.6 Ethics

All four studies were approved by the Regional Committee for Medical and Health Research Ethics, Central Norway (REC)[4]. The participants gave their written informed consent to participate in the studies in Papers I-III. Paper III, the only clinical trial of the four studies was registered in the ClinicalTrials.gov (NCT NCT03460314). The Norwegian Medicines Agency confirmed that the study did not require their approval.

Data in Paper IV came from the comprehensive and mandatory national patient database for which research is one of its purposes. Patients do not consent to research based on this material. The data is anonymized for researchers. Nevertheless, measures were taken to minimize the risk of indirect identification of patients from the material.

[4] Paper I: REC ref. 2010/1191; Paper II: REC ref 4.2005.33; Paper III: REC ref. 2012/1744; Paper IV: REC ref. 2015/1473.

3 DISCUSSION

3.1 What words do obese patients prefer? – Paper I

At first, the words we use may seem clinically insignificant. Yet, words are fundamental in communicating. Potentially, they serve as the starting point towards behavioural changes. Poor or inappropriate use of words may make patients uncomfortable, reticent, upset or unwilling to cooperate. In that direction, words may delay therapeutic change, and thereby, contribute towards further deterioration of the patients' health. Words matter.

The denotation of a word refers to its literal meaning, e.g., its definition according to the dictionary. Connotations, however, are the words' emotional and imaginary associations. While the denotation of 'obesity' could be BMI above 30 kg/m^2, the word may trigger an emotional response based on the individual's interpretation and experience of being heavy. Words may spark a range of negative or positive connotations.

In the following, 'word' refers both to singular words (e.g., 'weight') or expressions consisting of several words (e.g. 'weight problem') describing excess weight.

3.1.1 Politically correct

Research take place in a cultural context. Since the 1950s, there has been a shift of attitudes in the doctor-patient relationship from medical paternalism towards patient autonomy. This new paradigm emphasizes shared decision-making and the patients' rights to accept or decline recommended treatments. Sometimes referred to as the "new age of patient autonomy". Optimally, the physician and the patient *co-produce care* which is based on reciprocal trust (132). One way for clinicians to build trust is to be attentive to their verbal and non-verbal messages (133).

According to the Cambridge Dictionary, a politically correct word is an "expression … used instead of another one to avoid being offensive" (134). An area illustrating this is the discourse about immigration. The politically correct words describing someone of

another cultural origin have changed rapidly over the last years; some researchers characterize the nomenclature as a minefield (135). Despite the ontological differences, both immigrants and obese are at risk of stigmatization due to unfortunate use of words due to some external features.

In contrast to the immigration discourse, there are in Norway no strong stakeholders advocating the use of more sensitive words for obesity. Few people are organized in the national patient organization for overweight and obese persons, which makes their impact minimal. In contrast to the situation in the UK and US, there is no *Fat Acceptance* movement in Norway. That movement promotes the word 'fat', which was rated very negatively in the studies. This makes sense when considering that the movement's goal is to normalize 'fat bodies'. Self-identifying as a fat person can be seen as an act of empowerment and a marker of self-respect (136).

The lack of a public discourse about obesity and the related terminology in Norway is one of several arguments for mapping the patients' word desirability, i.e., their preference for words about obesity. The fact that there is no public voice advocating their cause, may leave us blind to the significance of word desirability when a person takes the initial steps towards medical treatment to obtain weight loss. The general idea that respectful clinical communication skills are essential for professionalism in health care, is another argument for investigating this matter.

3.1.2 Desirable or motivating?

Patients' preferences for a certain words may not seem like the most relevant information for the GP. The concept "desirability", which has been the focus in most of the studies (42-45), does not necessarily provide information about the words' motivational effects. In interviews with those being overweight or obese, Gray et al. express doubts about the assumption that the most favourable words for obesity motivate weight loss. 'Obese', which is associated to being massively overweight and lazy, was reported by the interviewees to be legitimate and possibly motivating *if used in a medical context* (48).

A recent study focusses on the words' effects on self-efficacy for diet change. Self-efficacy in this context would be the belief a person holds regarding his or her innate ability to change eating behaviours. The study found the word 'obesity' to be associated with a greater sense of self-efficacy than 'weight' (137). The authors speculate that words with more clinical connotations can be perceived as acknowledging obesity as a medical condition.

The study that best illustrates the contrast between desirable and motivating words was probably carried out by Puhl et al. Interestingly, while 'weight' was the most desirable word in her study, it was rated to be the second least motivating one. Conversely, 'morbidly obese', which was rated as the least desirable word, was rated among the most motivating ones (46).

3.1.3 Rating of words

'Weight' was the word rated as the most appropriate among the obese Norwegian patients; this is quite similar to the findings of five US-studies (42-46). A likely reason for why 'weight' stands out as positive in several studies, in different languages and cultural settings, is probably its neutral quality. 'Weight' per se does not reflect a state of *excess*; it can refer to any weight across the spectrum, and it appears as less judgmental. In their discussion, Lydecker et al. suggested an alternative explanation: Its neutral content makes it easier for individuals to avoid the emotional discussion about their weight. If the patient in response to 'weight' signals no willingness to discuss the topic, this probably indicates that the use of more precise and obesity-specific words could jeopardize further collaboration (43).

Most of the words rated next to 'weight' tend to be either negatively charged (e.g. 'weight *problem'* and '*too* heavy') or may have denotations associated with excess weight (e.g. 'overweight' and 'obesity'). Some words may be unfamiliar to the patients, like 'obesitas'. In the questionnaire next to this word, a considerable number of patients had added question marks or commented that it made no sense to them.

It is likely that the negative ratings of words ranked next to ‘weight’ reflect some negative perceptions, and sometimes, they may even trigger a sense of shame – see Figure 2.

Similar to five other studies on word desirability, our study applied a 5-point Likert scale for the rating of the various words. Although ‘weight’ reached the highest positive rating across all studies, it did not get the maximum score (+2 points). This may indicate a general unease when discussing body weight independent of what words are being used.

Four of the existing studies stand out by giving ‘weight’ a higher desirability rating - see Figure 3 below. These are studies of clinical samples. By estimating the confidence intervals of the ratings of ‘weight’ across these studies, we see that non-clinical samples (green bars in Figure 2) tend to rate ‘weight’ lower than the clinical ones (red bars). Studies of clinical samples consist of people with higher BMI; they are more likely to have struggled a long time with weight issues. Respondents with less body weight may not have been mentally sensitized to the same extent; they may perceive *any* labels of excess weight as unwelcome.

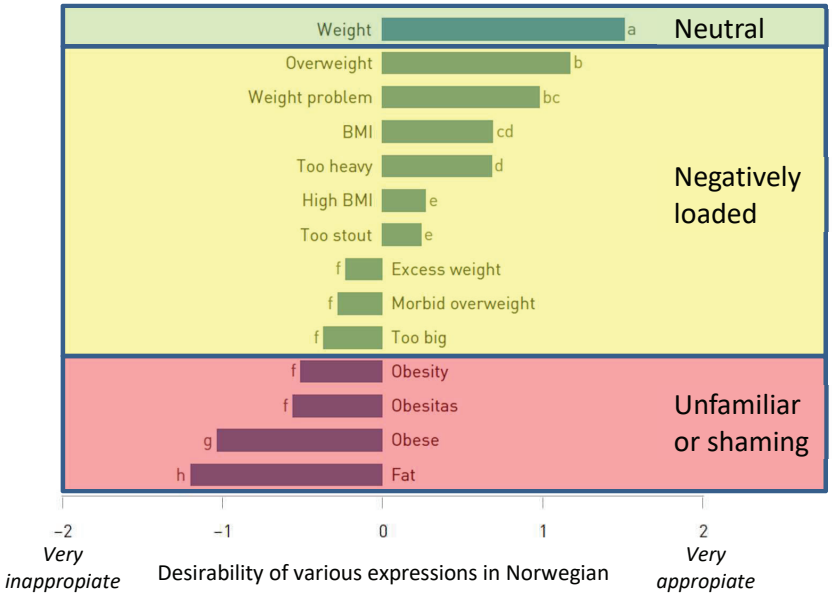


Figure 2 is an elaboration of Figure 1 in Paper I. The coloured bar chart shows Norwegian patients' ratings of words referring to excess weight. The background colours indicate that the neutral word 'weight' is the most preffered one, followed by words that in some ways are negatively loaded, and, finally, the words that are perceived as unfamiliar or shame-related.

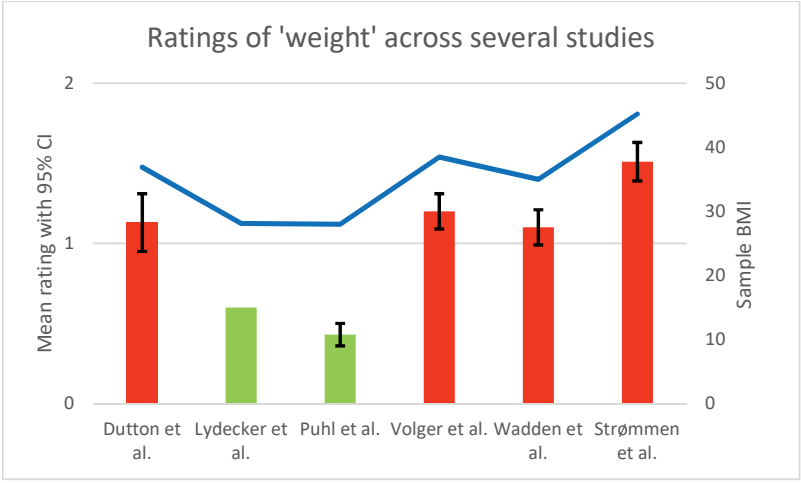


Figure 3: Patients' ratings of the word 'weight' across six studies. The bars (left vertical axis) show the mean rating with 95% CI (2 = most desirable; 0 = neutral). The line graph (right vertical axis) show the samples' mean BMI. Red bars are studies with treatment-seeking patients, while green bars display non-clinical samples. Only the study by Puhl et al reported confidence intervals. For the other studies, 95% CI was estimated based on SD and N.

3.1.4 Design and setting

In our study, a vignette introduced the responder to a hypothetical situation in which the physician brings up the topic about the patient's excess weight. Different words were suggested to be used by the physician, and the responder was to rate them on a Likert scale from *Very desirable* to *Very undesirable*. Despite that same-day test-retest reliability indicated consistency in the patients' responses, a frequent objection from researchers has been related to the use of a hypothetical situation as the introduction to the questionnaire; it may bring in an element that is remote from real life situations.

Alternatively, video recordings would provide observation data of both verbal and non-verbal communication. In addition, the patient and the physician could easily discuss the recording immediately after the consultation. However, video recordings would have required far more resources than what was available for our study, and it would probably not have added much more about the words' relative nuances. The primary interest of this study was to capture the emotional loadings of various words. Thus, a simple questionnaire seems to be a viable and cost-effective approach to map the word desirability.

3.1.5 Generalizability of findings

The GP may be the first clinician ever to initiate a serious discussion about a patient's excess weight and the words used at that time may make a difference. The participants in Paper I, however, were patients referred to obesity treatment in secondary care; probably, they are mentally more ready to handle discussions about obesity. This raises questions about the generalizability. In the following I will briefly discuss differences between clinical and non-clinical samples, and, finally, the generalizability of the findings from this study in relation to the other Scandinavian languages.

Research suggests that obese persons seeking obesity treatment perceive their health to be worse than that of obese persons who do not seek treatment (138). It has also been reported that those seeking BS score lower on the quality of life compared to obese patients in out-patient medical programmes (139). BMI may potentially mediate the differences between groups as the BMI tends to be higher among treatment seekers.

However, one study that compared BMI-matched treatment-seeking persons with persons who did not seek treatment found more psychopathology among those opting for treatment (140). Hence, the decision to seek treatment is likely driven by the person's total health burden as opposed to body weight alone. If treatment-seekers systematically differ from non-seekers, this may undermine some of our findings' generalizability.

Although differences exist between treatment-seekers and non-seekers, the distinction should not mask the heterogeneity within the non-clinical population. Among those not seeking treatment are also persons who are more psychologically vulnerable, e.g., people for whom shame represents a barrier towards seeking help. They represent an important sub-population to reach out to. Choosing words carefully could for some make the difference between acceptance of professional help or rejecting of it; the latter would leave the patient alone in battling the complexity of obesity. Even studying word desirability in a census population, as Puhl et al. did online (46), may not provide a comprehensive insight into the most vulnerable within the non-clinical population.

Another question about the generalizability is whether the Norwegian findings have relevance in other Scandinavian languages. Mainland Scandinavia (Norway, Sweden, Denmark) have many cultural features in common. The Scandinavian languages mostly share a common syntax with similar meaning of many words. In line with the findings about word desirability in the US and Norway, it is likely that obese patients in Sweden and Denmark also would prefer 'vægt'(DK)/'vikt'(S). 'Weight' across languages seem to carry a neutral value that is appreciated.

However, for words that are less desirable, the generalizability between languages seems less likely. Even though demeaning words were omitted from the study, words in the lower range of desirability are likely to trigger negative emotional responses due to their connotations rather than due to their denotations. This is illustrated by the two least desirable Norwegian words, 'fet' (monophtong) and 'feit' (diphthong). Although the words' denotations are the same – meaning 'fat' – their connotations are rather different. Diphthongs in Norwegian tend to characterize more vulgar expressions. Even though this may be a typical Norwegian phenomenon, the statistically significantly

different ratings of ‘fet’ and ‘feit’ illustrates that culturally specific connotations can impact patients’ perceptions.

To conclude, although the non-clinical population is likely to differ in many ways from treatment seekers, it seems advisable to apply desirable words to reach out to those who find help-seeking difficult. Our study may have some relevance also in the other Scandinavian countries.

3.1.6 Application of findings

The study of the desirability of words can provide guidance for clinicians and other health workers when raising the subject about excess weight with the patient. In particular, applying the word ‘weight’ seems to be a neutral choice when addressing the issue for the first time. As the dialogue on weight proceeds, the clinician may widen or adapt the vocabulary on excess weight by using the words that the patient accepts and uses himself or herself.

3.2 Motivation for treatment – Paper II

This paper is likely the first to explore how treatment motivation may sway the patient choice about treatment modalities. The qualitative data revealed substantial variation in the patients’ motivation and provided a basis for identifying eight subgroups of patients, four with those opting for conservative treatments and four with those opting for surgery. Two subgroups stood clearly out: those whose primary motivation seemed to be avoidance of the alternative treatment modality, i.e., one group had strong reasons to avoid surgery and the other had strong reasons for avoiding conservative treatment. These two avoidance groups had significantly higher levels of psychopathological symptoms than all other subgroups opting for the same treatment.

3.2.1 Negative motivation or the lesser evil

The most noticeable finding was the fearful avoidance, labelled *negative motivation*. The patients were either those opting for lifestyle treatment due to fear of dying during surgery, or those motivated for surgery to avoid the shame of social exposure in the group-based lifestyle programmes. Both options seemed driven by anxiety, fearful avoidance either for dying or social exposure. The statistical analyses of the HADS total-scores supported these assumptions.

The findings indicate that studies dichotomizing patients only according to their treatment choice may conceal clinically relevant psychological information that may be of relevance. For a patient with several comorbidities, fear can be rational due to increased risk for complications related to surgery. However, anxiety can also be the product of irrationality, misinformation or misinterpretation of information. For surgery, e.g., the patient may not understand the concept of mortality rates, despite objective and correct information. Improved patient education may reduce this fear. However, fear can also display a more generalized state of anxiety with a skewed interpretation bias that preferably should be addressed before the final choice. Anxiety has been defined as apprehensive expectation.

Two subgroups reported fear of surgery. One subgroup expressed fear of postoperative complications, the other reported fear of dying in the operating room. One patient even wrote that if there had been no mortalities so far, the patient expected to the first one ever to die. Those afraid of dying (N=4) reported very high symptom scores (HADS-T=23.0), while the patients fearing surgical complications (N=11) had more modest HADS scores (HADS-T=15.2). The small number of patients in each subgroup may explain why the differences did not reach statistical significance.

3.2.2 Patient motives and clinician's attention

The most frequent idea reported by those choosing the surgical modality (64% of SurgP), was that an operation implies a 'permanent solution'. This subgroup seemed to include two different motives, illustrated by the two quotes in Table 3 of Paper II. The first quote refers to their exhausted hopes after numerous diets. The second implies a

kind of resignation coupled with the belief that the modified gastro-intestinal anatomy will prevent their overeating. Typically, the surgically induced anatomical constraints appeared to them to be an absolute and permanent solution to their eating problems that they have been unable to handle by will and lifestyle.

This motive has a rational component; RYGB involves bypassing 95% of the stomach and causes a rise in several anorexigenic peptides (141). Accordingly, the patients will feel full after smaller meals. However, eating is not only a response to hunger, but may also be a maladaptive strategy to regulate difficult emotions (142). A relevant question is therefore if gastro-intestinal surgery can resolve the underlying emotional problems. If food has served the purpose of comfort or has been a tool to regulate emotions, the behaviour that stem from these propensities are likely to remain unchanged by surgery, and accordingly, they are likely to reoccur after the operation (143). In the second postoperative year, a study found that some patients felt the physical constraining effects of the operation started to fade (144).

The belief that surgery is an absolute and permanent solution may be problematic and built on false assumptions. What is permanent, however, is that patients – independently of the weight loss – are in a post-surgery state of risk for the rest of their lives. In other words, they must deal with several long-term complications to surgery without necessarily achieving the intended weight loss. Examples of such complications are, e.g., osteoporosis and post-prandial hypoglycaemia.

Putting on substantial weight after surgery is another concern. Their weight trajectories may have dropped significantly towards nadir about 12-18 months after surgery. Naturally, the weight loss comes to an end at some point, but often not at the low point the patient had expected (60). The discrepancy between the real and the wished weight, may after surgery trigger even stronger negative emotions than an unsuccessful diet. As surgery often is thought of as the ultimate solution, the feeling of failure after surgery may be psychologically quite devastating; the patients may see themselves as out of any further options.

When newly operated and losing weight, the patient may feel enthusiastic about the increase in positive attention from family and peers. However, when the weight

trajectory tapers off or even turns, the attention from others may become a burden and the situation may even precipitate a clinical depression. The tendencies towards self-blame may return and inadequate eating behaviour may be re-initiated. Mitchell et al. proposed that this kind of disappointment may in part explain the increased occurrence of postsurgical suicide rates (145).

Lastly, there is a risk of developing alcohol problems. The RYGB is proposed to reverse obesity-induced dysregulated dopamine reward processing. Before surgery, the dopamine reward signalling was chronically stimulated by large meals and palatable foods. This can cause reduced reward sensitivity, leading to more over-eating (146). After RYGB, both the physical constraint of the stomach and the post-surgical rise in the levels of anorexigenic peptides can drive the patient towards other reward agents than food, e.g., alcohol or other addictive substances. Combined with an increased dopamine sensitivity, the susceptibility to seek non-food rewards like alcohol increases (146). This issue is elaborated further in Paper IV.

3.2.3 The time factor in treatment decisions

According to the European guidelines for BS (147), failed non-surgical attempts to lose weight are required for being accepted for BS. Accordingly, surgical patients are expected to report several weight loss attempts prior to surgery. The horizontal axis in Figure 4A represents schematically a pre-surgical history of unsuccessful dieting leading to surgery.

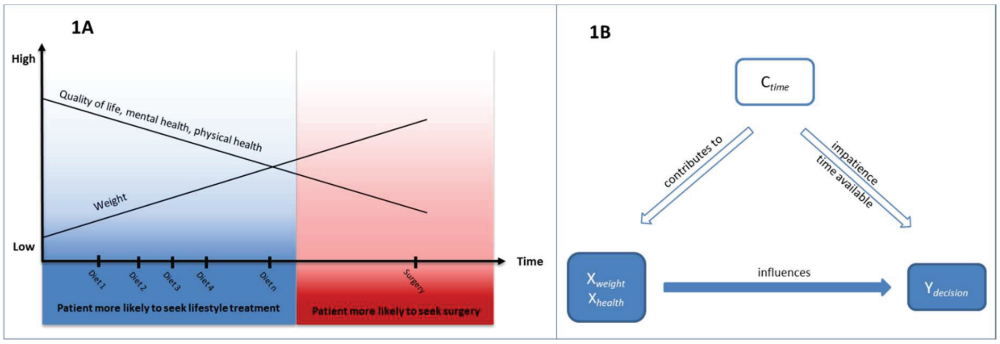


Figure 4A: The figure visualizes a potential patient's progression after several dieting attempts before finally seeking surgery.
Figure 1B: Time may be a confounder contributing to increased weight and to deteriorated health; both factors may directly influence the treatment decision.

Considering that obesity is a chronic, progressive disease (9), we would expect a net weight increase as time passes for many patients who have been using diets. At the same time, perceived stigma, gradual loss of functionality, and the emerging comorbidities will probably worsen the patients' health and quality of life. Although Figure 4A is simplified, it illustrates how elapsing time may affect the decision to take the step from diets to BS.

Paper II suggests that time may be a confounding factor; it tends to influence the patients' weight and health but may also sway their treatment decision more directly. Among those hoping that surgery to be a final and permanent solution, many reported years of attempts to lose weight by non-surgical means. Time was also a relevant factor for those having responsibilities for care or work: They felt that they did not have the time to go for a type of treatment with poor chances of success.

For the patients with negative motivation, i.e., those avoiding treatment due to anxiety, time did not seem to play much of a role in their decisions. The reluctance towards being socially exposed in group treatment acted as a strong driver towards surgery. Indirectly, this also meant saving time by not pursuing treatments they assume would be ineffective for them. However, this position tends to undermine the unproven potential to achieve significant health benefits without surgery. Accordingly, the fear of dying during surgery seemed to keep some patients away from considering this treatment option at all. Even after numerous failed non-surgical attempts, the patient may still

hope for the desired weight loss if they only would discover "the correct diet". This also underscores that time was not too important for them.

The eight subgroups identified in Paper II and the related analysis helps us understand some of the complexity of the underlying motivational mechanisms behind the patients' treatment decisions. To sum up, simple dichotomization of patients only based on their choice of treatment may mask subgroups of patients for whom the emotional and cognitive drivers strongly influence their treatment decisions. More knowledge and understanding of patients' motivation and the underlying psychological assumptions or ideas may perhaps pave the way for more personalized treatment approaches and hopefully for improved treatment outcomes.

3.2.4 Methodical considerations

The methods used in Paper I, III and IV reflect a positivistic research paradigm; the methods rely on the assumption that an objective and measurable reality can be explored. The mixed methods of Paper II, however, partly represent an alternative research paradigm referred to as *pragmatism* (148). While the epistemological debate between positivists and constructivists relate to the measurable reality vs. the subjective pluralities, pragmatists argue for the *utility* of research rather than how reality best may be explored. Mixed methods research aims to transcend the dichotomy between qualitative and quantitative methods (148).

Paper II contains a multi method study with a *sequential exploratory design* (149), and its table 2 provides an account of methods and the analyses. 'Sequential' implies that the study started qualitatively, in our case with textual data, which later were categorized and analysed quantitatively. The qualitative data were the basis for generating subgroups related to motivation and hypothesis about them. The statistical testing validated the qualitative categorization and hypothesis.

The qualitative data consisted of written responses to an open-ended question. Compared to an interview situation, textual data deprive the researcher of the opportunity to explore emerging themes further, and when in doubt about the meaning,

the chance to validate the information with the interviewee is not available. The free text was analysed according to the thematic analysis. In their summary, Nowell et al. describe this analysis as less anchored in a particular epistemology compared to other schools for qualitative analyses such as grounded theory or phenomenology (113). This theoretical freedom contributes to the method's flexibility. The last step of the qualitative analysis is *quantitizing* of the textual data, i.e., it implies the transition from text to numerical data, e.g., in a spread sheet. Statistical analyses of the data can enable validation of the qualitative data and generate new hypotheses.

In Paper II, we statistically tested whether the subgroups reporting negative motivation differed from the other subgroups within each treatment modality. In multiple comparisons, the error rate can pose a problem. If all subgroups (k) within each treatment modality were to be compared, this would yield $k(k\text{-}1)/2$ or six comparisons. However, Dunnett's test was applied, which allowed the testing of negative motivation; did they differ from those in the other subgroups. In this situation, there is only (k-1) or three comparisons, which reduces the familywise error rate (150).

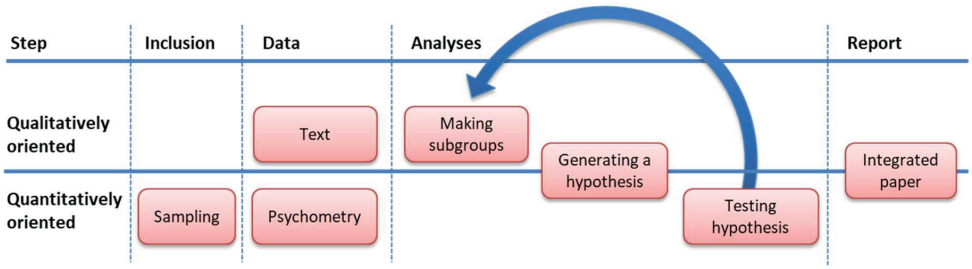


Figure 5: The figure illustrates the study's phases in Paper II and their relations to either qualitative or quantitative research.

Our study shows a way to subgroup patients according to their motivation for treatment. There have been studies looking into motivation for one single treatment option, e.g., the review of BS patients by Cohn et al. (151). However, the motivation may play out differently when the patients are faced with the choice between different treatment modalities. As modern medicine moves towards higher degrees of personalized treatment, there is the need for more adequate classification of patients. This paper is built on the assumption that the motivational-behavioural link is essential.

3.2.4.1 Randomization in obesity studies

The randomised controlled trial has been considered the 'gold standard' for the outcomes of interventions (152). However, only a small number of randomised controlled trials compares BS to non-surgical treatments for obesity (153). Although 30-day mortality after BS rates are very low today, the unlikely fatal outcome still represents a dilemma when randomizing between treatments of which one of them is quite invasive.

