Promoting energy balance related behavior after transplantation

BALANCE

Promoting energy balance related behavior after liver transplantation:

Development of a behavioral intervention based on physical activity and diet to support effective weight management and a healthy lifestyle - A multiphase mixed method research program

Inaugural dissertation

to

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Chapter 4 has been published as study protocol. The final results will be submitted to a scientific journal.

Chapter 6 will be submitted to a scientific journal.

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List of Abbreviations

AUROC	Area Under the Receiver Operating Characteristic Curve
BMI	Body Mass Index
CCM	Chronic Care Model
CI	Confidence Interval
CSA	Cyclosporine
CVE	Cardiovascular Events
GWAS	Genome Wide Association Study
HR	Hazard Ratio
IQR	Interquartile Range
LTx	Liver Transplantation
MELD	Model for End-Stage Liver Disease
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NODAT	New Onset Diabetes after Transplant
OR	Odds Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSQ	Psychosocial Questionnaire
SD	Standard deviation
STCS	Swiss Transplant Cohort Study
SNP	Single nucleotide polymorphisms
TAC	Tacrolimus
Tx	Transplantation
UK	United Kingdom
US	United States
WHO	World Health Organization
w-GRS	weighted genetic risk scores

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Sonja Beckmann, 2017

Summary

Obesity has become a global health concern not only in the general population but also among liver transplant (Tx) recipients. For more than 2 decades, rates of obesity in liver Tx candidates have been rising;[1] and post-Tx weight gain is contributing to a rising prevalence of post-Tx obesity in this group compared to pre-Tx measurements.[2-4]

While obesity predicts morbidity and mortality in the general population,[5-8] this relationship has not been reported consistently in liver Tx recipients. Regarding the impact of pre- and post-Tx obesity on metabolic or cardiovascular comorbidities, current evidence is mixed.[9-11] However, the few studies examining post-Tx weight gain found that it increased the burden of disease and predicted both nonalcoholic fatty liver disease[12,13] and metabolic syndrome.[12,14]

Metabolic syndrome occurs in 44% to 58% of liver Tx recipients,[12] contributing to an increased risk of cardiovascular disease and mortality.[12] Indeed, cardiovascular events (CVEs) are a leading cause of mortality after liver Tx.[15-18] And while first-year post-Tx patient and graft survival rates have been increasing steadily for decades, long-term outcomes have not echoed these improvements.[19] This progress gap is attributed partly to the post-Tx development of comorbidities such as hypertension, diabetes, and dyslipidemia–due largely to the side effects of long-term immunosuppressive medication intake accompanied by lifestyle factors (e.g., physical inactivity, unhealthy eating).[12,14,20-22]

To reduce post-Tx morbidity risks, the Tx community has called for action to tackle weight gain and obesity via lifestyle interventions.[22-25] Expressed as a deceptively simple equation, weight gain most commonly results from an energy imbalance whereby energy intake surpasses energy expenditure.[26] Although a web of interconnected variables are involved, behavioral factors related to energy balance, such as physical activity and diet, are among the most influential and can be targeted via interventions. Intervention research on this topic is rare regarding the liver Tx population. To date, only one study has tested an intervention using individual counseling on exercise and diet after liver Tx;[27] however, its authors did not examine the intervention's impact in relation to weight gain prevention.

The systematic development of a behavioral weight management intervention is no easy task: such interventions are typically complex, and should be informed by a theoretical model.[28,29] However, the crucial first step in developing any behavioral intervention is to build a sound understanding and definition of the problem in behavioral

terms. Also, in the context of weight gain after liver Tx, two clinical questions remain unanswered: “How important is the prevention of weight gain after Tx?” and “Which factors are related to weight gain and obesity after Tx?”

The overall aim of this dissertation was to generate evidence to answer these questions and facilitate the development of a behavioral intervention focusing on physical activity and diet to support effective post-Tx weight management. To achieve this aim, this dissertation was designed as a multiphase mixed method research project including three data analyses of the prospective nationwide Swiss Transplant Cohort Study (STCS), and one systematic review with meta-analysis. The results (summarized below) promise to facilitate evidence-based decision-making towards the development of a behavioral intervention to prevent post-Tx weight gain.

Body weight parameters vary considerably among solid organ Tx populations and geographical regions. However, a rigorous comparison of these parameters’ evolution between organ groups and throughout the course of Tx is limited due to methodological and terminological differences between the relevant studies (e.g., single center versus database studies, different timeframes for follow up measures, diverse operational definitions). Therefore, to compare all solid organ Tx populations concurrently, we conducted a descriptive longitudinal study **(Chapter 3)** using data from the STCS, a prospective nationwide cohort study. The STCS’s long-term prospective design allowed comparison of weight change patterns among organ groups and among patients in different body mass index (BMI) categories to assess weight parameters in relation to settings and patient groups. Changes in weight and BMI category were compared to the reference values at 6 months post-Tx.

We included 1359 adult kidney (58.3%), liver (21.7%), lung (11.6%), and heart (8.4%) recipients. Compared to data on international Tx groups, the majority of our Swiss Tx recipients had lower post-Tx weight gain. However, their cumulative incidence of obesity at 3 years after kidney, liver, lung, and heart Tx was 18.1%, 38.1%, 15.3%, and 13.3%, respectively. At 3 years post-Tx, in relation to their BMI categories at 6 months, normal weight and obese liver Tx patients, followed by underweight kidney, lung and heart Tx patients, showed the greatest weight gains. Compared to all other organ groups, liver Tx recipients showed both the greatest weight gain (mean 4.8 ± 10.4 kg), with 57.4% gaining >5% of their body weight, and the highest incidence of obesity (38.1%). Although weight gain patterns varied both within and across organ Tx groups, long-term monitoring of weight is indicated in all solid organ Tx populations to prevent weight gain leading to obesity.

Weight gain and obesity are the result of complex interactions between genetic, sociodemographic, behavioral, biomedical, psychological, and environmental factors. Therefore, a clear knowledge of factors influencing weight gain and other body weight parameters in Tx is important in view of tailoring interventions to avoid or modify these factors. As weight gain in this group has never been the subject of a systematic review, though, evidence on risk factors in the liver Tx population remains non-explicit. In our systematic review **(Chapter 4)**, then, we summarized the available evidence in view of factors associated with post-liver Tx BMI, obesity, and weight gain. Meta-analysis techniques were applied to relationships investigated at least 5 times. Of the 16495 articles retrieved, 43 assessed risk factors for body weight parameters. These identified a total of 82 separate factors, most of which either biomedical (e.g., etiology of liver disease, metabolic comorbidities before liver Tx) or sociodemographic (e.g., age, gender, pre- and post-Tx education).

In view of energy balance-related behaviors, not one of the 43 retrieved studies examined eating behavior; but 4 examined physical activity in relation to BMI or obesity after liver Tx. Overall, extensive variation in risk factor definitions limited the combination of factors to groups of at least 5 studies. The final meta-analyses focused on two risk factors–tacrolimus and cyclosporine–in 6 studies (median sample size: n = 171 (range: 63–455); 3 from Europe, 3 from the United States; publication era: 1997 – 2015). Post-Tx obesity was neither significantly associated with tacrolimus (odds ratio (OR), 0.75; 95% confidence interval (CI), 0.47-1.21; p = 0.24) nor cyclosporine (OR, 1.40; 95% CI, 0.89-2.18; p = 0.14). Evidence on factors related to post-liver Tx body weight parameters is still limited and warrants further investigation. It is recommended that future research be guided by theoretical frameworks to facilitate a systematic examination of interrelationships among selected factors.

Genetic factors also interact with clinical and psychosocial variables. To examine associations between weighted genetic risk scores and BMI up to 1 year after Tx **(Chapter 5)**, we studied 2 patient samples. Sample A (n = 995) consisted of kidney, liver, heart, lung and multi-organ Tx patients from the STCS; sample B (n = 156) included only kidney, liver and lung Tx patients enrolled between 2003 and 2005 from the Tx center of the University Hospital of Lausanne. Calculation of genetic risk scores used data on Tx candidate genes and single nucleotide polymorphisms (SNPs) associated with BMI in genome-wide association studies. Classified by the number of BMI risk alleles identified (range: 0 – 2), the genotypes were coded as 0, 1 or 2. Based on the assumption that each SNP effects BMI separately, SNPs were then weighted by

allele effect (β-coefficient), leading to the calculation of the final weighted genetic risk score.

The weighted genetic risk scores were associated with BMI increase for each additional risk allele in both samples (p-values < 0.008). Additionally, compared to the models incorporating no genetic factors, those using genetic risk scores better predicted weight gain at 1 year post-Tx. This result highlights the complexity of weight gain and the importance of incorporating a range of factors that influence post-Tx weight gain. Further research will be necessary to examine the genetic risk score and post-Tx body weight parameters in relation to patient outcomes.

In addition to studying weight gain per se, we examined the impact of new-onset obesity on cardiovascular events (CVEs) and patient survival to identify related post-liver Tx sociodemographic, behavioral, biomedical, psychological and genetic risk factors **(Chapter 6).** Based on STCS data on 253 liver Tx patients, the cumulative incidence of new-onset obesity was 21.3%, while that of CVE was 28.1%. Independent of the CVE status at liver Tx, risk factors for post-Tx CVEs were new-onset obesity (Hazard Ratio (HR) 2.95; 95% CI, 1.47-5.95; p = 0.002) and higher age at liver Tx (HR, 1.05; 95% CI, 1.02-1.08; p < 0.001). In patients without pre-Tx CVEs (n = 214), risk factors for post-Tx CVEs also included new-onset obesity (HR, 2.59; 95% CI, 1.21-5.53; p = 0.014) and higher age (HR, 1.04; 95% CI, 1.02-1.07; p = 0.001). However, survival itself was not associated with new-onset obesity (HR, 0.84; 95% CI, 0.34-2.04; p = 0.696). Independent predictors of new-onset obesity were male gender (HR, 0.39; 95% CI, 0.16-0.93; p = 0.034) and alcoholic liver disease (HR, 3.37; 95% CI, 1.17-9.71; p = 0.025). The genetic risk score was available in a subsample of 114 patients. In this analysis, male gender (HR, 0.26; 95% CI, 0.076-0.889; p = 0.032) and the genetic risk score (HR, 21.83; 95% CI, 1.50-317.64; p = 0.024) predicted new-onset obesity. Given the link between new-onset obesity and CVEs, the prevention of new-onset obesity by effective early weight management programs could probably lead to improved post-Tx cardiovascular outcomes.

In conjunction with the existing evidence, the findings of this dissertation contributed to the development of a behavioral weight management intervention. The COM-B model and the behavior change wheel served as theoretical guidance.[28,29] While COM-B is an explanatory model, characterizing the sources of behavior (i.e., capability, opportunity, and motivation), the behavior change wheel informed the intervention's systematic development and evaluation. Beginning with a theoretical introduction, **Chapter 7** follows the three stages of the behavior change wheel, leading to the suggestion of the BALANCE intervention in the liver Tx population.

In conclusion, this dissertation contributed to the evidence base regarding weight gain and obesity after solid organ Tx. For the first time, we simultaneously compared the evolution of body weight parameters up to 3 years after kidney, liver, heart and lung Tx to identify patterns of interest among these four populations. By studying the impact of new-onset obesity on cardiovascular morbidity and patient survival after liver Tx, we increased the limited evidence on the impact of post-Tx body weight parameters on patient health outcomes. In 3 studies, all guided by our theoretical framework, we systematically examined biomedical, behavioral, sociodemographic, psychological and genetic risk factors leading to weight gain, obesity and new onset obesity after Tx, thereby highlighting the cross-category interplay of factors. These studies' findings highlighted various implications for future research and clinical practice. Based on these findings, we recommend organizing post-Tx follow-up care based on a chronic care model, supported by eHealth technology. Such a care model has the potential not only to support effective weight management, but also to improve long-term patient outcomes.

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Chapter 1. Introduction

1.1 Obesity – a global epidemic

The term *globesity* expresses the magnitude of obesity, which has become a global public health issue in recent decades.[1,2] Based on age-standardized estimates for national and global obesity rates, between 1980 and 2013, Ng et al. reported that the number of overweight and obese adults (≥20 years) increased from 857 million to 2.1 billion over that 33-year period.[3]

The geographic differences are particularly noteworthy. In 2013, about one-third of the population of the United States (US) (female: 33.9%; male: 31.6%) were obese, with a slightly higher prevalence among women. In Central, Western and Eastern Europe, obesity was also more prevalent in women (20.7% - 21%) compared to men (14.8% - 20.5%), while in Switzerland the estimates for women and men were 17% and 18.4%, respectively. A 2017 report from the Organization for Economic Co-operation and Development (OECD) projected an increasing prevalence of obesity until at least 2030.[1] While obesity rates in Switzerland are low by global standards, they are expected to increase faster than other countries.

As a simple and easily comparable classification of body weight, the World Health Organization (WHO) proposed the body mass index (BMI). This is calculated by dividing a person's weight in kilograms by the square of their height in meters, i.e., kg/m^2. The WHO's BMI categories are: underweight (<18.5 kg/m^2), normal weight (18.5 – 24.9 kg/m^2), overweight (25 – 29.9 kg/m^2), and obese (≥30 kg/m^2). Obesity can be further differentiated into class I (30 – 34.9 kg/m^2), class II (34.9 – 39.9 kg/m^2), and class (III ≥40 kg/m^2).[4] As BMI is easy to determine, it is the most commonly used classification system for body weight not only in clinical practice but also in research.

Accounting for age, sex and race-ethnicity, the BMI corresponds well to the percentage of body fat;[5] however, certain shortcomings limit its use in severely ill people. E.g., its poor differentiation between fat and lean body mass hinders identification of ascites or edema.[6] Therefore, BMI is recommended not as a diagnostic measure but for screening alongside complementary measures,[7] e.g., bioelectrical impedance, to distinguish between total body water, fat-free body mass, body weight and body fat. Additionally, waist circumference and skin-fold thicknesses are easy assessable, while dual X-ray absorptiometry, magnetic resonance imaging, and computed tomography are among the more sophisticated (and expensive) techniques.[8] Although a variety of measures are in use, practical and budgetary considerations make BMI the most popular for studies.

1.2 Obesity and weight gain in the course of transplantation

The rising prevalence of obesity in the general population is mirrored in all solid organ transplant (Tx) populations. From 1990 to 2003, the proportion of obese (BMI >30 kg/m^2) candidates on the US liver Tx waiting list increased from 15% to 25% (National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation database);[9] and a 2015 report identified 35.8% of candidates in the database of the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients as obese at Tx.[10] The same development has been reported separately in US kidney,[11] heart,[12] and lung[13] transplant patients.

After Tx, weight gain is common, resulting in a higher prevalence of post-Tx obesity. In liver Tx, for example, excessive weight gain in the first year post-Tx (mean weight gain: 5 – 9 kg) leads to double the prevalence of pre-Tx obesity.[14-16] Beyond 1 year, body weight tends to increase less steadily; however, it has been reported that at 2 and 3 years after liver Tx, 21.6% and 31%, respectively, of initially non-obese recipients became obese.[15,16] Independent of BMI category at Tx, weight gain occurs in all patients after Tx. Still, it appears that those who were overweight or obese before Tx tend to gain more weight compared than those who were initially under- or normal weight.[14]

Weight parameters vary considerably among geographic regions and organ groups. For example, at 1 year post-Tx, while kidney Tx recipients in France had a mean weight gain of 2.7 kg,[17] their US counterparts had gained 10.3 kg[18]. Weight gain variations in the first year post-Tx have also been shown across organ groups in the US, e.g., 1.1 kg in heart[19] versus 9.2 kg in liver recipients.[20] The same differences apply to the prevalence of obesity. For example, in the US, approximately 30% of kidney[21] and liver[22] Tx patients were obese at Tx, compared to, respectively, 22.7% and 15.2% of heart[23] and lung recipients.[24]

Comparison of body weight parameter evolution between organ groups is hampered by variations among studies in view of design (e.g., single center versus database related studies), sampling methods, operational definitions and measurement methods.

Chapter 3 describes and compares the evolution of weight parameters within and among adult kidney, liver, lung, and heart Tx recipients up to 3 years post-Tx. The analysis used data from the nationwide, open, and prospective Swiss Transplant Cohort Study (STCS). The standardized methodology of the STCS data collection allowed a substantiated comparison of all organ groups.

1.3 Morbidity and mortality associated with weight gain and obesity

The widely accepted health risks of weight gain and obesity relate to their association with comorbidities including cancer, musculoskeletal disorders, cardiovascular dysfunction and metabolic diseases.[2,25-27] Figure 1 depicts obesity's most important relationships with medical complications. Further, Flegal et al.'s 2013 meta-analysis found a significant association between obesity (BMI ≥30 kg/m^2) and increased all-cause mortality in the general adult population.[28] However, when that study's BMI categories were examined separately, only values ≥35 kg/m^2 remained associated with higher mortality; and BMIs of 25 – 29.9 kg/m^2 were actually associated with significantly lower all-cause mortality than normal ones.