A way around this would be to identify the patients' willingness to be allocated by chance. Ternovits et al. found that only 21% of the patients would accept to be randomised to different *bariatric surgical procedures* (63). Hence we can assume that even fewer patients are willing to be randomised between treatments as radically different as bariatric surgery and conservative treatment. Furthermore, no patients in Paper II reported indifference to the choice of treatment. There are, however, study designs like the *patient preference trial* that initially randomize patients, then allow them to self-select treatment. The advantage is that this design produces additional information about the acceptability of two different treatments. On the negative side, this design may increase the size and cost of the trial as they involve two more groups of patients: patients randomized to treatment A; patients preferring treatment A; patients randomized to treatment B; and, patients preferring treatment B (154).

Another relevant issue is whether a comparative testing of surgery vs. conservative treatment challenges the principle of equipoise; there should be a genuine uncertainty among the investigators about the comparative therapeutic merits of the different treatments. In terms of weight loss and several other outcomes, surgery is expected to produce significantly better results (153). Randomisation would, therefore, pose an ethical dilemma if the investigator believes that one treatment outperforms the other (155). The null hypothesis, stating no difference between the treatments, should reflect a genuine uncertainty about the benefits.

3.2.5 Application of findings

For clinicians, the patients' motivation may open a door to important psychological and behavioural issues that can influence the outcome of the treatment. Knowing the patients' motivation would also reveal the patients expectations, a topic that should be addressed together with the patient before a decision about treatment is made.

Research papers mainly report outcomes in terms of means. Not knowing the patients' motivations for treatment may disguise relevant factors about the treatment effects. A detailed understanding of the patients' motivational-behavioural links may allow a more tailored obesity treatment. Since psychological-behavioural aspects seem to interfere with the outcome of both surgery and conservative treatments, insights into the patients' motivation may prove to be useful for the development of new therapeutic approaches.

3.3 Substitution therapy and bariatric surgery – Paper III

The patient on methadone illustrates how clinicians occasionally face situations where limited knowledge can guide their decisions. Yet, decisions must sometimes be made. The intuitive idea that BS may impair the absorption of essential drugs seemed legitimate for denying operation to certain patients. In our case, if the patient does not reach sufficient serum levels of the drug after surgery, the substitution therapy could be jeopardized. This was later demonstrated recently in a case using buprenorphine (156). On the other hand, denying the patient surgery could pave the way for increased body weight and major comorbid conditions.

The GP had referred the patient to the university hospital for a second opinion, which is granted by law in Norway (jfr. pasientrettighetsloven). As hospitals also have a statutory responsibility for research in addition to provide treatment (spesialisthelsetjenesteloven), clinicians at university hospitals are expected to be on the outlook for opportunities to fill existing gaps of knowledge. One such gap was the documentation of serum concentrations of drugs after bariatric surgery. While the pharma industry is obliged to provide data on the association between *dose* and effect (157), altered absorption following BS may drastically increase the variability in serum concentrations even though the dose remains the same. For this patient, we could have

consulted pharmacologists for drug monitoring. That would have provided data for dose adjustments. Instead, in collaboration with the Department for pharmacology, we designed this small study.

When less patients are available than what is required for statistical power in a sound trial, data sharing is relevant. A fundamental idea is that data from clinical trials should be regarded as a *public good* instead of the sponsors' property (158). Clinicians sharing anonymized, individual patient data from rare diseases or uncommon conditions can provide enough cases for proper statistical inferences. This presupposes that the data are collected in standardized manners, which is possible with PK-series. This was the thinking behind this single case study.

The clinically significant findings inspired the initiation of a large-scale PK-study of patients using analgesics, psychotropic and antihypertensive drugs. As of September 2020, the BAR-MEDS study[5] has reached 88 patients from four different hospitals in the region for testing 46 different drugs. For patients giving their consent, their participation provides them with an extended follow-up due to drug monitoring up to 12 months after surgery.

3.3.1 Methadone and body weight

In this case study, the patient had put on considerable weight after being prescribed methadone. Weight gain has previously been reported after opiate substitution therapy (77). Methadone (ATC code N07B C02) is a strong agonist used in the treatment of opiate addiction. The drug suppresses the abstinence syndrome by connecting to the mu-opioid receptor (159). The observed weight gain may in part be due to neuro-pharmaceutical effects; chronic exposure to mu-opioid agonists strengthens the taste preference for sweet foods. The opposite observation, i.e., a decreased taste preference for sweet foods has been seen in patients taking mu-opioid antagonists. Together, these reports suggest that methadone stimulates calorie intake (160). Occasional referrals for

[5] The BAR-MEDS website: www.legemiddelopptak.no

BS of patients on opiate substitution therapy is therefore to be expected. A large study from the US found 0.8% of the patients undergoing BS were using some kind of medication typically prescribed for opiate addiction (161). Based on the total number of BS procedures in 2016 (30), about 5,000 patients worldwide underwent BS while being on this group of medication.

For patients on opiate substitution therapy, other factors add to the risks of being denied surgery. According to the European guidelines for BS, substance dependence is listed as a contraindication (147). Less clear is the wording of the latest American guidelines. They state that substance abuse or dependence presupposes a formal mental health evaluation (162) with no further specification. Thus, no existing guidelines address issues related to patients treated with opioid agonists. Some clinicians consider opiate substitution therapy as just another form of dependence (163).

A history of illicit drug use can leave a person with stigma that may influence clinical decisions. Our patient had an extensive history both with mental and physical trauma as well as illicit drug use since her teens. A recent review, however, concluded that a history of substance abuse does not seem to influence the postoperative weight more than in patients with no such history. Also, it suggests that the majority of patients (68%) with a postoperative substance misuse or dependence had not experienced misuse problems prior to surgery, i.e., the misuse was a new onset. Among those with a preoperative history of substance use disorders, many did not fulfill those criteria three years after RYGB (164). The interpretation of these findings is limited since the substances were not specified in the studies. However, the results indicate that the link between previous misuse and problems with misuse after surgery may be weak. Regarding patients on opioid substitution therapy, there is no solid research documenting the outcome of BS. The absence of evidence can easily make treatment decisions based on assumptions.

3.3.2 Bioavailability of orally administered drugs

The strongest argument against surgery for this patient was that RYGB could decrease the absorption of methadone. The referral of the patient coincided with the introduction

of the SG at our hospital. At the time of referral, however, there was little available knowledge about the physiological implications of SG.

RYGB and SG are both invasive procedures; they significantly reduce the gastric emptying time, in particular for liquids. RYGB also seems to reduce the secretion and cause the gastric pH to increase. Furthermore, RYGB involves bypassing of both the duodenum and the proximal jejunum. The mucosa in these gut segments plays an active role in the pre-systemic metabolism of several drugs including methadone. RYGB could reduce gut metabolism (F_G) for compounds metabolized via CYP3A, an iso-enzyme in the cytochrome P450 enzyme group. The SG, on the other hand, maintains the original anatomy located distal to the pyloric sphincter. The motility of the small intestine may be reduced with RYGB, which would increase the transit time. The comparisons of PK factors of different surgical procedures as suggested by Darwich et al., does not mention that SG would influence the motility of the small intestine (3).

The changes in motility and secretion are direct effects of surgery; they can affect the bioavailability via the drug absorption (f_a) and the metabolization in the mucosa (F_G). However, the patients' subsequent weight loss may also influence bioavailability indirectly. Losing weight reduces the volume of drug distribution. It may also reduce the liver size. Reduced intrahepatic fat may affect the function of the liver and cause increased drug clearance.

For many patients, weight loss means the end of a chronic, low-grade inflammation associated with obesity. The reduction of inflammatory adipokines may lead to stronger expression of the CYP3A enzymes, iso-enzymes that seem to be inversely correlated with the body weight (74). Accordingly, BS may influence a range of factors that affects in particular the drug absorption. Specific characteristics of the drug such as solubility and lipophility (97) may add to the complexity, and predicting the bioavailability becomes difficult after BS.

Although there is still limited knowledge about the physiological consequences of SG compared to RYGB, several factors mentioned above may have contributed to changes in the methadone PKs. Normally, the mean bioavailability of methadone is high (75%) and the average half-life (25 hours) allows one daily administration (165). Serum

concentrations revealed, however, that this patient was preoperatively below the 10th percentile of patients taking a dose of 120 mg/d[6]. This was likely due to her CYP-polymorphism (CYP3A5 *1/*3-genotype) which means that she had a high capacity for pre-systemic metabolism of CYP3A-substrates like methadone. If the patient would have normal preoperative bioavailability (about 75%), the potential relative increase in bioavailability due to the operation would have been smaller. Paradoxically, only finding a modest rise in bioavailability would have made it more difficult to interpret which physiological mechanisms were involved.

Our suggested explanation for what happened after surgery was related to reduced gastric emptying time for liquids, occurring after SG (3). When ingesting methadone as a bolus dose, the mixture may have reached the CYP3A-active segments of the duodenum so quickly that it overwhelmed the metabolizing capacity of the mucosa. This left a higher proportion of the methadone to be absorbed. In hindsight, a relevant question is whether splitting the bolus dose into several smaller portions to be taken separately some minutes apart, would have caused less increase in the absorption. If so, this would support the theory that reduced gastric emptying time is a significant factor.

3.3.3 More research needed

The existing literature is scarce on how surgery may influence the patients' drug responses (74, 75). This poses a problem as patients risk being denied treatment if surgeons fear altered drug responses from essential medications. The dilemma was present in the case of Paper III. To be on the safe side, a denial of operation may be justifiable if there are no resources to monitor the drug therapy postoperatively. On the other hand, not to provide surgery (status quo-option) is a decision that can have grave consequences for the patients, e.g., increased weight, comorbidities, and shorter life span. The clinician needs to consider several uncertainties, not only the patient's current situation, but also her future. To establish collaboration with pharmacologists for drug response monitoring could avoid adverse events for patients with unknown PK effects.

[6] According to unpublished data from Avdeling for klinisk farmakologi, St. Olav Hospital.

Another difficult situation after surgery is when the patients experience altered drug responses. Limited awareness about this potential side-effect of surgery may lead to situations in which inadequate medication can go on undetected. In cases where patients use medication for which the therapeutic effect are not measured directly, e.g., the blood pressure in hypertensive patients, the patients may feel mistrusted when reporting insufficient effects. In particular, this pertains to medication with a potential for addiction or other adverse effects. We can assume that most patients trust their physicians when it comes to the dosing of the medication. When clinicians do not possess enough knowledge about the pharmacological effects related to surgery, they may inadvertently cause health problems in their patients. Since data on PKs and surgery is not required for the pharmaceutical companies to get marketing approvals, this line of research depends mostly on academic trials.

A third issue is safety. Altered drug responses may cause serious adverse effects. In particular, this is relevant for drugs for which high concentrations are toxic, or it can apply to situations in which the therapy relies on steady plasma concentrations. For oral administration of morphine (mixture) in patients undergoing RYGB, a study reported that the T_{max} was reduced after surgery from 53 minutes before to 7 minutes at 12 months after the operation. During the same period, the C_{max} rose from 11.3 to 38.1 µg/L. Although the total exposure (AUC) increased more moderately (55.5%), the study underlines caution when administrating immediate-release solutions for acute pain to avoid sedation and respiratory depression (166). Similar to our methadone case, morphine was given as a mixture, but the surgical procedure differed. The review by Azran et al. (73) recommends to switch from solid to liquid immediate release oral drugs. Their argument is that gastric processes in general do not influence the drug release in liquid formulations. Although it may be correct that surgery has little impact on drug release, our study suggests that it can increase the absorption to a large degree. In other words, several factors need to be considered.

3.3.4 Methodical considerations

Methodically, studies reporting a case or a series of cases hold the place as the weakest evidence in the medical design hierarchy (152). Nonetheless, these hierarchies are also

criticized as the design per se does not guarantee quality in terms of data and procedures (167). A common critique of case studies are that they are not scientifically designed from the start, but cover the experience of an investigator or clinician. Another major objection is how patients are selected. Contrasting case studies to randomized controlled trials, the latter strive to achieve balance between unknown prognostic factors. Accordingly, case studies cannot provide clear evidence. The lack of controls makes inferences difficult as it cannot be ruled out that the observed changes could have happened spontaneously (152). In the context of the PK effects of BS, however, case studies are referred to as valuable as they give some directions for future research (168) and may help to frame better research questions for planned studies.

The critique related to few patients is unarguably valid. However, our paper also differs from many case studies as it was a planned, interventional study per protocol and not the retrospective reporting of an unexpected observation. Its prospective direction opened for comprehensive preoperative testing which became reference for postsurgical comparisons. Furthermore, the idea that surgery potentially could impact PK, and that intestinal functionality possibly could change with time, led to the design with repeated follow-ups planned at +1 week, +1 month, +6 months, and +12 months. In hindsight, the repeated measurements demonstrated that drugs do not necessarily enter a steady state situation immediately after surgery. This has implications for how long drug monitoring is required. Unfortunately, a complete 12 month test series of our patient was not carried out due to difficulties with blood sampling; her veins were compromised after self-administering opiates for a decade. Even if there had been only a single postoperative follow-up, this would have made us draw the conclusion that the PK data represents an absolute and lasting change. The observed continuous and progressing changes, however, suggested that there is a gradual alteration in the intestinal functionality with impact on the PK of drugs.

Another strength of this case study was the CYP-genotyping. Mapping the patients' capacity to metabolize drugs was essential to understand the inter-individual variability. However, even in this single case, to identify her CYP3A5 polymorphism became a key to understand the observed PK changes. Normal indications for CYP-genotyping are when major side-effects are observed, or when the expected therapeutic results do not

appear. In retrospect, as the patient was prescribed a relatively high dose of methadone, we can speculate that identifying her polymorphism prior to therapy would have aided the process to find the adequate dose. Especially when prescribing psychotropic drugs, CYP-genotyping may be a cornerstone to achieve personalized therapy (169).

3.3.5 Application of findings

Drug monitoring could avoid unnecessary refusals for BS in those patients that are relying on drug therapy. This is particularly relevant for patients depending on stable plasma concentrations or when the therapeutic range of the drug is narrow. Until this is done systematically, it is vital that the relevant patients are informed about altered drug absorption as a possible side-effect. In the longer perspective, information about patients' CYP-genotypes and the different physiological effects of unlike surgical procedures could form the basis for an algorithm aiding the clinicians' decisions about which surgery to recommend or elevate the awareness about when close monitoring of pharmacological therapy would be required. Joint research collaboration between several hospitals can provide the required evidence base for such algorithms.

3.4 Alcohol related diagnoses after bariatric surgery – Paper IV

3.4.1 Severity of alcohol problems

Alcohol represents a major risk factor for several diseases (170). From a nutritional perspective, alcohol intake is undesirable. Alcohol is energy dense, carrying 7 kcal/g but contains 'empty calories', i.e., they are without any nutritional value. Furthermore, people who drink tend not to compensate for the alcohol-related calories by eating less (171) and may instead increase their food intake due to the disinhibiting effects of alcohol (172).

Alcohol may also reduce safety, in particular if the bioavailability increases post-operatively. RYGB causes a stronger and more rapid intoxication ($\uparrow C_{max}$, $\downarrow T_{max}$) (104-107). When more ethanol enters the systemic circulation, the time until regained sobriety will be longer. One activity in which safety may be jeopardized, is driving; the

patient will reach ethanol blood concentrations above acceptable limits after less intake and time than before. The precautions a person is used to take regarding drinking and driving, e.g., counting hours, do not apply as before. One study found that among patients who developed AUD after BS, one third reported having been driving while intoxicated (95).

Keeping in mind the poor mental health of many treatment seeking obese patients (173, 174), stronger alcohol effects may increase psychopathology, and co-occur with depression, loneliness and low self-esteem (175). About a third of the attempted suicides are committed under the influence of alcohol (176), and AUD is common among people who complete the suicide (177). In the acute phase of the alcohol intoxication, feelings of despair may increase while alcohol weakens the "brakes". Thus, impulsivity tend to increase while limiting the ability to see alternatives (175). Assuming a dose-response relationship between intoxication and suicidal behaviour, increased ethanol bioavailability after surgery may be particularly harmful. Increased bioavailability of ethanol has been suggested as an explanation for the increased risk of post-surgery suicide (145) together with the PK changes of psychotropic medications (76).

A study by Adams et al. on the long-term mortality after RYGB showed that the mortality risk due to accidents and suicide was significantly higher in operated patients compared to severely obese controls (178). Both accidents and suicides are statistically accompanied by alcohol intake. The authors did not discuss alcohol as a possible cause for the high numbers.

Heritability is assumed to explain 50 to 60% of alcohol dependence (179). This possible genetic predisposition is independent of any surgical procedure. However, if BS increases the ethanol bioavailability, underlying predispositions for substance abuse may develop more frequently than what would otherwise be expected.

BS procedures may inflict major alcohol problems on some patients. To put things into perspective, about 1 percent of the population in the Nord-Trøndelag County had undergone BS (180). These patients live on for decades after surgery, and an accumulated number of patients will be living with the post-surgery risks. Some of

those risks will materialize. Patients as well as clinicians should be aware of the potential complications in the aftermath of surgery and to the best of their ability try to avoid them.

3.4.2 Stealth phenomenon

There may be many reasons for the lack of awareness about alcohol abuse as a complication to BS. To my knowledge, only two large prospective studies exist on the topic (83, 86). Other related studies have had very low response rates (94, 181). The patients' unwillingness to respond to sensitive questions may lead to response errors (182). Patients tend to be reticent about sharing this type of problematic information about themselves.

The current ways patients are being followed-up may render AUD-detection difficult. In both a Swedish and a US sample, the alcohol intake had increased significantly two years after the RYGB (83, 85). Two years after BS, most public hospitals in Norway have terminated their active follow-up. This reduces the likelihood of detecting alcohol complications. To diminish misuse of alcohol in BS patients probably require a longer follow-up.

In Norway, about 1000 bariatric operations are performed annually in the private hospitals (183); they are not reported to the NPR. Accordingly, Paper IV includes no information about their health status. The follow-up programmes of private clinics tend to be less comprehensive and shorter compared to those of the public hospitals. Another group not registered by NPR are patients getting BS abroad. BS has become part of medical tourism as the procedures cost less and require less preoperative screening (184). The competitive costs also include less post-operative follow-up (185). For patients, this option may seem like a rational choice: They get the treatment faster, they have fewer appointments with the clinicians, and it is cheaper. However, operations abroad are more likely to increase the amount of undetected post-operative problems, also those related to alcohol misuse.

The information given to patients about BS and alcohol varies. If the awareness of the risk of AUD is low, such problems may be identified too late. A well-known reason for delayed help-seeking is that the severity of drinking is not admitted by the patient (186). Recently, several authors have advocated that targeted patients should be informed about the potential risks of alcohol problems (83, 86, 95). Information about these risks should probably also include their next of kin as they may be the first to discover altered drinking behaviours in the BS patient. In the general population, the majority of individuals with AUD never undergo any alcohol treatment (187).

3.4.3 Different operationalisations of AUD cases

In research, AUD cases have been operationalised in very different ways. See Table 3 for an overview. Below, I will briefly comment on this diversity as it is likely to influence the conclusions.

In Paper IV, an AUD-case was defined as a person with "*any registered alcohol-related diagnose"*. Theoretically, my definition would produce more cases than the register studies of Backman et al (116) and Östlund et al (188); they based caseness on a registered AUD treatment. Examples of patients included in Paper IV may have alcohol-related organ damages, or they were treated for injuries or self-harm under the influence of alcohol.

As Table 3 shows, smaller studies tend to use diagnostic interviews to determine caseness, sometimes supplemented by questionnaires. Three studies applied parts of the SCID, the psychiatric Structured Clinical Interview for DSM-IV, to determine AUD (95, 181, 189). Worth noticing for future studies is that while the fourth revision of the DSM described AUD as two distinct disorders, alcohol abuse and alcohol dependence, the two are merged into one disorder in the next version, DSM-5 (190). Mid-size studies mostly utilize questionnaires to define AUD-cases.

3.4.4 Methodical issues when comparing across studies

Another issue to consider when comparing findings across studies applying different operationalisations of AUD pertains to the questions asked when focusing on the consumed *volume of alcohol*.

Question from DSM-IV and DSM-5:

> *Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?*

Questions from AUDIT (Alcohol Use Disorder Identification Test) (191):

> Q2: *How many drinks containing alcohol do you have on a typical day when you are drinking?*
> Q3: *How often do you have six or more drinks on one occasion?*

Considering that one unit of alcohol will yield higher blood alcohol concentrations after than before surgery, the response to questions like those above after surgery can easily be misinterpreted. In practice this means that when a patient is reporting identical alcohol intake pre- and post-surgery, the response fails to disclose that the systemic exposure of alcohol is probably increased. While a threshold of 8 points has been recommended for achieving high sensitivity and an acceptable specificity for the AUDIT (191), a lower cut-off would apply for AUDIT postoperatively. Consequently, phrases like the ones referred above, are not likely to contribute adequately to the detection of de-novo post-surgery AUD.

Table 3: Studies exploring prevalence or risk of post-operative alcohol problems with their operational definitions of alcohol problems.

Paper	Construct	Method	Data source	N	Surgery	Findings/comment
Backman et al. (2016) (116)	AUD	Admissions for alcohol use disorder	Register data	16,755	RYGB	After surgery, RYGB-patients had higher risk of inpatient care for AUD compared to the general population. The RYGB-sample contained all patients undergoing RYGB in Sweden in the period 2001-2010.
Ertelt et al. (2008) (94)	Alcohol abuse Alcohol dependence	Study-specific questionnaire with some questions from DSM-IV	Questionnaire	70	RYGB	Current alcohol dependence after surgery 8.6%. Retrospective study with low response rate (28%).
King et al. (2017) (86)	AUD-symptoms	AUDIT ≥ 8 or any symptom of alcohol dependence or harm (AUDIT)	Questionnaire	2,348	RYGB, gastric banding	20.8% 5-year cumulative incidence of post-surgery onset AUD-symptoms among RYGB-patients.
Mitchell et al. (2015) (189)	AUD	SCID SCID+AUDIT ≥ 8 or any alcohol-related harm	Structured interview combined with questionnaire	201	RYGB	When applying SCID, 8% developed AUD 3 years after surgery of whom 44% had no previous AUD history. Adding AUDIT, numbers were 18% and 40%, respectively.
Smith et al. (2017) (95)	Alcohol abuse Alcohol dependence Alcohol use	SCID AUDIT > 8, MAST > 5 AUI, HAS	Structured interview Questionnaire	26	RYGB, SG	Post-operatively all patients display problematic alcohol use; alcohol abuse or dependence found in 46%, one third show a de-novo diagnose. No comparisons between types of surgery as the authors had no individual data on surgical procedure.
Strømmen et al. (2020) (192)		Alcohol-related diagnose	Register data	10,208	RYGB, SG	First register study on SG. RYGB and SG
Suzuki et al. (2012) (181)	AUD	SCID	Structured interview	51	RYGB, gastric banding	Current AUD after surgery 11.8%. All AUD-cases had RYGB. Retrospective study with low response rate (11%).
Svensson et al. (2013) (83)	Moderate or high alcohol consumption Alcohol problems	Daily alcohol consumption above > 20/40 g/day (women/men) Question: Do you think you have alcohol problems? (yes/no)	Questionnaire Questionnaire	2,010	RYGB, vertical banded gastroplasty, gastric banding,	RYGB-patients compared to non-operated controls had increased risk of: 1) alcohol abuse diagnoses (HR=4.97), 2) alcohol consumption ≥ medium WHO medium risk level (HR=2.69), 3) alcohol problems (HR=5.91).

	Alcohol abuse	ICD-diagnosis related to alcohol abuse	Register data		non-operated controls	
Östlund et al. (2013) (188)	Alcohol abuse	Inpatient care for alcohol abuse	Register data	11,115	RYGB, vertical banded gastroplasty, gastric banding	RYGB-patients compared to patients with restrictive surgery had increased risk of inpatient care for alcohol abuse (HR=2.3)

Abbreviations: AUD, Alcohol Use Disorder; AUI, Alcohol Use Interview; HAS, Hangover and Sensitivity to Alcohol Questionnaire; MAST, Michigan Alcohol Screening Test; SCID, Structured Interview for DSM-IV; SG, vertical sleeve gastrectomy; ICD, International Classification of Diseases and Related Health Problems; RYGB, Roux-en-Y gastric bypass

3.4.6 Application of findings

In line with the ideal of more personalized medicine, decisions about which surgical procedure to recommend to a patient should be made in accordance with the patient's health parameters. Those predisposed for addictions should be informed that BS potentially can increase the ethanol bioavailability. We did not find any significant difference in the hazard ratios for registered diagnoses related to alcohol or other substances after RYGB and SG; our data did not favor the recommendation of one procedure over the other. However, the relatively short observation time of SG compared to RYGB call for epidemiological studies with longer observation time of the patients after the operation.

3.5 Closing remarks

This thesis underscores the complexity and diversity of the challenges related to the obese patient population. The four papers are aligned with the idea of *obesities*; they are focusing on the many and diverse challenges that go beyond the operating room.

The first paper may aid clinicians to avoid addressing obesity patients verbally in counter-productive ways. Approaching obese patient adequately early on, may for some mean the difference between a continued hard and prolonged, lonely struggle against obesity – or a better life if referred for professional treatment and support. The second paper sheds light on the covert motives behind the patient's choice of treatment. Exploring the underlying motives may open some new doors that may lead to more tailor-made approaches and treatments with a better outcome. The study may also add some clues for future research. The third paper illustrates in a single patient the interplay between surgical procedure, medication, and the patient's genotype. Understanding the PK effects of BS seems important and may prevent unfortunate pharmacological side-effects that can jeopardize the outcome. The final paper uses registry data from a large number of patients; it maps their possible alcohol related health problems in the aftermath of surgery. The study sheds light on a group of potential complications that many follow from BS.

Although these four papers investigate different topics, they present corroborations that may aid in the development of a more comprehensive algorithm for patient selection and treatment. Thereby, they reflect and underscore the idea of more personalized treatment.

REFERENCES

1. Obesity. Preventing and managing the global epidemic. Geneva: World Health Organisation, 2000 894 Contract No.: Tecnical Report Series 894.
2. Simonsen T, Aarbakke J, Lysaa R. Illustrert farmakologi Bind 1. 3 ed. Bergen: Fagbokforlaget; 2010.
3. Darwich AS, Pade D, Ammori BJ, Jamei M, Ashcroft DM, Rostami-Hodjegan A. A mechanistic pharmacokinetic model to assess modified oral drug bioavailability post bariatric surgery in morbidly obese patients: Interplay between CYP3A gut wall metabolism, permeability and dissolution. J Pharm Pharmacol. 2012;64(7):1008-24.
4. Christopoulou-Aletra H, Papavramidou N. Methods used by the hippocratic physicians for weight reduction. World J Surg. 2004;28(5):513-7.
5. Allison DB, Downey M, Atkinson RL, Billington CJ, Bray GA, Eckel RH, et al. Obesity as a disease: a white paper on evidence and arguments commissioned by the Council of the Obesity Society. Obesity (Silver Spring). 2008;16(6):1161-77.
6. Heshka S, Allison DB. Is obesity a disease? Int J Obes. 2001;25:1401-4.
7. Kopelman PG, Finer N. Reply: Is obesity a disease? Int J Obes. 2001(25):1405-6.
8. Bray GA. Obesity is a chronic, relapsing neurochemical disease. Int J Obes Relat Metab Disord. 2004;28(1):34-8.
9. Bray GA, Kim KK, Wilding JPH. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. Obes Rev. 2017;18(7):715-23.
10. Jastreboff AM, Kotz CM, Kahan S, Kelly AS, Heymsfield SB. Obesity as a Disease: The Obesity Society 2018 Position Statement. 2019;27(1):7-9.
11. Puhl RM, Liu S. A national survey of public views about the classification of obesity as a disease. Obesity (Silver Spring). 2015;23(6):1288-95.
12. Sobal J. The medicalization and demedicalization of obesity. In: Maurer D, Sobal J, editors. Eating agendas Food and nutrition as social problems. New York: Aldine de Gruyter; 1995.
13. Obesity as a disease [press release]. American Medical Association, 18. June 2013 2013.
14. Aronne LJ, Nelinson DS, Lillo JL. Obesity as a disease state: A new paradigm for diagnosis and treatment. Clinical Cournerstone.9(4):9-29.
15. Parsons T. Social structure and dynamic process: The case of modern medical practice. The social system. The social system: The Free Press of Glencoe; 1964.
16. National Center for Health S. Health, United States. Health, United States, 2015: With Special Feature on Racial and Ethnic Health Disparities. Hyattsville (MD): National Center for Health Statistics (US); 2016.
17. Midthjell K. Trends in overweight and obesity over 22 years in a large adult population: The HUNT-study, Norway. Clinical Obesity. 2013;3:12-20.
18. Malik VS, Willett WC, Hu FB. Global obesity: trends, risk factors and policy implications. Nat Rev Endocrinol. 2013;9(1):13-27.
19. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384(9945):766-81.
20. Finkelstein EA, Khavjou OA, Thompson H, Trogdon JG, Pan L, Sherry B, et al. Obesity and severe obesity forecasts through 2030. Am J Prev Med. 2012;42(6):563-70.

21. Stefater MA, Wilson-Pérez HE, Chambers AP, Sandoval DA, Seeley RJ. All bariatric surgeries are not created equal: Insights from mechanistic comparisons. Endocr Rev. 2012;33(4):595-622.
22. Franco JV, Ruiz PA, Palermo M, Gagner M. A review of studies comparing three laparoscopic procedures in bariatric surgery: sleeve gastrectomy, Roux-en-Y gastric bypass and adjustable gastric banding. Obes Surg. 2011;21(9):1458-68.
23. Deitel M. A brief history of the surgery for obesity to the present, with an overview of nutritional implications. J Am Coll Nutr. 2013;32(2):136-42.
24. Vincent RP, le Roux CW. Changes in gut hormones after bariatric surgery. Clin Endocrinol (Oxf). 2008;69(2):173-9.
25. Hofsø D, Fatima F, Borgeraas H, Birkeland KI, Gulseth HL, Hertel JK, et al. Gastric bypass versus sleeve gastrectomy in patients with type 2 diabetes (Oseberg): a single-centre, triple-blind, randomised controlled trial. The lancet Diabetes & endocrinology. 2019;7(12):912-24.
26. Colquitt J, Pickett K, Loveman E, Frampton GK. Surgery for weight loss in adults. Cochrane Database Syst Rev. 2014;8.
27. Picot J, Jones J, Colquitt JL, Gospodarevskaya E, Loveman E, Baxter L, et al. The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation. Health Technol Assess. 2009;13(41):1-190, 215-357, iii-iv.
28. Carlsson LMS, Sjöholm K, Jacobson P, Andersson-Assarsson JC, Svensson P-A, Taube M, et al. Life Expectancy after Bariatric Surgery in the Swedish Obese Subjects Study. 2020;383(16):1535-43.
29. O'Brien PE, McPhail T, Chaston TB, Dixon JB. Systematic review of medium-term weight loss after bariatric operations. Obes Surg. 2006;16:1032-40.
30. Angrisani L, Santonicola A, Iovino P, Vitiello A, Higa K, Himpens J, et al. IFSO Worldwide Survey 2016: Primary, Endoluminal, and Revisional Procedures. Obes Surg. 2018;28(12):3783-94.
31. Sandvik J. Langtidsresultater etter gastrisk bypass og gastrisk sleeve. Kirurgen. 2017(1):18-21.
32. Phelan SM, Burgess DJ, Yeazel MW, Hellerstedt WL, Griffin JM, van Ryn M. Impact of weight bias and stigma on quality of care and outcomes for patients with obesity. Obes Rev. 2015;16(4):319-26.
33. Pont SJ, Puhl R, Cook SR, Slusser W. Stigma experienced by children and adolescents with obesity. Pediatrics. 2017;140:e20173034.
34. Drury CAA, Louis M. Exploring the association between body weight, stigma of obesity, and health care avoidance. J Am Acad Nurse Pract. 2002;14(12):554-61.
35. Gudzune KA, Bennett WL, Cooper LA, Bleich SN. Patients who feel judged about their weight have lower trust in their primary care providers. Patient Educ Couns. 2014;97:128-31.
36. Hayward LE, Neang S, Ma S, Vartanian LR. Discussing weight with patients with overweight: Supportive (not stigmatizing) conversations increase compliance intentions and health motivation. Stigma and Health. 2019.
37. Gudzune KA, Beach MC, Roter DL, Cooper LA. Physicians build less rapport with obese patients. Obesity. 2013;21:2146-52.
38. Bertakis KD, Azari R. The impact of obesity on primary care visits. Obes Res. 2005;13(9):1615-23.
39. Agborsangaya CB, Majumdar SR, Sharma AM, Gregg EW, Padwal RS. Multimorbidity in a prospective cohort: prevalence and associations with weight loss and health status in severely obese patients. Obesity (Silver Spring). 2015;23(3):707-12.

40. Elliott JP, Gray EL, Yu J, Kalarchian MA. Medication Use Among Patients Prior to Bariatric Surgery. Bariatr Surg Pract Patient Care. 2015;10(3):105-9.
41. Aycock DM, Sims TT, Florman T, Casseus KT, Gordon PM, Spratling RG. Language Sensitivity, the RESPECT Model, and Continuing Education. J Contin Educ Nurs. 2017;48(11):517-24.
42. Dutton GR, Tan F, Perri MG, Stine CC, Dancer-Brown M, Goble M, et al. What words should we use when discussing excess weight? Journal of the American Board of Family Medicine : JABFM. 2010;23(5):606-13.
43. Lydecker JA, Galbraith K, Ivezaj V, White MA, Barnes RD, Roberto CA, et al. Words will never hurt me? Preferred terms for describing obesity and binge eating. Int J Clin Pract. 2016;70(8):682-90.
44. Volger S, Vetter ML, Dougherty M, Panigrahi E, Egner R, Webb V, et al. Patients' preferred terms for describing their excess weight: Discussing obesity in clinical practice. Obesity. 2012;20:147-50.
45. Wadden TA, Didie E. What's in a name? Patients' preferred terms for describing obesity. Obes Res. 2003;11(9):1140-6.
46. Puhl RM, Peterson J, Luedicke J. Motivating or stigmatizing? Public perceptions of weight-related language used by health providers. Int J Obes. 2013;37:612-9.
47. Pearl RL, Walton K, Allison KC, Tronieri JS, Wadden TA. Preference for people-first language among patients seeking bariatric surgery. JAMA Surg. 2018:E2.
48. Gray CM, Hunt K, Lorimer K, Anderson AS, Benzeval M, Wyke S. Words matter: a qualitative investigation of which weight status terms are acceptable and motivate weight loss when used by health professionals. BMC Public Health. 2011;11:513.
49. Carels RA, Young KM, Wott CB, Harper J, Gumble A, Wagner Hobbs M, et al. Internalized weight stigma and its ideological correlates among weight loss treatment seeking adults. Eating & Weight Disorders. 2009;14:e92-e7.
50. Jolles SA, Alagoz E, Liu N, Voils CI, Shea G, Funk LM. Motivations of Males with Severe Obesity, Who Pursue Medical Weight Management or Bariatric Surgery. J Laparoendosc Adv Surg Tech A. 2019;29(6):730-40.
51. Holgerson AA, Clark MM, Ames GE, Collazo-Clavell ML, Kellogg TA, Graszer KM, et al. Association of Adverse Childhood Experiences and Food Addiction to Bariatric Surgery Completion and Weight Loss Outcome. Obes Surg. 2018;28(11):3386-92.
52. Pitzul KB, Jackson T, Crawford S, Kwong JCH, Sockalingam S, Hawa R, et al. Understanding disposition after referral for bariatric surgery: when and why patients referred do not undergo surgery. Obes Surg. 2014;24(1):134-40.
53. Roberson DW, Neil JA, Pories ML, Rose MA. Tipping point: factors influencing a patient's decision to proceed with bariatric surgery. Surg Obes Relat Dis. 2016;12(5):1086-90.
54. Sadhasivam S, Larson CJ, Lambert PJ, Mathiason MA, Kothari SN. Refusals, denials, and patient choice: reasons prospective patients do not undergo bariatric surgery. Surg Obes Relat Dis. 2007;3(5):531-5; discussion 5-6.
55. Schauer DP, Arterburn DE, Wise R, Boone W, Fischer D, Eckman MH. Predictors of bariatric surgery among an interested population. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2014;10(3):547-52.
56. Dixon JB, Laurie CP, Anderson ML, Hayden MJ, Dixon ME, O'Brien PE. Motivation, readiness to change, and weight loss following adjustable gastric band surgery. Obesity. 2009;17(4):698-705.

57. Figura A, Ahnis A, Stengel A, Hofmann T, Elbelt U, Ordemann J, et al. Determinants of Weight Loss following Laparoscopic Sleeve Gastrectomy: The Role of Psychological Burden, Coping Style, and Motivation to Undergo Surgery. Journal of Obesity. 2015;2015:626010.
58. Libeton M, Dixon JB, Laurie C, O'Brien PE. Patient motivation for bariatric surgery: characteristics and impact on outcomes. Obes Surg. 2004;14(3):392-8.
59. Peacock JC, Perry L, Morien K. Bariatric patients' reported motivations for surgery and their relationship to weight status and health. Surg Obes Relat Dis. 2018;14(1):39-45.
60. Aelfers SCW, Schijns W, Ploeger N, Janssen IMC, Berends FJ, Aarts EO. Patients' Preoperative Estimate of Target Weight and Actual Outcome after Bariatric Surgery. Obes Surg. 2017;27(7):1729-34.
61. Gelinas BL, Delparte CA, Hart R, Wright KD. Unrealistic weight loss goals and expectations among bariatric surgery candidates: The impact on pre- and postsurgical weight outcomes. Bariatric Surgical Patient Care. 2013;8(1):12-7.
62. Ren CJ, Cabrera I, Rajaram K, Fielding GA. Factors influencing patient choice for bariatric operation. Obes Surg. 2005(15):202-6.
63. Ternovits CA, Tichansky DS, Madan AK. Band versus bypass: randomization and patients' choices and perceptions. Surg Obes Relat Dis. 2006;2(1):6-10.
64. Fischer L, Wekerle A-L, Sander J, Nickel F, Billeter AT, Zech U, et al. Is there a Reason Why Obese Patients Choose Either Conservative Treatment or Surgery? Obes Surg. 2017;27(7):1684-90.
65. Bancheri L, Patrizi B, Kotzalidis GD, Mosticoni S, Gargano T, Angrisani P, et al. Treatment choice and psychometric characteristics: differences between patients who choose bariatric surgical treatment and those who do not. Obes Surg. 2006;16(12):1630-7.
66. Matthews-Ewald MR, Myers VH, Newton RL, Jr., Beyl R, Waldo K, Dufour CM, et al. Predictors for selection of insurance-funded weight loss approaches in individuals with severe obesity. Obesity (Silver Spring). 2015;23(6):1151-8.
67. Miras AD, Al-Najim W, Jackson SN, McGirr J, Cotter L, Tharakan G, et al. Psychological characteristics, eating behavior, and quality of life assessment of obese patients undergoing weight loss interventions. Scandinavian journal of surgery : SJS : official organ for the Finnish Surgical Society and the Scandinavian Surgical Society. 2015;104(1):10-7.
68. Stout AL, Applegate KL, Friedman KE, Grant JP, Musante GJ. Psychological correlates of obese patients seeking surgical or residential behavioral weight loss treatment. Surg Obes Relat Dis. 2007;3(3):369-75.
69. Castellini G, Godini L, Amedei SG, Galli V, Alpigiano G, Mugnaini E, et al. Psychopathological similarities and differences between obese patients seeking surgical and non-surgical overweight treatments. Eat Weight Disord. 2014;19(1):95-102.
70. Gradaschi R, Noli G, Cornicelli M, Camerini G, Scopinaro N, Adami GF. Do clinical and behavioural correlates of obese patients seeking bariatric surgery differ from those of individuals involved in conservative weight loss programme? Journal of human nutrition and dietetics : the official journal of the British Dietetic Association. 2013;26 Suppl 1:34-8.
71. Buchwald H. The evolution of metabolic/bariatric surgery. Obes Surg. 2014;24(8):1126-35.
72. Guedes BLdS, Montanha MC, Teixeira JJV, Diniz A, Silva SRB, Previdelli I, et al. Clinicians' prescribing practices for bariatric surgery patients: is there an issue? 2015;40(1):104-9.
73. Azran C, Wolk O, Zur M, Fine-Shamir N, Shaked G, Czeiger D, et al. Oral drug therapy following bariatric surgery: an overview of fundamentals, literature and clinical recommendations. Obes Rev. 2016;17(11):1050-66.

74. Angeles PC, Robertsen I, Seeberg LT, Krogstad V, Skattebu J, Sandbu R, et al. The influence of bariatric surgery on oral drug bioavailability in patients with obesity: A systematic review. 2019;20(9):1299-311.
75. McLachlan LA, Chaar BB, Um IS. Pharmacokinetic changes post–bariatric surgery: A scoping review.n/a(n/a).
76. Bland CM, Quidley AM, Love BL, Yeager C, McMichael B, Bookstaver PB. Long-term pharmacotherapy considerations in the bariatric surgery patient. Am J Health Syst Pharm. 2016;73(16):1230-42.
77. Fenn JM, Laurent JS, Sigmon SC. Increases in body mass index following initiation of methadone treatment. J Subst Abuse Treat. 2015;51:59-63.
78. Sogg S. Alcohol misuse after bariatric surgery: Epiphenomenon or "Oprah" phenomenon? Surg Obes Relat Dis. 2001;3(3):366-8.
79. Moshiri M, Osman S, Robinson TJ, Khandelwal S, Bhargava P, Rohrmann CA. Evolution of bariatric surgery: a historical perspective. AJR Am J Roentgenol. 2013;201(1):W40-8.
80. Saules KK, Wiedemann AA, Ivezaj V, Hopper JA, Foster-Hartsfield J, Schwarz D. Bariatric surgery history among substance abuse treatment patients: prevalence and associated features. Surg Obes Relat Dis. 2010(6):615-21.
81. Kalarchian MA, Marcus MD, Levine MD, Courcoulas AP, Pilkonis PA, Ringham RM, et al. Psychiatric disorders among bariatric surgery candidates - relationship to obesity and functional health status. The American Journal of Psychiatry. 2007;164(2):328-34.
82. Mühlhans B, Horbach T, de Zwaan M. Psychiatric disorders in bariatric surgery candidates: a review of the literature and results of a German prebariatric surgery sample. Gen Hosp Psychiatry. 2009;31(5):414-21.
83. Svensson PA, Anveden A, Romeo S, Peltonen M, Ahlin S, Burza MA, et al. Alcohol consumption and alcohol problems after bariatric surgery in the Swedish Obese Subjects (SOS) study. Obesity (Silver Spring). 2013.
84. Bhatti JA, Nathens AB, Thiruchelvam D, Grantcharov T, Goldstein BI, Redelmeier DA. Self-harm Emergencies After Bariatric Surgery: A Population-Based Cohort Study. JAMA Surg. 2016;151(3):226-32.
85. King WC, Chen J-Y, Mitchell JE, Kalarchian MA, Steffen KJ, Engel SG, et al. Prevalence of alcohol use disorders before and after bariatric surgery. JAMA. 2012;307(23):2516-25.
86. King WC, Chen JY, Courcoulas AP, Dakin GF, Engel SG, Flum DR, et al. Alcohol and other substance use after bariatric surgery: prospective evidence from a U.S. multicenter cohort study. Surg Obes Relat Dis. 2017;13(8):1392-402.
87. Fogger SA, McGuinness TM. The relationship between addictions and bariatric surgery for nurses in recovery. Perspect Psychiatr Care. 2012;48(1):10-5.
88. Ivezaj V, Saules KK, Schuh LM. New-onset substance use disorder after gastric bypass surgery: rates and associated characteristics. Obes Surg. 2014;24(11):1975-80.
89. Ivezaj V, Saules KK, Wiedemann AA. "I didn't see this coming": Why are postbariatric patients in substance abuse treatment? Patients' perceptions of etiology and future recommendations. Obes Surg. 2012;22:1308-14.
90. Reslan S, Saules KK, Greenwald MK, Schuh LM. Substance misuse following Roux-en-Y gastric bypass surgery. Subst Use Misuse. 2014;49(4):405-17.
91. Wiedemann AA, Saules KK, Ivezaj V. Emergence of New Onset substance use disorders among post-weight loss surgery patients. Clin Obes. 2013;3(6):194-201.
92. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Arch Gen Psychiatry. 2005;62:593-602.

93. Acevedo MB, Eagon JC, Bartholow BD, Klein S, Bucholz KK, Pepino MY. Sleeve gastrectomy surgery: when 2 two alcoholic drinks are converted to 4. Surg Obes Relat Dis. 2018;14:277-83.
94. Ertelt TW, Mitchell JE, Lancaster K, Crosby RD, Steffen KJ, Marino JM. Alcohol abuse and dependence before and after bariatric surgery: a review of the literature and report of a new data set. Surg Obes Relat Dis. 2008;4(5):647-50.
95. Smith KE, Engel SG, Steffen KJ, Garcia L, Grothe K, Koball A, et al. Problematic Alcohol Use and Associated Characteristics Following Bariatric Surgery. Obes Surg. 2017.
96. Spadola CE, Wagner EF, Varga LM, Syvertsen JL, De La Cruz Munoz NF, Messiah SE. A Qualitative Examination of Increased Alcohol Use after Bariatric Surgery among Racially/Ethnically Diverse Young Adults. Obes Surg. 2017.
97. Slørdal L, Spigset O. Grunnleggende farmakokinetikk - absorpsjon. Tidsskr Nor Lægeforen. 2005;125(7):886-7.
98. Kalant H. Pharmacokinetics of ethanol: Absorption, distribution, and elimination. In: Begleiter H, Kissin B, editors. The pharmacology of alcohol and alcohol dependence. Oxford: Oxford University Press; 1996.
99. Oneta CM, Simanowski UA, Martinez M, Allali-Hassani A, Pares X, Homann N, et al. First pass metabolism of ethanol is strikingly influenced by the speed of gastric emptying. Gut. 1998;43(5):612-9.
100. DiPadova C, Worner TM, Julkunen RJ, Lieber CS. Effects of fasting and chronic alcohol consumption on the first-pass metabolism of ethanol. Gastroenterology. 1987;92(5 Pt 1):1169-73.
101. Frezza M, Padova Cd, Pozzato G, Terpin M, Baranova E, Lieber C. High blood alcohol levels in women. The role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. N Engl J Med. 1990;322(2):95-9.
102. Fraser A. Pharmacokinetic interactions between alcohol and other drugs. Clin Pharmacokinet. 1997;33(2):79-90.
103. Caballeria J, Frezza M, Hernandez-Munoz R, DiPadova C, Korsten MA, Baraona E, et al. Gastric origin of the first-pass metabolism of ethanol in humans: effect of gastrectomy. Gastroenterology. 1989;97(5):1205-9.
104. Hagedorn JC, Encarnacion B, Brat GA, Morton JM. Does gastric bypass alter alcohol metabolism? Surg Obes Relat Dis. 2007;3(5):543-8; discussion 8.
105. Klockhoff H, Naslund I, Jones AW. Faster absorption of ethanol and higher peak concentration in women after gastric bypass surgery. Br J Clin Pharmacol. 2002;54(6):587-91.
106. Steffen KJ, Engel SG, Pollert GA, Cao L, Mitchell JE. Blood alcohol concentrations rise rapidly and dramatically after Roux-en-Y gastric bypass. Surgery for obesity and related diseases. 2013:Online ahead of print.
107. Woodard GA, Downey J, Hernandez-Boussard T, Morton JM. Impaired alcohol metabolism after gastric bypass surgery - A case-crossover trial. J Am Coll Surg. 2011;212:209-14.
108. Changchien EM, Woodard GA, Hernandez-Boussard T, Morton JM. Normal alcohol metabolism after gastric banding and sleeve gastrectomy: a case-cross-over trial. J Am Coll Surg. 2012;215(4):475-9.
109. Gallo AS, Berducci MA, Nijhawan S, Nino DF, Broderick RC, Harnsberger CR, et al. Alcohol metabolism is not affected by sleeve gastrectomy. Surg Endosc. 2015;29(5):1088-93.
110. Maluenda F, Csendes A, De Aretxabala X, Poniachik J, Salvo K, Delgado I, et al. Alcohol absorption modification after a laparoscopic sleeve gastrectomy due to obesity. Obes Surg. 2010;20(6):744-8.

111. Nygaard E, Kårikstad V. Prioriteringsveileder sykelig overvekt. 2009.
112. Prioriteringsveileder sykelig overvekt. Oslo: Helsedirektoratet, 2009.
113. Nowell LS, Norris JM, White DE, Moules NJ. Thematic Analysis: Striving to Meet the Trustworthiness Criteria. International Journal of Qualitative Methods. 2017;16(1):1609406917733847.
114. Sim J, Wright C. Research in Health Care - Consepts, Designs and Methods. Cheltenham: Nelson Thornes; 2000.
115. NIH Definition of Clinical Trial Case Studies 2019 [updated 01.07.201902.07.2020]. Available from: https://grants.nih.gov/policy/clinical-trials/CT-Definition-Case-Studies_1.7.19.pdf.
116. Backman O, Stockeld D, Rasmussen F, Naslund E, Marsk R. Alcohol and substance abuse, depression and suicide attempts after Roux-en-Y gastric bypass surgery. Br J Surg. 2016.
117. van Hout GC, van Oudheusden I, van Heck GL. Psychological profile of the morbidly obese. Obes Surg. 2004;14(5):579-88.
118. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.
119. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002;52(2):69-77.
120. Mykletun A, Stordal E, Dahl AA. Hospital Anxiety and Depression (HAD) scale: factor structure, item analyses and internal consistency in a large population. Br J Psychiatry. 2001;179:540-4.
121. Olssøn I, Mykletun A, Dahl AA. The Hospital Anxiety and Depression Rating Scale: a cross-sectional study of psychometrics and case finding abilities in general practice. BMC Psychiatry. 2005;5:46.
122. Ambwani S, Boeka AG, Brown JD, Byrne TK, Budak AR, Sarwer DB, et al. Socially desirable responding by bariatric surgery candidates during psychological assessment. Surg Obes Relat Dis. 2013;9(2):300-5.
123. Fabricatore AN, Sarwer DB, Wadden TA, Combs CJ, Krasucki JL. Impression management or real change? Reports of depressive symptoms before and after the preoperative psychological evaluation for bariatric surgery. Obes Surg. 2007;17(1213-1219).
124. Grønning I. Fedmefortellinger. Sosiologisk tidsskrift. 2014(3):227-48.
125. Fabricatore AN, Crerand CE, Wadden TA, Sarwer DB, Krasucki JL. How do mental health professionals evaluate candidates for bariatric surgery? Survey results. Obes Surg. 2006;16:567-73.
126. Ware JEj, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.
127. Ware JE, Jr. SF-36 health survey update. Spine. 2000;25(24):3130-9.
128. Loge JH, Kaasa S, Hjermstad MJ, Kvien TK. Translation and performance of the Norwegian SF-36 health survey in patients with rheumatoid arthritis. I. Data quality, scaling assumptions, reliability and construct validity. J Clin Epidemiol. 1998;51(11):1069-76.
129. Corica F, Corsonello A, Apolone G, Lucchetti M, Melchionda N, Marchesini G. Construct validity of the Short Form-36 Health Survey and its relationship with BMI in obese outpatients. Obesity (Silver Spring). 2006;14(8):1429-37.
130. Karlsen TI, Tveita EK, Natvig GK, Tonstad S, Hjelmesaeth J. Validity of the SF-36 in patients with morbid obesity. Obes Facts. 2011;4(5):346-51.
131. Kolotkin RL, Crosby RD, Kosloski KD, Williams GR. Development of a brief measure to assess quality of life in obesity. Obes Res. 2001;9(2):102-11.