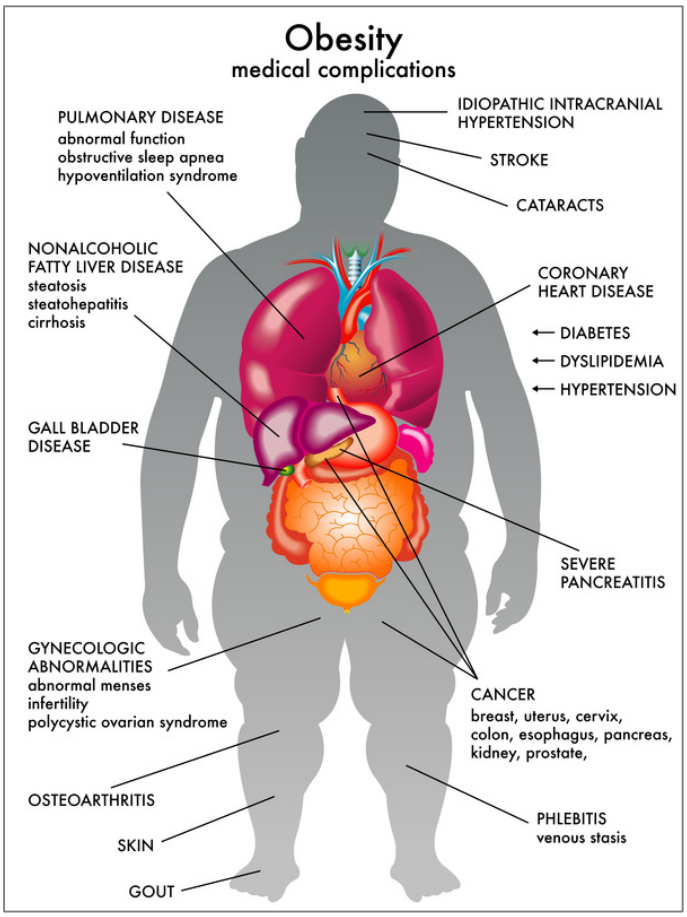

Figure 1. Obesity and its association with medical complications.
Source: http://www.glsurgical.com.sg/weight-loss-procedure/why-weight-loss-procedure/

Metabolic and cardiovascular diseases after liver transplantation

Metabolic diseases such as hypertension, diabetes mellitus and dyslipidemia commonly occur after liver Tx.[29,30] One of the most common post-Tx complications–affecting 44% to 58% of liver Tx recipients[29]–is metabolic syndrome, i.e., the occurrence of ≥3 of the following symptoms: impaired glucose tolerance, hypertriglyceridemia, high blood pressure, low high density lipoprotein levels, or abdominal obesity.[31-33] Still, although obesity is used as a diagnostic component of metabolic syndrome,[34] the impacts of body weight parameters on its development are mixed. While pre- and post-Tx obesity rates were both significant in univariate analysis;[35] multivariate analyses indicated that pre-Tx BMI[35,36] and post-Tx weight gain[29,30] were both independent predictors of metabolic syndrome. Other factors consistently related to post-Tx metabolic syndrome are immunosuppressive drugs (which are required lifelong to prevent graft rejection episodes),[37-39] lifestyle factors (e.g., physical inactivity, unhealthy dietary habits, and a history of smoking) and various non-modifiable factors including higher age, gene polymorphisms or end-stage organ disease.[29,30]

The clinical impact of metabolic syndrome is substantial: it contributes to overall and cardiovascular mortality after liver Tx, and to an increased risk of cardiovascular disease.[29,39,40] Among liver graft recipients, cardiovascular events (CVEs) such as myocardial infarction, cerebrovascular accidents, cardiac arrests, atrial fibrillation, pulmonary embolism, heart failure, and/or stroke have been reported as leading causes of mortality.[41-44] A recent systematic review of 29 studies summarized the incidence rates of CVEs in relation to time after liver Tx.[45] In the first 6 months post-Tx, the average incidence was 22% (range: 1.1% – 50%); after 6 months, that figure fell to 11.8% (range 0 to 31.4%). The wide range of incidence rates reflected variations in outcome definitions applied in the individual studies. Although obesity is a well-described risk factor for cardiovascular disease in the general population,[46] this relationship has not yet been verified in liver Tx, as only one study identified obesity at Tx as a predictor for CVE.[47] In fact, few studies have corroborated this or various other apparent relationships, i.e., in most studies, multivariate analyses have indicated no associations between CVE and obesity at Tx, BMI before or after Tx,[45]or post-Tx weight gain.[48]

One possible explanation for this lack of corroboration is that researchers focus predominantly on pre-Tx body weight parameters, but may not adjust for fluid-altering conditions. For example, given that ascites and edema are common in patients with end-stage liver disease, unless measurements are corrected for abnormal fluid levels, pre-Tx body weight parameters as outcome-predictive factors are limited.[40] Therefore, it may be more appropriate to measure CVE in relation not to BMI at Tx but to accurately measured obesity or new-onset obesity after Tx. To date, no such relationship has been examined.

Nonalcoholic fatty liver disease before and after liver transplantation

Raising additional concerns, obesity also contributes to another epidemic: nonalcoholic fatty liver disease (NAFLD), i.e., macrovesicular hepatic steatosis with >5% fat in the liver in the absence of significant alcohol intake (20 g/day in men, 10 g/day in women), viral infection, or any other specific etiology of liver disease.[49] NAFLD is the hepatic manifestation of metabolic syndrome, often occurring simultaneously with obesity, dyslipidemia and insulin resistance.[50] Obese people have 3.5 times the risk of developing NAFLD compared to normal weight people.[51] Along with rates of obesity increasing worldwide, NAFLD has become the most common liver disease, with a global prevalence of 25.2%.[52] The progressive version of NAFLD is nonalcoholic steatohepatitis (NASH). NASH is associated with hepatocellular carcinoma development and in-

creased mortality, liver-related disease, cardiovascular disease and malignancy in the general population.[53-55]

NASH-related cirrhosis is now the fastest increasing indication for liver Tx in Europe and the US, where it is expected to overtake Hepatitis C as the leading cause in 10 – 15 years.[56-58] Liver graft recipients transplanted because of NASH have either similar[58] or better long-term patient survival compared to those transplanted for other reasons.[59] However, diagnosis of NAFLD after Tx–either the recurrence of liver steatosis or the development of *de novo* NAFLD–is a new health issue, affecting 25% – 60% of liver Tx recipients.[60] Its underlying mechanisms are complex, and its pathogenesis in transplanted grafts is not yet fully understood. Still, along with genetic factors, NASH cirrhosis as the primary indicator for Tx is associated with post-Tx NAFLD.[60] Of note, one of the most consistent predictors of NAFLD is post-Tx weight gain,[29,60] which is congruent with evidence in the general population.[27]

Post-operative outcomes and survival after liver transplantation

Pre-Tx obesity has been associated with increased risk for post-operative complications (i.e., operative complications, infections), and increased length of intensive care unit and hospital stays.[61] However, a recent meta-analysis found no association–even after adjustment for ascites or severity of liver disease–between patient survival and pre-Tx BMI, noting similar survival rates across BMI categories and obesity classes.[62] To date, to the best of our knowledge, no study examined the impact of post-Tx body weight parameters on patient survival.

In conclusion, the discord between the research results noted above might be explained by methodological differences among the studies, e.g., variations in measurement points (e.g., short- or long-term outcomes after Tx), the dominant use of cross-sectional study design, the diversity of diagnostic criteria (e.g., for metabolic syndrome, cardiovascular disease, NAFLD) and the measurement of body weight parameters. Especially before Tx, the measurement of body weight (and the further calculation of the BMI) may be skewed by the presence of ascites and edema. While the impact of pre-Tx BMI and obesity have been examined extensively in the literature, post-Tx body weight parameters such as weight gain and subsequent obesity are not well understood. Finally, evidence is either scant or contradictory regarding how post-Tx weight gain and new-onset obesity impact patient outcomes such as metabolic and cardiovascular diseases or patient and graft survival.

Chapter 6 presents the results of an STCS analysis aimed at and examining the impact of new-onset obesity on CVE and patient survival, and determining risk factors for the development of new-onset obesity after liver Tx. Longitudinal data from the Swiss cohort allowed a time-dependent analysis of outcomes and predictors.

1.4 Factors influencing weight gain and energy balance

The regulation of body weight follows the first law of thermodynamics, i.e., the principle that energy can be transformed from one form to another, but cannot be created or destroyed. This leads to the energy balance equation: energy storage = energy intake - energy expenditure.[63] In physiology, weight change results from an imbalance between energy intake (calories consumed) and expenditure (calories expended) over time.[64] Therefore, maintaining a stable weight, i.e., balancing energy intake with expenditure, may appear a simple matter of adherence to energy balance related behaviors, e.g., healthy eating (energy intake) and physical activity (energy expenditure). In fact, effective weight management is extremely complex: the etiology of weight gain, leading to overweight and obesity, depends on a multitude of interconnected factors.

One of the most comprehensive overviews of weight-influencing factors and their interrelationships is presented in the 2007 United Kingdom (UK) *Foresight* report's obesity system map (Figure 2, the interactive version is available on http://www.shiftn.com/obesity/Full-Map.html.).[65] The center of the diagram is energy balance, embedded in a dense tangle of 108 variables from 10 source types: media, social, psychological, economic, food, activity, infrastructure, developmental, biological and medical. Among the variables, positive or negative influences are depicted via 304 causal linkages. Finally, the variables are grouped into 8 superior clusters: social psychology, individual psychology, individual physical activity, physical activity environment, food production food consumption, physiology and individual physiology.

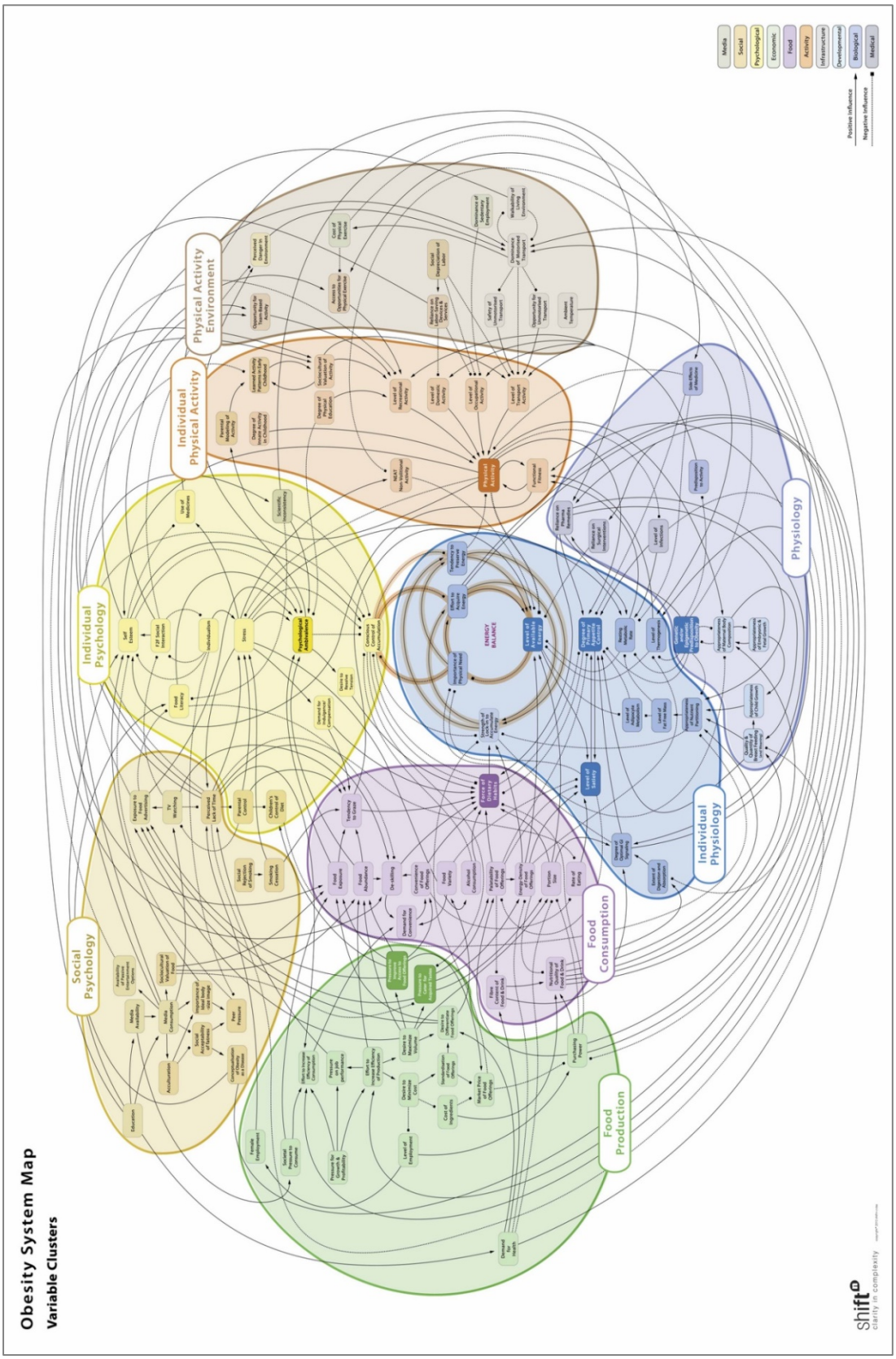

Figure 2. Obesity system map in the UK *Foresight* report. To highlight the different variable clusters, the system map was redesigned by ShiftN
Source: (http://www.shiftn.com)

Based on the *Foresight* report and current literature, we developed a simplified framework (Figure 3) to guide the design and research of the studies conducted within this PhD project and described in chapters 4 and 6 below. This framework covers 6 categories of variables related to weight gain: genetic, sociodemographic, behavioral, biomedical, psychological, and environmental.[66-69] The framework is intended for use as a working model, and should be adapted according to the most compelling available evidence.

To date, few studies have examined factors influencing post-liver Tx weight gain in ways that would add information to our framework. The examination of **genetic** factors in relation to weight gain is only beginning in Tx populations. One genomic study in liver Tx found that recipients carrying at least one D allele of the ACE gene had a nearly 4 times the risk of weight gain compared to those with no D allele.[70] This study also found a gene-age effect, as weight gain was particularly prevalent in patients aged >55. These results call for further research to test findings such as in kidney Tx populations. E.g., when Cashion et al. examined gene expression profiles in subcutaneous adipose tissue, they found 4 genes positively (CPE, LEP, NPY1R, NPY5R), and 2 genes negatively (APOM, CRP) correlated with post-Tx weight gain.[71]

Regarding **sociodemographic** influences, evidence of major factors' impact on post-Tx weight gain can be contradictory. For example, the impacts of age and gender remain controversial;[14-16,20] however, other factors, such as BMI before liver disease onset, higher weight/BMI before Tx, family history of overweight and being married have been consistently associated with weight gain.[14,15,20,72]

Surprisingly few studies have examined **behavioral** factors, and especially energy balance-related behaviors; and some of those few have made counter-intuitive findings. Perhaps most notably, in Anastacio et al.'s cross-sectional study, neither dietary intake nor daily physical activity could be related to post-liver Tx overweight or obesity.[72] In another case, Ferreira et al. prospectively assessed energy intake and expenditure in 17 recipients before liver Tx and during the first year after.[73] Compared to the pre-Tx measurement, energy intake increased post-Tx, while expenditure remained rather stable. This resulted in a positive energy balance and by 12 months post-Tx, mean weight had increased from 69.6 ± 17.2 kg to 74.2 ± 17.7 kg. Unfortunately, the relationship between energy balance and weight gain was not analyzed. Another behavioral factor examined with weight gain was current and former smoking; however the results remain inconclusive.[14,15,72]

Most studies have examined **biomedical** factors, especially immunosuppressive medication use. In general, one side effect commonly attributed to prednisone is a craving for sweets and increasing weight, especially when prescribed at >5 mg/day.[74] However, little evidence in liver Tx supports this relationship. While a number of studies have reported that the cumulative prednisone dose at 1 year post-Tx predicts obesity, weight gain, weight change or a decrease of fat-free body mass,[15,75] others have found no such association.[14,16,20,76,77] Results for other immunosuppressive drugs such as cyclosporine tend to be similarly inconsistent.[14,20,72] Only tacrolimus is generally agreed to have no impact on post-Tx weight gain.[14,15,20,72,77]

Our literature study uncovered no studies that examined post-liver Tx weight gain in relation to **psychological** or **environmental** factors.

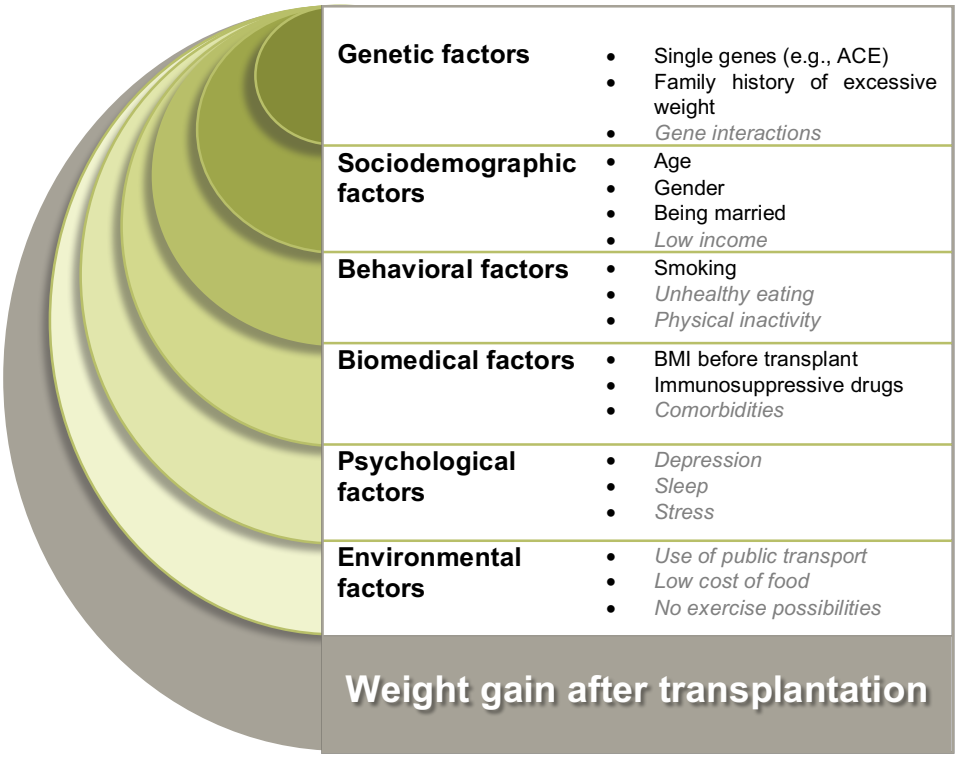

Figure 3. Theoretical framework of factors influencing weight gain in the BALANCE project. The variables assigned to the 6 main categories are examples from the liver Tx population and selected variables from the general population (in grey color and italics). Source: Own Illustration.

Overall, the evidence regarding weight gain influencing factors remains scarce; and it is not yet clear which variables predict weight gain after Tx as the few existing results are partly conflicting. This might be explained by methodological reasons, e.g., most studies used cross-sectional designs, which precludes the detection or inference of causal relationships. In view of the content gaps, most single center and also database-related studies are limited regarding data collection to mainly sociodemographic

and biomedical variables. As such limitations obscure the complexity of weight gain, they limit any examination of predictive factors and their interrelationships. Additionally, to the best of our knowledge, no study has yet examined associations between post-Tx weight gain and energy balance-related behavior, psychological or environmental factors.

Chapter 4 describes the results of our systematic literature review and meta-analysis investigating the risk factors regarding post-liver Tx changes in BMI, weight gain and obesity. This is the first summary and synthesis of the current evidence regarding risk factors in liver Tx. Guided by our theoretical framework, the data were extracted according to the 6 main categories. The results guided the adaption of the framework according to the evidence provided by the meta-analysis.

Chapter 5 provides the results of a study using data from the STCS to examine associations between genetic factors and weight gain after Tx. This study shows the importance of including genetic factors in risk factor models in order to strengthen predictive power.

Chapter 6 presents a study about outcomes and risk factors of new-onset obesity after liver Tx. This study identified patients at risk for weight gain and subsequent new-onset obesity. The results highlight the importance of preventing weight gain and the development of new-onset obesity as it was associated with post-Tx CVE.