132. Kilbride MK, Joffe S. The New Age of Patient Autonomy: Implications for the Patient-Physician Relationship. JAMA. 2018;320(19):1973-4.
133. Grob R, Darien G, Meyers D. Why Physicians Should Trust in Patients. JAMA. 2019;321(14):1347-8.
134. Meaning of politically correct in English: Cambridge Dictionary. Available from: https://dictionary.cambridge.org/dictionary/english/politically-correct.
135. Sætre S. Fy-norsk ordliste. Morgenbladet. 2008 7. januar 2008.
136. Meadows A, Daníelsdóttir S. What's in a word? On weight stigma and terminology. Frontiers in Psychology. 2016;7:1527.
137. Hopkins CM, Bennett GG. Weight-Related Terms Differentially Affect Self-Efficacy and Perception of Obesity. Obesity (Silver Spring). 2018;26(9):1405-11.
138. Fontaine KR, Bartlett SJ, Barofsky I. Health-related quality of life among obese persons seeking and not currently seeking treatment. Int J Eat Disord. 2000;27(1):101-5.
139. Kolotkin RL, Crosby RD, Williams GR. Health-related quality of life varies among obese subgroups. Obes Res. 2002;10(8):748-56.
140. Fitzgibbon ML, Stolley MR, Kirschenbaum DS. Obese people who seek treatment have different characteristics than those who do not seek treatment. Health Psychol. 1993;12(5):342-5.
141. Hutch CR, Sandoval D. The Role of GLP-1 in the Metabolic Success of Bariatric Surgery. Endocrinology. 2017;158(12):4139-51.
142. Dingemans A, Danner U, Parks M. Emotion Regulation in Binge Eating Disorder: A Review. Nutrients. 2017;9(11):1274.
143. Geraci AA, Brunt A, Marihart C. The Work behind Weight-Loss Surgery: A Qualitative Analysis of Food Intake after the First Two Years Post-Op. ISRN obesity. 2014;2014:427062.
144. Engström M, Forsberg A. Wishing for deburdening through a sustainable control after bariatric surgery. International Journal of Qualitative Studies on Health and Well-being. 2011;6(1):5901.
145. Mitchell JE, Crosby R, de Zwaan M, Engel S, Roerig J, Steffen K, et al. Possible risk factors for increased suicide following bariatric surgery. Obesity (Silver Spring). 2013;21(4):665-72.
146. Blackburn AN, Hajnal A, Leggio L. The gut in the brain: the effects of bariatric surgery on alcohol consumption. Addiction biology. 2017;22(6):1540-53.
147. Fried M, Yumuk V, Oppert JM, Scopinaro N, Torres A, Weiner R, et al. Interdisciplinary European guidelines on metabolic and bariatric surgery. Obes Surg. 2014;24(1):42-55.
148. Feilzer MY. Doing Mixed Methods Research Pragmatically: Implications for the Rediscovery of Pragmatism as a Research Paradigm. Journal of Mixed Methods Research. 2009;4(1):6-16.
149. Creswell JW, Clark VL, Gutmann ML, Hanson WE. Advanced mixed methods research designs. In: Tashakkori A, Teddlie C, editors. Handbook of mixed methods in social and behavioral research. Thousand Oaks, California: SAGE; 2003.
150. Dunnett CW. A Multiple Comparison Procedure for Comparing Several Treatments with a Control. Journal of the American Statistical Association. 1955;50(272):1096-121.
151. Cohn I, Raman J, Sui Z. Patient motivations and expectations prior to bariatric surgery: A qualitative systematic review. 2019;20(11):1608-18.
152. Machin D, Fayers PM. Randomized clinical trials: Design, practice and reporting. Chichester: Wiley-Blackwell; 2010.

153. Gloy VL, Briel M, Bhatt DL, Kashyap SR, Schauer PR, Mingrone G, et al. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. BMJ. 2013;347:f5934.
154. Torgerson DJ, Sibbald B. Understanding controlled trials. What is a patient preference trial? BMJ. 1998;316(7128):360.
155. Freedman B. Equipoise and the ethics of clinical research. The New England journal of medicine. 1987;317(3):141-5.
156. Krabseth H-M, Strømmen M, Spigset O, Helland A. Effect of Sleeve Gastrectomy on Buprenorphine Pharmacokinetics: a Planned Case Observation. Clin Ther. 2020.
157. Rudberg I, Solberg DK, Refsum H. CYP-genotyping ved psykofarmakologisk behandling. Tidsskr Nor Laegeforen. 2005;125(21):2953-5.
158. Rodwin MA, Abramson JD. Clinical Trial Data as a Public Good. JAMA. 2012;308(9):871-2.
159. Methadone 1mg/ml oral solution sugar-free [Internet]. emc. [cited 13-5.2020].
160. Mysels DJ, Sullivan MA. The relationship between opioid and sugar intake: Review of evidence and clinical applications. J Opioid Manag. 2010;6(6):445-52.
161. King WC, Chen J-Y, Belle SH, Courcoulas AP, Dakin GF, Flum DR, et al. Use of prescribed opioids before and after bariatric surgery: prospective evidence from a U.S. multicenter cohort study. Surgery for Obesity and Related Diseases. 2017;13(8):1337-46.
162. Mechanick JI, Apovian C, Brethauer S, Garvey WT, Joffe AM, Kim J, et al. Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures – 2019 update: cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists. Surgery for Obesity and Related Diseases. 2020;16(2):175-247.
163. Steiro A, Hestevik CH, Shrestha M, Muller AE. Erfaringer blant pasienter og helsepersonell med legemiddelassistert rehabilitering (LAR): En systematisk oversikt over kvalitative studier. Oslo: Folkehelseinstituttet, 2020.
164. Kanji S, Wong E, Akioyamen L, Melamed O, Taylor VH. Exploring pre-surgery and post-surgery substance use disorder and alcohol use disorder in bariatric surgery: a qualitative scoping review. Int J Obes. 2019;43(9):1659-74.
165. Kapur BM, Hutson JR, Chibber T, Luk A, Selby P. Methadone: a review of drug-drug and pathophysiological interactions. Crit Rev Clin Lab Sci. 2011;48(4):171-95.
166. Lloret-Linares C, Hirt D, Bardin C, Bouillot JL, Oppert JM, Poitou C, et al. Effect of a Roux-en-Y gastric bypass on the pharmacokinetics of oral morphine using a population approach. Clin Pharmacokinet. 2014;53(10):919-30.
167. Evans D. Hierarchy of evidence: a framework for ranking evidence evaluating healthcare interventions. J Clin Nurs. 2003;12(1):77-84.
168. Roerig JL, Steffen K. Psychopharmacology and Bariatric Surgery. European eating disorders review : the journal of the Eating Disorders Association. 2015;23(6):463-9.
169. Tømmerbakke SG. Gentestet pasientene - endret medikament eller dose hos syv av ti. Dagens Medisin. 2020 6.5.2020.
170. Griswold MG, Fullman N, Hawley C, Arian N, Zimsen SRM, Tymeson HD, et al. Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet. 2018;392(10152):1015-35.
171. Rose AK, Hardman CA, Christiansen P. The effects of a priming dose of alcohol and drinking environment on snack food intake. Appetite. 2015;95:341-8.

172. Hetherington MM, Cameron F, Wallis DJ, Pirie LM. Stimulation of appetite by alcohol. Physiol Behav. 2001;74(3):283-9.
173. Dawes AJ, Maggard-Gibbons M, Maher AR, Booth MJ, Miake-Lye I, Beroes JM, et al. Mental Health Conditions Among Patients Seeking and Undergoing Bariatric Surgery: A Meta-analysis. JAMA. 2016;315(2):150-63.
174. Dreber H, Reynisdottir S, Angelin B, Tynelius P, Rasmussen F, Hemmingsson E. Mental distress in treatment seeking young adults (18-25 years) with severe obesity compared with population controls of different body mass index levels: cohort study. Clin Obes. 2017;7(1):1-10.
175. Norstrom T, Rossow I. Alcohol Consumption as a Risk Factor for Suicidal Behavior: A Systematic Review of Associations at the Individual and at the Population Level. Archives of suicide research : official journal of the International Academy for Suicide Research. 2016:1-18.
176. Boenisch S, Bramesfeld A, Mergl R, Havers I, Althaus D, Lehfeld H, et al. The role of alcohol use disorder and alcohol consumption in suicide attempts--a secondary analysis of 1921 suicide attempts. European psychiatry : the journal of the Association of European Psychiatrists. 2010;25(7):414-20.
177. Pirkola SP, Isometsa ET, Heikkinen ME, Lonnqvist JK. Suicides of alcohol misusers and non-misusers in a nationwide population. Alcohol Alcohol. 2000;35(1):70-5.
178. Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, et al. Long-term mortality after gastric bypass surgery. N Engl J Med. 2007;357(8):753-61.
179. Dick DM, Bierut LJ. The genetics of alcohol dependence. Current Psychiatry Reports. 2006;8:151-7.
180. Børstad J, Trana K. Bekymret for antall fedmeoperasjoner i Norge: NRK.no; 2015 [23.6.2020]. Available from: https://www.nrk.no/trondelag/bekymret-for-antall-fedmeoperasjoner-i-norge-1.12633899.
181. Suzuki J, Haimovici F, Chang G. Alcohol use disorders after bariatric surgery. Obes Surg. 2012;22(2):201-7.
182. Cannell CF, Marquis KH, Laurent A. A summary of studies of interviewing methodology. Vital Health Stat 2. 1977(69):i-viii, 1-78.
183. Årsrapport for 2016 med plan for forbetringstiltak. Bergen: Helse-Bergen, 2017 20. September 2017. Report No.
184. Birch DW, Vu L, Karmali S, Stoklossa CJ, Sharma AM. Medical tourism in bariatric surgery. Am J Surg. 2010;199(5):604-8.
185. Østmoe H. Fedmeturisme til lav pris og høy risiko. Adresseavisen [Internet]. 2011.
186. Grant BF. Barriers to alcohol treatment: Reasons for not seeking treatment in a general population sample. J Stud Alcohol. 1997;58:365-71.
187. Cohen E, Feinn R, Arias A, Kranzler HR. Alcohol treatment utilization: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. Drug Alcohol Depend. 2007;86(2-3):214-21.
188. Östlund MP, Backman O, Marsk R, Stockeld D, Lagergren J, Rasmussen F, et al. Increased admission for alcohol dependence after gastric bypass surgery compared with restrictive surgery. JAMA Surg. 2013;148(4):374-7.
189. Mitchell JE, Steffen K, Engel S, King WC, Chen JY, Winters K, et al. Addictive disorders after Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2015;11(4):897-905.
190. Diagnostic and statistical manual of mental disorders, DSM 5. 5 ed. Arlington: American Psychiatric Publishing; 2013.

191. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. AUDIT. The Alcohol Use Disorders Identification Test. Geneva: WHO Department of Mental Health and Substance Dependence, 2001.
192. Strømmen M, Bakken IJ, Klöckner C, Sandvik J, Kulseng B, Holen A. Diagnoses related to abuse of alcohol and addictive substances after gastric bypass and sleeve gastrectomy: a nation-wide registry study from Norway. Surgery for Obesity and Related Diseases. 2020;16(4):464-70.

PAPERS I-IV

Paper I

Magnus Strømmen, Inger Johanne Bakken, Ellen Andenæs, Christian A Klöckner, Ronald Mårvik, Bård Kulseng, Are Holen. ***Fet, feit eller bare overvektig?*** Tidsskrift for den norske legeforening (2015) 135, 1732-1736
DOI: 10.4045/tidsskr.14.0828

Fet, feit eller bare overvektig?

BAKGRUNN Det kan være utfordrende å drøfte fedme med pasienten uten at dette oppleves som krenkende. Forebygging av livsstilssykdommer gjør det påkrevd å ta opp temaet overfor dem dette gjelder. I denne studien undersøkes pasienters uttrykkssensitivitet, det vil si hvor passende eller upassende de opplever ulike uttrykk for fedme, og hvilke pasientkarakteristika som er knyttet til uttrykkssensitivitet.

MATERIALE OG METODE Undersøkelsen er del av en femårig studie med pasienter i Midt-Norge som ble behandlet for sykelig fedme. Uttrykkene i studien var foreslått av Overvektsforeningen. Data om uttrykkssensitivitet ble innsamlet ved hjelp av et spørreskjema ett år etter behandling.

RESULTATER Av 206 deltakere returnerte 157 spørreskjemaet. Gjennomsnittlig kroppsmasseindeks (BMI) (SD) var 37,6 kg/m^2 (7,3 kg/m^2). Uttrykkssensitiviteten overfor 14 ulike betegnelser varierte. «Vekt», «overvekt» og «vektproblem» kom best ut, mens «obesitas», «fet» og «feit» ble vurdert som mest upassende. Mest uttrykkssensitive var kvinner, de som utviklet overvekt tidlig i livet, de med høyere utdanning og de som ikke var tilfreds med vekten.

FORTOLKNING Det var stor variasjon i hvordan ulike uttrykk for overvekt og fedme ble oppfattet. Kunnskap om temaet kan være relevant for leger og annet helsepersonell i forebygging og behandling av fedme.

Magnus Strømmen
magnus.strommen@stolav.no
Institutt for nevromedisin
Det medisinske fakultet
Norges teknisk-naturvitenskapelige universitet
og
Senter for fedmeforskning
Kirurgisk klinikk
St. Olavs hospital

Inger Johanne Bakken
Institutt for nevromedisin
Det medisinske fakultet
Norges teknisk-naturvitenskapelige universitet

Ellen Andenæs
Institutt for språk og litteratur
Det humanistiske fakultet
Norges teknisk-naturvitenskapelige universitet

Christian A. Klöckner
Psykologisk institutt
Fakultet for samfunnsvitenskap
og teknologiledelse
Norges teknisk-naturvitenskapelige universitet
og
Senter for fedmeforskning
Kirurgisk klinikk
St. Olavs hospital

Ronald Mårvik
Senter for fedmeforskning
Kirurgisk klinikk
St. Olavs hospital
og
Nasjonalt senter for avansert laparoskopisk kirurgi
Kirurgisk klinikk
St. Olavs hospital

Bård Kulseng
Senter for fedmeforskning
Kirurgisk klinikk
St. Olavs hospital

Are Holen
Institutt for nevromedisin
Det medisinske fakultet
Norges teknisk-naturvitenskapelige universitet
og
Smertesenteret
St. Olavs hospital

Engelsk oversettelse på www.tidsskriftet.no

Overvekt er i dagligtale ofte synonymt med både overvekt og fedme, to tilstander som skiller seg med hensyn til etiologi, prognose og behandling. Klinikere bruker gjerne WHOs klassifisering av kroppsmasse basert på kroppsmasseindeks (Body Mass Index, BMI) og nyanserer mellom overvekt og varierende grader av fedme (1). I møte med pasienter kan presise uttrykk være utfordrende, og det kan tenkes at ordbruken kan ha betydning for samarbeidsklima og behandlingsutfall.

Mange med overvekt og fedme innser at de løper en risiko for å utvikle sykdom. Like fullt er livsstilsendring vanskelig for noen. Siden 66 % av befolkningen går årlig til lege, kan fastlegen spille en nøkkelrolle (2). En amerikansk studie viste at pasienter med høy kroppsmasseindeks oftere avbestiller legetimen hvis veiing inngår (3). Fra legens side er komorbiditet snarere enn kroppsmasseindeks avgjørende for om vekt tematiseres (4–6). Det kan være en negativ sammenheng mellom pasientens kroppsmasseindeks og legens bruk av tid til konsultasjonen (7). I sum kan dette tyde på at både pasient og lege har en tendens til å vike unna overvekt som tema, og at overvekt tematiseres først når komplikasjoner oppstår.

Hvordan man oppfatter sin egen kroppsstørrelse, varierer fra person til person. Oppfatningen varierer dessuten med livsfase, kjønn (8, 9) og alder (10). Det er også en generell tendens til å underrapportere vekten (11). Økt prevalens av overvekt nå for tiden kan bidra til sosial normalisering av tilstanden og gjøre at færre ser på seg selv som overvektig.

Dessuten kompliseres trolig samtalen mellom lege og pasient av at ulike dagligdagse uttrykk om overvekt og fedme kan oppfattes som krenkende. Tematisering av kroppen rører ved den enkeltes selvfølelse, noe som aktualiseres ytterligere av at depresjon er utbredt blant mennesker med uttalt fedme (12). Generelt sett er samfunnets holdninger til overvekt negative, det innbefatter også helsevesenet (13). Selv om det eksisterer delte oppfatninger blant klinikere om hvordan overvekt bør omtales overfor pasienter (14, 15), foreligger det lite empiri på området. I to amerikanske studier er pasienters uttrykkssensitivitet kartlagt (16, 17), men forskjeller i språk og kultur gir liten overføringsverdi til norske forhold. Det er ingen norske studier på feltet.

I denne studien har vi undersøkt hvordan norske pasienter opplevde ulike fedmeuttrykk. Dette omtales som *uttrykkssensitivitet*, her forstått som hvor passende eller upassende de opplever ulike betegnelser.

Vi forsøker å gi svar på følgende spørsmål:

- I hvilken grad har pasienter med sykelig fedme opplevd at fastlegen har tematisert deres fedme?
- Hvor upassende finner fedmepasienter bruk av ulike uttrykk?
- Er uttrykkssensitivitet relatert til bakenforliggende variabler som kjønn, alder, utdanning, samlivsstatus, mental helse, vurdering av egen vekt og/eller når i livet man utviklet overvekt?

Materiale og metode

Deltakere

Analysen av uttrykkssensitivitet var et sekundært endepunkt i en femårig studie

HOVEDBUDSKAP

De fleste av pasientene mente at det var riktig av legen å ta initiativ til en samtale om fedme og dens helsemessige konsekvenser

Uttrykk som obesitas, fet og feit ble opplevd som upassende, vekt og overvekt ble vurdert som mer passende

Spesielt følsomme for uttrykkene var kvinner, personer med høyere utdanning og de som utviklet overvekt tidlig i livet

med pasienter som opprinnelig var henvist til St. Olavs hospital for behandling av sykelig fedme. Av 206 deltakere returnerte 157 spørreskjemaet (svarrate 76 %). Skjemaet ble tilsendt i forkant av ettårsundersøkelsen med oppfordring om å returnere det ved oppmøtet, hvorpå det forelå komplette opplysninger hos 142 pasienter fra Midt-Norge. Grunnet suksessiv inklusjon strakte studien seg fra 2005 til 2013. I en tidligere artikkel beskrives behandlingen pasientene gjennomgikk og de helsemessige effekter av den (18). Alle pasientene oppfylte kriteriet for sykelig fedme og hadde ved inklusjonstidspunktet BMI > 35 kg/m^2.

Studien er godkjent av regional etisk komité (REK) Midt-Norge.

Tabell 1 Sosiodemografiske og antropometriske data for de 157 inkluderte pasientene, som alle hadde gjennomgått vektreduserende behandling ett år tidligere

Alder (år) – gjennomsnitt ± SD	42,6 ± 9,2
Kvinner – antall (%)	119 (75,8)
Menn – antall (%)	38 (24,2)
Samboende/gift – antall (%)	96 (57,0)
Utdanning tilsvarende bachelorgrad eller mer – antall (%)	54 (35,7)
Overvektsdebut i barndom/ungdomstid – antall (%)	108 (71,5)
BMI (kg/m^2) – gjennomsnitt utgangsverdi ± SD	45,2 ± 5,7
BMI (kg/m^2) – gjennomsnitt ett år etter behandling ± SD	37,6 ± 7,3

Data

Følgende variabler inngikk i analysen av uttrykkssensitivitet: kjønn, alder (kontinuerlig variabel), utdanningsnivå (grunnskole/yrkesskole eller videregående skole/høyere utdanning), samlivsstatus (aleneboende eller samboende), tidspunkt for overvektsdebut (barndom/ungdomstid eller voksen alder) og tilfredshet med vekttapet etter behandling (tilfreds eller utilfreds).

Videre inngikk dimensjonen sosial funksjonsevne fra SF-36, basert på spørsmålene om hvorvidt fysisk helsetilstand eller følelsesmessige problemer har påvirket ens sosiale omgang. SF-36 er et generisk livskvalitetsinstrument bestående av 36 spørsmål som gir grunnlag for åtte ulike erfaringsdimensjoner (19).

Vi anvendte symptomintensitet for angst målt med HADS (Hospital Anxiety and Depression Scale) (20). Både SF-36 og HADS (angstdimensjonen) inngikk i analysen som kontinuerlige variabler. Kun angstdimensjonen fra HADS ble tatt inn i regresjonsanalysen på grunn av multikollinearitet mellom denne og depresjon.

Grunnlaget for utvalget av variabler til analysen var hva vi hypotetisk antok kunne spille inn. Variabeltilfanget var også prisgitt rammene av de opprinnelige data i den femårige (hoved)studien som uttrykksstudien utgikk fra, siden denne delen av studien ble integrert etter studiestart.

Uttrykkssensitivitet

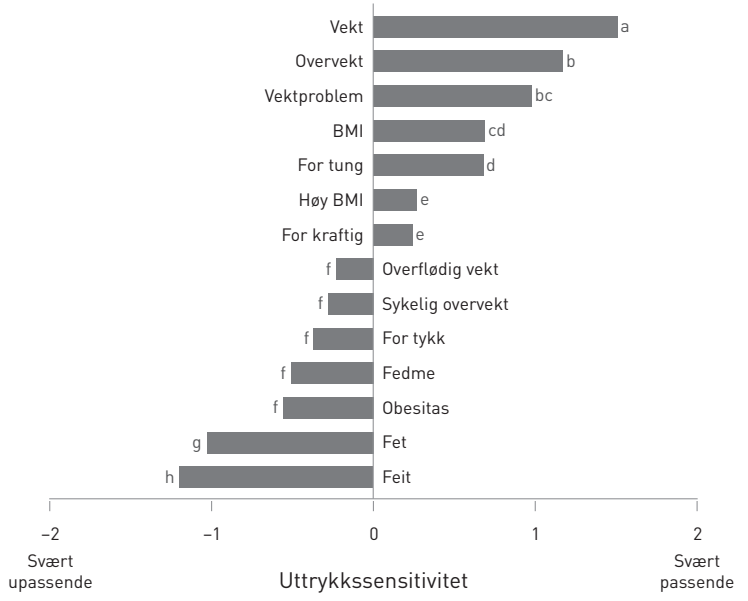
Spørsmålene om uttrykkssensitivitet var inspirert av en amerikansk studie (16). Skjemaet ble utviklet for denne studien, og test-retest-analyse av 33 personer viste høy korrelasjon.

I skjemaet ble pasientene bedt om å se for seg følgende situasjon: «Du er hos fastlegen til ordinær kontroll. Dette skjedde før du ble henvist til sykehuset for behandling av overvekt. På eget initiativ ønsker fastlegen å snakke med deg om din overvekt og om konsekvensene dette kan ha for helsen. Du har ikke snakket med fastlegen om overvekt tidligere.»

Så fulgte 14 ulike uttrykk for overvekt eller fedme som var tenkt brukt av legen. Hvert uttrykk ble av pasienten skåret for uttrykkssensitivitet i henhold til en fempunkts skala med responsalternativer fra *svært upassende (–2)* til *svært passende (+2)*. Uttrykkene var innhentet fra Overvektsforeningen, som i forkant av studien ble oppfordret til å komme med betegnelser som kunne oppfattes som positive eller negative. Uttrykk som primært forekommer som skjellsord ble utelatt.

Følgende uttrykk inngikk i skjemaet, i denne rekkefølgen: «overvekt», «vektproblem», «BMI», «høy BMI», «fedme», «sykelig overvekt», «obesitas», «overflødig vekt», «for tung», «fet», «feit», «tykk», «kraftig» og «vekt».

Skjemaet inneholdt også følgende spørsmål (med svaralternativene ja/nei/vet ikke): Om legens valg av uttrykk ville ha hatt betydning for pasient-lege-relasjonen, om det er riktig av legen å initiere en samtale om



Figur 1 *Uttrykkssensitivitet for 14 uttrykk for overvekt og fedme vurdert av pasienter behandlet for sykelig fedme (N = 157). Søyler med ulike bokstaver er signifikant ulike (p < 0,001), det vil si illustrerer uttrykk som oppleves ulikt av pasientene. Eksempel: «Vekt» oppleves forskjellig fra alle andre uttrykk, mens det er ingen forskjell mellom opplevelsen av «overvekt» og «vektproblem»*

Tabell 2 Hvem var mest sensitive for de dårligst likte fedmeuttrykkene? Multippel lineær regresjon med uttrykkssensitivitet predikert av ulike pasientkarakteristika hos 142[1] pasienter som hadde gjennomgått vektreduserende behandling. 95 % konfidensintervall

	B[2]	95 % KI av B
Utdanning (0[3] = grunnskole/yrkesskole; 1 = videregående skole)	–1,92	–2,92 — –0,90
Fedmedebut (0 = barndom/ungdomstid; 1 = voksen alder)	1,59	0,29 — 2,82
Kjønn (0 = kvinne; 1 = mann)	1,58	0,39 — 2,86
Vurdering av egen vekt (0 = utilfreds; 1 = tilfreds)	1,24	0,27 — 2,23
Sosial funksjonsevne (SF-36)	–0,06	–0,11 — 0,01
Angstsymptomer (HADS)	–0,11	–0,22 — 0,01
Samlivsstatus (0 = enslig; 1 = parforhold)	0,55	–0,32 — 1,52
Alder (år)	–0,00	–0,06 — 0,06

[1] Fullstendige data for regresjonsanalysen kun for 142 deltakere

[2] Beta er regresjonsvekt og utgjør forskjell i uttrykkssensitivitet når variabelen endres med én enhet mens alle andre variabler holdes konstante. Positive verdier tilsier at man er mindre uttrykkssensitiv, mens negative verdier tilsier økt sensitivitet

[3] For dikotome variabler er 0 referansekategorien. Eksempel: Personer med videregående skole (eller mer utdanning) liker i gjennomsnitt uttrykkene nesten to poeng dårligere enn personer kun med grunnskole/yrkesskole når de andre faktorene er like

fedme og om pasienten selv hadde opplevd at leger faktisk hadde tatt slikt initiativ.

Statistiske analyser

Uttrykkssensitiviteten kunne angis i fem kategorier. Vi benyttet Friedmans ANOVA etterfulgt av Wilcoxons signed-rank test for å vurdere forskjeller mellom uttrykkene. På grunn av et høyt antall parvise tester (n = 91) ble signifikansnivået justert til 0,001. De tre uttrykkene som totalt sett oppnådde den mest negative skåringen ble slått sammen til én variabel, for mer å kunne se på selve fenomenet uttrykkssensitivitet fremfor det enkelte uttrykk. En slik samlevariabel reduserer samtidig risikoen for tilfeldige målefeil.

Ved hjelp av multippel lineær regresjon undersøkte vi så om uttrykkssensitivitet var assosiert med bakenforliggende faktorer (signifikansnivå 0,05). På grunn av utvalgets begrensede størrelse gjorde vi gjentatte tilfeldige utvalg (bootstrapping), en teknikk som gir konfidensintervaller estimert av den virkelige fordelingen i materialet og ikke på en antakelse om normalfordeling. Statistiske beregninger ble utført i PASW Statistics 18 (SPSS Inc., 2009, Chicago, IL).

Resultater

Undersøkelsen er basert på 157 personer (76,2 %) som returnerte skjemaet om uttrykkssensitivitet. Ved testtidspunktet (ett år ute i studien) hadde deltakernes kroppsmasseindeks i gjennomsnitt (SD) falt fra 45,2 kg/m^2 (5,7 kg/m^2) til 37,6 kg/m^2 (7,3 kg/m^2).

I tabell 1 vises sosiodemografiske og antropometriske data om utvalget.

Pasientenes erfaringer med at legen tematiserer overvekt og fedme

I alt mente 124 pasienter (80 %) at legens evne til å formulere seg var av betydning for samarbeidsrelasjonen, og 145 (92 %) vurderte det som riktig av legen å ta initiativ til en samtale om fedme og dens helsemessige konsekvenser. 52 pasienter (33 %) rapporterte at de hadde opplevd at legen tok slikt initiativ.

Pasientenes vurdering av ord og uttrykk

Test av den totale variasjonen mellom uttrykkene var statistisk signifikant, $\chi^2(13) = 857{,}8$, $p < 0{,}001$. I figur 1 fremstilles detaljer i uttrykkssensitivitet. Av uttrykkene kom «vekt» best ut, med snittskåren (SD) 1,51 (± 0,7) – dette var signifikant forskjellig ($p < 0{,}001$) fra andre uttrykk. Deretter fulgte «overvekt» med 1,17 (± 1,0), «vektproblem» med 0,98 (± 1,1); «BMI» med 0,69 (± 1,1); «for tung» med 0,68 (± 1,2); «høy BMI» med 0,27 (± 1,2) og «for kraftig» med 0,24 (± 1,2).

«Feit» ble vurdert som det mest upassende, med snittskår –1,20 (± 1,2). «Feit» var dessuten signifikant forskjellig fra «fet», som hadde skår –1,03 (± 1,2). Derpå fulgte fem uttrykk som innbyrdes ikke var signifikant forskjellige: «obesitas» –0,56 (± 1,2); «fedme» –0,51 (± 1,4); «for tykk» –0,37 (± 1,3); «sykelig overvektig» –0,28 (± 1,4) og «overflødig vekt» –0,23 (± 1,3).

Mest uttrykkssensitive var kvinner, de som utviklet overvekt tidlig i livet, de med høyere utdanning og de som ikke var tilfreds med vekten (tab 2). Alder, samlivsstatus, angstsymptomer og sosial funksjonsevne nådde ikke signifikans i modellen. Regresjonen er basert på de 142 deltakerne vi hadde fullstendige data på.

Diskusjon

Studien vår viser at mange pasienter mente det er riktig at legen tar initiativ til en samtale om overvekt og fedme. Samtidig var pasientene sensitive for flere uttrykk som beskriver fedme. Mange mente at feil ordvalg påvirker relasjonen til legen negativt. Som sagt var det kvinnene som var mest uttrykkssensitive, og de som ble overvektige tidlig i livet, de med høyere utdanning og de som var utilfreds med vekten.

Hver tredje pasient rapporterte at legen tok initiativet til å snakke om fedme. Tallet er lavt når man tar deltakernes betydelige vekt i betraktning. En annen studie har vist at vekt var tema i kun 17 % av konsultasjonene med overvektige pasienter (21). Pasienters og legers oppfatning av hvorvidt vekt i det hele tatt har vært tema i konsultasjonen kan dessuten variere. I en studie fant man at pasientene langt sjeldnere enn legene mente at vekten ble omtalt. Mest avvikende oppfatning hadde pasienter som i liten grad hadde forsøkt å gå ned i vekt på egen hånd (22), hvilket understreker kompleksiteten ved å samtale om dette.

Fastleger kvier seg for å diskutere overvekt med pasienter av frykt for å støte (5, 23). Mest utfordrende er dette når legen kjenner pasienten dårlig (4). Det å lykkes med forebygging krever at temaet blir tatt opp tidlig nok. Antar man at overvektige, men ellers friske personer i mindre grad besøker fastlegen enn fete med tilleggssykdommer, betyr dette at samtalen om vekt må tas med pasienter man kjenner dårlig. Dette bør skje også i tilfeller der pasienten selv ikke tar et slikt initiativ. Funn om at komorbiditet snarere enn kroppsmasseindeks er utslagsgivende for om legen tematiserer fedme (4–6), understreker behovet for forebygging. Ni av ti pasienter i vår studie mente det var riktig av legen å ta et slikt initiativ.

At det er større uttrykkssensitivitet hos kvinner, kan relateres til kjønnsforskjeller når det gjelder selvbilde og kroppsbevissthet. Kvinner er mer kritiske til sin egen kropp (8, 9), mens menn i større grad underestimerer vekten sin (24). Det er også vist at menn foretrekker et mer direkte språk enn kvinner gjør (25).

En medvirkende årsak til økt sensitivitet hos dem med høyere utdanning kan være at de, i motsetning til personer med lavere utdanning, i mindre grad underestimerer egen vekt (24). Derfor kan det være at uttrykk i større grad oppleves som treffende. Et språksosiologisk perspektiv på dette funnet kan være at direkte språkbruk er mer utbredt i miljøer med lavere utdanning og at de med høyere utdanning derfor mangler en viss her-

ding. En tredje forklaring på hvorfor de med høyere utdanning relativt sett synes overvekt er mer belastende, er opplevelsen av å falle utenfor sosialt aksepterte normer (26).

Noe uventet fant vi ingen prediktiv verdi av angstsymptomer målt med HADS-skalaen. Det samme gjaldt for sosial funksjonsevne, alder og samlivsstatus.

Det var klar sammenheng mellom det å være overvektig tidlig i livet og uttrykkssensitivitet. Dette kan trolig føres tilbake til erfaringer med stigmatisering på grunn av overvekt (27), noe som dermed kan ha fått en formende innflytelse på identitetsutviklingen. Mennesker som utvikler overvekt i voksen alder internaliserer neppe samfunnets holdninger med samme styrke.

Data var innsamlet ved ettårsoppfølgingen etter fedmebehandling. Pasientene opplyste da om graden av tilfredshet med egen vekt/vekttap på det tidspunktet. Initiale vekttap kan være oppmuntrende og styrke pasientens selvbilde, noe som delvis kan forklare hvorfor de som var misfornøyd med vekten, var mer uttrykkssensitive.

Tradisjonelt har leger aktivt forvaltet utviklingen av fagterminologien (28), og klinikere tilstreber gjerne språklig presisjon. Våre funn viser imidlertid at uttrykk som for klinikere burde ha en klar denotasjon til BMI > 30 kg/m^2, vekker negative reaksjoner hos pasientene.

Mens «overvekt/overvektig» er presise uttrykk for en kroppsmasseindeks på 25–30 kg/m^2, vil det være korrekt å bruke betegnelser som «fedme/fet/feit», «adipositas/adipøs» og «obesitas» ved BMI > 30 kg/m^2. Klinikere unngår trolig uttrykkene «adipositas/obesitas», da disse er fremmede for folk flest. De unngår kanskje også «fedme/fet/feit» av frykt for å støte. Snarere anvendes ukorrekte uttrykk som «overvekt» og «sykelig overvekt» også ved en BMI > 30 kg/m^2. Er det riktig å la pasientenes oppfatning av uttrykkene styre helsepersonellets språkbruk?

Spørsmålet kan ses i lys av *protection motivation theory*, hvor bekymring for egen helse tenkes ha en positiv verdi (29). Sentralt i teorien er individets trusselvurdering – opplevelsen av helserisiko (*vulnerability*) og konsekvensenes alvorlighetsgrad (*severity*). Det å være bekymret for helsen ses som en ressurs til endring av helseskadelig atferd. Man kan tenke seg at bruk av mer presise uttrykk har større potensial for uro.

Men teorien har en viktig forutsetning: Man skal på samme tid veilede og støtte ny atferd. Teorien legitimerer dermed ikke ukritisk bruk av uttrykk når behandlerrelasjonen enten vil opphøre eller ikke vektlegger endring av helseatferd. Isolert sett kan krenkende uttrykk virke mot sin hensikt (30). Samtidig er det studier som viser at fedmepasienter faktisk oppfatter direkte uttrykk som mer motiverende for endring enn eufemismer (31, 32). Slik kan det forsvares å bruke et mer direkte, kanskje konfronterende språk overfor pasientene, iallfall når det gjelder menn.

Isolert sett vil valg av uttrykk neppe ha direkte betydning for graden av vekttap, men de kan bidra til påvirkning av tankeprosesser som er med på å fremskynde atferdsendring. Det å høre legen si at man er fet, kan få pasienten til å innse alvoret i situasjonen. En slik forståelse er også i samsvar med hva vi vet om relativ sykdomsrisiko (33).

Vi vet fra før at menn og yngre generelt foretrekker en mer direkte uttrykksmåte (31). Vår studie bekrefter kjønnsforskjellen, men viser også andre faktorer av betydning. Hvor grensen går mellom hva som er motiverende og hva som bare er krenkende, er vanskelig å si. Opplever pasienten å bli stigmatisert, kan reaksjoner bli unngåelse av konsultasjoner eller legebytte. Slik kan en uheldig språkbruk i verste fall ha negative helsekonsekvenser (32).

Denne studien tok utgangspunkt i pasienter med sykelig fedme. Funnene kan ikke uten videre generaliseres til den atskillig større populasjonen av overvektige som ikke er behandlingssøkende. Vi må dessuten ta i betraktning at et av spørsmålene var knyttet til forhold som ligger noe tilbake i tid og at det kan ha innvirket på svarene. Utvalget av variabler til regresjonsanalysen var begrenset av data innsamlet før denne delstudien ble satt i gang. Flere variabler som vi ikke hadde tilgang til, kan tenkes å påvirke uttrykkssensitiviteten og ville derfor ha kunnet påvirke resultatet.

Funnene er etter vårt syn relevante – særlig for fastleger. De ser ofte pasientens vektutvikling og har en oppgave i å forebygge. Kunnskap om hvordan språkbruken oppleves, kan senke terskelen for å tematisere kroppsvekt på et tidlig tidspunkt og slik kanskje gjøre forebygging mer effektivt.

Forskningsfondet ved Unimed Innovation og St. Olavs hospital har gitt økonomisk støtte til studien.

Magnus Strømmen (f. 1973)
er ph.d.-student i klinisk medisin, m.sc. og forskningssykepleier.
Forfatter har fylt ut ICMJE-skjemaet og oppgir ingen interessekonflikter.

Inger Johanne Bakken (f. 1968)
er dr.ing. innen biofysikk og medisinsk teknologi og seniorrådgiver innen registerepidemiologi ved Folkehelseinstituttet.
Forfatter har fylt ut ICMJE-skjemaet og oppgir ingen interessekonflikter.

Ellen Andenæs (f. 1951)
er førsteamanuensis i anvendt språkvitenskap, leder for Seksjon for språklig kommunikasjon og koordinator for forskergruppe i helsekommunikasjon og etikk ved Norges teknisk-naturvitenskapelige universitet.
Forfatter har fylt ut ICMJE-skjemaet og oppgir ingen interessekonflikter.

Christian A. Klöckner (f. 1972)
er professor i sosialpsykologi og kvantitative metoder og metodekonsulent ved Senter for sykelig overvekt i Midt-Norge.
Forfatter har fylt ut ICMJE-skjemaet og oppgir ingen interessekonflikter.

Ronald Mårvik (f. 1949)
er spesialist i gastroenterologi og i generell kirurgi og avdelingsoverlege.
Forfatter har fylt ut ICMJE-skjemaet og oppgir ingen interessekonflikter.

Bård Kulseng (f. 1951)
er spesialist i endokrinologi, professor ved Institutt for kreftforskning og molekylær medisin og leder av Senter for fedmeforskning.
Forfatter har fylt ut ICMJE-skjemaet og oppgir ingen interessekonflikter.

Are Holen (f. 1945)
er spesialist i psykiatri og professor.
Forfatter har fylt ut ICMJE-skjemaet og oppgir ingen interessekonflikter.

Litteratur

1. Obesity. Preventing and managing the global epidemic. Genève: World Health Organisation, 2000.
2. Nossen JP. Hva foregår på legekontorene? Konsultasjonsstatistikk for 2006. Oslo: Arbeids- og velferdsdirektoratet, 2007.
3. Olson CL, Schumaker HD, Yawn BP. Overweight women delay medical care. Arch Fam Med 1994; 3: 888–92.
4. Kristeller JL, Hoerr RA. Physician attitudes toward managing obesity: differences among six specialty groups. Prev Med 1997; 26: 542–9.
5. Michie S. Talking to primary care patients about weight: a study of GPs and practice nurses in the UK. Psychol Health Med 2007; 12: 521–5.
6. Potter MB, Vu JD, Croughan-Minihane M. Weight management: what patients want from their primary care physicians. J Fam Pract 2001; 50: 513–8.
7. Hebl MR, Xu J. Weighing the care: physicians' reactions to the size of a patient. Int J Obes Relat Metab Disord 2001; 25: 1246–52.
8. Grover VP, Keel PK, Mitchell JP. Gender differences in implicit weight identity. Int J Eat Disord 2003; 34: 125–35.
9. Pingitore R, Spring B, Garfield D. Gender differences in body satisfaction. Obes Res 1997; 5: 402–9.
10. Reboussin BA. Correlates of satisfaction with body function and body appearance in middle-and older aged adults: The Activity Counseling Trial (ACT). Psychol Health 2000; 15: 239–54.
11. Niedhammer I, Bugel I, Bonenfant S et al. Validity of self-reported weight and height in the French GAZEL cohort. Int J Obes Relat Metab Disord 2000; 24: 1111–8.

>>>

12. Onyike CU, Crum RM, Lee HB et al. Is obesity associated with major depression? Results from the Third National Health and Nutrition Examination Survey. Am J Epidemiol 2003; 158: 1139–47.
13. Puhl RM, Heuer CA. The stigma of obesity: a review and update. Obesity (Silver Spring) 2009; 17: 941–64.
14. Guide to authors. The Obesity Society. http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1930-739X/homepage/ForAuthors.html (14.9.2015).
15. Holmén J. Den som lider av fetma är fet! Läkartidningen 1999; 96: 3081.
16. Volger S, Vetter ML, Dougherty M et al. Patients' preferred terms for describing their excess weight: discussing obesity in clinical practice. Obesity (Silver Spring) 2012; 20: 147–50.
17. Wadden TA, Didie E. What's in a name? Patients' preferred terms for describing obesity. Obes Res 2003; 11: 1140–6.
18. Martins C, Strømmen M, Stavne OA et al. Bariatric surgery versus lifestyle interventions for morbid obesity – changes in body weight, risk factors and comorbidities at 1 year. Obes Surg 2011; 21: 841–9.
19. Ware JE Jr. SF-36 health survey update. Spine 2000; 25: 3130–9.
20. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67: 361–70.
21. Scott JG, Cohen D, DiCicco-Bloom B et al. Speaking of weight: how patients and primary care clinicians initiate weight loss counseling. Prev Med 2004; 38: 819–27.
22. Greiner KA, Born W, Hall S et al. Discussing weight with obese primary care patients: physician and patient perceptions. J Gen Intern Med 2008; 23: 581–7.
23. Tailor A, Ogden J. Avoiding the term 'obesity': an experimental study of the impact of doctors' language on patients' beliefs. Patient Educ Couns 2009; 76: 260–4.
24. Kuchler F, Variyam JN. Mistakes were made: misperception as a barrier to reducing overweight. Int J Obes Relat Metab Disord 2003; 27: 856–61.
25. Kirtley MD, Weaver JB. Exploring the impact of gender role self-perception on communication style. Women's. Stud Commun 1999; 22: 190–209.
26. Ross CE. Overweight and depression. J Health Soc Behav 1994; 35: 63–79.
27. Latner JD, Stunkard AJ. Getting worse: the stigmatization of obese children. Obes Res 2003; 11: 452–6.
28. Myking J. Terminologiutvikling – kulturpolitikk og sosialpolitikk. Tidsskr Nor Legeforen 2008; 128: 850.
29. Norman P, Boer H, Seydel ER. Protection motivation theory. I: Conner M, Norman P, red. Predicting health behaviour. New York, NY: McGraw-Hill Education, 2005.
30. Boer H, Seydel ER. Protection motivation theory. I: Conner M, Norman P, red. Predicting health behaviour. New York, NY: McGraw-Hill Education, 2005.
31. Gray CM, Hunt K, Lorimer K et al. Words matter: a qualitative investigation of which weight status terms are acceptable and motivate weight loss when used by health professionals. BMC Public Health 2011; 11: 513.
32. Puhl R, Peterson JL, Luedicke J. Motivating or stigmatizing? Public perceptions of weight-related language used by health providers. Int J Obes 2013; 37: 612–9.
33. Wilson PWF, D'Agostino RB, Sullivan L et al. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. Arch Intern Med 2002; 162: 1867–72.

Mottatt 27.6. 2014, første revisjon innsendt 2.12. 2014, godkjent 14.9. 2015. Redaktør: Tor Rosness.

Paper II

Magnus Strømmen, Bård Kulseng, Einar Vedul-Kjelsås, Harald Johnsen, Gjermund Johnsen, Ronald Mårvik. ***Bariatric surgery or lifestyle intervention? An exploratory study of severely obese patients' motivation for two different treatments.*** Obesity Research & Clinical Practice (2009) 3, 193-201
DOI: 10.1016/j.orcp.2009.04.004

Obesity Research & Clinical Practice (2009) **3**, 193—201

ELSEVIER

http://www.iotf.org/oonet/aoaso.htm

ORIGINAL ARTICLE

Bariatric surgery or lifestyle intervention? An exploratory study of severely obese patients' motivation for two different treatments

Magnus Strømmen[a,*], Bård Kulseng[a], Einar Vedul-Kjelsås[b,c], Harald Johnsen[d], Gjermund Johnsen[a,e,f], Ronald Mårvik[a,e,f]

[a] *Centre for Obesity, Dept. of Surgery, St. Olavs University Hospital, Norway*
[b] *Dept. of Neuroscience, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Norway*
[c] *Dept. of Research and Development, Division of Psychiatry, St. Olavs University Hospital, Norway*
[d] *Dept. of Medical Imaging, St. Olavs University Hospital, Norway*
[e] *National Center for Advanced Laparoscopic Surgery, St. Olavs University Hospital, Norway*
[f] *Future Operating Rooms, St. Olavs University Hospital, Norway*

Received 2 January 2009; received in revised form 31 March 2009; accepted 25 April 2009

KEYWORDS
Overweight;
Obesity;
Gastric bypass;
Lifestyle intervention;
Mental health;
Mixed methods research;
Sequential exploratory design

Summary
Background: In the complex field of treating severe obesity, motivation is receiving increased attention. This explorative study aims to highlight what influences the preferences of severely obese patients deciding for either gastric bypass surgery or lifestyle treatment.
Methods: Patients awaiting laparoscopic gastric bypass were presented with an 18-week inpatient lifestyle programme alternative to gastric bypass. Questionnaires provided qualitative data (reasons for choosing one treatment over another) and quantitative data (mental health assessment using the Hospital Anxiety and Depression Scale). The material was analysed according to a sequential exploratory design involving thematic analysis of patients' arguments, validation using HADS, and statistical computations (hypothesis testing) with one-way ANOVA followed by Dunnett's post hoc test.
Results: 159 participants (mean BMI 47.2 kg/m^2) returned questionnaires of which 32% wanted the lifestyle treatment alternative to surgery. Reasons for choosing the two treatments varied widely as did also the corresponding data on mental health. Two subgroups stood out with particularly high mental symptom scores,

* Corresponding author at: St. Olavs University Hospital, Centre for Obesity, Dept. of Surgery, Olav Kyrres gate 17, NO-7006 Trondheim, Norway. Tel.: +47 9170 1010; fax: +47 7386 7428.
E-mail address: magnus-s@online.no (M. Strømmen).

1871-403X/$ — see front matter
doi:10.1016/j.orcp.2009.04.004

namely patients choosing surgery due to reluctance to engage in social interaction in lifestyle treatment, and patients preferring lifestyle treatment due to the fear of dying during general anaesthesia. These two subgroups showed significantly higher symptom scores than other subgroups within their therapy-of-choice group. The number of comorbid diseases was also found to impact upon motivation.
Conclusions: Patients carry different incentives for choosing the same type of treatment. On a subgroup level, psychopathological symptoms seem to follow motivational patterns. Analysing motivation and mental health may provide measures for identifying subgroups with various prospects for therapy outcome.

Introduction

Dental anxiety is known to limit or even prevent the utilisation of oral health care services [1], often entailing severe consequences for both oral health and quality of life [2]. While dental anxiety is a well recognised problem within the dental profession, little has been done to document similar anxiety mechanisms among patients in need of bariatric treatment. Over the years, we have occasionally met patients who are reluctant to accept or even turn down bariatric procedures, however we have never approached these cases in a systematic fashion with the express objective of trying to understand the impact of anxiety on patient decisions. Paradoxically the potential consequences of morbid obesity are more detrimental to the patients' health than neglected oral health care.

We located only one study looking into reasons why obese patients turn down treatment. Sadhasivam et al. found that the most frequent cause for not undergoing bariatric surgery was related to patients' financial coverage [3]. Consequently, this does not explain withdrawals experienced within our public health service where treatment is free of charge. Also, as this study was based on participants recruited from a bariatric clinic, it is likely that patients reluctant to undergo surgery were not referred to the clinic in the first place.

Although bariatric surgery is the recommended treatment for the most severely obese [4,5], Norwegian health authorities have instructed public hospitals with bariatric units also to provide non-surgical alternatives (i.e. lifestyle alteration). In our process of organising a comprehensive alternative to try to match gastric bypass, we found it necessary to learn more about patients' motivation for treatment. Recent research reveals an increased interest for obese patients' motivation with publications on topics including patients' expectations to and how patients value different treatment outcomes [6]; patients' reasons for wanting to loose weight [7—9]; and the possible link between motivation and treatment outcome [10]. However, literature provide only limited insight into why obese patients refuse treatment [3], and none at all on why they choose one treatment rather than another.

To shed light upon how patients' make their choices of therapy, we set an explorative study asking referred patients hypothetically to choose between these two very different, yet none the less comprehensive, treatments. The first alternative was the laparoscopic gastric bypass procedure. Alternatively, they were offered an extensive non-surgical lifestyle modification programme involving an 18-week stay at a clinic. Financially, the gastric bypass procedure and the 18-week stay at the clinic cost approximately the same. However, patients were not presented with these costs as inpatient medical treatment in Norway is largely free of charge.

Due to fundamental differences between these two treatments, we anticipated that patients opting for one treatment rather than another would show characteristic differences in motivation. Due to our occasional experience with patients reporting anxiety about the bariatric procedure, we also anticipated to find differences in psychological functioning. Accordingly, the research questions in this explorative study were (A) Do patients choosing the same treatment share mutual rationales? and (B) If not, do patients differ in outcomes on psychological measures according to different rationales?

Materials and methods

Setting and participants

In March 2005, 209 patients in Central Norway referred to the Obesity Clinic at St. Olavs University Hospital were asked to fill in a questionnaire

Table 1 Sample characteristics of participants ($N = 150$).

	N	Mean (SD)	%
Age		41.2 (10.5)	
Gender			
Female	111		74
BMI		47.2 (5.8)	
Obesity onset			
In childhood	105		70
In adulthood	40		27
Diet attempts (last 5 years)			
None	6		4
1—5 diets	68		45
6—10 diets	47		31
11 diets or more	21		14
Wanted EWL[a]			
Less than 50%	5		3
50—100%	103		69
More than 100%	29		19
Family			
Living alone/single	56		37
One or more children	108		72
Level of education			
Primary school	30		20
College/vocational training	84		56
University-level 1—3 years	26		17
University-level ≥4 years	10		7
Comorbidity history[b]			
Asthma	54		36
Arthritis	29		19
Diabetes	41		27
Heart disease	12		8
Hypertension	61		41
Sleep apnoea	24		16
Gall disease	26		17
Mental disorder	54		36
HADS[c]			
Anxiety, possible cases[d]	72		48
Depression, possible cases[e]	62		41
Total symptom intensity[f]		14.9 (7.7)	

[a] Excess weight loss; referring to a BMI of 25. Formula: $[(\text{weight} - \text{wished weight})/25(\text{height})^2]100$.
[b] Self-reported: ''Has a physician ever told you that you have any of these diseases?''.
[c] Hospital Anxiety and Depression Scale.
[d] HADS anxiety score ≥8.
[e] HADS depression score ≥8.
[f] HADS-total symptom score, HADS-T.

sent to them by post. One reminder was sent to non-responders. In all, 159 forms were returned yielding a response rate of 76%. Sample characteristics are summarised in Table 1. Nine participants were excluded, leaving a total of 150 participants. Reasons for exclusion from the study were (1) failure to express which treatment was wanted, (2) contradictory arguments (arguments favouring one treatment but choosing the other), or (3) prior history of bariatric surgery that might cause them to be biased. The study was approved by the Regional Committee for Research Ethics.