1.5 Energy balance-related behaviors

Although the multiplicity of factors influencing weight gain has been acknowledged, energy balance-related behaviors such as dietary intake and physical activity are still perceived as the most important dynamics related to energy balance and weight management.[2,78] So far, though, no evidence indicates that any specific diet can effectively prevent weight gain.[79,80] The general recommendations to maintain a stable weight are to adjust caloric intake to match one's expenditures (i.e., decreased intake during periods of reduced physical activity), adhere to a well-balanced diet (i.e., including vegetables, fruits, beans and pulses, whole grains and fish), and limit intake of energy-dense foods (e.g., fats and sugars).[81] Following a particular diet such as Mediterranean style, low-fat, low-carbohydrate, or low glycemic index is important for overweight and obese people who aim to lose weight.[7] Regarding physical activity, guidelines recommend for healthy adults a minimum of 150 min of moderate-intensity physical activity with per week[78,82]–an activity level associated with healthy normal weight and general health benefits such as reduced risk for cardiovascular disease.[81,83]

In the liver Tx population, factors including immunosuppressive medication increase the risk for metabolic and cardiovascular comorbidities. Therefore, to maintain normal weight and prevent comorbidities, graft recipients need to adopt a particularly healthy post-Tx lifestyle, adhering to energy balance-related behaviors such as a healthy diet and physical activity.[84] Despite the known benefits of healthy eating and physical activity after Tx, non-adherence with recommendations is well documented.[85]

A small number of small studies have examined healthy eating over the course of liver Tx, measured by short-term self-reported dietary intake, i.e., 3-day food intake records. In one study with 31 participants, the total number of calories consumed remained stable from pre-Tx to 6 months post-Tx;[86] however, two others reported increases in energy intake at 9 months (n=23)[87] and 1 year post-Tx (n=17).[73] While carbohydrate and protein consumption remained rather stable, fat intake increased. As a result, body weight and fat mass increased in both study samples.[73,87] Similarly, a German cross-sectional study examined 42 liver Tx recipients' total energy intake and macronutrients compared to the general population's consumption patterns and the recommendations of the German Nutrition Society.[76] Tx recipients (median time after Tx: 50 months; range: 17.7 – 100.6) consumed more total energy than national recommendations (2389 kcal/d versus 2200 kcal/d), with higher proportional fat intake (41%) than either the recommendations (30%) or the general population (36%).

Regarding physical activity, roughly half of US liver Tx recipients engage in regular physical activity; however, activity levels still remain below those recommended in US public health guidelines.[88,89] A subgroup analysis in liver recipients more than 1 year after Tx showed very similar results, suggesting that decreased post-liver Tx physical activity levels are independent of physical limitations in the early recovery phase.[88] These results are worrisome: low physical activity has been associated with metabolic syndrome after liver Tx,[88] as well as cardiovascular and all-cause mortality after kidney Tx.[90] Conversely, post-Tx physical activity has been associated with beneficial effects such as increased health-related quality of life, self-efficacy, personal fitness, muscle strength and functional performance.[89,91-94] Few studies have linked increased physical activity to reductions in the incidence of hepatic steatosis in individuals with NAFLD;[95-97] however, this has not been examined in the Tx population.

1.6 Behavioral interventions in weight management

Three approaches drive weight management: (1) the prevention of weight gain; (2) short-term weight loss due to a temporary negative energy balance; and (3) long-term

weight loss maintenance due to re-achieving continuous energy balance at a reduced level. Experts and guidelines consistently advise a focus on weight gain prevention.[25,78,81,98] This strategy is based on physiological mechanisms, which compensate during phases of energy shortage. I.e., while reduced energy intake by food restriction leads to short-term weight loss, homoeostatic factors drive a feedback loop by changing body energy requirements and increasing appetite.[99-101] Behavioral factors (e.g., challenges to retain changes, especially with regard to diet and physical activity), as well as environmental variables (e.g., availability of energy-dense foods, increased portion sizes, epigenetic modifications such as higher risk for obesity and metabolic diseases after intrauterine exposure to very low or very high maternal nutrition[102]) add to the complexity of the underlying physiology.[100]

Based on these mechanisms, weight loss is commonly followed by weight regain.[103,104] Even in behavioral intervention studies applying state-of-the-art recommendations, sustainable weight loss maintenance remains a major problem.[101,105] Middleton et al.'s 2012 meta-analysis synthesized 11 randomized-controlled trials examining the effects of extended care (i.e., continued therapist contact to prevent weight regain following initial loss) on weight loss maintenance.[106]The trials' follow-up lengths varied; however, the 5 that used 18 months of follow-up reported lower mean weight regain in their intervention groups (from 1.2 kg to 4.5 kg) compared to their controls (from 3.3 kg to 7.2 kg).

Comprehensive lifestyle interventions have become a cornerstone of weight gain and obesity prevention.[7] To tackle individual, environmental and systemic drivers, a multilevel approach has been recommended.[67] On the individual level, interventions focusing on health behaviors are suggested.[67] Three systematic reviews examined effective patient-level interventions and their key components to prevent weight gain in adults.[80,107,108] Their findings indicated that multicomponent interventions (combining dietary advice, physical activity and promotion of behavior change) are more effective than single component interventions. However, few of the included behavior change interventions were based on underlying theories,[107] nor was their development comprehensively described.

Studies focusing on energy balance-related interventions in the liver Tx population are scarce. Still, even while the Tx community calls for assistance in weight gain and obesity management to prevent comorbidities,[39,84,96,109] the development and implementation of structured, noninvasive, multidisciplinary weight management programs has virtually stalled. Since 2006, only one randomized controlled trial (in 119 liver Tx recipients) has examined the effects of a combined dietary and physical activity

intervention on exercise capacity, muscle strength, body composition, nutritional intake and health-related quality of life.[110] That intervention included individual counseling on exercise prescription (e.g., walking or cycling for 30 min per session with increasing intensity, at least three times per week), and nutrition recommendations (caloric balance, fat intake ≤30% of total caloric intake, and additional dietary recommendations). The 10-month follow-up was based on home-based exercise and dietary modification. Although exercise capacity increased only in the intervention group, body weight, BMI and fat mass significantly increased in both groups. However, even though the trial was not powered to detect changes in body composition, the intervention group's increase of fat mass was slower than that of the usual care group, suggesting a favorable intervention effect. And while the authors did not explicitly address behavior change within the intervention, the counseling session comprised several components that could be assigned and coded to behavior change techniques: short and long-term goal setting, self-monitoring with exercise logs and 3-day food diaries, review of current behaviors, recommendations for program progression, discussion of problems and barriers, suggestions for changes and encouragement for continued participation, and a newsletter offering information and tips for adherence.

The overall aim of this dissertation was to generate evidence that would facilitate the development of a behavioral intervention based on physical activity and diet to support effective weight management and a healthy lifestyle after liver Tx.

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Chapter 2. Aims

The overall aim of this dissertation was to generate evidence that would facilitate the development of a behavioral intervention focusing on physical activity and diet to support effective weight management and a healthy lifestyle after liver Tx.

Based on the gaps described in the introduction regarding body weight parameter evolution among solid organ Tx populations, the complex mechanisms leading to post-Tx weight gain and obesity, and body weight parameter's impacts on patient outcomes, the specific aims were as follows:

1) To examine the evolution of body weight parameters up to 3 years after Tx within and among adult kidney, liver, lung, and heart Tx patients in the STCS **(Chapter 3).**
2) To summarize and synthesize the current literature in view of risk factors for post-Tx BMI, weight gain and obesity in the liver Tx population **(Chapter 4).**
3) To examine weight gain in the first year after solid organ Tx in the STCS from a genomic perspective **(Chapter 5).**
4) To determine clinical and psychosocial risk factors for post-liver Tx new-onset obesity and examine its impact on outcomes including patient survival and CVEs in the STCS **(Chapter 6).**

Chapter 3. Evolution of Body Weight Parameters up to Years after Solid Organ Transplantation: The Prospective Swiss Transplant Cohort Study

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3.1 Abstract

Obesity and weight gain are serious concerns after solid organ transplantation (Tx); however, no unbiased comparison regarding body weight parameter evolution across organ groups has yet been performed. Using data from the prospective nationwide Swiss Transplant Cohort Study, we compared the evolution of weight parameters up to 3 years post-Tx in 1359 adult kidney (58.3%), liver (21.7%), lung (11.6%), and heart (8.4%) recipients transplanted between May 2008 and May 2012. Changes in mean weight and body mass index (BMI) category were compared to reference values from 6 months post-Tx. At 3 years post-Tx, compared to other organ groups, liver Tx recipients showed the greatest weight gain (mean 4.8 ± 10.4 kg), 57.4% gained >5% body weight, and they had the highest incidence of obesity (38.1%). After 3 years, based on their BMI categories at 6 months, normal weight and obese liver Tx patients, as well as underweight kidney, lung and heart Tx patients had the highest weight gains. Judged against international Tx patient data, the majority of our Swiss Tx recipients' experienced lower post-Tx weight gain. However, our findings show weight gain pattern differences, both within and across organ Tx groups that call for preventive measures.

3.2 Background

As the number of obese patients awaiting solid organ transplantation (Tx) has steadily increased over the past decades[1-4] and considerable post-Tx weight gain has been described in all Tx populations,[5] patient weight parameters (e.g., obesity and weight gain) are relevant factors to investigate over the Tx continuum. Moreover, obesity and weight gain have been associated with serious health issues across all solid organ Tx populations.[6] Conclusive evidence links pre-Tx obesity with worse post-Tx outcomes, for example, increased risk of graft dysfunction and post-Tx surgical, cardiovascular or metabolic complications.[6] Over the post-Tx course, obesity and weight gain at 1 year after kidney Tx are associated with increased risks of cardiovascular and all-cause mortality,[7-9] as well as graft failure.[7-10]

Weight parameters vary considerably among organ groups. In the United States (US), for example, approximately 30% of kidney[11] and liver[12] Tx patients are obese at the time of Tx, while the numbers in heart[13] and lung Tx[14] are 22.7% and 15.2%, respectively. Also mean weight gain in the first year after Tx varies across organ groups, for example, 1.1 kg in heart[15] versus 9.2 kg in liver Tx,[16] and across geographic regions, e.g., 2.7 kg weight gain in kidney Tx recipients in France[8] versus 10.3 kg in the US.[17]

Recent reviews highlight the challenges of comparing different studies' results as definitions, measurements and sampling methods might vary.[6,18] Body mass index (BMI in kg/m^2) and weight change in kilogram or in percent are the weight parameters most often used. *BMI categories* applied in adults, according to the World Health Organization (WHO) are underweight (<18.5 kg/m^2), normal weight (18.5 – 24.9 kg/m^2), overweight (25 – 29.9 kg/m^2), and obese (≥30 kg/m^2).[19] Although the BMI is easy to calculate, it has considerable limitation for example, it provides no information about the distribution of weight or fat, and it fails to differentiate between muscle mass, fat, or extracellular water.[20] In a Tx candidate with ascites or edema, a high BMI may reflect fluid overload rather than increased fat mass. Especially in the liver Tx population the pre-Tx BMI should be corrected for ascites to avoid misclassification regarding BMI category.[3] Still, flawed though it may be, BMI is certainly worth monitoring. In the kidney Tx population, a BMI increase in >5%, independent of pre-Tx BMI, has been associated with graft loss.[8]

Another commonly used weight parameter in the Tx literature is post-Tx *weight change,* expressed as the calculated difference in kilogram over time. This is a rather crude measure, as it disregards differences in baseline weight (e.g., a 5 kg weight gain in an underweight patient is clinically dissimilar from a similar weight gain in an obese

patient). One useful weight parameter to consider would be weight change in percent related to baseline weight. In this regard, a weight gain of ≥5% functions well as a clinically relevant cutoff, as it has been identified as a risk factor for cardiovascular and metabolic disorders in overweight or obese adults. In the same populations, losses of 5 – 10% are associated with health benefits.[21] In the literature, one limitation of percentage weight change related to baseline weight remains the limited consideration of baseline BMI category (e.g., 5 – 10% weight gain in underweight vs obese patients). Importantly, few studies addressing weight parameters in solid organ Tx have examined weight changes longer than 1-year post-Tx. Additionally, except for a small number of notable exceptions,[5,15,22] the vast majority of studies focus on individual centers and on a solitary Tx population only.

The absence of a standard methodology to assess the evolution of various post-Tx weight parameters, including the longer-term post-Tx course, precludes firm conclusions on the prevalence and evolution of relevant weight parameters between organ groups. Across solid organ Tx groups, identifying these patterns will allow researchers to determine how and in which groups to first invest their efforts for preventive measures. Using data from the nationwide, open, and prospective Swiss Transplant Cohort Study (STCS), including all patients transplanted in any of the six Swiss Tx centers since 2008, we aim to describe and compare the evolution of weight parameters within and among adult kidney, liver, lung, and heart Tx recipients up to 3 years post-Tx.

3.3 Methods

Patients and Methods

The STCS includes all patients transplanted in Switzerland since 2008. Data in the STCS are collected at Tx, at 6 and 12 months post-Tx, then yearly thereafter. Follow-up ends with the patient's death or dropout. The STCS was approved by all relevant cantonal ethic committees. More details about the design and methodology of the STCS are described elsewhere.[23,24] Inclusion criteria for this analysis were as follows: age ≥18 years, data available about weight and height at Tx, and receiving a first kidney, liver, lung, or heart Tx between May 5th 2008 and May 31st 2012, thus allowing a 3-year follow-up in all participants. Patients who supplied no informed consent for further data analysis, or who were receiving multiple grafts were excluded.

Variables and measurement

Body weight parameters

Height and weight at Tx, 6 months, 1, 2, and 3 years post-Tx were used to calculate patients' BMIs (weight in kilogram divided by height in meters squared). *BMI categories* were determined according to the WHO definition.[19] Changes in weight parameters over time (i.e., mean weight or BMI category) were examined in relation to the measurements at 6 months post-Tx. Using these figures as reference values allowed an unbiased and comparative examination of changes between all four organ groups, as no correction for pre-Tx ascites or edema was possible using STCS data.

Weight change in kilogram was calculated for each patient as the difference between the reference weight at 6 months post-Tx and the weight at Tx, 1, 2, and 3 years post-Tx. The means of weight changes were then calculated for each organ group and for the BMI subgroups, respectively, which were defined based on the reference BMI category at 6 months.

Weight change in % was calculated for each patient as the difference between the weight at 3 years post-Tx multiplied by 100 and divided by the 6-month reference weight. Means were then calculated for each organ group and for the BMI subgroups, which were again based on the reference BMI category at 6 months, and categorized as follows: weight loss (loss of >5% weight), stable weight (weight change between -5% and 5%), and weight gain (gain of >5% weight).

The *evolution of BMI* over time was examined using two analyses. First, as the proportion of patients in each of the BMI categories at Tx, 6 months, 1, 2, and 3 years post-Tx. As patients can shift from one BMI category to another at different measurement points, this presentation does not necessarily represent individual changes. Consequently, we examined the evolution of BMI on an individual level and analyzed at 3 years post-Tx the proportions of patients who remained in their 6-month reference BMI categories versus those who shifted between categories.

Clinical and socio-demographic variables

To describe the sample at time of Tx, we extracted following variables from the STCS database: age, gender, length of follow-up, donor type (deceased or living, only in kidney and liver Tx), and ethnicity (Caucasian, African, Asian, and other race) and end-stage organ disease leading to Tx. Death, graft loss, and rejection were recorded from Tx until the end of the 3-year follow-up period. Rejection for each organ group was defined according to the definition used by the STCS: kidney: acute humoral or cellular rejection; liver: clinically suspected and biopsy-proven rejection; lung: bronchoalveolar

lavage or clinically suspected and biopsy-proven rejection; and heart: biopsy-proven rejection from grade 1a to grade 4.

Statistical analysis

Based on measurement level and data distribution, descriptive statistics including frequencies and percentages, means and standard deviations (SD) were used to describe both the sample and the evolution of BMI and weight. In the STCS dataset, the variables weight and height were missing in 4.3% and 3.0% of the cases, respectively. Missing variables were not imputed, nor were patients with missing values excluded from further analysis. All analyses were performed using SPSS Version 23.0 statistical software (IBM Corp., Armonk, NY, USA).

3.4 Results

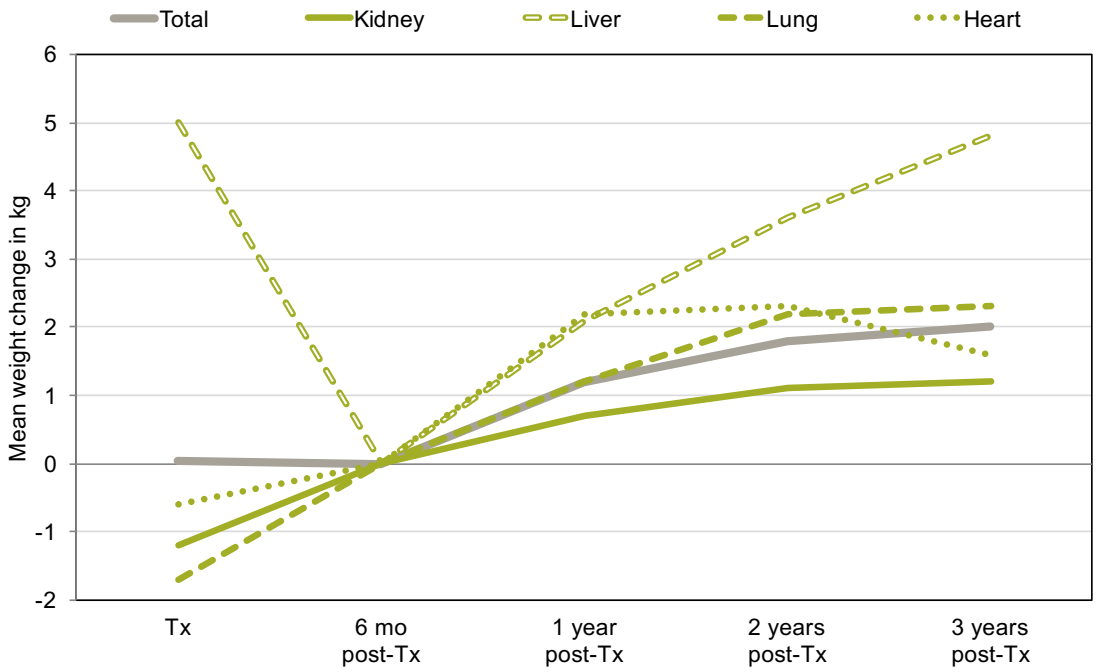
In August 2015, the STCS database included 3315 patients. After the exclusion of n = 1956 patients based on the application of our inclusion and exclusion criteria, a total of 1359 patients were eligible for the final analysis (kidney = 58.3%, liver = 21.7%, lung = 11.6%, and heart = 8.4%). The most common underlying end-stage organ diseases were as follows: in kidney patients, glomerulonephritis (22.9%), polycystic kidney disease (21.6%), and nephrosclerosis (13.8%); in liver patients, viral hepatitis (35.9%), alcoholic liver disease (22.7%), and hepatocellular carcinoma (8.5%); in lung patients, chronic obstructive pulmonary disease (30.4%), cystic fibrosis (24.1%), and idiopathic pulmonary fibrosis (20.3%); and in heart patients, cardiomyopathy (55.3%) and ischemic heart disease (28.9%). Further sample characteristics are summarized in Table 1.