Measures

Participants were presented with information about gastric bypass surgery and an 18-week inpatient lifestyle programme. They were then asked, hypothetically, in a questionnaire to choose between ILP (Inpatient Lifestyle Programme) and LGB (Laparoscopic Gastric Bypass), as well as to list the grounds for their choice in an open-ended question. In addition, they also gave self-reported data on anthropometry (height, weight), sociodemography (educational level, marital status), comorbidity (checking for a list of diseases associated with obesity) and mental health applying HADS (the Hospital Anxiety and Depression Scale).

HADS

The Norwegian version of HADS has demonstrated good psychometric properties [11] and was used for assessing mental health. The instrument consists of fourteen questions sensitive for anxiety and depression [12]. Each question is followed by four possible responses which are summed according to Likert-scoring (0123). For our purpose we calculated the total score, indicating global emotional distress. Using HADS for screening purposes, there is reported good positive predictive value for any mental disorder using a cut-off of 17 or more [13].

Analysis

The study has a sequential exploratory design [14] combining qualitative and quantitative data. More specifically, the qualitative material was analysed thematically [15]. The quantitative data served as a basis for validation as well as giving grounds for hypothesis generation. Finally, the material from different data sources was integrated to make statistical computations possible (hypothesis testing). The process is schematically accounted for in Table 2.

Qualitative analysis

The participants' answers to the open-ended question about why they would choose LGB or ILP represented an extensive textual material, ranging from scant, concise answers consisting of only three words, up to long explanations of more than 150 words. The thematic analysis was performed by

Table 2 Process of analysis—a sequential exploratory study to investigate severely obese patients' motivation for either bariatric surgery or lifestyle intervention.

Step	Analysis	Description	Methodical strengths/weaknesses
Qualitative analysis	*Thematic analysis*: Mapping all different reasons for choice of treatment.	The qualitative material consisted of participants' answers to an open-ended question. The material was read repeatedly noting all aspects of motivation emerging from the data.	This trial combines qualitative and quantitative data from the same sample. The sample was bigger than normal for qualitative studies. As the field of interest was unexplored, this increases the chance of achieving thematic saturation.
	Reduction: Classification and condensation, leaving only one reason per participant	The reduction process involved disclosing the common themes in the reported aspects. While some participants reported only one reason, others reported several. Only one reason was kept per participant.	Reducing the complexity of motivation to only one reason per participant is oversimplifying human nature, yet it eases statistical inferences.
	Quantitising: Numerical representation	Themes emerging from the qualitative material were coded and entered into the statistical software.	As only one researcher analysed the qualitative data, inter-rater reliability tests and consensus making were not possible. Instead authors developed a protocol for theme selection.
Validation	*Comparison*: Does other data support the classifications of the qualitative material?	As some subgroups' motivation seemed to reflect symptoms of psychopathology, we calculated mean symptom scores for each subgroup using HADS. When ranging subgroups according to symptom intensity, a pattern emerged with higher scores for subgroups reporting psychological reasons for their choice, and lower scores for patients reporting mostly social reasons.	The quantitative material contained HADS. Bringing in a validated tool for psychometric measurement provided objective data as grounds for validations of the qualitative analysis.
Hypothesis	*Generating hypothesis*	The hypothesis *Symptoms of psychopathology influence upon choice of treatment* followed the validated qualitative analysis.	In this study there was no basis for making a questionnaire with pre-defined categories. The relatively large sample size and combination of qualitative and quantitative data, proved fruitful for completing an explorative study. The findings may give direction to an interview guide for in depth analysis of patients' reasoning as well as incorporating categories into a questionnaire allowing a better quantitative research design.
	Testing hypothesis	The null hypothesis *No significant differences in psychopathology between the subgroups* was rejected.	

Table 3 Treatment rationales with corresponding levels of psychological distress among participants preferring gastric bypass ($N = 102$), sorted by descending symptom scores.

Subgroup rationale with representative quotation	Caseness HADS-T[a] ≥17	Comparisons[b] HADS-T, mean (SD)	*p*
Rationale 1—*social reluctance* ($n = 4$)			
''I've got difficulties coping in groups of people. I also find it hard to deal without my wife and don't want to leave her.''	100%	23.8 (2.5)	
Rationale 2—*the permanent solution* ($n = 65$)			
''I loose weight easily. But I also gain it just that easy. I've tried every diet there is and consider surgery to be a better solution for me.''	36%	14.7 (7.5)	0.041
''The gastric bypass creates a physical constriction which prevents over eating.''			
Rationale 3—*familial considerations* ($n = 28$)			
''I'm a single parent for four small children. Some of them are ill. Their situation is too complex for leaving them into someone else's care.''	36%	14.2 (7.2)	0.037
Rationale 4—*work* ($n = 5$)			
''Autumn is high season for me at work. Participation in the lifestyle programme would cause a great economical loss that I cannot afford.''	20%	10.0 (9.2)	0.015

[a] HADS-T, Hospital Anxiety and Depression Scale, total score.
[b] Pairwise comparisons of mean scores using the subgroup with social reluctance as control. Method: Dunnett's test following one-way ANOVA: $F_{3,95} = 2.70$, $p = 0.050$.

the first author and was initially aimed at identifying all reasons behind treatment choice. Among the reasons, some common themes emerged. As some participants gave several reasons for their choice of treatment and the intention was to classify each participant according to his or her main argument, the authors setup a protocol for how this reduction should take place. According to this protocol the

Table 4 Treatment rationales with corresponding levels of psychological distress among participants preferring lifestyle treatment ($N = 36$), sorted by descending symptom scores.

Subgroup rationale with representative quotation	Caseness HADS-T[a] ≥17	Comparisons[b] HADS-T, mean (SD)	*p*
Rationale 1—*fear of anaeshesia* ($n = 4$)			
''I'm terrified of the surgery. I'm so obese that I'm afraid of dying during the procedure.''	100%	23.0 (3.4)	
Rationale 2—*fear of complications* ($n = 11$)			
''I fear that other diseases I have make the surgical procedure risky.''	46%	15.2 (7.2)	NS
Rationale 3—*normality* ($n = 14$)			
''I don't have any weight related physical afflictions, so I think it's possible for me to loose weight without surgery. But I lack the right attitude.''	23%	13.1 (5.7)	0.014
''I find surgery to be an excuse for doing nothing and should be the last resource if nothing else works.''			
Rationale 4—*followup* ($n = 7$)			
''Long term support is necessary to adapt a new lifestyle.''	14%	12.8 (1.8)	0.030

[a] HADS-T, Hospital Anxiety and Depression Scale, total score.
[b] Pairwise comparisons using the subgroup with procedure related anxiety as control. Method: Dunnett's test following one-way ANOVA: $F_{3,28} = 3.31$, $p = 0.034$.

first reason listed was decisive unless another reason clearly stood out as more important. The list of reasons served as basis for classification. Finally, the material was quantitised [16] i.e. coded numerically to enable statistical computations.

Statistical analysis

We conducted a contingency table test to see if men and women differed in choice of treatment. One-way ANOVA followed by Dunnett's post hoc tests were applied for multiple comparisons of mental symptom intensity between subgroups of participants to one control group, yet maintaining the family-wise error rate. Finally a contingency test followed by a test for trend was conducted to see if the number of diseases influenced patient motivation. Statistical analyses were performed using software (SPSS for Windows, Rel. 13.0. 2004. Chicago: SPSS Inc.). All statistical tests were two-tailed, with significance set at an α-level of 0.05.

Results

Sample characteristics are presented in Table 1. Thirty-two percent of the patients preferred lifestyle treatment over gastric bypass. There was no significant difference in choice of treatment between men and women ($\chi^2 = 0.078$, $p = 0.78$).

The qualitative material condensed into a total of nine different categories of arguments for treatment. Five of these were arguments for surgical treatment; denominated *Social Reluctance, A Permanent Solution, Familial Considerations*, *Work Situation,* and *Being Physically Disabled*, whereas four arguments promoted lifestyle therapy; *Fear of Anaesthesia, Fear of Complications, Desire for Normality*, and *Desire for Follow Up*. The participants were divided into subgroups according to these arguments. However, the five participants choosing surgery due to physical handicaps were not included in the further analysis since their treatment decision did not reflect motivational issues as much as physical functionality. Rationales as well as typical quotations for pro-surgery and pro-lifestyle participants are presented in Tables 3 and 4, respectively.

The qualitative analysis revealed two subgroups giving reasons for their choice of therapy which placed their mental health in question. In the pro-lifestyle category, this was the subgroup reporting death anxiety related to the surgical procedure, while in the pro-surgery category those strongly wanting to avoid social intimacy with other patients stood out. HADS-total, as an indicator of global emotional distress, was calculated for each subgroup to see if the score validated our interpretation of the qualitative data. In Tables 3 and 4, subgroups with their representative quotations are listed according to decreasing symptom intensity. In addition, the tables present data on probable caseness (in terms of any mental disorder) according to a cut-off score of 17 and higher.

In the case of participants oriented towards surgical treatment, statistical analysis showed symptom intensity to differ significantly between the subgroups (one-way ANOVA: $F_{3,95} = 2.70$, $p = 0.050$). Dunnett's test found significantly higher symptom scores among participants with social reluctance when compared to all other subgroups (Table 3). Concerning participants preferring lifestyle therapy, the analysis also showed these subgroups to differ significantly (one-way ANOVA: $F_{3,28} = 3.31$, $p = 0.034$), although here the subgroup fearing for complications from surgery did not differ statistically significantly from those afraid of dying during the procedure (Table 4). Three outliers were excluded from the lifestyle group before running the analysis.

Another finding in the qualitative data was that some patients reported positive motivation (i.e. choosing treatment A because they regarded treatment A as good for them) while others carried negative motivation (i.e. choosing treatment A to avoid treatment B). Typically, negatively motivated patients seeking lifestyle treatment often referred to how their disease would increase the risk of complications during surgery. On the other hand, negatively motivated patients seeking surgery often explained how diseases had made exercising difficult and consequently impaired their physical functionality. Finally, we did a statistical test to see if the number of diseases increased the risk of being negatively motivated and found a significant linear trend of medium association ($\chi^2 = 5.88$, $p = 0.015$; Cramer's $V = 0.22$, $p = 0.041$).

Discussion

Participants reported significantly different rationales for choosing the same type of treatment. The mental symptom scores varied according to rationale, supporting the view that the diverse rationales reflected distinctly different subgroups within which some have particular psychological problems that influence choice of treatment.

Thirty-two percent of the participants preferred a lifestyle alternative to bariatric surgery. There is reason to believe that the demand for treatments varies according to the specific therapy and how it is presented. It is worth noticing that at the time of this study, bariatric surgery was the standard treat-

ment offered by the Norwegian public healthcare system. Thus, the participants may have been in a process of mental preparedness, making an alternative choice to surgery less likely. This may bias the material in favour of bariatric surgery. However, this should not influence the described motivational traits which were the focus of this study.

Different reasons for same type of treatment

To our knowledge, no one has yet explored how motivation differs between obese people opting for different obesity treatments. Consequently, we had no basis for incorporating pre-defined response categories in a questionnaire. As to the different reasons reported (Tables 3 and 4), arguments varied widely. This suggests that a crude dichotomisation of the material into pro-lifestyle and pro-surgical treatment could conceal important patient characteristics. The sample's moderate size, later divided into no less than eight subgroups according to therapy rationale, produced some groups of very few participants. Nevertheless, as this was an explorative study, we chose to keep data divided into subgroups, although aware that this led to an unbalanced study design.

Mental health and its influence upon motivation for treatment

HADS is primarily a mental health screening instrument made for detecting possible/probable cases as well as assessing change in emotional state [12]. Thus, HADS is insufficient for diagnostic purposes. In our material, 40% were labelled 'possible cases' of mental disorder. Bearing in mind the general tendency of not seeking professional help for mental problems [17], the fact that 36% of the participants reported having at some time been diagnosed with mental disorder (Table 2) support the high HADS-scores.

When comparing symptom intensity of the two subgroups carrying highest scores to that of the other subgroups within their respective choice of treatment, most differences reached statistical significance (Tables 3 and 4). Accompanied by the qualitative data, this suggests that motivation for treatment can be a way to identify qualitatively different subgroups of obese patients. An earlier study investigating psychological underpinnings of the choice of therapy found no differences in psychopathology between patients seeking bariatric surgery and patients seeking a non-surgical treatment [18]. Our study has shown that mental health does vary according to choice of treatment, but requires analysis on a subgroup level.

Physical disease is in general correlated to impaired mental health [19], with severe obesity specially associated with increased risk of depression [20,21]. Based upon the degree of obesity as well as the number of comorbidities reported in this material, we expected high symptom scores. Participants reporting fear of dying during surgery (denominated *Fear of Anaesthesia*) scored considerably, yet statistically non-significantly, higher on symptom intensity than participants mainly afraid of complications from the procedure. Although the finding is statistically non-significant, we chose to include a comment as the qualitative data validated by the HADS clearly suggest two subgroups experiencing rather different types of worries about bariatric surgery: feeling some concern about possible complications from surgery may be a sign of soundness. However, when the fear of dying in the operating room excludes surgery as a potential treatment, the magnitude of this worry may be of a pathological character. By turning down obesity treatment, the patient is at high risk of serious comorbidities and decreased longevity. While fear of surgery and anaesthesia in general has been known for a long time [22], our findings suggest that in the field of bariatric surgery, this fear actually make patients refuse treatment.

In general, when assessing subgroups according to decreasing symptom intensity, a shift in motivation occurs from mainly psychological aspects (anxiety, fear, reluctance) to more social issues (working situation, family, follow up-services). It also illustrates that if anxiety is present, this may influence choice of therapy. However, in such cases, what therapy actually is preferred is determined by what triggers the anxiety.

In a recent study by Adams et al. [23], cause-specific mortality related to accidents and suicide were 58% higher among gastric bypass patients than among matched obese controls. While some psychological distress is expected to follow from the severe physical and psychosocial limitations of being obese, mental health and quality of life is found to improve with weight loss [24,25]. Even though Adams' findings probably reflect a subset of patients with more grave mental problems, it is clear that there is more to treating obesity than reducing weight. Psychological screening may help identifying both patients of poor mental health as well as those who need more guidance before entering a treatment programme. Today, there are no uniform guidelines for optimal psychological screening. Consequently, this is implemented differently across clinics [26]. Based upon the finding

from our study, the bariatric nurses at our clinic systematically ask new patients about their feelings on general anaesthesia as well as intimacy in group settings. Patients with such issues are referred to our psychologist.

Physical health and its influence upon motivation for treatment

In the qualitative material we also see the contours of a more superior trait, namely sign of motivation. The reported reasons appeared to be *either* positively or negatively oriented. By positive motivation we mean the wish to achieve something desirable based on the chosen treatment. This is self-evident and will not be exemplified. The opposite, denominated negative motivation, is primarily fuelled by the wish to avoid an undesirable treatment. The two subgroups that stood out with respect to poor mental health, i.e. participants with anxiety of the surgical procedure, and participants with a high level of social reluctance, are examples of carriers of negative motivation: they pick the lesser of two evils. Keeping in mind that all patients, independently of type of obesity treatment, sooner or later face challenges that threaten to reverse the modified behaviour, this particular subset of patients may be questioned as to their readiness to participate in treatment. Their motivation for treatment reveals a rather limited view on therapies that potentially provide life-long effects. Also, their strikingly high symptom scores underline the need to examine their motivation more thoroughly as it may express a more profound and possibly undetected mental health problem.

As negatively motivated patients often based their argument on obstacles caused by comorbidities, we found statistical evidence supportive of such a dichotomisation into positively or negatively motivation when testing whether the number of diseases influenced motivation. The psychological mechanism behind this could be that patients suffering from different diseases experience a shift in focus away from possibilities and over to disease driven limitations. Whether *negatively motivated* patients have poorer prospects in terms of weight loss, is yet to be determined. It is likely, however, that individual motivation is a key mechanism for maintaining the necessary alterations in diet and activity.

Consequence for trials comparing different treatments

Participants' reasons for choice of treatment were characterised by unambiguous rationales. Few participants showed signs of doubt, indicating that most were convinced as to what type of therapy would be best in their case. Such absolute certainty has implications for research designs when evaluating effects of lifestyle therapy compared to bariatric surgery. Unless there is a sufficient pool of patients indifferent to type of treatment, making a patient preference trial design possible [27], two considerations point against randomisation in comparative studies.

Firstly, as both bariatric surgery and lifestyle modification programmes require great personal efforts, randomising patients against their preferred choice increases the risk of non-compliance. Then, there is also an important ethical consideration: in general, patients should not be randomised to treatment they do not want when this therapy involves considerably higher risk of complications than other alternatives. In this case, gastric bypass clearly means a higher risk both for morbidity and mortality. This dilemma is recently also raised by Sjöström et al. [5]. Thus, in cases where patients already have made up their mind about what treatment they want, both methodical and ethical considerations point toward selection based on preferred choice rather than randomisation.

Conflicts of interest

No conflict of interest to declare.

References

[1] Berggren U, Meynert G. Dental fear and avoidance: causes, symptoms, and consequences. J Am Dent Assoc 1984;109:247—51.
[2] Nicolas E, Collado V, Faulks D, Bullier B, Hennequin M. A national cross-sectional survey of dental anxiety in the French adult population. BMC Oral Health 2007;7:12.
[3] Sadhasivam S, Larson CJ, Lambert PJ, Mathiason MA, Kothari SN. Refusals, denials, and patient choice: reasons prospective patients do not undergo bariatric surgery. Surg Obes Relat Dis 2007;3:531—5 [discussion: 5—6].
[4] Colquitt J, Clegg A, Loveman E, Royle P, Sidhu MK. Surgery for morbid obesity. Cochrane Database Syst Rev 2005:CD003641.
[5] Sjostrom L, Narbro K, Sjostrom CD, Karason K, Larsson B, Wedel H, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med 2007;357:741—52.
[6] Wee CC, Jones DB, Davis RB, Bourland AC, Hamel MB. Understanding patients' value of weight loss and expectations for bariatric surgery. Obes Surg 2006;16:496—500.
[7] Brink PJ, Ferguson K. The decision to lose weight. West J Nurs Res 1998;20:84—102.
[8] Munoz DJ, Lal M, Chen EY, Mansour M, Fischer S, Roehrig M, et al. Why patients seek bariatric surgery: a qualitative and quantitative analysis of patient motivation. Obes Surg 2007;17:1487—91.

[9] O'Brien K, Venn BJ, Perry T, Green TJ, Aitken W, Bradshaw A, et al. Reasons for wanting to lose weight: different strokes for different folks. Eat Behav 2007;8:132—5.
[10] Libeton M, Dixon JB, Laurie C, O'Brien PE. Patient motivation for bariatric surgery: characteristics and impact on outcomes. Obes Surg 2004;14:392—8.
[11] Mykletun A, Stordal E, Dahl AA. Hospital anxiety and depression (HAD) scale: factor structure, item analyses and internal consistency in a large population. Br J Psychiatry 2001;179:540—4.
[12] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361—70.
[13] Harter M, Woll S, Wunsch A, Bengel J, Reuter K. Screening for mental disorders in cancer, cardiovascular and musculoskeletal diseases. Comparison of HADS and GHQ-12. Soc Psychiatry Psychiatr Epidemiol 2006;41:56—62.
[14] Creswell JW, Clark VL, Gutmann ML, Hanson WE. Advanced mixed methods research designs. In: Tashakkori A, Teddlie C, editors. Handbook of mixed methods in social and behavioral research. Thousand Oaks, CA: Sage; 2003.
[15] Pope C, Mays N, Popay J. Synthesizing qualitative and quantitative health evidence. A guide to methods. Maidenhead, Berkshire: Open University Press; 2007.
[16] Teddlie C, Tashakkori A. Major issues and controversies in the use of mixed methods in the social and behavioral sciences. In: Tashakkori A, Teddlie C, editors. Handbook of mixed methods in social and behavioral research. Thousand Oaks, CA: Sage; 2003.
[17] Roness A, Mykletun A, Dahl AA. Help-seeking behaviour in patients with anxiety disorder and depression. Acta Psychiatr Scand 2005;111:51—8.
[18] Bancheri L, Patrizi B, Kotzalidis GD, Mosticoni S, Gargano T, Angrisani P, et al. Treatment choice and psychometric characteristics: differences between patients who choose bariatric surgical treatment and those who do not. Obes Surg 2006;16:1630—7.
[19] Yates WR. Epidemiology of psychiatric disorders in the medically ill. In: Robinson RG, Yates WR, editors. Psychiatric treatment of the medically ill. New York: Marcel Dekker; 1999.
[20] Dong C, Sanchez LE, Price RA. Relationship of obesity to depression: a family-based study. Int J Obes Relat Metab Disord 2004;28:790—5.
[21] Onyike CU, Crum RM, Lee HB, Lyketsos CG, Eaton WW. Is obesity associated with major depression? Results from the Third National Health and Nutrition Examination Survey. Am J Epidemiol 2003;158:1139—47.
[22] Regel H, Rose W, Hahnel S, Krause A. Evaluation of psychological stress before general anesthesia. Psychiatr Neurol Med Psychol (Leipz) 1985;37:151—5.
[23] Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, et al. Long-term mortality after gastric bypass surgery. N Engl J Med 2007;357:753—61.
[24] Kolotkin RL, Meter K, Williams GR. Quality of life and obesity. Obes Rev 2001;2:219—29.
[25] van Gemert WG, Severeijns RM, Greve JW, Groenman N, Soeters PB. Psychological functioning of morbidly obese patients after surgical treatment. Int J Obes Relat Metab Disord 1998;22:393—8.
[26] Bauchowitz AU, Gonder-Frederick LA, Olbrisch ME, Azarbad L, Ryee MY, Woodson M, et al. Psychosocial evaluation of bariatric surgery candidates: a survey of present practices. Psychosom Med 2005;67:825—32.
[27] Torgerson DJ, Sibbald B. Understanding controlled trials. What is a patient preference trial? BMJ 1998;316:360.

Paper III

Magnus Strømmen, Arne Helland, Bård Kulseng, Olav Spigset. ***Bioavailability of methadone after sleeve gastrectomy: A planned case observation.*** Clinical Therapeutics (2016) 38, 1532-1536
DOI: 10.1016/j.clinthera.2016.04.033

Case Report

Bioavailability of Methadone After Sleeve Gastrectomy: A Planned Case Observation

Magnus Strømmen, RN, MSc[1,2]; Arne Helland, MD[3,4]; Bård Kulseng, MD, PhD[1]; and Olav Spigset, MD, PhD[3,4]

[1]*Centre for Obesity Research, Clinic of Surgery, St. Olav University Hospital, Trondheim, Norway;* [2]*Department of Neuroscience, NTNU, Norwegian University of Science and Technology, Trondheim, Norway;* [3]*Department of Clinical Pharmacology, Clinic of Laboratory Medicine, St. Olav University Hospital, Trondheim, Norway; and* [4]*Department of Laboratory Medicine, Children's and Women's Health, NTNU, Norwegian University of Science and Technology, Trondheim, Norway*

ABSTRACT

Objective: Morbidly obese patients on opioid-replacement therapy may be at risk for treatment refusal with regard to bariatric surgery. However, patients on opioid replacement may have the personal skills to facilitate the lifestyle changes required for successful outcomes after bariatric surgery. This planned case observation assessed the effects of sleeve gastrectomy on the pharmacokinetic properties of methadone.

Methods: A white woman in her 40s on methadone maintenance therapy and with morbid obesity was referred for bariatric surgery. Serial blood samples for methadone concentration measurements were obtained before and at 5 days and 1, 7, and 11 months after surgery.

Findings: Serum methadone concentrations increased from before to 5 days after surgery and continued to increase for 7 months thereafter. The predose measurement at 11 months postoperatively suggests a further increase compared with the previous predose measurements.

Implications: Clinicians should beware the potential for altered effects of methadone after bariatric surgery. We recommend that serum concentrations be routinely measured pre- and postoperatively, and that the dose be adjusted according to these measurements and regular clinical assessments. (*Clin Ther.* 2016;38:1532–1536) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: bariatric surgery, methadone, opioid replacement, pharmacokinetics.

INTRODUCTION

Although there are no absolute contraindications to bariatric surgery,[1] most bariatric surgeons consider that patients with ongoing illicit drug use should not undergo such procedures.[2] The lack of clear recommendations within this field makes morbidly obese patients on opioid-replacement therapy a subgroup at risk for treatment refusal.

There is little evidence to provide guidance on these matters. Of the few relevant studies that exist, one found patients with past substance abuse to be at higher risk for dropout during the assessment process before bariatric surgery.[3] However, a study evaluating weight loss 2 years after gastric bypass found that patients who previously and successfully had participated in treatment for substance abuse (alcohol or drugs) achieved more weight loss compared with patients with no history of substance abuse.[4] The authors hypothesized that patients with such a history can gain valuable insight into personal skills relevant for lifestyle change, as well as draw strength from their experience with abstinence support programs.

Both preclinical and clinical studies have reported that chronic exposure to opioid μ-receptor agonists leads to sweet taste preference.[5] It is also known that patients

Accepted for publication April 19, 2016.
http://dx.doi.org/10.1016/j.clinthera.2016.04.033
0149-2918/$ - see front matter

entering methadone maintenance therapy gain weight: One study found that women 2 years into treatment had increased on average 17.5% in weight.[6] Consequently, occasional referrals of patients on methadone maintenance are likely to occur in bariatric clinics.

Clinicians may be reluctant to provide bariatric surgery in patients on opioid-replacement therapy, for fear of adverse outcomes. Uncertainties concerning the effects of the procedure on pharmacokinetics may contribute to such hesitation. Several mechanisms of bariatric surgery may influence the bioavailability of pharmaceuticals, such as shifts in gastric pH, changes in gastrointestinal transit time, reduced absorptive surface area, and altered presystemic drug metabolism. The effects of bariatric surgery on pharmacokinetic properties are known for only a few medications.[7] Neither methadone nor buprenorphine, the drugs most commonly used for opioid-replacement therapy, are among these.

This planned case observation is the first systematic evaluation of the possible effects of sleeve gastrectomy on methadone pharmacokinetics.

CASE DESCRIPTION

A white woman in her 40s on methadone maintenance therapy and with morbid obesity was referred for bariatric surgery at a Norwegian university hospital. She had a 27-year history of illicit drug abuse and had injected heroin for 10 years before she entered a rehabilitation program that included opioid-replacement therapy with methadone ~10 years before presentation. After starting methadone therapy, she had gained ~30 kg in weight. At referral to hospital, her height was 159 cm, her weight was 127.8 kg, and her body mass index (BMI) was 50.6 kg/m^2. She presented with multiple complications of morbid obesity, including type 2 diabetes mellitus, obstructive sleep apnea, and depression. She also had hyperparathyroidism and was hepatitis B and C positive. In addition to methadone 120 mg/d (a dose that had been stable for several years), her drug therapy consisted of metformin 1600 mg/d and sitagliptin 100 mg/d for diabetes, fesoterodine 16 mg/d for urinary incontinence, pregabalin 900 mg/d for neuralgia, and lactulose as needed for constipation.

The patient underwent a multidisciplinary review, including a psychiatric assessment, in the bariatric clinic. She was informed about the lack of scientific evidence concerning the effects on the pharmacokinetic properties of methadone, and provided written consent to undergo surgery, including being followed up for 15 years for the evaluation of long-term effects. The authors also received approval for performing the study from the regional ethics committee. After completing a mandatory patient-education program, the patient was scheduled for laparoscopic sleeve gastrectomy and followed a liquid very-low-calorie diet the 3 weeks before surgery.

The patient's preoperative weight and BMI were 117.0 kg and 46.3 kg/m^2. Surgery took place with the patient under general anesthesia, and the patient had an epidural catheter placed for postoperative pain relief. The need for epidural analgesia prolonged her hospitalization, extending the regular stay of 1 to 2 days to 8 days. She received her regular dose of 120 mg methadone both on the day of surgery and on the subsequent in-hospital days.

One year after surgery, her weight and BMI had decreased to 92.1 kg and 36.4 kg/m^2, respectively, representing a 46.3% loss of her excess weight (using the upper BMI limit for normal weight, i.e. 25 kg/m^2, as reference). Her physical functioning had improved and she had stopped taking antidiabetic medication. The methadone dose was kept unchanged at 120 mg/d throughout the first postoperative year.

Serial blood samples for methadone concentration measurements were obtained at 8 days preoperatively, as well as at 5 days, 1 month, and 7 months postoperatively. Sampling took place at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, and 24 hours after methadone ingestion. Moreover, a single sample was obtained 24 hours after methadone ingestion at 11 months postoperatively. Serum concentrations of total methadone as well as of its enantiomers *R*-methadone and *S*-methadone were measured with an LC/MS method developed at our laboratory.[8] Key pharmacokinetic variables of methadone were calculated by means of the pharmacokinetic analysis software package Kinetica version 5.0 (Thermo Scientific, Waltham, Massachusetts). The patient was genotyped for the cytochrome P-450 (CYP) enzymes CYP2B6, CYP3A4, and CYP3A5, which are involved in the metabolism of methadone,[9] by allele-specific polymerase chain reaction (PCR).[10,11]

RESULTS

The time–concentration curve of methadone in this patient is presented in the Figure. In general, the serum concentrations of methadone were increased from the sampling preoperatively to 5 days postoperatively,

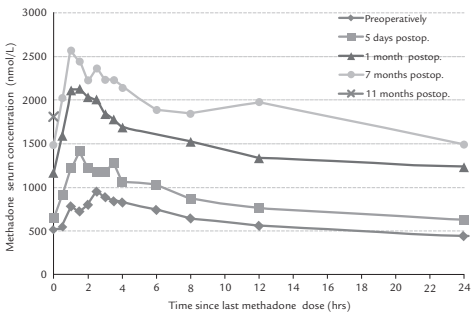


Figure. Serum concentrations of methadone in a woman undergoing bariatric surgery by sleeve gastrectomy.

and continued to increase during the first 7 months after surgery. The single predose measurement 11 months postoperatively suggested a further increase compared with the previous predose measurements. Key pharmacokinetic data are presented in the Table.

The AUC of the active enantiomer *R*-methadone increased less than did that of total methadone, with 14%, 114%, and 163% increases at 5 days, 1 month, and 7 months after surgery, respectively. In accordance with this finding, the proportion of *R*-methadone of the total methadone concentration decreased sharply shortly after surgery, and then remained stable. The proportions of *R*-methadone of the total methadone concentration were 76% at t_0 and 62% at T_{max} preoperatively, and 65% at t_0 and 52% at T_{max} postoperatively. Genotyping revealed the following genotypes: CYP2B6, *1/*1; CYP3A4, *1/*1; and CYP3A5, *1/*3.

As methadone is known to prolong the QT interval on ECG in a dose-related manner, increasing the risk for torsades de pointes ventricular tachycardia,[8] we obtained pre- and postoperative ECGs. Immediately preoperatively, the QT interval corrected for heart rate (QTc) was 425 ms, whereas it was 435 ms at 10 months postoperatively.

DISCUSSION

In this planned case observation, we observed marked changes in the pharmacokinetic properties of methadone after the patient had undergone sleeve gastrectomy, with a large increase in drug exposure and a shorter T_{max} compared with baseline. The total drug exposure, as expressed by the AUC, increased progressively throughout the postoperative period, and 7 months postoperatively it was 3-fold the baseline value. This large increase can be explained only by a substantially greater bioavailability. The T_{max} decreased from 2.5 hours before surgery to 1 hour at 7 months after surgery. The $t_{1/2}$ increased slightly immediately postoperatively, then it remained stable. The active enantiomer, *R*-methadone, showed similar changes, but to a somewhat lesser extent.

In most patients, methadone bioavailability is >80%; thus, the overall potential for increased bioavailability of methadone would be expected to be low and generally not exceed a 20% increase. However, a large interindividual variability in bioavailability, with values ranging from 36% to 100%, has been described.[9] Genotyping showed that the patient had the CYP3A5 *1/*3 genotype, signifying an increased metabolic capacity for CYP3A substrates such as methadone compared with the general white population.[12] In patients expressing active CYP3A5, the presence of this enzyme increases the presystemic metabolism of CYP3A substrates, leading to lesser bioavailability.[12] This finding is in accordance with the low preoperative serum concentration of methadone in the present patient (a concentration below the 10th percentile among patients taking a dose of 120 mg/d, according to unpublished data from our laboratory's therapeutic drug monitoring database, 2015). The potential for large increases in the bioavailability of drugs metabolized by CYP3A after bariatric surgery, particularly in patients who express active CYP3A5, has been reported previously for atorvastatin.[13]

Sleeve gastrectomy decreases gastric volume without inducing malabsorption. No portion of the small intestine is bypassed, and the pyloric function remains intact.[14] Thus, it may seem surprising that such a procedure could dramatically influence drug bioavailability. Logically, because no part of the intestine is removed or bypassed, the amount of CYP3A in the intestinal wall and thus the extent of presystemic metabolism would be expected to be unaffected. However, sleeve gastrectomy is associated with a more rapid emptying of gastric contents into the intestine after ingestion,[15] a phenomenon often referred to as "dumping." The decrease in T_{max} confirms the occurrence of this mechanism in our

Table. Pharmacokinetic variables based on the concentrations of total ($R + S$) methadone and of the active enantiomer *R*-methadone in a woman undergoing bariatric surgery with sleeve gastrectomy.

Parameter	Preoperatively (Baseline)	Postoperative Day 5	Postoperative Month 1	Postoperative Month 7
Total ($R + S$) methadone				
C_0, nmol/L	508	645	1166	1481
C_{max}, nmol/L	945	1414	2128	2564
C_{max}/C_0 ratio	1.86	2.19	1.82	1.73
T_{max}, h	2.5	1.5	1.5	1.0
AUC_{0-24}, nmol/L × h	14,368	20,198	34,920	44,983
AUC_{0-24}, % increase*	0	41	143	213
$t_{½}$, h	29.3	36.5	37.1	37.2
R-methadone				
C_0, nmol/L	402	423	766	940
C_{max}, nmol/L	616	748	1206	1379
C_{max}/C_0 ratio	1.53	1.77	1.57	1.47
T_{max}, h	2.5	1.5	1.5	1.0
AUC_{0-24}, nmol/L × h	10,453	11,946	22,401	27,460
AUC_{0-24}, % increase*	0	14	114	163
$t_{½}$, h	43.9	48.4	59.4	54.8

*Compared to AUC_{0-24} preoperatively.

patient. Rapid gastric emptying after sleeve gastrectomy may lead to a substantially greater drug concentration in the duodenum after methadone intake. We hypothesize that the increased drug concentration may overwhelm CYP3A enzyme capacity in the intestinal wall and possibly also during the first pass through the liver, causing a higher proportion of the drug to reach the systemic circulation.

Other possible explanations for the observed pharmacokinetic changes should be taken into consideration. Systemic inflammation may downregulate the expression of both CYP enzymes and drug transporters such as p-glycoprotein and increase the plasma concentration of the acute phase protein α_1-acid glycoprotein, to which methadone is highly bound.[9] Such changes may possibly have contributed to the increased serum concentration of methadone immediately postoperatively. However, this concept cannot explain the further increases in methadone concentration during the subsequent months. Moreover, we cannot rule out the possibility that inadequate medication adherence contributed to the observed changes. However, because the methadone concentrations at t_0 and t_{24} were almost identical in all 4 sample series, nonadherence does not seem likely. The patient's considerable weight loss has reduced the total volume of distribution of the methadone. However, as the concentration at steady state is primarily related to clearance and not to the volume of distribution, the key question is whether a weight loss like this could reduce clearance, such as via a decrease in liver mass. The patient's lean body mass was reduced by 9.3% from 1 to 7 months postoperatively. Even if the total liver mass would be expected to have decreased by the same order of magnitude, we consider that the contribution of such an effect would explain only a small part of the observed increases in the methadone concentration. Finally, to our knowledge, the patient did not at any point use medications known to influence CYP3A metabolism, which could otherwise have influenced the pharmacokinetic properties of methadone.

Pre- and postoperative ECGs did not reveal a significant increase in the QT interval; however, the risk for QT prolongation in such patients should definitively be borne in mind as it is a known dose-dependent adverse effect of methadone.[8] A higher and more rapidly occurring peak concentration might increase the rewarding and intoxicating effects of methadone, which could be detrimental in previous addicts, and might even cause respiratory depression. Unfortunately, we do not have systematic clinical observations of the patient during the postoperative period.

CONCLUSION

We conclude that sleeve gastrectomy has the potential to significantly increase the bioavailability of and decrease the T_{max} of methadone, probably due to accelerated gastric emptying. This finding especially applies to individuals with a low preoperative bioavailability, such as that caused by genetically determined or pharmacologically induced increased CYP3A metabolism. Clinicians should beware the potential for altered drug effects of methadone after bariatric surgery. We recommend that serum concentrations be routinely measured pre- and postoperatively, and that the dose be adjusted according to these measurements and regular clinical assessments.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

ACKNOWLEDGMENT

We thank the staff at the Clinical Research Facility at St. Olav University Hospital, Trondheim, Norway, for clinical and technical support. There were no external sources of funding.

REFERENCES

1. SAGES Guidelines Committee. SAGES guideline for clinical application of laparoscopic bariatric surgery. *Surg Endosc*. 2008;22:2281–2300.
2. Bauchowitz AU, Gonder-Frederick LA, Olbrisch ME, et al. Psychosocial evaluation of bariatric surgery candidates: a survey of present practices. *Psychosom Med*. 2005;67:825–832.
3. Sockalingam S, Cassin S, Crawford SA, et al. Psychiatric predictors of surgery non-completion following suitability assessment for bariatric surgery. *Obes Surg*. 2013;23:205–211.
4. Clark MM, Balsiger BM, Sletten CD, et al. Psychosocial factors and 2-year outcome following bariatric surgery for weight loss. *Obes Surg*. 2003;13:739–745.
5. Mysels DJ, Sullivan MA. The relationship between opioid and sugar intake: Review of evidence and clinical applications. *J Opioid Manag*. 2010;6:445–452.
6. Fenn JM, Laurent JS, Sigmon SC. Increases in body mass index following initiation of methadone treatment. *J Subst Abuse Treat*. 2015;51:59–63.
7. Edwards A, Ensom MH. Pharmacokinetic effects of bariatric surgery. *Ann Pharmacother*. 2012;46:130–136.
8. Stallvik M, Nordstrand B, Kristensen O, et al. Corrected QT interval during treatment with methadone and buprenorphine — relation to doses and serum concentrations. *Drug Alcohol Depend*. 2013;129:88–93.
9. Kapur BM, Hutson JR, Chibber T, et al. Methadone: a review of drug-drug and pathophysiological interactions. *Crit Rev Clin Lab Sci*. 2011;48:171–195.
10. Crettol S, Deglon JJ, Besson J, et al. Methadone enantiomer plasma levels, CYP2B6, CYP2C19, and CYP2C9 genotypes, and response to treatment. *Clin Pharmacol Ther*. 2005;78:593–604.
11. Lunde I, Bremer S, Midtvedt K, et al. The influence of CYP3A, PPARA, and POR genetic variants on the pharmacokinetics of tacrolimus and cyclosporine in renal transplant recipients. *Eur J Clin Pharmacol*. 2014;70:685–693.
12. De Fazio S, Gallelli L, De Siena A, et al. Role of CYP3A5 in abnormal clearance of methadone. *Ann Pharmacother*. 2008;42:893–897.
13. Skottheim IB, Jakobsen GS, Stormark K, et al. Significant increase in systemic exposure of atorvastatin after biliopancreatic diversion with duodenal switch. *Clin Pharmacol Ther*. 2010;87:699–705.
14. Stefater MA, Wilson-Pérez HE, Chambers AP, et al. All bariatric surgeries are not created equal: insights from mechanistic comparisons. *Endocr Rev*. 2012;33:595–622.
15. Melissas J, Leventi A, Klinaki I, et al. Alterations of global gastrointestinal motility after sleeve gastrectomy: a prospective study. *Ann Surg*. 2013;258:976–982.

Address correspondence to: Magnus Strømmen, RN, MSc, Centre for Obesity Research, Clinic of Surgery, St. Olav University Hospital, PO Box 3250 Sluppen, Trondheim 7006, Norway. E-mail: magnus.strommen@stolav.no

Paper IV

Magnus Strømmen, Inger Johanne Bakken, Christian A Klöckner, Jorunn Sandvik, Bård Kulseng, Are Holen. ***Diagnoses related to abuse of alcohol and addictive substances after gastric bypass and sleeve gastrectomy – A Nation-Wide Registry Study from Norway*.**
Surgery for Obesity and Related Diseases (2020) 16, 464-470
DOI: 10.1016/j.soard.2019.12.011

ELSEVIER

SURGERY FOR OBESITY AND RELATED DISEASES

Surgery for Obesity and Related Diseases 16 (2020) 464–470

Original article

Diagnoses related to abuse of alcohol and addictive substances after gastric bypass and sleeve gastrectomy: a nation-wide registry study from Norway

Magnus Strømmen, M.Sc.[a,b,*], Inger Johanne Bakken, Ph.D.[c], Christian Klöckner, Ph.D.[a,d], Jorunn Sandvik, M.D.[a,e,f], Bård Kulseng, M.D., Ph.D.[a,f], Are Holen, M.D., Ph.D.[b]

[a]*Centre for Obesity Research, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway*
[b]*Department of Mental Health, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway*
[c]*Centre for Fertility and Health, Norwegian Institute of Public Health, Oslo, Norway*
[d]*Department of Psychology, Faculty of Social and Educational Sciences, Norwegian University of Science and Technology, Trondheim, Norway*
[e]*Clinic of Medicine and Rehabilitation, Møre and Romsdal Hospital Trust, Ålesund, Norway*
[f]*Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway*

Received 29 May 2019; accepted 6 December 2019

Abstract

Background: After Roux-en-Y gastric bypass (RYGB) patients are at higher risk of alcohol problems. In recent years, sleeve gastrectomy (SG) has become a common procedure, but the incidence rates (IRs) of alcohol abuse after SG are unexplored.

Objectives: To compare IRs of diagnoses indicating problems with alcohol or other substances between patients having undergone SG or RYGB with a minimum of 6-month follow-up.

Setting: All government funded hospitals in Norway providing bariatric surgery.

Methods: A retrospective population-based cohort study based on data from the Norwegian Patient Registry. The outcomes were ICD-10 of Diseases and Related Health Problems diagnoses relating to alcohol (F10) and other substances (F11–F19).

Results: The registry provided data on 10,208 patients who underwent either RYGB or SG during the years 2008 to 2014 with a total postoperative observation time of 33,352 person-years. This corresponds to 8196 patients with RYGB (27,846 person-yr, average 3.4 yr) and 2012 patients with SG (5506 person-yr; average 2.7 yr). The IR for the diagnoses related to alcohol problems after RYGB was 6.36 (95% confidence interval: 5.45–7.36) per 1000 person-years and 4.54 (2.94–6.70) after SG. When controlling for age and sex, adjusted hazard ratio was .75 (.49–1.14) for SG compared with RYGB. When combining both bariatric procedures, women <26 years were more likely to have alcohol-related diagnoses (3.2%, 2.1–4.4) than women of 26 to 40 years (1.6%, 1.1–2.1) or women >40 (1.3%, .9–1.7). The IR after RYGB for the diagnoses related to problems with substances other than alcohol was 3.48 (95% confidence interval: 2.82–4.25) compared with 3.27 (1.94–5.17) per 1000 person-years after SG. Controlling for age and sex, the hazard ratio was .99 (.60–1.64) for SG compared with RYGB.

Conclusions: In our study, procedure-specific differences were not found in the risks (RYGB versus SG) for postoperative diagnoses related to problems with alcohol and other substances within the available observation time. A longer observation period seems required to explore these findings

St. Olavs Hospital, Trondheim University Hospital, Norway, funded the study.

*Correspondence: Magnus Strømmen, P.O. Box 3250 Torgarden, N-7030 Trondheim, Norway.

E-mail address: magnus.strommen@stolav.no (M. Strømmen).

https://doi.org/10.1016/j.soard.2019.12.011

further. (Surg Obes Relat Dis 2020;16:464–470.)

Key words: Bariatric surgery; Gastric bypass; Sleeve gastrectomy; Alcohol; Addiction

For obesity, bariatric surgery is superior in terms of weight loss compared with nonsurgical interventions [1]. For most patients, surgery effectively relieves or resolves co-morbid diseases [2]. Worldwide, surgical weight loss operations have doubled from 2008 to 2016 [3], and are likely to increase further in the future. Consequently, more people will be at risk for late complications.

One such complication is alcohol problems. Patients with the Roux-en-Y gastric bypass (RYGB) in abuse treatment programs report higher alcohol intake than nonbariatric patients [4]. Compared with patients with gastric banding, RYGB patients have been found to increase their alcohol consumption after surgery [5,6], they have more symptoms of alcohol use disorder [5] and higher risk for being in alcohol abuse treatment after surgery [7]. Such findings suggest alcohol problems after surgery may be a procedure-specific complication.

Recently, increased dopamine sensitivity due to hormonal effects of RYGB, have been proposed as a possible explanation for alcohol abuse [8]. Besides this direct effect on the brain, a number of studies have shown that the RYGB modifies the bioavailability of ethanol as follows: the C_{max} (maximum serum concentration) is significantly elevated [9–11], and furthermore, the t_{max} (time for reaching C_{max}) is reduced [12]. Normally, ethanol undergoes a presystemic metabolism in the gastrointestinal tract due to gastric mucosal alcohol dehydrogenase activity [13]. RYGB seems to potentiate ethanol toxicity via impaired first-pass metabolism.

The 2 most common bariatric procedures today are RYGB and sleeve gastrectomy (SG) [3]. The existing data on SG and its effects on ethanol bioavailability are inconclusive. Two studies found the peak alcohol concentration to increase significantly after SG [14,15], although similar changes were not observed in other studies [16,17].

Despite high numbers of surgical procedures, no published data exists so far on procedure-specific associations between SG and diagnoses related to abuse of alcohol or other substances. The main aim of this study was to compare the incidence rates (IRs) of diagnoses related to abuse of alcohol and other substances after SG or RYGB. Also, we explored potential links between age and sex to abuse diagnoses independent of surgical procedure.

Methods

This is a retrospective, population-based cohort study based on comprehensive data from the Norwegian Patient Registry (NPR), a national database covering somatic and mental health services. All hospitals and clinics reimbursed by the government report their diagnoses to NPR. For bariatric surgery, approximately two thirds of the operations in Norway are performed in such hospitals.

The population was defined using the Nordic Medico-Statistical Committee Classification of Surgical Procedures (NCSP) published by the Nordic Medico-Statistical Committee. There were 11,392 adult patients in Norway registered with the NCSP-codes JFD (intestinal bypass operations) and JDF (bariatric operations on stomach) from 2008 to 2014. Due to invalid personal identification numbers, 25 patients were excluded, leaving a total of 11,367 patients with 515,432 hospitalizations or outpatient consultations.

The sample was further reduced to patients with the specific NCSP-codes JDF10/11 (RYGB), JDF96/97 (SG), and JFD03/04 (duodenoileal bypass with duodenal switch), leaving out other kinds of surgeries (n = 163). Due to the small number of biliopancreatic diversions in the observation period (n = 121), patients with codes JFD03/04 were excluded. Patients with 2 different bariatric surgeries on the same day (n = 35) were also excluded. Finally, for the calculation of IRs, we excluded patients with <6 months follow-up time after surgery (n = 840) and patients who had their first diagnosis related to alcohol or other substances during these first 6 months (alcohol: n = 6; other substances: n = 5). This left us with 10,208 patients who underwent either RYGB (n = 8196) or SG (n = 2012) in Norway within the targeted time frame.

Regarding abuse categories, the first category included patients ‘registered with an alcohol-related diagnosis’, that is, the F10*-diagnoses (mental and behavioral disorders due to alcohol). A few patients were also included with other diagnoses indirectly indicating alcohol problems, including G62.1 (alcoholic polyneuropathy), K29.2 (alcoholic gastritis), K70 (alcoholic liver disease), K86.0 (alcohol-induced chronic pancreatitis), Z71.4 (alcohol abuse counseling and surveillance), and Z72.1 (problems related to alcohol use).

The second category ‘registered with other substance-related diagnoses’ included F11* to F19*, except F17* (tobacco). There are several reasons to leave tobacco out. Despite the addictive properties of nicotine, it has a limited effect on the central nervous system compared with the other substances in the category. Thus, categorizing tobacco

together with much heavier substances would render the interpretation of the data more difficult. Furthermore, the use of tobacco is legal and available without strict regulations, and considering the social acceptance for tobacco, we assume that physicians to a large degree do not register F17 diagnoses.

The sample was divided into the following 3 age cohorts: patients 18 to 25 years (n = 684) representing the youngest patients and a period often involving experimentation with alcohol and other addictive substances; patients 26 to 40 years (n = 3974), a phase when settling down and often starting a family; and patients >40 years (n = 6390). In addition to age, sex was also included in the analyses. The NPR did not provide data on other potential confounders or covariates.

Ethical approval for using registry data was obtained from the Regional Committee for Medical and Health Research Ethics in Central Norway (ref. 2015/1473). The identity of the individuals in the sample were never available to the researchers.

Analysis

Differences between age groups and sex were calculated by analysis of variance with Games-Howell post hoc tests. IR for those registered with relevant diagnoses were the number of cases divided by observation time (person-yr at risk). Crude hazard ratios (HR) were calculated by dividing IR of SG by the corresponding IR for RYGB (reference category). An inspection of log-minus-log survival curves did not indicate violation of the proportional hazards assumption, allowing the use of Cox regression to estimate the HR adjusted for age and sex. The patients were followed either until a reported event of registered alcohol abuse (model 1), or a reported event of other substance abuse (model 2), time of death, or end of observation period (December 31, 2014), whichever occurred first. Risk estimates were calculated with 95% confidence intervals (CI). The analyses were done with SPSS version 23 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA).

Results

The total annual number of bariatric procedures doubled from 2008 to 2014 from 957 to 1955 procedures (RYGB and SG). However, the frequencies of the different procedures developed differently. While the number of SG increased by 678% (from 91 to 708 procedures), RYGB rose only by 44% (from 866 to 1247 procedures). The frequency of the duodenal switch gradually tapered off during the observation period (from 43 to 4 procedures).

The total postoperative observation time for those with bariatric surgery was 33,352 years (see Table 1). Average postoperative observation time for RYGB was 3.4 and 2.7 years for SG. Women represented 72.4% of the total sample. Mean age (standard deviation) was 42.5 (10.4) years. There was high consistency (99.4%) between NCSP codes used to define the sample and the expected 10th revision of the International Statistical Classification of Diseases and Related Health Problems code E66*.

Diagnoses related to alcohol and other substances

From January 1, 2008 until the time of surgery, 67 patients were registered with alcohol-related diagnoses and 83 with diagnoses related to other substances. From the time of surgery until December 31, 2014, 202 patients were assigned alcohol diagnoses. This corresponds to a postoperative IR of 6.06 per 1000 person-years for alcohol diagnoses. In the same period 115 were assigned diagnoses related to other substances, corresponding to a postoperative IR of 3.45 per 1000 person-years. The different postoperative substance diagnoses (number of patients) were F11-opioids (76); F12-cannabinoids (19); F13-sedatives/hypnotics (70); F14-cocaine (1); F15-other stimulants (35); F16-hallucinogens (1); F17-tobacco (17); F18-volatile solvents (1); and F19-multiple drug use (43).