Variables	Total group n = 1359	Kidney Tx n = 792	Liver Tx n = 295	Lung Tx n = 158	Heart Tx n = 114
Age at Tx, mean ± SD	52.0 ± 13.3	52.5 ± 13.8	52.7 ± 11.3	49.7 ±13.8	49.1 ±14.5
Male, n (%)	888 (65.3)	530 (66.9)	192 (65.1)	77 (48.7)	89 (78.1)
Ethnicity					
Caucasian, n (%)	1283 (94.4)	736 (92.9)	279 (94.6)	156 (98.7)	112 (98.2)
Black, n (%)	36 (2.6)	26 (3.3)	8 (2.7)	1 (0.6)	1 (0.9)
Asian, n (%)	34 (2.5)	24 (3.0)	8 (2.7)	1 (0.6)	1 (0.9)
Other, n (%)	6 (0.4)	6 (0.8)	0	0	0
Death, n (%)	159 (11.7)	51 (6.4)	44 (14.9)	38 (24.1)	26 (22.8)
Graft loss, n (%)	95 (7.0)	44 (5.6)	21 (7.1)	19 (12.0)	11 (9.6)
Rejection, n (%)	613 (45.1)	288 (36.4)	138 (46.8)	97 (61.4)	90 (78.9)
Deceased donor, n (%)		438 (55.3)	276 (93.6)	158 (100)	114 (100)
Weight					
at Tx, mean ± SD	73.8 ± 16	75.3 ± 15.5	74.9 ± 16.4	62.8 ± 15.3	75.5 ±14.2
BMI					
at Tx, mean ± SD	25.3 ± 4.7	25.8 ± 4.6	25.5 ± 4.5	22.3 ± 4.9	25.3 ± 4.1
at 6mo, mean ± SD (n)	25.3±4.6 (1280)	26.3±4.7 (777)	23.8±4.0 (255)	22.9±4.2 (151)	25.5±3.9 (97)
at 1y, mean ± SD (n)	25.7±4.8 (1209)	26.4±4.9 (738)	24.6±4.4 (238)	23.4±4.1 (143)	26.2±4.6 (90)
at 2y, mean ± SD (n)	26.0±4.9 (1114)	26.5±4.9 (688)	25.5±4.9 (209)	23.7±4.0 (128)	26.2±4.8 (89)
at 3y, mean ± SD (n)	26.1±5.0 (995)	26.6±5.0 (628)	25.7±4.9 (170)	23.9±4.5 (116)	25.9±5.0 (81)

Tx, transplant; BMI, body mass index; SD, standard deviation; y, year

Table 1. Demographic and clinical patient characteristics.
Source: Own Illustration.

Weight changes in kilogram compared to the reference weight at 6 months after kidney, liver, lung, and heart Tx are shown in Figure 1. With regard to the period between Tx and 6 months, kidney, lung, and heart Tx patients were already gaining weight in the early post-Tx phase, while liver Tx patients showed a different pattern, with a mean weight loss of −5 kg (± 8.5 kg). From 6 months to 3 years post-Tx, all organ groups gained weight (overall mean weight gain: 2.0 ± 7.5 kg). However, the amount of weight gain differed between groups. Liver Tx recipients gained the most weight (4.8 ± 10.4 kg), while kidney Tx patients gained the least (1.2 ± 6.3 kg).



	From Tx to 6 mo	Reference at 6 mo	From 6 mo to 1 year	From 6 mo to 2 years	From 6 mo to 3 years
Total sample weight change / kg mean ± SD, range, (n)	**0.03 ± 7.3 -30 - 37.7, (1280)**	**0 ± 0, (1280)**	**1.2 ± 4.8 -32 - 19, (1188)**	**1.8 ± 6.3 -30 - 37.1, (1095)**	**2.0 ± 7.5 -40.1 - 43.3, (983)**
Kidney weight change / kg mean ± SD, range, (n)	-1.2 ± 5.8 -27 - 17.7, (777)	0 ± 0, (777)	0.7 ± 4.6 -32 - 19, (73)	1.1 ± 5.5 -30 - 21.5, (684)	1.2 ± 6.3 -40.1 - 21.6, (624)
Liver weight change / kg mean ± SD, range, (n)	5 ± 8.5 -20 - 37.7, (255)	0 ± 0, (255)	2.1 ± 5.4 -12.5 - 18.9, (225)	3.6 ± 8.2 -24.7 - 37.1, (197)	4.8 ± 10.4 -38 - 43.3, (162)
Lung weight change / kg mean ± SD, range, (n)	-1.7 ± 7.5 -30 - 18.9, (151)	0 ± 0, (151)	1.2 ± 4.9 -21 - 14.7, (140)	2.2 ± 6.7 23.1 - 25.7, (125)	2.3 ± 8.0 -27.9 - 25, (116)
Heart weight change / kg mean ± SD, range, (n)	-0.6 ± 8.2 -19.4 - 20.4, (97)	0 ± 0, (97)	2.2 ± 4.6 -11.5 - 14, (90)	2.3 ± 6.5 -11.5 - 22.1, (89)	1.6 ± 7.5 -16.5 - 27.1, (81)

Tx, transplant; SD, standard deviation; y, year; mo, month

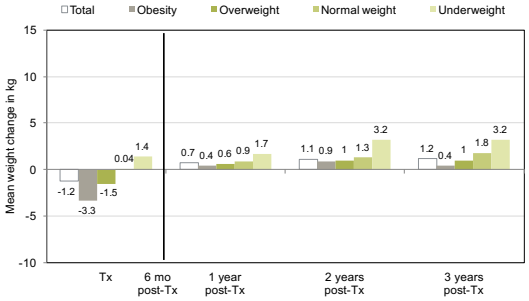
Figure 1. Mean weight changes in kg compared to the reference weight at 6 months after kidney, liver, lung and heart Tx.
Source: Own Illustration.

Mean weight changes in kilogram compared to the 6-month reference weight by BMI category at 6 months after kidney, liver, lung, and heart Tx are shown in Figure 2. In kidney, lung, and heart Tx, patients who were underweight at 6 months post-Tx subsequently gained the most weight compared to those in higher BMI categories. Obese liver Tx patients at 6 months post-Tx gained the most weight up to 2 years post-Tx, while at 3 years, patients who had normal weight at 6 months post-Tx showed the highest increase in weight. Lung Tx patients who were obese at 6 months post-Tx lost weight during the observation period.

Weight changes in percent categories by BMI category at 6 months after kidney, liver, lung, and heart Tx are shown in Figure 3. From 6 months to 3 years post-Tx, 55.3% of kidney Tx patients maintained a stable weight, compared with 45.7% of lung, 33.3% of heart, and 30.2% of liver Tx patients. The liver Tx group had the largest proportion of patients who gained >5% weight (57.4%) over the observation period, compared with the lung (37.9%), heart (33.3%), and kidney Tx (29.8%) groups. A more detailed examination revealed that in kidney, lung, and heart Tx, the underweight patients were the largest fraction gaining >5% weight, while liver Tx, these were the recipients who were normal weight or obese at 6 months. In lung and liver Tx, obese patients formed the largest proportion of the weight loss group.

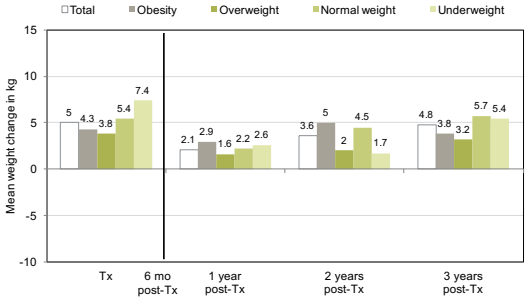
The proportion of patients per BMI category at each measurement from Tx to 3 years after kidney, liver, lung, and heart Tx is shown in Figure 4. The distribution of BMI categories at time of Tx among kidney, liver, and heart Tx candidates is comparable, while in lung Tx, a higher proportion of underweight (28.5%) and a lower proportion of obese patients (5.7%) were observed. From Tx to 6 months post-Tx, the prevalence of obesity decreased in the liver and heart Tx groups (from 17.3% to 5.9% and from 14.9% to 11.3%, respectively). However, during the entire observation period, the prevalence of overweight and obesity increased in all organ groups except heart Tx, where the prevalence of obesity peaked at 2 years post-Tx.

Kidney Tx



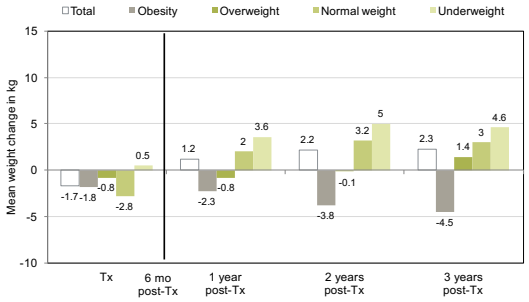
	Tx	1 year post-Tx	2 years post-Tx	3 years post-Tx
Total, n (SD)	777 (5.8)	733 (4.6)	684 (5.5)	624 (6.3)
Under-weight, n (SD)	19 (3.1)	19 (2.5)	17 (6.1)	17 (6.3)
Normal weight, n (SD)	309 (5.2)	299 (4.1)	277 (4.9)	246 (5.4)
Over-weight, n (SD)	292 (5.7)	274 (4.2)	263 (4.7)	248 (5.4)
Obesity, n (SD)	157 (6.7)	141 (6.3)	127 (7.6)	113 (9.0)

Liver Tx



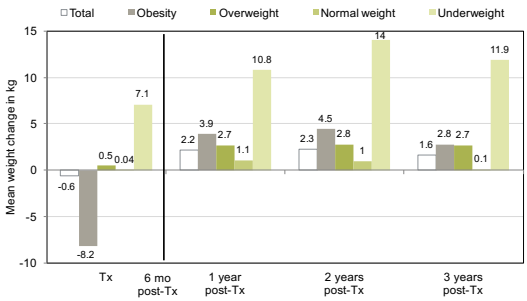
	Tx	1 year post-Tx	2 years post-Tx	3 years post-Tx
Total, n (SD)	255 (8.5)	225 (5.4)	197 (8.2)	162 (10.4)
Under-weight, n (SD)	18 (6.5)	16 (4.9)	12 (3.3)	11 (10.2)
Normal weight, n (SD)	150 (8.1)	131 (5.0)	109 (7.4)	93 (8.7)
Over-weight, n (SD)	72 (9.1)	64 (6.1)	62 (9.0)	48 (10.6)
Obesity, n (SD)	15 (11.4)	14 (6.3)	14 (12.5)	10 (21.0)

Lung Tx



	Tx	1 year post-Tx	2 years post-Tx	3 years post-Tx
Total, n (SD)	151(7.5)	140 (4.9)	125(6.7)	116 (8.0)
Under-weight, n (SD)	22 (5.9)	20 (5.0)	18 (7.7)	13 (8.3)
Normal weight, n (SD)	81 (7.1)	76 (3.9)	68 (5.6)	67 (6.7)
Over-weight, n (SD)	40 (8.0)	36 (5.3)	33 (7.3)	29 (9.1)
Obesity, n (SD)	8 (10.9)	8 (6.6)	6 (7.1)	7 (11.4)

Heart Tx

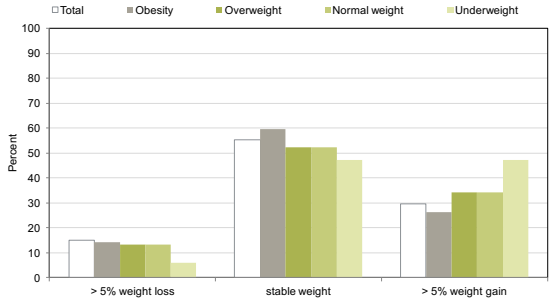


	Tx	1 year post-Tx	2 years post-Tx	3 years post-Tx
Total, n (SD)	97 (8.2)	90 (4.6)	89 (6.5)	81 (7.5)
Under-weight, n (SD)	2 (4.2)	2 (1.1)	2 (4.2)	2 (4.3)
Normal weight, n (SD)	48 (6.7)	44 (3.5)	45 (4.8)	41 (5.8)
Over-weight, n (SD)	36 (8.1)	34 (4.6)	33 (7.1)	30 (8.1)
Obesity, n (SD)	11 (11.0)	10 (6.7)	9 (8.9)	8 (11.1)

Footnote: Mean weight changes in kg were calculated as the differences between each measurement point and the reference weight at 6 months post-Tx, which is the initial value in the graph. At the time of Tx, the bars with positive values indicate a higher mean weight compared to the measure at 6-months post-Tx, corresponding to weight loss between Tx and 6 months thereafter. Bars with a negative value indicate a lower mean weight, corresponding to weight gain in this timeframe. After Tx, the bars with positive values indicate a higher mean weight compared to the measure at 6-months post-Tx, corresponding to weight gain beyond 6 months. Bars with a negative value indicate a lower mean weight, corresponding to weight loss.
Tx, transplant; SD, standard deviation

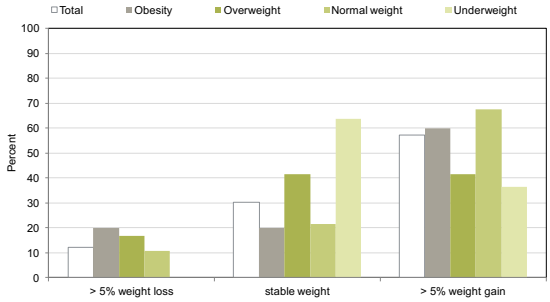
Figure 2. Mean weight changes in kg compared to the 6-month reference weight by BMI category at 6 months after kidney, liver, lung and heart Tx**.**
Source: Own Illustration

Kidney Tx



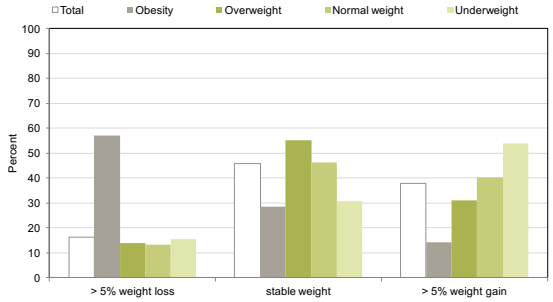
	>5% weight loss	stable weight	>5% weight gain
Total, n	93	345	186
Underweight, n	1	8	8
Normal weight, n	33	129	84
Overweight, n	35	148	65
Obesity, n	24	60	29

Liver Tx



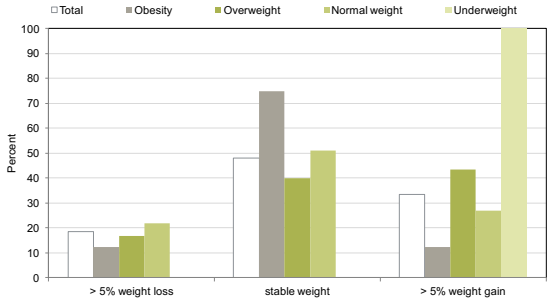
	>5% weight loss	stable weight	>5% weight gain
Total, n	20	49	93
Underweight, n	0	7	4
Normal weight, n	10	20	63
Overweight, n	8	20	20
Obesity, n	2	2	6

Lung Tx



	>5% weight loss	stable weight	>5% weight gain
Total, n	19	53	44
Underweight, n	2	4	7
Normal weight, n	9	31	27
Overweight, n	4	16	9
Obesity, n	4	2	1

Heart Tx

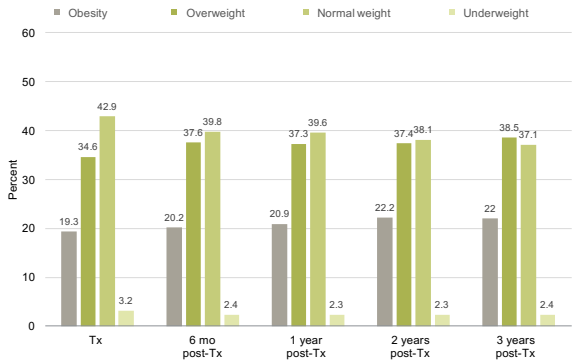


	>5% weight loss	stable weight	>5% weight gain
Total, n	15	39	27
Underweight, n	0	0	2
Normal weight, n	9	21	11
Overweight, n	5	12	13
Obesity, n	1	6	1

Footnote: Mean weight changes in % categories were calculated as differences between the measure at 6 months and 3 years post-Tx. Weight categories were defined as weight loss (losing >5% weight), stable weight (weight change between -5% and 5%), and weight gain (gaining >5% weight).