Age and sex

We first tested the impact of age and sex independent of type of surgery. The omnibus test for analysis of variance indicated that age influenced the risk for alcohol diagnoses for women ($F_{2,7418} = 6.257$, $P = .002$). The difference in risk did, however, not reach statistical significance in the post hoc analyses (Games-Howell test) when comparing women <26 years (3.5%, 95%CI: 2.3–4.7) to women 26 to 40 years old (1.7%, 1.2–2.2, $P = .096$). Neither was there any difference between the women 26 to 40 years old and women >40 (1.4%, .9–1.8, $P = .504$). For the analysis of the youngest age group compared with those >40, the difference reached statistical significance ($P = .034$). For men, the omnibus test indicated no significant differences between the different age groups ($F_{2,2841} = .957$, $P = .384$) as follows: men <26 years (3.5%, 1.2–5.8); men 26 to 40 years (2.3%, 1.3–3.2); and men >40 (3.2%, 2.5–3.8). However, alcohol-related diagnoses were more frequent among men >40 years compared with women of the same age ($F_{1,5905} = 22.163$, $P < .001$).

Whereas the omnibus tests indicated that age influenced the risk for diagnoses related to substances other than alcohol (women: $F_{2,7401} = 4.915$, $P = .007$; men: $F_{2,2849} = 6.432$, $P = .002$), the post hoc tests did not support such differences statistically. The following comparisons were done: women <26 years (2.3%, 1.3–3.2) compared with women 26 to 40 years (1.4%, 1.0–1.8, $P = .453$), and with women >40 (.9%, .5–1.2, $P = .107$); and women 26 to 40 years old with women >40 years ($P = .092$). And for men, <26 years (2.8%, 1.1–4.6) with men 26 to 40 years (1.7%, 1.0–2.4, $P = .704$) and men >40 years

Table 1
Incidence rates per 1000 person-years (IR) and hazard ratios (HR) with associated 95% confidence intervals (CI) for patients registered with diagnoses related to alcohol or other substances after Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) in hospitals covered by the Norwegian National Insurance Scheme in the years 2008–2014 (n = 10,208)

Covariate	Surgical procedure	Person-years at risk	Alcohol							Other substances						
			Cases	Overall		Crude		Adjusted†		Cases	Overall		Crude		Adjusted†	
				IR	(95%CI)	HR*	(95%CI)	HR (*P*)	(95%CI)		IR	(95%CI)	HR*	(95%CI)	HR (*P*)	(95%CI)
Total																
	Both procedures	33,352	202	6.06	(5.23–6.95)					115	3.45	(2.85–4.14)				
	RYGB (n = 8196)	27,846	177	6.36	(5.45–7.36)	1.00				97	3.48	(2.82–4.25)	1.00			
	SG (n = 2012)	5506	25	4.54	(2.94–6.70)	.71	(.45–1.09)	.75 (.182)	(.49–1.14)	18	3.27	(1.94–5.17)	.94	(.53–1.56)	.99 (.969)	(.60–1.64)
Sex																
Men	RYGB (n = 2254)	8085	73	9.03	(7.08–11.35)	1.00				22	2.74	(1.71–4.12)	1.00			
	SG (n = 543)	1605	9	5.61	(2.56–10.64)	.62	(.27–1.24)	.66 (.234)	(.33–1.32)	6	3.74	(1.37–8.14)	1.37	(.46–3.49)	1.31 (.562)	(.52–3.28)
Women	RYGB (n = 5898)	19,762	104	5.26	(4.30–6.38)	1.00				75	3.80	(2.99–4.76)	1.00			
	SG (n = 1453)	3901	16	4.10	(2.34–6.66)	.78	(.43–1.33)	.82 (.455)	(.48–1.39)	12	3.08	(1.59–5.37)	.81	(.40–1.50)	.89 (.698)	(.48–1.63)
Age																
<26 yr	RYGB (n = 454)	1463	20	13.67	(8.35–21.11)	1.00				11	7.52	(3.75–13.45)	1.00			
	SG (n = 169)	450	2	4.44	(.54–16.05)	.33	(.04–1.34)	.36 (.168)	(.08–1.54)	4	8.89	(2.42–22.76)	1.18	(.27–3.99)	1.40 (.568)	(.44–4.46)
26–40 yr	RYGB (n = 2995)	10,638	55	5.17	(3.89–6.73)	1.00				46	4.32	(3.17–5.77)	1.00			
	SG (n = 701)	2006	11	5.48	(2.74–9.81)	1.06	(.50–2.05)	1.14 (.697)	(.59–2.18)	9	4.49	(2.05–8.52)	1.04	(.45–2.15)	1.12 (.757)	(.55–2.30)
>40 yr	RYGB (n = 4703)	15,746	102	6.48	(5.28–7.86)	1.00				40	2.54	(1.81–3.46)	1.00			
	SG (n = 1126)	3050	12	3.93	(2.03–6.87)	.61	(.30–1.11)	.66 (.116)	(.36–1.20)	5	1.64	(.53–3.83)	.65	(.20–1.64)	.69 (.442)	(.27–1.76)

* RYGB as reference category.
† Adjusted for the covariates sex and/or age.

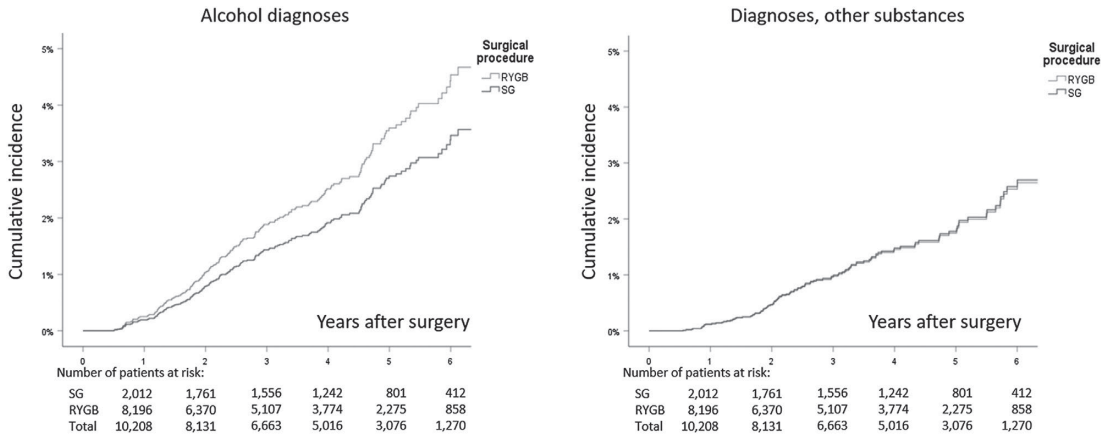


Fig. 1. Kaplan-Meier failure curves for time of registration with diagnoses related to alcohol (left) and substances other than alcohol (right), divided by surgical procedure. RYGB = Roux-en-Y gastric bypass; SG = sleeve gastrectomy.

(.5%, .1–1.0, $P = .237$); and, last, men 26 to 40 years old compared with men >40 years ($P = .045$).

Diagnoses by operation method

The Kaplan-Meier curves in Fig. 1 illustrate the cumulative incidences for diagnoses related to alcohol and other substances. For alcohol, the curves visually indicate that RYGB involved a higher risk for alcohol diagnoses than SG. The difference in risks was, however, not supported statistically as the adjusted HR of .71 for patients undergoing SG compared with RYGB was nonsignificant (95%CI: .45–1.09) (see Table 1). For other substances, the Kaplan-Meier curve gave no visual indication of difference in risk for diagnoses dependent on type of surgery. The HR for patients undergoing SG compared with RYGB was .94 (95% CI: .53–1.56).

Discussion

This study is the first to compare IR of diagnoses related to abuse of alcohol and other substances after SG and RYGB. It was based on comprehensive registry data from 10,208 patients who have undergone RYGB or SG in Norway. There were no procedure-specific differences in risks for diagnoses related to problems with alcohol or other substances within the 33,352 years of observation time. After bariatric surgery, alcohol diagnoses were more frequent among women <26 years compared with older women. In patients >40 years, men showed higher risks for alcohol diagnoses than women.

Primary outcome: abuse-related diagnoses

Clinicians and patients share a common interest in knowing potential complications related to surgical procedures. Therefore, we aimed to investigate if there were procedure-specific differences in the risks for diagnoses related to alcohol abuse or of other substances after RYGB and SG. However, the higher incidence of alcohol-related diagnoses after RYGB compared with SG, was not statistically significant. However, it is notable how the Kaplan-Meier curves for RYGB and SG diverge with time with alcohol diagnoses occurring more frequently among RYGB patients.

Both because surgery probably causes permanent changes in ethanol bioavailability, and because previous studies have shown that alcohol problems increases with time since surgery [5], a longer observation period may be required to conclude with more certainty whether RYGB and SG involve different risks. Östlund et al. [7], with their study on admission for alcohol dependence, did find a significant increased risk in RYGB patients compared with patients with a restrictive procedure. This study, however, had a substantially longer follow-up time (8.6 yr). Furthermore, in terms of ethanol and bioavailability, RYGB and SG may be physiologically more similar than RYGB and the restrictive procedures in the Swedish study.

The frequency of bariatric surgery increased from 2008 to 2014; most patients had their surgery toward the end of the observation period. Accordingly, our data contain a rather short postoperative observation time. During the observation period there was a shift in surgical procedures from almost exclusively RYGB toward more SG, while the duodenal switch phased out. This makes a skewed curve and RYGB constitutes 83% of the total observation time.

An abuse-related diagnosis in a data material only covering approximately 3 years of follow-up time indicates several circumstances. First, abuse emerged shortly after surgery. Moreover, the patient must have used health services in which the patient or the physician chose to bring up the issue. Postoperative alcohol use disorder was first

addressed in the medical guidelines for bariatric surgery in 2008 [18]. Hence, several years after this, many clinicians may not have been aware of the association between bariatric surgery and alcohol abuse. Consequently, this topic may not have been emphasized enough in the patient education and clinicians may not actively have been looking for symptoms of abuse. For the patients experiencing alcohol problems, lacking the understanding of the association while also feeling shame, could have made help-seeking difficult. Although patient education and alcohol screening both pre- and postsurgery are recommended [19], the quality of the information and types of screening varies between clinics. If these assumptions are reasonable, our study likely underestimates the true incidence of abuse problems.

Other factors may also contribute to the underreporting of alcohol problems. Only a minority of those with alcohol problems seek adequate treatment [20]. The associated stigma and the belief that these problems should be managed by oneself, are likely contributing factors [21]. The National Epidemiologic Survey on Alcohol and Related Conditions found <12% with a lifetime history of alcohol use disorders had ever used professional treatment. On average, it took 4 years from onset of alcohol use disorders to treatment [20], which exceeds our postoperative observation time. Several factors support the notion that IRs of diagnoses grossly underestimate the magnitude of alcohol problems. However, this would not influence the HR when comparing the 2 procedures, as we are not aware of any systematic differences between the patient groups having undergone RYGB and SG.

On the other side, patients may also develop alcohol problems independent of surgery. And there may be patients with alcohol problems before or even present at the time of surgery who were assigned their first diagnosis in the follow-up period. By excluding patients who had their first alcohol diagnosis registered during the first 6 months after surgery, we tried to prevent that such cases inflated the IR.

Several studies have found RYGB to increase the risk of postsurgery alcohol problems both compared with those treated with restrictive surgery [5,7,22] and controls [23]. Our study suggests that RYGB and SG may involve similar risks for alcohol-related complications, although our findings shed no light on the underlying mechanisms. There are strong indications that RYGB and SG have some common key physiologic effects despite surgical and anatomic dissimilarities [24].

Secondary outcome: differences in age and sex

Younger women had higher risks for obtaining alcohol diagnoses than older women, which is in line with a previous study, which found younger age to be a predictor of postoperative alcohol use disorder [25]. Hazardous drinking behavior is more common among younger people, with heavier drinking in a single session and drinking until intoxication [26]. We also speculate whether an impaired ability to self-regulate in general could be a stronger obesity-driving factor among people with early- compared with late-onset obesity. Unfortunately, the NPR provide no information on at what time in life patients put on weight.

Higher risks for alcohol diagnoses observed among the young after surgery may reflect more partaking in social situations involving alcohol. As bariatric surgery may potentiate intoxication of ethanol [9–11], pharmacologic effects of surgery may limit significantly the drinking capacity of young operated persons. Social consequences of weight loss may complicate this further as patients may explore new social arenas where alcohol is common. Both lack of experience with drinking and insufficient knowledge about the pharmacologic effects of surgery, make young patients more prone to intoxications.

Strengths and limitations

To our knowledge, this is the first national-based registry study comparing risks for abuse-related diagnoses after SG to RYGB. By using nation-wide registry data, we could follow patients' treatments and additional diagnoses in the public healthcare system. There was high concordance between codes for treatment and the relevant disease diagnoses; this supports the validity of our findings.

One limitation is that alcohol disorders are generally difficult to detect, and registry data on such diagnoses underestimates the magnitude of alcohol problems, particularly the first years after onset.

Our data start in 2008, which prevents calculations of pre- versus postoperative HRs as this would require data at least back to the patients' adolescence. Thus, our data give no support to say whether bariatric surgery per se increases the risk of abuse diagnoses.

As studies show increased drinking behavior during the second postoperative year [5,6,22], our observation period should ideally have been longer. Moreover, change in surgical procedures led to major differences in the number of RYGB observation years compared with SG.

The merging of all nonalcohol substances into 1 single category may conceal details related to particular types of substances; low numbers of cases left insufficient opportunity for further analyses.

This study had no control group, which would have eased the interpretation of the findings.

Conclusion

This study contributes to the understanding of the postoperative complications of bariatric surgery. Based on the observation time available, our data give no clear support for recommending one type of surgery to reduce risks of postoperative abuse. However, a longer observation period seems warranted to conclude with more certainty whether RYGB and SG involve different risks.

Alcohol is the most prevalent substance of abuse. Hence, screening for alcohol use should be a regular part of the patient care pre- and postsurgery. Accordingly, the duration of the follow-up should be long enough to ensure that alcohol problems are adequately identified and treated.

Acknowledgments

Data from the NPR have been used in this publication. The interpretation and reporting of data are the sole responsibility of the authors, and no endorsement by the NPR is intended or should be inferred.

Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

References

[1] Colquitt J, Pickett K, Loveman E, Frampton GK. Surgery for weight loss in adults. Cochrane Database Syst Rev 2014;8(8):CD003641.
[2] Lopes EC, Heineck I, Athaydes G, Meinhardt NG, Souto KE, Stein AT. Is bariatric surgery effective in reducing comorbidities and drug costs? A systematic review and meta-analysis. Obes Surg 2015;25(9):1741–9.
[3] Angrisani L, Santonicola A, Iovino P, et al. IFSO worldwide survey 2016: primary, endoluminal, and revisional procedures. Obes Surg 2018;28(12):3783–94.
[4] Saules KK, Wiedemann AA, Ivezaj V, Hopper JA, Foster-Hartsfield J, Schwarz D. Bariatric surgery history among substance abuse treatment patients: prevalence and associated features. Surg Obes Relat Dis 2010;6(6):615–21.
[5] King WC, Chen JY, Courcoulas AP, et al. Alcohol and other substance use after bariatric surgery: prospective evidence from a U.S. multicenter cohort study. Surg Obes Relat Dis 2017;13(8):1392–402.
[6] Svensson PA, Anveden A, Romeo S, et al. Alcohol consumption and alcohol problems after bariatric surgery in the Swedish Obese Subjects (SOS) study. Obesity (Silver Spring) 2013;21(12):2444–51.
[7] Östlund MP, Backman O, Marsk R, et al. Increased admission for alcohol dependence after gastric bypass surgery compared with restrictive surgery. JAMA Surg 2013;148(4):374–7.
[8] Polston JE, Pritchett CE, Tomasko JM, et al. Roux-en-Y gastric bypass increases intravenous ethanol self-administration in dietary obese rats. PloS One 2013;8(12):e83741.
[9] Hagedorn JC, Encarnacion B, Brat GA, Morton JM. Does gastric bypass alter alcohol metabolism? Surg Obes Relat Dis 2007;3(5):543–8; discussion 548.
[10] Klockhoff H, Naslund I, Jones AW. Faster absorption of ethanol and higher peak concentration in women after gastric bypass surgery. Br J Clin Pharmacol 2002;54(6):587–91.
[11] Woodard GA, Downey J, Hernandez-Boussard T, Morton JM. Impaired alcohol metabolism after gastric bypass surgery - a case-crossover trial. J Am Coll Surg 2011;212(2):209–14.
[12] Steffen KJ, Engel SG, Pollert GA, Cao L, Mitchell JE. Blood alcohol concentrations rise rapidly and dramatically after Roux-en-Y gastric bypass. Surg Obes Relat Dis 2013;9(13):470–3.
[13] Frezza M, Padova Cd, Pozzato G, Terpin M, Baranova E, Lieber C. High blood alcohol levels in women. The role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. N Engl J Med 1990;322(2):95–9.
[14] Acevedo MB, Eagon JC, Bartholow BD, Klein S, Bucholz KK, Pepino MY. Sleeve gastrectomy surgery: when 2 two alcoholic drinks are converted to 4. Surg Obes Relat Dis 2018;14:277–83.
[15] Maluenda F, Csendes A, De Aretxabala X, et al. Alcohol absorption modification after a laparoscopic sleeve gastrectomy due to obesity. Obes Surg 2010;20(6):744–8.
[16] Changchien EM, Woodard GA, Hernandez-Boussard T, Morton JM. Normal alcohol metabolism after gastric banding and sleeve gastrectomy: a case-cross-over trial. J Am Coll Surg 2012;215(4):475–9.
[17] Gallo AS, Berducci MA, Nijhawan S, et al. Alcohol metabolism is not affected by sleeve gastrectomy. Surg Endosc 2015;29(5):1088–93.
[18] Mechanick JI, Kushner RF, Sugerman HJ, et al. American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery Medical Guidelines for Clinical Practice for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient. Surg Obes Relat Dis 2008;4(5 Suppl):S109–84.
[19] Parikh M, Johnson JM, Ballem N. ASMBS Position statement on alcohol use before and after bariatric surgery. Surg Obes Relat Dis 2016;12(2):225–30.
[20] Cohen E, Feinn R, Arias A, Kranzler HR. Alcohol treatment utilization: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. Drug Alcohol Depend 2007;86(2-3):214–21.
[21] Wallhed Finn S, Bakshi AS, Andreasson S. Alcohol consumption, dependence, and treatment barriers: perceptions among nontreatment seekers with alcohol dependence. Subst Use Misuse 2014;49(6):762–9.
[22] Conason A, Teixeira J, Hsu CH, Puma L, Knafo D, Geliebter A. Substance use following bariatric weight loss surgery. JAMA Surg 2013;148(2):145–50.
[23] Backman O, Stockeld D, Rasmussen F, Naslund E, Marsk R. Alcohol and substance abuse, depression and suicide attempts after Roux-en-Y gastric bypass surgery. Br J Surg 2016;103(10):1136–42.
[24] Stefater MA, Wilson-Pérez HE, Chambers AP, Sandoval DA, Seeley RJ. All bariatric surgeries are not created equal: insights from mechanistic comparisons. Endocr Rev 2012;33(4):595–622.
[25] King WC, Chen J-Y, Mitchell JE, et al. Prevalence of alcohol use disorders before and after bariatric surgery. JAMA 2012;307(23):2516–25.
[26] Bauman A, Phongsavan P. Epidemiology of substance use in adolescence: prevalence, trends and policy implications. Drug Alcohol Depend 1999;55(3):187–207.

Begrepsbruk

Tenk deg følgende situasjon:
Du er hos fastlegen for en ordinær kontroll. Dette skjedde for du ble henvist til overvektssenteret for behandling av overvekt. Fastlegen ønsker denne dagen, på eget initiativ, å snakke med deg om din overvekt og konsekvensene dette kan ha for din helse. Du har ikke snakket med fastlegen om overvekt tidligere.

Bakgrunnen for at vi henvender oss til dere om dette er at vi ønsker å klargjøre hva overvektige selv opplever er en ok måte å formulere dette på. Siden enkelte uttrykk for overvekt kan oppleves støtende, kan måten man ordlegger seg på ha betydning for dialogen videre. Begrepene i eksemplene nedenfor er alle foreslått av overvektige selv.

Sett ett kryss pr linje som uttrykker hvordan du opplever legens formulering.

Fastlegen sier: "I dag vil jeg gjerne snakke med deg om …"

	Svært passende	Passende	Verken eller	Upassende	Svært upassende	
"…din overvekt"	☐	☐	☐	☐	☐	
"…ditt vektproblem"	☐	☐	☐	☐	☐	
"…din BMI"	☐	☐	☐	☐	☐	
"…din høye BMI"	☐	☐	☐	☐	☐	
"…din fedme"	☐	☐	☐	☐	☐	
"…din sykelige overvekt"	☐	☐	☐	☐	☐	
"…din obesitas"	☐	☐	☐	☐	☐	
"…din overflødige vekt"	☐	☐	☐	☐	☐	**SNU ARKET!**

	Svært passende	Passende	Verken eller	Upassende	Svært upassende
"…at du er for tung"	☐	☐	☐	☐	☐
"…at du er fet"	☐	☐	☐	☐	☐
"…at du er feit"	☐	☐	☐	☐	☐
"…at du er for tykk"	☐	☐	☐	☐	☐
"…at du er for kraftig"	☐	☐	☐	☐	☐
"…vekten din"	☐	☐	☐	☐	☐

	Ja	Nei	Vet ikke
Har legens måte å formulere seg på betydning for din relasjon til legen?	☐	☐	☐
Mener du det er riktig at *fastlegen tar initiativ* til å drøfte dette?	☐	☐	☐
Mener du det er riktig om *fastlegen aldri* gjør overvekt til et tema?	☐	☐	☐
Stemmer det med din erfaring at fastlegen tar opp dette på eget initiativ?	☐	☐	☐

	Svært passende	Passende	Verken eller	Upassende	Svært upassende
Hvis ja, hvordan opplevde du det?	☐	☐	☐	☐	☐

ERRATA (1)

25th of August 2020 the managing editor of Surgery for Obesity and Related Disorders was informed about an error in Table 1, Paper IV. I recommended to update the online version with a revised table and this text: "We regret to inform that there is an error in Table 1: The age and sex cohorts do not add up to the total sample (N=10,208). This is corrected now."

Table 1: Incidence rates per 1,000 person-years (IR) and hazard ratios (HR) with associated 95% confidence intervals (CI) for patients registered with diagnoses related to alcohol or other substances following Roux-n-Y Gastric Bypass (RYGB) or Sleeve Gastrectomy (SG) in hospitals covered by the Norwegian National Insurance Scheme in the years 2008-2014. (N=10,208)

Covariate	Surgical procedure	Person-years at risk	Alcohol							Other substances						
			Cases	IR/95% CI		Crude HR[a]/95% CI		Adjusted[b] HR(p)/95% CI		Cases	IR/95% CI		Crude HR[a]/95% CI		Adjusted[b] HR(p)/95% CI	
Total																
	Both procedures	33,352	202	6.06	(5.23 – 6.95)					115	3.45	(2.85 – 4.14)				
	RYGB (N=8,196)	27,846	177	6.36	(5.45 – 7.36)	1.00				97	3.48	(2.82 – 4.25)	1.00			
	SG (N=2,012)	5,506	25	4.54	(2.94 – 6.70)	0.71	(0.45 – 1.09)	0.75 (.182)	(0.49 – 1.14)	18	3.27	(1.94 – 5.17)	0.94	(0.53 – 1.56)	0.99 (.969)	(0.60 – 1.64)
Sex																
Men	RYGB (N=2,272)	8,085	73	9.03	(7.08 – 11.35)	1.00				22	2.74	(1.71 – 4.12)	1.00			
	SG (N=548)	1,605	9	5.61	(2.56 – 10.64)	0.62	(0.27 – 1.24)	0.66 (.234)	(0.33 – 1.32)	6	3.74	(1.37 – 8.14)	1.37	(0.46 – 3.49)	1.31 (.562)	(0.52 – 3.28)
Women	RYGB (N=5,924)	19,762	104	5.26	(4.30 – 6.38)	1.00				75	3.80	(2.99 – 4.76)	1.00			
	SG (N=1,464)	3,901	16	4.10	(2.34 – 6.66)	0.78	(0.43 – 1.33)	0.82 (.455)	(0.48 – 1.39)	12	3.08	(1.59 – 5.37)	0.81	(0.40 – 1.50)	0.89 (.698)	(0.48 – 1.63)
Age																
< 26 years	RYGB (N=456)	1,463	20	13.67	(8.35 – 21.11)	1.00				11	7.52	(3.75 – 13.45)	1.00			
	SG (N=170)	450	2	4.44	(0.54 – 16.05)	0.33	(0.04 – 1,34)	0.36 (.168)	(0.08 – 1.54)	4	8.89	(2.42 – 22.76)	1.18	(0.27 – 3.99)	1.40 (.568)	(0.44 – 4.46)
26-40 years	RYGB (N=3,011)	10,638	55	5.17	(3.89 – 6.73)	1.00				46	4.32	(3.17 – 5.77)	1.00			
	SG (N=708)	2,006	11	5.48	(2.74 – 9.81)	1.06	(0.50 – 2.05)	1.14 (.697)	(0.59 – 2.18)	9	4.49	(2.05 – 8.52)	1.04	(0.45 – 2.15)	1.12 (.757)	(0.55 – 2.30)
>40 years	RYGB (N=4,729)	15,746	102	6.48	(5.28 – 7.86)	1.00				40	2.54	(1.81 – 3.46)	1.00			
	SG (N=1,134)	3,050	12	3.93	(2.03 – 6.87)	0.61	(0.30 – 1.11)	0.66 (.116)	(0.36 – 1.20)	5	1.64	(0.53 – 3.83)	0.65	(0.20 – 1.64)	0.69 (.442)	(0.27 – 1.76)

IR=incidence rate; HR=hazard ratio; CI=confidence interval; RYGB=Roux-n-Y gastric bypass; SG=sleeve gastrectomy

[a] RYGB as reference category; [b] Adjusted for the covariates sex and/or age

ISBN 978-82-326-6109-1 (printed ver.)
ISBN 978-82-326-6236-4 (electronic ver.)
ISSN 1503-8181 (printed ver.)
ISSN 2703-8084 (online ver.)

NTNU
Norwegian University of
Science and Technology