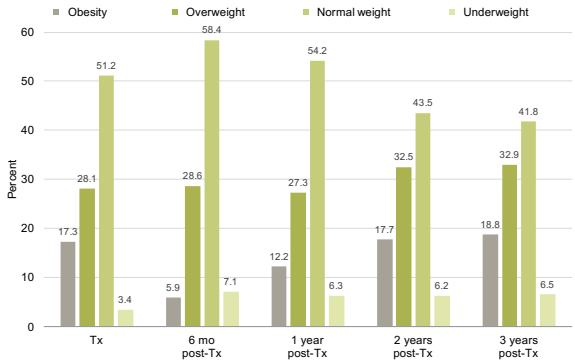
Figure 3. Weight changes in % categories from 6 months to 3 years after kidney, liver, lung and heart Tx using 6 month BMI category as reference value.
Source: Own Illustration

Kidney Tx



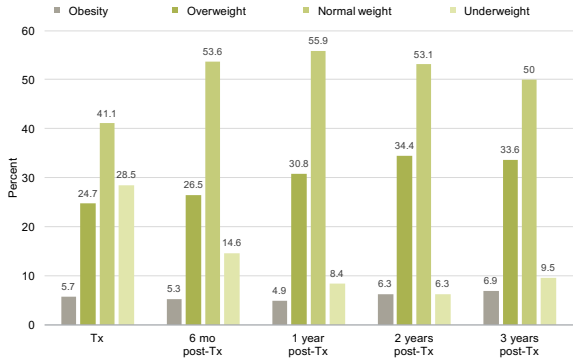
	Tx	6 mo post-Tx	1 year post-Tx	2 years post-Tx	3 years post-Tx
Total, n	792	777	738	688	628
Underweight, n	25	19	17	16	15
Normal weight, n	340	309	292	262	233
Overweight, n	274	292	275	257	242
Obesity, n	153	157	154	153	138

Liver Tx



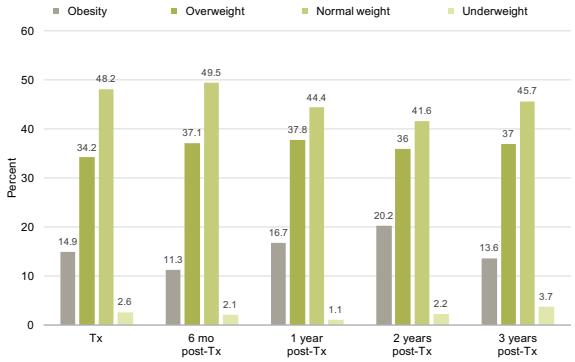
	Tx	6 mo post-Tx	1 year post-Tx	2 years post-Tx	3 years post-Tx
Total, n	295	255	238	209	170
Underweight, n	10	18	15	13	11
Normal weight, n	151	149	129	91	71
Overweight, n	83	73	65	68	56
Obesity, n	51	15	29	37	32

Lung Tx



	Tx	6 mo post-Tx	1 year post-Tx	2 years post-Tx	3 years post-Tx
Total, n	158	151	143	128	116
Underweight, n	45	22	12	8	11
Normal weight, n	65	81	80	68	58
Overweight, n	39	40	44	44	39
Obesity, n	9	8	7	8	8

Heart Tx

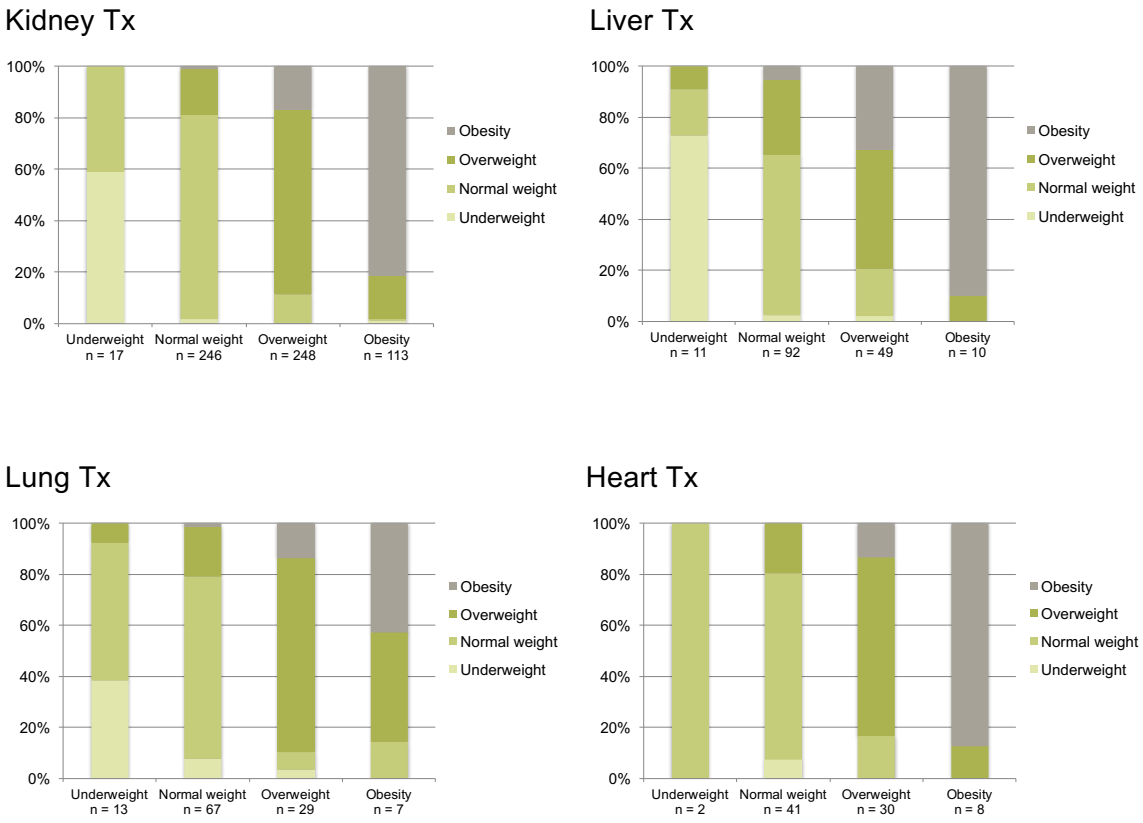


	Tx	6 mo post-Tx	1 year post-Tx	2 years post-Tx	3 years post-Tx
Total, n	114	97	90	89	81
Underweight, n	3	2	1	2	3
Normal weight, n	55	48	40	37	37
Overweight, n	39	36	34	32	30
Obesity, n	17	11	15	18	11

Tx, transplant

Figure 4. Proportion of patients per BMI category at each measurement from Tx to 3 years after kidney, liver, lung and heart Tx
Source: Own Illustration.

The shift among BMI categories from 6 months to 3 years after kidney, liver, lung, and heart Tx is shown in Figure 5. Shifting upwards one or even two BMI categories over the observation period was common in all organ groups. In liver and lung Tx, 9.1% and 7.7% of underweight patients became overweight, respectively. In kidney, liver, and lung Tx, 1.2%, 5.4%, and 1.5% of normal weight patients became obese, respectively. In all organ groups, the majority of patients who were obese at 6 months post-Tx remained obese at 3 years post-Tx (i.e., kidney: 81.4%; liver: 90%; lung: 42.9%, and heart 87.5%). The cumulative incidence of obesity at 3 years after kidney, liver, lung, and heart Tx was 18.1%, 38.1%, 15.3%, and 13.3%, respectively.



Footnote: This analysis included only patients with data at 6 months and 3 years post-Tx. The bars reflect patients' individual weight change trajectories between the two measurement points, leading to a possible subsequent shift to another BMI category.

Figure 5. Shift among BMI categories from 6 months to 3 years after kidney, liver, lung and heart Tx**.**
Source: Own Illustration.

3.5 Discussion

In a nationwide prospective cohort, we simultaneously examined the evolution of different weight parameters such as weight in kg and % categories as well as BMI up to 3 years after kidney, liver, lung, and heart Tx, thereby allowing a rigorous comparison of the results among all four Tx groups. Although post-Tx weight gain was common in all populations, our analysis revealed differing patterns among and within the specific organ groups.

Weight changes related to the reference weight at 6 months

All organ Tx groups had a steep weight increase from 6 months to 1 year post-Tx that leveled off on average after 2 years post-Tx. Importantly, kidney and lung Tx patients had already gained a comparable amount of weight in the very early postoperative period, that is, in the first 6 months following Tx. Liver Tx recipients showed a different pattern of weight loss, which might be explained by the loss of ascites and edema following Tx. Our results confirm previous findings of post-Tx weight gain, especially in the first year after Tx.[7,15,25] However, with regard to the timeframe used in our analysis (from 6 months to 1 year), the mean weight gain in the Swiss Tx populations is still slightly lower than that of international studies in liver (means of 3 kg and 4 kg),[16,25] lung (mean 3.4 kg),[15] and heart Tx patients (mean 2.3 kg).[15] Studies in kidney Tx examined post-Tx weight gain only from time of Tx to 1 year post-Tx (means ranging from 2.3 kg to 10.3 kg).[7,8,17,26,27] Considering the era from Tx to 1 year after Tx, the kidney Tx patients in our study would have gained 2 ± 6.8 kg, which is lower compared to the European and US samples.[7,8,17,26,27] The relatively low mean weight gain in our Swiss cohort is an encouraging result, as it may reflect a rather healthy lifestyle and high self-perceived general state of health, as has been reported in the Swiss general population.[28]

While there is consensus that post-Tx weight gain occurs independently of pre-Tx BMI, the analysis based on BMI categories provided a more detailed picture. Some studies in kidney, liver, lung, and heart Tx have reported the highest weight gain in patients who were under- or normal weight at the time of Tx.[5,9,27,29] Our findings in kidney, lung, and heart Tx are congruent with those studies, although our analyses were based on weight change in relation to BMI category at 6 months post-Tx. In liver Tx, we found the highest post-Tx weight gain in those who were normal weight or obese at 6 months after Tx. This result was also reflected in the analysis of weight change by percentage category. Nearly 60% of the whole liver Tx population gained >5% weight between 6 months and 3 years post-Tx. This group mainly consisted of patients who were normal

weight (67.7%) or obese (60%) at 6 months post-Tx, while the majority of underweight patients retained a stable weight. Again, this pattern differed from those of the other organ groups, in which by the majority the underweight patients were among those who gained >5% weight.

Moderate weight gain, especially in underweight patients, can be desirable, as it reflects a state of recovery after severe illness or malnutrition. Therefore, weight gain at 1 year post-Tx has been associated with increased 5-year patient and graft survival after liver Tx[30] and with better patient survival in after lung Tx.[31] However, independent of initial BMI, excessive weight gain carries also risks that may contradict such benefits. A >5% BMI increase at 1 year post-kidney Tx increased the risk of graft loss threefold;[8] and a ≥10% weight gain at 2 years post-Tx was associated with subsequent mortality.[7] As post-Tx weight gain is also associated with negative patient outcomes, our detailed results facilitate the premature identification of patients who might be at increased risk of higher post-Tx weight gain.

The evolution of BMI categories

Our analysis of cross-category BMI shifts showed that 41.2% of underweight kidney Tx patients who gained weight between 6 months and 3 years post-Tx managed to achieve normal weight. Two underweight patients - from the liver and lung Tx groups - actually even became overweight. In non-underweight patients, weight gain contributed to an incidence of obesity between 13.3% and 18.1% at 3 years post-Tx, with liver Tx patients having the highest incidence, at 38.1%. This finding exceeds the results of a UK study (n = 597) that reported a 26.3% incidence of obesity at 3 years post-Tx among liver patients who were non-obese at the time of Tx.[32] Interestingly, that study reported higher post-Tx weight gain than ours from 6 months to 3 years (median: 7.7 versus 4 kg).

Among all organ groups, the majority of patients who were overweight or obese at 6 months post-Tx remained so over time, which is in line with previous results.[5] Considering that we calculated our patients' reference BMI at 6 months post-Tx, this is particularly worrisome, as by that time they should have recovered from potential ascites and edema, and a BMI ≥30 kg/m^2 could be considered as an unbiased measure of obesity. Given that Tx recipients with higher BMI values are already at increased risk of post-Tx metabolic and cardiovascular comorbidities[6], these results call for interventions to reduce or prevent post-Tx obesity. However, we also found a promising result in lung Tx patients. Of that group's obese patients, 57.2% shifted downwards to overweight or normal weight. Drivers for this development might include either close Tx

center follow-up care, which supports the implementation of weight loss behaviors, or the recipients' renewed ability to engage in physical activity. Although exercise capacity remains limited after lung Tx,[33] previous studies showed that the amount and intensity of post-Tx physical activity increased significantly compared to pre-Tx.[34]

Still despite a small proportion of obese Tx recipients who lost weight over time, our overall prevalence of obesity increased after kidney, liver, and lung Tx. Although obesity has become a global public health issue, its prevalence varies tremendously across national populations[35] and is reflected in national Tx populations.[36] Due to these disparities and additional methodological challenges (e.g., operationalization of variables, study design, inclusion criteria), a reliable comparison to previous studies is normally difficult. However, a German study also examined the four solid organ Tx groups simultaneously up to 1 year post-Tx.[5] In their graphs, they showed equal pre-Tx obesity rates in kidney and liver Tx, while their prevalence in lung and especially in heart Tx was clearly lower compared to our results. With regard to the evolution of BMI over the first year after Tx, the German Tx population showed the same pattern as our Swiss samples.

In order to better classify the results of our study, we compared our patients' BMI with the general Swiss population. The most recent rate for overweight in Swiss persons 16 or older is 30.8%.[28] In liver and lung Tx groups, the rates were similar to that of the general population, while in kidney and heart Tx, the percentages of overweight patients were higher at all measurement points. With regard to obesity, the comparison between Tx patients and the general population was more alarming. As the national average is 10.3%, obesity in kidney Tx was roughly twice this value at all measurement points. Although the prevalence rates of obesity in liver and heart Tx were lower compared to the kidney Tx patients, their values later than 1 year post-Tx were still above the level of the Swiss general population.

This study is subject to several limitations. First, BMI subgroup analyses are based on small sample sizes, especially in the heart and lung Tx groups. Second, the STCS dataset provides no measures on waist circumference or body composition. Third, an earlier measurement than 6 months post-Tx might have been a more appropriate proxy to adjust the weight and BMI for pre-Tx ascites and edema. The examination of long-term pre-Tx data, preferably dating to before the onset of end stage organ disease, would provide more accurate information about the evolution of patients' body weight parameters. Despite these limitations, the STCS's systematic and homogeneous methodology limited the risk of bias and offered a unique opportunity to study and compare all four solid organ groups simultaneously. Our recommendations for future

research would be to investigate the evolution of body weight parameters in the long-term period after Tx and also examine predictors for weight gain in the specific organ groups such as pharmacological, behavioral, or genetic risk factors. Additionally, it would be important to incorporate the measurement of body composition and waist circumference, as this would allow a more detailed analysis regarding changes in the distribution of water, body fat, or muscle mass.

Conclusion

In our four Swiss solid organ Tx populations we found a relatively low mean post-Tx weight gain compared to international data. Nevertheless, the prevalence of obesity increased in all except the heart Tx group. The use of different weight parameters in our in-depth analyses revealed different patterns among the organ groups and BMI subgroups. Compared to kidney, lung, and heart Tx, the liver recipients had the highest post-Tx weight gain. They were the largest group of patients to increase their body weight by >5%, and had the highest incidence of obesity. Based on the BMI category at 6 months, underweight kidney, lung, and heart Tx patients gained more weight after Tx compared to those with a higher BMI category, while in liver Tx the obese and normal weight patients gained most weight. Except in lung Tx, the proportion of obese Tx patients was mostly higher compared to the Swiss general population. Our findings highlight the need for preventive interventions. Especially normal, overweight, and obese liver Tx should be targeted for interventions as they experience highest weight gain after Tx.

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Chapter 4. Pre- and Post-Transplant Factors Associated with Body Weight Parameters after Liver Transplantation – A Systematic Review and Meta-Analysis

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4.1 Abstract

Background: Weight gain and obesity can increase liver transplant (LTx) recipients' disease burden. We aimed to summarize and synthesize the evidence on pre- and post-transplant factors related to post-LTx BMI, weight gain, and obesity.

Methods: For this systematic review and meta-analysis we searched Medline via PubMed, Cochrane library, CINAHL, PsycINFO, and EMBASE for original quantitative studies on 6 classes of factor (i.e., genetic, sociodemographic, behavioral, biomedical, psychological, and environmental) linked to body weight parameters in adult first-time LTx patients. A 19-item instrument was used for quality assessment. Effect sizes and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for relationships investigated in ≥5 studies. Factors investigated in <5 studies were summarized and described.

Results: Of 16495 articles retrieved, 43 assessed factors in liver transplantation. These examined 82 mainly biomedical and sociodemographic factors. However, variation between definitions allowed inclusion of only 2 factors (i.e., tacrolimus, cyclosporine) in our meta-analyses of 6 studies examining a shared parameter for body weight (median patient sample: 171 (range: 63 - 455); Europe n = 3; United States n = 3; publication years: 1997 - 2015). Neither tacrolimus (OR, 0.75; 95% CI, 0.47-1.21; p = 0.24) nor cyclosporine (OR, 1.40; 95% CI, 0.89-2.18; p = 0.14) were related significantly with post-LTx obesity.

Conclusions: Evidence on factors, especially modifiable ones, related to post-LTx body weight parameters is still scarce, as heterogeneity among factor definitions limits data extraction and the performance of meta-analyses. To facilitate future research, studies should apply theoretical frameworks to guide their study design, select variables of interest and systematically examine interrelationships among selected factors.

4.2 Background

Obesity, defined as a body mass index (BMI) ≥30 kg/m^2, has become a major health issue in the liver transplant (LTx) population. An analysis of the Scientific Registry of Transplant Recipients in the United States (US) revealed that, from 2001 to 2011, reflecting a general worldwide trend towards rising BMI values,[1] the prevalence of obesity in LTx candidates rose from 29% to 34.4%.[2] Post-LTx weight gain increases this figure further in the recipients. Independent of geographical region or research era, obesity increased from pre-LTx to 1 year post-LTx in studies from the US (14.5% to 23.8%),[3] the United Kingdom (12.6% to 23.7%),[4] and Poland (1.3% to 14.7%).[5] However, these

values must be evaluated carefully, as their reported measurements do not necessarily account for pre-LTx fluid overload (e.g., edema), which biases measurement of BMI, i.e., body weight in kilograms divided by the square of height in meters (kg/m^2). As this would falsely inflate the prevalence of obesity at LTx, the rise of its post-LTx prevalence may be even more pronounced. In fact, a recent Swiss prospective cohort study measuring weight gain between 6 months and 3 years post-LTx noted a mean weight gain of 4.8 kg, which increased the prevalence of obesity in their sample from 5.9% to 18.8%.[6]

In general, weight gain is the result of complex interactions between biological (including genetic), behavioral, social and environmental factors.[7] Post-LTx weight gain is often attributed to immunosuppressive medication–especially prednisone, as its side effects include enhanced appetite, a craving for sweets and increased intake of high-fat foods.[8,9] However, not all available evidence supports this relationship.[10,11] Conflicting results have also been reported in view of other biomedical (cyclosporine),[5,11,12] socio-demographic (age and gender)[3-5,11], and behavioral factors (current and former smoking).[3,11,12] However, a clear understanding of post-LTx body weight factors is important as both weight gain and obesity are associated with metabolic syndrome.[13,14] As the LTx population is already exposed to a higher risk for metabolic and cardiovascular diseases because of the immunosuppressive medications,[15-19] the possibility that obesity might exacerbate their burden of disease, is worrisome.

Examining risk factors for post-LTx body weight parameters offers three main advantages: it identifies patients at risk for weight gain and subsequent obesity; it facilitates understanding of pathways to weight gain; and it exposes modifiable risk factors. Together, these provide a firm basis upon which to develop preventive interventions against weight gain and obesity.[20,21] Therefore, the primary aim of this systematic review and meta-analysis was to summarize and synthesize the evidence regarding pre- and post-LTx risk factors influencing body weight parameters such as BMI, obesity, and weight gain.

4.3 Methods

The methodology of this systematic review and meta-analysis followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.[22] Reporting was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: PRISMA statement.[23] The review protocol was registered in the

international prospective register of systematic reviews (PROSPERO, registration number: CRD42014009151) and published.[24]

Information sources and search strategy

We searched the following electronic databases without limits: Medline via PubMed, Cochrane library, CINAHL, PsycINFO, and EMBASE. To identify relevant additional studies, we screened reference lists of studies in included in data extraction. The search string was developed according to PICOS criteria (Participants, Interventions/Exposure, Comparisons, Outcomes/Topics, Study design). To allow a broad variety of search results, search strings were restricted to two concepts: 'participants' and 'exposure'. The first string was developed for PubMed (see Table 1) and later translated for the remaining databases in collaboration with a librarian. The first search was conducted March 17, 2014 and updated February 3, 2016. As the project aimed to examine risk factors related to body weight parameters in kidney, liver, heart and lung transplant populations, the search strategy included all solid organ groups.[24] However, this article only reports the risk factors affecting the LTx population.

(("Body Mass Index"[Mesh] OR "obesity"[Mesh] OR "overweight"[MeSH Terms] OR "Weight Gain"[Mesh] OR "Body Weight Changes"[Mesh:noexp] OR "Body Weight"[Mesh:noexp]) OR ("BMI"[Text Word] OR "Body Mass Index"[Text Word] OR "obesity"[Text Word] OR "overweight"[Text Word] OR "weight gain"[text word] OR "body weight change*"[Text Word] OR "body weight"[Text Word] OR "weight"[Text Word] OR "Ideal Body Weight"[Mesh] OR "weight management"[Text Word] OR "body size"[Text Word]) AND ("organ transplant*"[Text Word] OR "transplant*"[Text Word] OR "heart transplant*"[Text Word] OR "liver transplant*"[Text Word] OR "lung transplant*"[Text Word] OR "kidney transplant*"[Text Word]) OR ("Kidney Transplantation"[Mesh] OR "Lung Transplantation"[Mesh] OR "Heart Transplantation"[Mesh] OR "Liver Transplantation"[Mesh] OR "Organ Transplantation"[Mesh:noexp] OR "Transplantation"[Mesh:noexp]))

Table 1. Detailed PubMed search string
Source: Own Illustration.

Inclusion and exclusion criteria

Studies were included if they met following criteria: (1) original quantitative or mixed-method study design; (2) first-time liver, heart, lung or kidney transplant candidates or recipients aged ≥18 years; (3) examination of risk factors or correlates associated with post-LTx body weight parameters; (4) study reported in English, German, Dutch or French; and (5) full text available. Studies with other than original quantitative or mixed-method study design (e.g., case reports, reviews, editorials, letters to the editor, qualitative research), focusing on re-transplanted or multi-organ transplant recipients, or not examining any relationship between body weight parameters and other variables, were excluded.

Study selection

In accordance with the inclusion and exclusion criteria, title and abstract screening (stage 1), then full text reading (stage 2) were performed by three researchers (SB, GD, NN) for the first search, and by two researchers for the 2016 search update (SB, GD). In both stages of the study selection process, the studies were divided into equal work packages. Each researcher independently evaluated the studies of the allocated work package. For feasibility reasons, as the first literature search retrieved 13367 hits, we deviated from the Cochrane Collaboration recommendation that at least two people should independently select studies and then verify all results.[22] For quality monitoring, the study selection process was first pilot-tested and evaluated in 50 studies for stage 1 and in 6 studies for stage 2. Researchers then cross-checked a random sample of 10% of one another's in- and exclusion decisions. Disagreements were resolved by discussions with a third researcher (SDG) until consensus was reached.

Data extraction and management

Data extraction was performed independently by two researchers (SB, GD). In case where an article provided either insufficient data for extraction or conflicting information, the author was contacted for additional information at most twice via e-mail or research network platforms. The following general variables were extracted: *general information* (author, year, journal, continent, country, language, setting, database, study design, time of transplant), *population* (donor, etiology of liver disease, model of end-stage liver disease score, sample size, age, gender, race, follow-up time, correction for ascites, definition of BMI categories), details on *statistical analysis*, and *body weight parameters* (BMI and BMI category at LTx and post-LTx, as well as post-LTx weight gain). For the purposes of this study, we defined the most commonly used BMI classification–that proposed by the World Health Organization (WHO)–as an accurate outcome measure: underweight: <18.5 kg/m^2; normal weight: 18.5-24.9 kg/m^2; overweight: 25-29.9 kg/m^2; and obesity ≥ 30 kg/m^2.[25]

As weight gain and obesity result from a complex interplay of factors,[7] we used a previous extensive overview[26] to develop a guiding framework, and categorized pre- and post-LTx factors as follows: *genetic* (e.g., single genes, family history of overweight), *sociodemographic* (e.g., age, gender, education, marital status, income level, working status), *behavioral* (e.g., energy intake, energy expenditure, physical activity, smoking), *biomedical* (e.g., BMI category, end-stage organ disease, hemodialysis, medication), *psychological* (e.g., stress, quality of life), and *environmental* (e.g., public transportation, availability of exercise areas).

Quality assessment

Study quality was assessed independently by two researchers (SB, GD) via a 19-item instrument (see table 2), which was adapted from two other tools: the 27-item Downs and Black checklist[27] and a quality assessment instrument used for Duerinckx et al.'s 2016 systematic review.[28] The results of the quality assessment were visualized via the Cochrane Risk of Bias summary figure provided by Cochrane Review Manager 5.3).[29]

No	Question	Definition	Rating
Aim			
1	Is the **hypothesis / aim / objective** of the study clearly described?		• Yes • No • Unable to determine
2	Does the study have a **prospective** design?	Yes: • Prospective data collection	• Yes • No • Unable to determine
Participants			
3	Are the **characteristics of** the **patients** included in the study clearly **described**?	Yes: • Cohort studies and trials: inclusion and/or exclusion criteria given • Case-control studies: a case-definition and source for controls is given No: • No information about precise age, multi-organ or re-transplant	• Yes • No • Partially
4	Were the **subjects asked / chosen** to participate in the study **representative of the entire population** from which they were recruited? Meaning: Identify the source population for patients and describe how the patients were selected	Yes: • Sample comprises the entire source population • Unselected sample of consecutive patients • Random sample • Patients from more than one center or study setting included No: • Single center setting Unable to determine: • Study does not report the proportion of the source population from which the patients are derived	• Yes • No • Unable to determine
5	Were the **patients** in different intervention groups (trials and cohort studies) or	Yes: • Patients for all comparison groups were selected from the same hospital / popula-	• Yes • No • Unable to de-

No	Question	Definition	Rating
	were the cases and controls (case-control studies) recruited **from the same population**?	tion / cohort Unable to determine: • In cohort and case-control studies: no information concerning the source of patients included	termine
6	Were study **subjects** in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) **recruited over the same period of time**?	Yes: • All patients recruited over the same period of time Unable to determine: • Time period over which patients were recruited for the study is not specified	• Yes • No • Unable to determine
7	Were **losses** of patients **to follow-up** taken into account?	Yes: • If the proportion lost to follow-up was too small to affect the main findings Unable to determine: • Numbers of patients lost to follow-up are not reported	• Yes • No • Unable to determine
Outcomes			
8	Are the **main outcomes** to be measured clearly **described in** the **introduction or methods** section?	No: • If main outcomes are first mentioned in the results • No cutoffs for BMI categories given	• Yes • No • Partially
9	Were the **main outcome measures** used **accurate** (valid and reliable)?	Yes: • Outcome measures clearly described (psychometrics, values) • Studies referring to other work or demonstrate the outcome measures are accurate (reference given) No: • Not WHO definition for BMI categories	• Yes • No • Unable to determine
10	Are the **variables of interest** clearly **described**?	Yes: Clear description of content such as • Changes of weight, BMI • Risk factors • Consequences / outcomes	• Yes • No • Partially
Results			
11	Are the **main findings** of the study clearly **described**?	Yes: • Simple outcome data reported for all major findings	• Yes • No • Partially

No	Question	Definition	Rating
		This question does not cover statistical tests.	
12	Have **actual probability values** been reported for the main outcomes **except** where the probability value is **< 0.001**?	Yes: • 0.035 rather than <0.05	• Yes • No • Partially
13	Does the study provide **estimates** of the **random variability** in the data for the main outcomes?	Yes: • According distribution of data, results include: – Non-normal: IQR – Normal: SE, SD or CI • If distribution of data is not described, it must be assumed that the estimates were appropriate	• Yes • No • Partially
14	Are **principal confounders** influencing the outcome clearly **described**?	Yes: • List of principal confounders is provided	• Yes • No • Partially
Analysis			
15	In trials and cohort studies, do the **analyses adjust for different lengths of follow-up** of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes: • Follow-up was the same for all study patients • Different lengths of follow-up were adjusted for (e.g. survival analysis) No: • Differences in follow-up are ignored	• Yes • No • Unable to determine
16	Were the **statistical tests** used to assess the main outcomes **appropriate** according to the data and the aims?	Yes: • Analysis clearly described • Little statistical analysis but no evidence of bias • Risk factors: Multivariate analysis • Small sample size: nonparametric methods • If distribution of the data is not described it must be assumed that the estimates used were appropriate	• Yes • No • Partially
17	Was there adequate **adjustment for confounding** in the **analyses** from which the main findings were	Randomized studies: No: • Main conclusions of the study were based on analyses of treatment rather than inten-	• Yes • No • Unable to determine

No	Question	Definition	Rating
	drawn?	tion to treat • Distribution of known confounders in the different treatment groups was not described or not taken into account in the analyses Non-randomized studies: No: • The effect of the main confounders was not investigated • Confounding was demonstrated but no adjustment was made in the final analyses	
18	Was the **sample size appropriate**?	Yes: • A priori sample size justification • At least 104+x if testing individual predictors variables • At least 50+8x subjects x is the number of independent/ predictors variables for testing a multiple correlation	• Yes • No • Unable to determine
19	**Reproducibility** of the study on the basis of the description of methods and outcomes	Yes: • Enough details described that the study could be repeated accurately • If yes in question: 18, 16, 10, 9, 8, 3	• Yes • No • Partially

BMI, Body Mass Index; WHO, World Health Organization; IQR, interquartile range; SE, standard error; SD, standard deviation; CI, confidence interval

Instrument adapted from the 27-item checklist by Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomized and non-randomized studies of health care interventions. J Epidemiol Community Health. 1998;52(6):377-384.

Table 2. Quality assessment instrument
Source: Own Illustration.

Data analysis

Study characteristics were presented using descriptive statistics. Where mean values for age or BMI were only provided for subgroups, a weighted mean was calculated for the total sample. Only risk factors assessed in ≥5 studies were included in the meta-analysis. Effect sizes were calculated to analyze the strengths and directions of relationships, and were expressed as odds ratios (OR) for associations between risk factors and post-LTx body weight parameters. All effect sizes were reported with the corresponding 95% confidence intervals (CIs). Because we expected sample heterogeneity among the primary studies, estimated effects were pooled using a random-effects model. The included studies' heterogeneity was assessed using both the Cochran Q test (with a p value <0.1 indicating significant heterogeneity) and I^2 statistics, with val-

ues of 25%, 50%, and 75% respectively indicating moderate low, moderate, and high heterogeneity.[30] Subgroup analyses using year of publication and geographical location as moderators were conducted with meta-analytic versions of regression (for continuous moderators) and ANOVA (for dichotomous moderators). Risk factors assessed in <5 studies were grouped within their categories and classed as significant or nonsignificant based on their relationship with the body weight parameter. The results were summarized graphically. All analyses were conducted using Comprehensive Meta-Analysis software (Biostat, Inc., Englewood, NJ, USA).

4.4 Results

Study selection and assignment to the categories

The study selection process is shown in Figure 1. Of 16495 initial references, 43 studies in LTx met the inclusion criteria. These assessed 82 distinct pre-and post-LTx factors in relation to any of the 3 body weight parameters (i.e., post-LTx BMI, obesity and weight gain). Overall, factor definitions varied hugely, which limited pooling to groups of at least 5 studies examining the same factor in relation to the same body weight parameter of interest. Two factors (i.e., tacrolimus and cyclosporine) were examined in 6 studies vis à vis post-LTx obesity, making them eligible for data extraction and meta-analysis.[13,31-35]

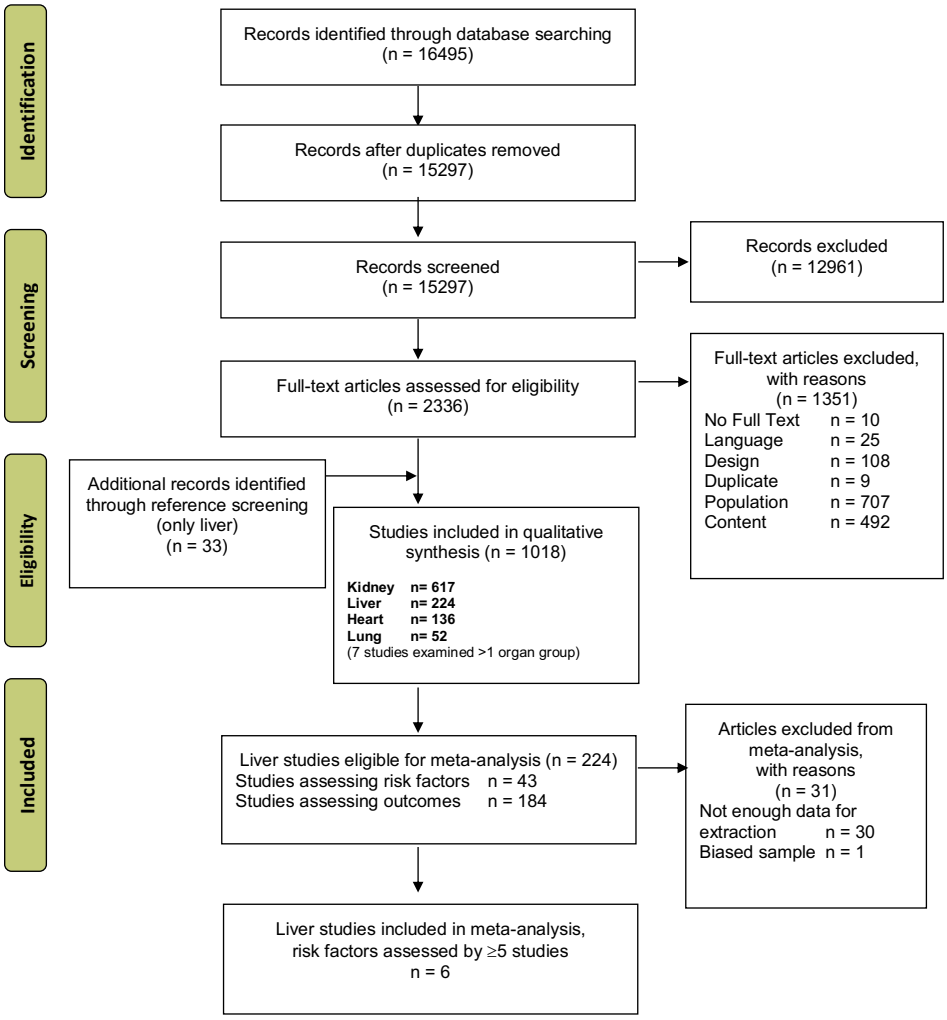
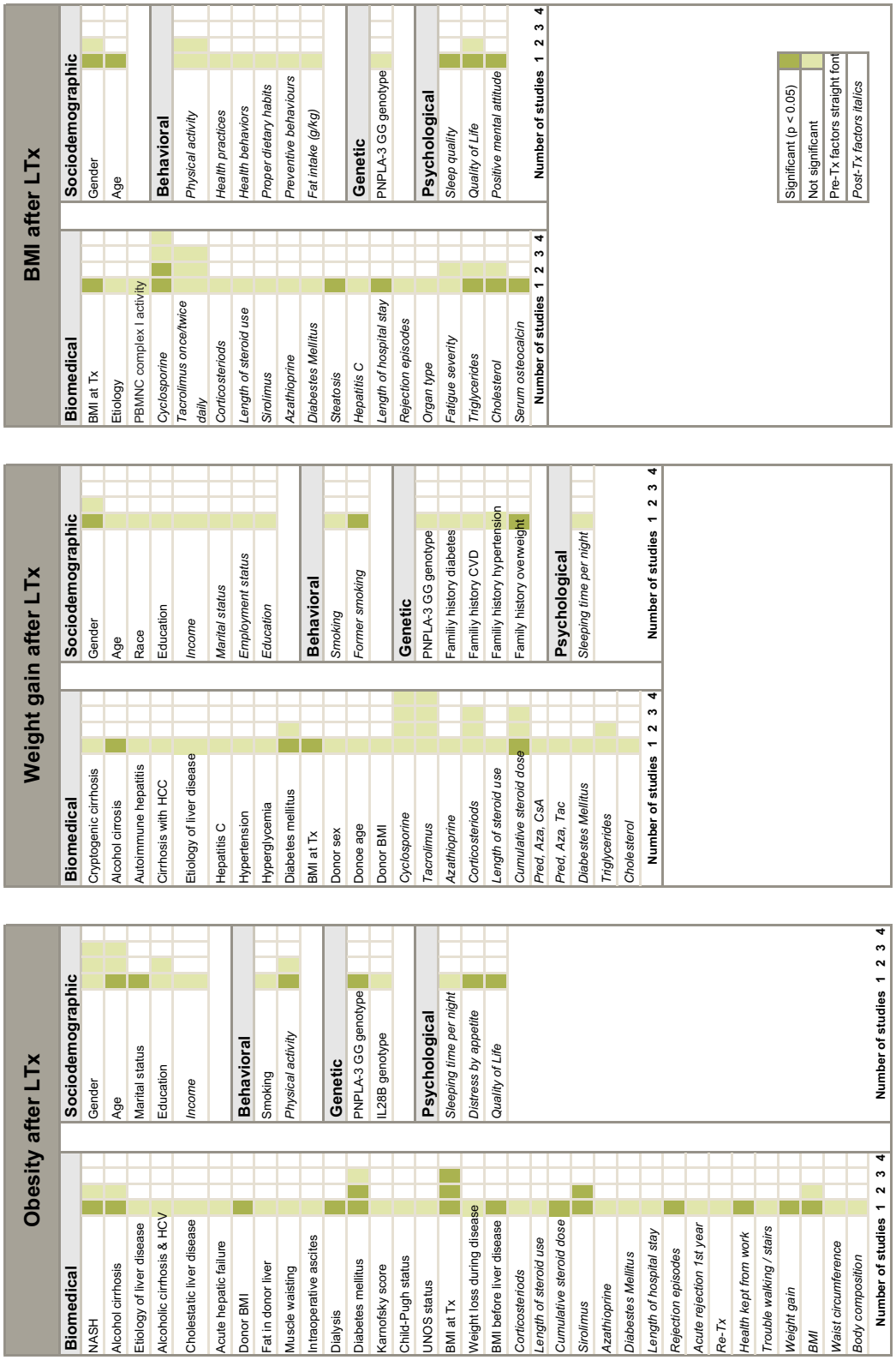


Figure 1. Flowchart according to PRISMA statement.
Source: Own Illustration.

Summary of factors examined in relation to post-LTx body weight parameters

Figure 2 shows an overview of factors studied in fewer than 5 studies in relation to post-LTx BMI, obesity and weight gain. The majority of factors examined were categorized as biomedical and sociodemographic. Within the pre-LTx biomedical factors, diabetes mellitus and BMI were studied 5 times in relation to either BMI, obesity or weight gain and represented the highest number of significant results relative to the total number of studies (respectively 3/5 and 5/5). Among the post-LTx biomedical factors of interest, 4 types of immunosuppressive medication were frequently examined in relation to the 3 body weight parameters, but generally yielded low proportions of significant results: steroids (2/12), cyclosporine (2/8), tacrolimus (0/7), and sirolimus (2/3). In the group of pre-LTx sociodemographic factors, gender and age were studied most frequently, both with mixed results regarding their impact (2/7 and 2/5). Very few studies examined behavioral, genetic or psychological risk factors; none examined environmental factors.



NASH, nonalcoholic steatohepatitis; HCV, hepatitis C Virus; BMI, body mass index; UNOS, United Network for Organ Sharing; Tx, transplantation; HCC, hepatocellular carcinoma; Pred, prednisone; Aza, Azathioprine, CsA, cyclosporine; Tac, Tacrolimus; CVD, cardiovascular disease

Figure 2. Pre- and post-LTx risk factors of post-LTx obesity, weight gain and BMI assessed by 1 to 4 studies.
Source: Own Illustration

Study Year	Country	Design Set-ting	Time of LTx	Follow up	Partici-pants, n	Male gender, (%)	Age at LTx, mean ± SD, median (range)	BMI at LTx, mean ± SD	Patients in different BMI categories[§] at LTx, n (%)
Akarsu et al. 2013	Turkey	Retrospective cohort study, single center	01.2001 - 01.2010	5 years	226	66.8	46.19 ± 10.2	25.7 ± 4.2	Underweight°: 13 (5.8) Normal weight[#]: 96 (42.5) Overweight: 84
Bianchi et al. 2006	Italy	Retrospective cohort study, single center	06.2001 - 09.2003	median 40 mo (range 6-164)	230	66.1	53 (18-66)	26 ± 4	Overweight: 120 (52) Obese: 25 (11)
Canzanello et al. 1997	U.S.	Retrospective cohort study, single center	NA	1 year	63	39.7	47.9*	25.98*	Obese": 15 (23.8)
Fernandez-Miranda et al. 2002	Spain	Case control study, single center	11.1986 - 03.1995	median 102 mo (range 60-168)	116	64.6	51.2 ± 12.6	26.2 ± 4.8	Obese: 26 (22.4)
Fussner et al. 2015	U.S.	Retrospective cohort study, single center	12.1998 - 12.2004	8 - 12 years	455	64	51.8 ± 10.3	26 ± 8	NA
Rabkin et al. 2002	U.S.	Case control study, single center	1994 - 1998	3 years	87	62	46.7*	NA	Obesity defined as indicated diagnosis, sample size NA

LTx, liver transplantation; SD, standard deviation; BMI, body mass index; NA, not available; mo, months
* Calculated weighted mean
§ categories defined according to WHO, otherwise indicated:
° BMI: <20 kg/m^2, # BMI: 20-24.9 kg/m^2, " ≥ 27.8 kg/m^2 in men, ≥ 27.3 kg/m^2 in women

Table 3. Characteristics of studies included in meta-analysis.

Characteristics of the studies included in meta-analysis

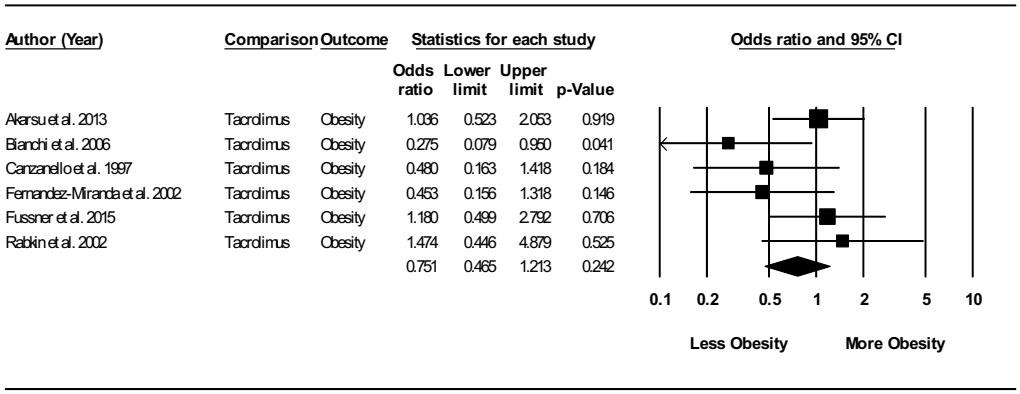
The characteristics of the 6 studies examining tacrolimus and cyclosporine as possible factors of post-LTx obesity are summarized in Table 3. All 6 were single-center studies from either Europe (n = 3, 50%) or the US (n = 3, 50%), and were published between 1997 and 2015. The median sample size was 171 patients (range, 63 – 455). Distributions of patients within BMI categories were not provided in all of the studies, nor were BMI category definitions used consistently. The final set of studies did not include companion papers.

Risk factors for post-LTx obesity

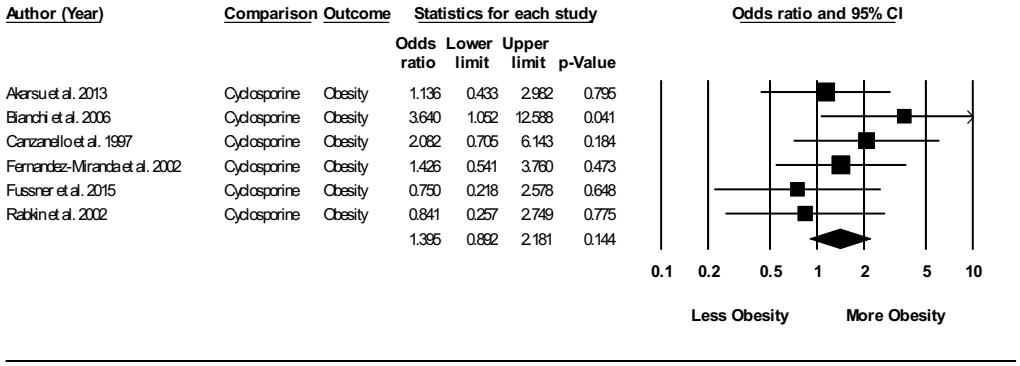
The 6 included studies, involving a total of 1177 participants, showed no association between tacrolimus and post-LTx obesity (OR, 0.75; 95% CI, 0.47-1.21; p = 0.24) (Figure 3). There was low but non-significant heterogeneity among the studies (Q, 7.12; I^2 = 29.75%; p = 0.21). Results of a subgroup analysis based on year of study publication was not significant (β = 0.05; p = 0.18); nor were those of a subgroup analysis based on where each study was conducted (Europe, including Turkey: mean OR, 0.56; 95% CI, 0.26-1.28; US: mean OR, 0.95; 95% CI, 0.506-1.791; p = 0.33).

Further, no association was shown between cyclosporine use and post-LTx obesity (OR, 1.40; 95% CI, 0.89-2.18; p = 0.14). Heterogeneity among the studies was non-significant (Q = 4.67; I^2 = 0.00%; p = 0.46). As with the tacrolimus analysis, cyclosporine yielded no significant differences in study effect sizes based on year of publication (β = -0.03, p = 0.34); and no difference was shown due to study location (Europe, including Turkey: mean OR, 1.64 95% CI, 0.871-3.088); US: mean OR, 1.15 05% CI, 0.59-2.25; p = 0.45).

Tacrolimus



Cyclosporine



CI, confidence interval

Figure 3. Forest plot of studies analyzing tacrolimus and cyclosporine in relation to post-LTx obesity in ≥5 studies.
Source: Own Illustration

Quality assessment

The results of the quality assessment are shown in Figure 4. All studies had retrospective study designs (n = 6, 100%); 4 (66.6%) had sample sizes large enough to test individual predictor variables. None used a theoretical framework to guide the research process or the selection of study variables; and none reported studying representative samples (selected via probability sampling). Three studies (50%) clearly described the patient characteristics needed to apply our systematic review's inclusion and exclusion criteria. All 6 adequately described the results and the variables of interest, i.e., the factors analyzed in relation to body weight parameters. Although 2 (33.3%) took confounders into account, none adjusted adequately for them in the analysis. Based on the methods described in the articles, 3 studies (50%) met the criteria for reproducibility.

4.5 Discussion

This systematic literature review summarized pre- and post-LTx factors relating to post-LTx BMI, obesity, and weight gain. In all, 82 factors were identified, mainly from the biomedical and sociodemographic categories. Behavioral, genetic or psychological factors were less frequently studied, while environmental factors were not examined in relation to any body weight parameter. As only tacrolimus and cyclosporine were addressed in more than 5 studies, they were the only factors eligible for meta-analysis. Neither tacrolimus nor cyclosporine was significantly associated with post-LTx obesity.

Examination of factors associated with body weight parameters

All factors were assigned to our predefined categories. As expected, the majority were biomedical or sociodemographic. Most are easily obtainable, as they are among the more common sample characteristics in single-center and database-related studies. In spite of a large initial search return, however, not enough articles were available to perform more meta-analyses, as the researchers' factor definitions varied too greatly. E.g., steroid use was defined as use of cortisone (yes/no), cumulative steroid dose, length of steroid use, or use of steroids in combination with other immunosuppressive drugs. This level of heterogeneity among definitions precluded meta-analyses to test for relationships between immunosuppressive drugs and weight-gain parameters, which still warrant further investigation.[9]

Following LTx, metabolic comorbidities such as diabetes, hypertension or dyslipidemia commonly occur as side-effects of immunosuppressive medication.[17] Although obesity is also classed as a metabolic disorder, few studies have examined possible relationships with it. Three out of 5 studies focusing on diabetes found that pre-LTx diabetes significantly related to post-LTx obesity and weight gain. Taking another perspective, in a recent systematic review, Li et al. examined risk factors for new-onset diabetes mellitus after LTx by meta-analyzing 7 studies with information on pre-LTx BMI.[36] The results suggest relationships between diabetes and body weight parameters, independent of when those parameters were measured; however, testing these relationships will require further investigation.

Nevertheless, body weight influencing parameters include far more than biomedical or sociodemographic factors. As weight gain and subsequent obesity are driven by multiple interrelated factors, a broader range of variables require consideration.[26] Evidence in the general population stresses the importance of socioeconomic (e.g., female gender with low income),[37,38] psychological (e.g., depression),[39] and genetic factors (e.g., BMI- and obesity-related genes such as FTO, MC4R, or BDNF).[40] Yet, the

examination of those specific factors in large samples is often limited because they are not included *per se* in standardized database or registry data collection.

Behavioral factors, e.g., healthy eating and physical activity, represent another important component in relation to body weight parameters. Still, while their value to prevent weight gain has been shown in the general population,[41,42] evidence in the LTx population is lacking. Two quantitative studies asked LTx recipients their opinions regarding the causes of weight gain after LTx.[16,43] Interestingly, increased food intake, constant hunger, and decreased daily physical activity where among the most common responses. Although these findings suggest that patients perceive behavioral factors as relevant to weight gain, this relationship needs further examination in both qualitative and quantitative research. Examining barriers to physical activity after transplantation, a small study in kidney recipients found that, alongside fear of injuring the new kidney, health problems such as pain were limiting post-LTx activity levels, as well as time constraints after they returned to work.[44] These findings not only provide preliminary insights regarding post-kidney transplant non-performance of physical activity, but also emphasizes behavior's relationships with other, e.g., psychological (i.e., fear, anxiety), biomedical (i.e., pain), and sociodemographic factors (i.e., return to work). Given the complexity of factors related to body weight parameters, future research should incorporate theoretical frameworks guiding the choice of study design and selection of variables of interest.

Overall, the alarming low amount of studies examining risk factors and body weight parameters in the LTx population indicates an urgent need for further investigation. Yet, methodological issues may be a barrier. Various genetic, sociodemographic, behavioral, biomedical, psychological, and environmental factors (e.g., epigenetic characteristics, monthly income, physical activity, immunosuppressive drugs, moving to another area) can change over the course of Tx: an adequately-sized prospective study cohort that can supply repeated measurements, thereby allowing multivariate analyses and the examination of interrelationships, would be optimal for this type of research.

Examination of various body weight parameters

Despite the broad choice of body weight parameters available for study, the majority of study authors chose to examine post-LTx obesity (BMI ≥30 kg/m^2). However, none differentiated between the WHO's three obesity classes (class I: BMI ≥30-34.9 kg/m^2; class II: BMI 35-39.9 kg/m^2; class III: ≥40 kg/m^2).[25] As BMI values ≥35 kg/m^2 have been associated with lower patient survival,[45] higher post-LTx morbidity and increased

healthcare utilization,[45-47] risk factors associated with obesity classes II and III warrant far more attention.

The small number of studies examining post-LTx weight gain–recognized as a health issue in LTx since the early 1990s[43]–was also somewhat surprising. Modifiable weight gain risk factors could be targeted by preventive interventions, which are widely accepted as the key strategy against weight gain and subsequent obesity.[48-50] The reason for this approach is the so-called yo-yo effect. In times of lower energy intake, e.g., during a diet, compensatory physiological mechanisms lead to reduced energy requirements. Afterwards, when energy intake increases to a normal level, to have a reserve available for future shortages, the body takes up more energy than actually needed, resulting in weight re-gain.[51] Based on the difficulty involved in overcoming these compensatory mechanisms, preventing weight gain should logically be easier than achieving and maintaining a target weight after weight loss.[52] Therefore, we propose the identification of risk factors associated with post-LTx weight gain as an important area for future research.

Risk factors for post-LTx obesity

The use of neither tacrolimus nor cyclosporine–both calcineurin inhibitors–was associated with post-LTx obesity. Following LTx, tacrolimus has become the immunosuppressive treatment of choice, as it is associated with improved patient and graft survival and reduced rejection.[53] Unfortunately, while functioning well as the major pathway of immunosuppression, calcineurin inhibition has also been associated with the development of metabolic comorbidities such as diabetes mellitus, hypertension, and hyperlipidemia.[54] However, our meta-analysis showed no association between either tacrolimus or cyclosporine and obesity as a metabolic disorder. Moreover, none of the other 8 studies examining tacrolimus or cyclosporine with weight gain after LTx found a significant association. Although heterogeneity was not statistically significant across our sample, the small number of studies included in the analysis (n = 6) might have contributed to an inadequate statistical power to detect differences across studies. Subgroup analyses considering year of study publication and geographical location found no differences.

However, several inter-study methodological and clinical disparities may also have impacted our analyses. First, from a *methodological perspective,* obesity alone might not be accurate enough as an outcome measure. We did not distinguish in our review between obesity per se (which might have been present pre-LTx) and new-onset obesity that developed post-LTx. Of the studies relevant to our meta-analyses,

only Akarsu et al. provided more detailed information about this differentiation, as they examined the factors related to obesity's development.[31] Second, the cutoff values defining obesity differed across the 6 studies–one of which provided no BMI cutoff.[35] Third, 3 studies were cross-sectional, examining the relationship between immunosuppressive drugs and post-LTx obesity only at one specific time point, i.e., either 1[13,33] or 3 years.[35] The other 3 assessed post-LTx obesity longitudinally between 1 and 168 months, weakening a precise definition of the outcome measured. Finally, as immunosuppressive medications are core treatment elements, preventing graft rejection after transplant, studies examining them often lack adequate control groups.

From a *clinical perspective*, the amount of immunosuppressive medication applied likely varied across the 6 studies and over time. Dosing usually decreases in the post-LTx course to minimize long-term medication-related side effects and comorbidities.[55] Also, in case of medication intolerance or other clinical, laboratory, or histological responses, a medication regimen might change radically.[17] Finally, based on a growing body of research and clinical experience, since the first uses of cyclosporine and tacrolimus–respectively in the late 1970s and late 1980s–, their application (i.e., amount of medication needed, combination of drugs) has improved continuously.[55] Considering that the 6 studies included in our meta-analysis studied LTx over more than 2 decades (1986 – 2010), this long-term development process implies heterogeneity in the prescription of both immunosuppressive agents. Neither of these clinical issues (e.g., possible changes of immunosuppressive regimen, dosing) was described explicitly in any of the 6 included studies.

Limitations

In addition to the shortcomings already mentioned in the discussion, this study has additional limitations. First, as noted, we could only include a small number of observational studies. Results should therefore be interpreted with caution. Second, the definitions and reporting methods varied across all 43 articles examining risk factors. This hindered the extraction of variables needed for the final meta-analysis. Additionally, as we applied no time limit for the search. This limited the data extraction from studies performed more than 10 years ago with information missing from their reports or articles, as authors did not typically archive their data. Third, the inclusion criteria that all participants be aged ≥18 led to the exclusion of a number of papers, especially from the earlier transplantation era, when adults were often defined as aged ≥16 years. Fourth, we were not able to include data on body composition or waist circumference, both of which are important and informative body weight parameters. Finally, due to the

small number of eligible studies, we were unable to perform more comprehensive subgroup analyses, examining moderators such as type of transplant, study setting, ethnicity, age, gender, adjustment for ascites or co-morbidities.

Conclusion

We identified 82 distinct pre- and post-LTx factors examined in relation to BMI, obesity and weight gain after LTx. The factors studied were mainly categorized as biomedical and sociodemographic. Unfortunately, strong variations in factor definitions limited the pooling to groups of at least 5 studies for meta-analysis. Only two factors were eligible for meta-analysis: tacrolimus and cyclosporine. Neither was significantly associated with post-LTx obesity. Subgroup analyses focusing on year of publication and geographical region yielded no significant results. Further research is necessary to identify modifiable factors associated with post-LTx weight gain and obesity, to facilitate development of preventive interventions. Future studies should apply theoretical frameworks to select variables of interest and systematically examine interrelationships among different factors.

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Chapter 5. Weighted Genetic Risk Scores and Prediction of Weight Gain in Solid Organ Transplant Populations

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5.1 Abstract

Background: Polygenic obesity in solid organ transplant (Tx) populations is considered a risk factor for the development of metabolic abnormalities and graft survival. Few studies to date have studied the genetics of weight gain in Tx recipients. We aimed to determine whether weighted genetic risk scores (w-GRS) integrating genetic polymorphisms from Genome Wide Association Studies (GWAS) (single nucleotide polymorphisms (SNP) group#1 and SNP group #2) and from Candidate Gene studies (SNP group#3) influence body mass index (BMI) in TX populations and if they predict ≥10% weight gain one year after Tx. To do so, two samples (n_A = 995, n_B = 156) were obtained from naturalistic studies and three w-GRS were constructed and tested for association with BMI over time. Prediction of 10% weight gain at one year after Tx was assessed with models containing genetic and clinical factors.

Results: w-GRS were associated with BMI in sample A and B combined (BMI increased by 0.14 and 0.11 units per additional risk allele in SNP group #1 and #2, respectively, p-values<0.008). w-GRS of SNP group#3 showed an effect of 0.01 kg/m^2 per additional risk allele when combining sample A and B (p-value 0.04). Models with genetic factors performed better than models without in predicting 10% weight gain at one year after Tx.

Conclusions: This is the first study in Tx evaluating extensively the association of w-GRS with BMI and the influence of clinical and genetic factors on 10% of weight gain one year after Tx, showing the importance of integrating genetic factors in the final model. Genetics of obesity among Tx recipients remains an important issue and can contribute to treatment personalization and prediction of weight gain after Tx.

5.2 Background

Obesity has become a worldwide major concern since it has more than doubled in the last decades. In 2014, 39% of adults were overweight (Body Mass Index (BMI) 25 - 29.9 kg/m^2) and 13% were obese (BMI ≥30 kg/m^2).[1] Obesity is a risk factor leading to other comorbidities such as diabetes, cardiovascular diseases and certain type of cancers.[1] Among solid organ transplant (Tx) recipients, the rate of overweight and obesity has increased over the past years. By 2011, 34% of liver Tx candidates were obese, compared to 29% in 2001.[2] Similar results have been found for kidney, heart and lung Tx recipients.[3-5] Although overweight and obesity prevalence are similar to those measured in general population studies, in Tx recipients the consequences are more serious. Indeed, obesity in Tx is an important risk factor for the development of New Onset Diabetes after Transplant (NODAT)[6] which has a deleterious effect on graft survival.[7,8] Moreover, it can be often associated with delayed graft function related to surgical and post-operative complications.[9]

Few longitudinal studies examining weight gain among Tx recipients have been conducted to date, most of them focusing on weight gain during the first year post-Tx. a weight gain ranging from 3.5 kg to 10 kg has been reported in heart, liver and kidney Tx recipients[10-14] and a mean of 10% weight gain during the first year after Tx was described in kidney Tx recipients.[15] A threshold of 10% increase of ideal body weight, defined as the metropolitan relative weight criteria,[16] has been related to a risk of developing cardiovascular disease in general populations followed for more than 25 years.[16,17] Ethnicity, sex, age in addition to specific factors such as transplanted organ, glucocorticoids and immunosuppressive treatments are some of the described factors influencing weight gain following Tx and NODAT,[18] as well as genetic factors. Most studies on Tx populations focused mainly on the NODAT rather than weight gain.[19,20] Regarding BMI-related phenotypes, a protocol for the first systematic literature review has been published. The aim is to condense and compare the current state of evidence on weight gain, overweight and obesity in Tx individuals including genetic and non-genetic factors.[21]

Regarding candidate gene approach, two single nucleotide polymorphisms (SNPs) and one insertion/deletion have previously been associated with BMI-related phenotypes.[22-24] These studies were conducted in three heterogeneous populations with small or moderate sample sizes (n<270), with different obesity-related outcomes and type of Tx organ. Furthermore, different polymorphisms were analyzed. To our knowledge, no Genome Wide Association Studies (GWAS) investigating BMI variants within Tx recipients have yet been published. Recently, a microarray study examining

gene expression in subcutaneous adipose tissue in kidney Tx recipients found that the expression of obesity-related genes was correlated with weight change.[25] The top 41 ranked genes were further associated with obesity through a text mining approach,[26] including genes related to diabetes, obesity and neurological concepts such as dopamine, nicotine, and cognition.[25] Interestingly, two of these genes (i.e., *MTCH2* and *TFAP2B*) were also found in the largest BMI GWAS meta-analysis conducted to date in the general population.[27] This meta-analysis was conducted in more than 300 000 individuals and reported 97 SNPs associated with BMI, also including 32 previously replicated BMI SNPs.[28-31] All 97 polymorphisms explained up to 2.7% of BMI variability within these individuals.[27] Since polygenic or common obesity is influenced by many genetic polymorphisms, genetic risk scores provide a useful tool summarizing risk-associated variations across the genome by aggregating information from multiple-risk SNPs, and they may improve the consistency and the power to determine genetic risk in polygenic diseases.[32,33]

In the present study, we aimed to study the association of three weighted genetic risk scores (w-GRS), integrating previously published SNPs, with BMI in two cohorts of Swiss transplanted individuals. In addition, we assessed whether these genetic polymorphisms could predict a ≥10% weight gain during the first year post-Tx.

5.3 Methods

Sample A

The Swiss transplant cohort study (STCS) is an ongoing prospective multicenter study (Basel, Bern, Geneva, Lausanne, St. Gallen and Zurich) started in May 2008 which enrolls Tx recipients with no particular eligibility or exclusion criteria other than having received an allotransplant and having signed the informed consent.[34] The present study (May 2008 - May 2011) included Tx recipients (i.e., kidney, liver, lung, heart, or multi-organ) with a functional graft for at least 12 months after Tx in order to have a sufficient period of follow-up. A total of 1294 patients were followed up in their respective Tx centers at baseline and at 6, 12, 24, 36 and 48 months after Tx. Lipid profile, BMI, blood pressure and patient characteristics were collected at the different time-points of the follow up. Further details have been published elsewhere.[34,35] Only Caucasians and recipients of 18 years or older were retained. If an individual was subjected to more than one Tx, only the first Tx was considered. A total of 995 patients were considered for analysis.

Sample B

A total of 197 Tx recipients (i.e., lung, liver and kidney) were enrolled between 2003 and 2005 from the outpatient clinic of the Tx center of the University Hospital of Lausanne, Switzerland. Only patients with a functional graft for more than 12 months were eligible to participate in the study. Further details can be found elsewhere.[35-37] Briefly, data regarding patients' age, gender, BMI, ethnicity, immunosuppressive treatments among others were collected retrospectively from the medical files. Additionally, data concerning weight, at baseline, at 1, 3, 6, 9, 12 and at the yearly follow-up during the 5 years after Tx were collected retrospectively from the medical files between October 2011 and April 2012. Blood samples were collected for further genotyping analysis. 156 individuals of 18 years or older for whom Caucasian ethnicity was reported and had clinical data available, were included in the analysis. This sample was considered as a replication sample. All patients gave their written informed consent and the studies were approved by the ethics committee of the Lausanne and Geneva University Hospitals.

Genotype selection and genotyping

SNP selection was done according to large Meta analyses of GWAS published on BMI. SNP group #1 included 32 BMI associated polymorphisms in general adult populations.[28] A second group consisted of 97 SNPs (SNP group #2) recently associated with BMI in general populations and which included the previous 32 SNPs (or its proxies).[27] Only SNPs significant at GWAS levels (i.e. $p < 5x10^{-8}$) were retained for the analysis. Additionally, 41 genes whose expression in subcutaneous adipose tissue has been previously associated with weight change in kidney Tx recipients[25] were included. A selection of tagging SNPs of these genes was obtained using HapMap Genome Browser (release 28). In order to avoid over representation of a particular gene, one tagging SNP per gene was selected based on the number of SNPs tagged and on the genotype availability in our samples. Six genes were excluded since no tagging SNPs were found in HapMap. Of note, two genes (i.e., *MTCH2*, *TFAP2B*) were also present in the GWAS mentioned previously (SNP group #1). Finally, 19 SNPs, for which genotype was available in both samples A and B, were retained in the SNP group#3.

For the sample A, genotypes were analyzed with the Human OmniExpress-24 BeadChip Kit as described by the manufacturer's protocol (Illumina, San Diego, CA). For the sample B, genotyping was performed using the Illumina 200K Cardiometabochip (Illumina, San Diego, CA). Briefly, the CardioMetabochip is a custom Illumina iSelect genotyping array designed to test DNA variation of 200'000 SNPs from regions

identified by large scale meta-analyses of GWAS for metabolic and cardiovascular traits.[38] Polymorphisms or proxies were chosen based on genotype availability. A Quality Control was done for the genotyped SNPs. Samples were excluded from the analysis if sex was inconsistent with genetic data from X-linked markers, and when genotype call rate was <0.96 and gene call score <0.15. GenomeStudio Data Analysis Software was used to export results generated by Illumina CardiometaboChip.

Construction of Genetic Risk Scores

Three genetic risk scores were built following a w-GRS method as previously described[28] with 32 SNPs (SNP group #1) and 97 SNPs (SNP group #2) both from GWAS, and 19 SNPs (SNP group#3) from candidate genes. Briefly, genotypes from each SNP were coded as 0, 1 or 2 according to the number of BMI risk alleles and each polymorphism was then weighted by its β-coefficient (allele effect) based on the assumption that all SNP of interest have independent effects and contribute in an additive manner on BMI. In order to facilitate interpretation, the genetic risk score was subsequently rescaled as previously described.[39] Thus, each unit increase in the genetic risk score corresponded approximately to one additional risk allele. Allele effects on BMI were obtained from those published in the literature for the SNPs group#1 and #2.[27,28] For the SNP group#3 allele effects were calculated from a large population based sample, GIANT, which consisted in a meta-analysis of GWAS with a discovery set of 123,865 individuals of European ancestry from 46 studies for height,[40] BMI[28] and waist-to-hip ratio.[41]

Statistical analysis

Descriptive analysis of quantitative data is presented as median and range unless otherwise specified whereas qualitative data is expressed as percentages. Chi-squared test or rank sum test were used for association studies within categorical data or non-parametric continuous variables, respectively. Hardy-Weinberg Equilibrium was determined for each polymorphism by a chi-square test. P-value threshold was set at <0.05 and Bonferroni multiple test correction was applied when necessary (i.e., 0.05/6; 2 tests of w-GRS in the whole sample A and 2 tests of w-GRS in two different subgroups). Due to the exploratory nature of the analysis conducted for the third GRS, in the present work we did not consider multiple test correction for this GRS.

For multivariate analysis, a Generalized Additive Mixed Model was used to deal with complex and non-linear BMI evolution at different time points and presence of multiple observations per individual introducing interdependence among observations. A

random effect at the subject level was also introduced to take the dependence structure of observed data into account. The models were fitted using the mgcv package of R (settings were fixed at package defaults). To be more conservative, the uncertainty of estimated parameters was assessed by 1'000 bootstraps on individuals.[42] Multivariate models were adjusted by gender, type of treatment, organ, living donor and CMV as previously described in the literature,[18] as well as genetic factors and time of follow-up. Because sex and age have been described as factors influencing weight gain,[15] further analyses were conducted stratifying by gender and the median age when the interactions with w-GRS were significant.

Prediction of ≥10% weight gain one year after transplantation in the sample A

A binary logistic regression model at 12 months after Tx was used to determine whether clinical and genetic factors influence a ≥10% weight gain one year after Tx for those cases where genetic components were significantly associated with BMI. The ability to discriminate between gainers of 10% weight versus those who did not gain 10% one year after Tx was assessed with the Area Under the Receiver Operating Characteristic Curve (AUROC) for a model containing only clinical covariates (i.e., age, sex, Tx organ, BMI at baseline, immunosuppressant treatment) and another model integrating clinical and genetic factors. For each pair of models compared (i.e., the non-genetic nested in its corresponding genetic model) the same number of individuals must be tested in order to be comparable. In addition, sensitivity (percentage of correctly predicted individuals with ≥10% weight gain among all individuals with ≥10% weight gain), specificity (percentage of correctly predicted individuals with <10% weight gain among all truly individuals with <10% weight gain) and accuracy (percentage of correctly classified gainers of ≥10% weight among all subjects) were obtained for each model using "pROC" R package.[43] An AUROC lower than 0.70 indicates low discriminative accuracy.[44] As previously described,[45,46] in order to assess the added value of selected SNPs in predicting a ≥10% weight gain one year after Tx (i.e. comparison of genetic and non-genetic models), likelihood ratio tests and Integrated Discrimination Improvement estimates with their respective p-values were calculated. Finally, the number needed to genotype (i.e. the average number of patients who need to be genotyped to detect one misclassified case of ≥10% weight gain one year after transplantation if using only clinical covariates) was calculated based on the inverse of the difference between the accuracy of clinical and genetic models.[47]

5.4 Results

Population description

The characteristics of sample A are presented in Table 1. Sixty-six percent were men, 17.0% were obese one year after Tx and 27.1% were diagnosed of NODAT. Similar patterns ($p > 0.05$) were observed in sample B (60.9%, 18.5% and 28.8%, respectively, Table 2). Twenty three percent of individuals in sample A gained ≥10% of weight the first year after Tx and 35% of individuals in sample B ($p < 0.001$). The mean of weight gain one year after Tx was 3.5% and 6.3% for samples A and B, respectively. Sample A included also heart and multi-organ Tx, individuals were older than in sample B (median age: 54 years compared to 48, $p < 0.001$) and there was a high prevalence of living donors (27.1% and 11.5%, respectively, $p < 0.001$). Tacrolimus (TAC) was more frequently prescribed in sample A, whereas cyclosporine (CSA) was more used in sample B (45.1% versus 34.6%, respectively for TAC and 19.6% versus 65.4%, respectively for CSA; $p < 0.05$). For sample A, individuals with at least 3 immunosuppressive treatments (i.e. CSA, TAC, glucocorticoids, azathioprine and/or mycophenolate) gained significantly more weight at one year after Tx compared to the others ($p = 0.01$). Of note, 99% of those with at least 3 immunosuppressants had a glucocorticoid treatment prescribed, possibly contributing to this weight gain. No significant results were found in sample B. Among those individuals with less than 3 immunosuppressant drugs, sample A had lower prescription of glucocorticoids than sample B, probably contributing to explain the differences of weight gain observed between both samples.

Characteristic	All n=995	Weight gain ≥10%* n=204	Weight gain <10%* n=673	p-value #
Recipient age at Tx (y), median (range)	54 (18 - 79)	51 (18 - 73)	55 (18 - 79)	**0.0001**
Recipient men, (%)	66.0	56.8	68.9	**0.001**
Period of follow up (mo), median (range)	12 (0 - 48)	12 (0 - 48)	12 (0 - 48)	0.55
Living donor (%)	27.1	27.9	29.6	0.6
Donor age (y), median (range)	53 (1 - 86)	50 (1 - 80)	53 (1 - 86)	**0.04**
Tx organ (%)				
Kidney	62.4	61.3	67.2	**<0.001**
Liver	15.9	10.3	14.7	
Lung	9.5	14.7	7.8	
Heart	6.5	11.3	4.6	
Multi-organ Tx	4.1	2.5	4.5	
Before Tx				
BMI (kg/m^2), median (range)	24.6 (13.7 - 41.2)	23.1 (14.9 - 37.4)	24.9 (14.3 - 41.2)	**0.0001**
Overweight (BMI 25 - 29.9 kg/m^2), %	30.7	23.0	32.5	**<0.001**
Obese (BMI ≥30 kg/m^2), %	15.3	9.3	16.8	
High-density lipoprotein (mmol/L), median (range)	1.2 (0.01 - 8)	1.2 (0.1 - 4.1)	1.2 (0.09 - 8)	0.7
Low-density lipoprotein (mmol/L), median (range)	2.2 (0.06 - 10.02)	2.2 (0.1 - 7.1)	2.2 (0.08 - 10)	0.3
Cholesterol (mmol/L), median (range)	4.2 (0.3 - 11.7)	4.0 (0.3 - 9.9)	4.2 (0.8 - 11.7)	0.2
At 12 months after Tx				
BMI (kg/m^2), median (range)	25.2 (15.3 - 44.6)	27.1 (18.8 - 44.6)	24.7 (15.3 - 44.3)	**0.0001**
Overweight (BMI 25 - 29.9 kg/m^2), %	34.7	39.0	33.0	**<0.001**
Obese (BMI ≥30 kg/m^2), %	17.0	27.0	14.0	
High-density lipoprotein (mmol/L), median (range)	3.5	1.3 (0.5 - 4.1)	1.3 (0.2 - 7.0)	0.08
Low-density lipoprotein (mmol/L), median (range)	1.3 (0.21 - 7)	2.6 (0.8 - 5.8)	2.6 (0.3 - 8.7)	0.8
Cholesterol (mmol/L), median (range)	2.6 (0.3 - 8.7)	5.0 (2.3 - 9.2)	4.8 (1.7 - 12.0)	**0.01**
Incidence of NODAT, (%)$	27.1	25.9	28.1	0.6
Cytomegalovirus serostatus (%)				
Recipient cytomegalovirus infection (R+)	57.1	21.8	23.7	0.9
Donor cytomegalovirus infection (D+)	53.0	20.8	20.6	
Recipient and Donor cytomegalovirus infection (R+D+)	32.6	33.2	33.1	
Calcineurin inhibitors (%)				
TAC	45.1	42.2	48.6	0.3
CSA	19.6	21.1	19.6	
None	35.2	36.8	31.8	

Tx, transplantation; BMI, body mass index; NODAT, new onset diabetes after transplant; y, year; mo, months; # comparison between weight gain ≥10% and weight gain <10%; *at 12 months after Tx, missing n=118; $ NODAT was diagnosed if patients were taking an antidiabetic treatment after Tx or if diabetes was reported in their case report forms. NODAT excluded those patients with diabetes previous to Tx

Table 1. Characteristics of Sample A (all and by 10% weight gain one year after Tx). Source: Own Illustration

Characteristic	All n = 156	Weight gain ≥10%* n = 42	Weight gain <10%* n = 78	p-value #
Recipient age at Tx (years), median (range)	48 (22 - 68)	47 (26 - 66)	49 (22 - 68)	0.4
Recipient men (%)	60.9	59.5	61.5	0.8
Period of follow up (months), median (range)	12 (1 - 60)	12 (1 - 60)	12 (1 - 60)	1
Living donor (%)	11.5	11.9	7.7	0.4
Donor age (years), median (range)	43.5 (10 - 73)	45 (10 - 65)	43 (11 - 69)	0.7
Tx organ (%)				
Kidney	65.4	76.2	60.3	**0.03**
Liver	23.7	7.1	26.9	
Lung	10.9	16.7	12.8	
Before Tx				
BMI (kg/m^2), median (range)	23.4 (15.8 - 37.3)	22.9 (18.7 - 33.5)	24.2 (15.8 - 37.3)	0.06
Overweight (BMI 25 - 29.9 kg/m^2), %	24.1	14.3	30.8	0.08
Obese (BMI ≥30 kg/m^2), %	10.9	9.5	12.8	
At 12 months after Tx				
BMI (kg/m^2), median (range)	25.2 (16.5 - 39.3)	26.8 (20.9 - 39.3)	24.3 (16.5 - 35.4)	**0.0006**
Overweight (BMI 25 - 29.9 kg/m^2), %	35.1	45.2	28.2	**0.004**
Obese (BMI ≥30 kg/m^2), %	18.5	28.6	14.1	
Incidence of NODAT, (%)	28.8	30.9	35.9	0.6
Cytomegalovirus serostatus (%)				
Recipient cytomegalovirus infection (R+)	49.3	30.8	36.1	0.6
Donor cytomegalovirus infection (D+)	61.5	23.1	15.3	
Recipient and Donor cytomegalovirus infection (R+D+)	27.6	30.8	27.8	
Calcineurin inhibitors (%)				
TAC	34.6	26.2	47.4	**0.02**
CSA	65.4	73.8	52.7	

Tx, transplantation; BMI, body mass index; NODAT, new onset diabetes after transplant; y, year; mo, months
comparison between weight gain ≥10% and weight gain <10%
* at 12 months after Tx, missing n = 36

Table 2. Characteristics of Sample B (all and by 10% weight gain one year after Tx). Source: Own Illustration

10% weight gain one year after Tx.

In both samples A and B, those gaining ≥10% of weight had lower BMI at baseline and higher BMI 12 months after Tx compared to those gaining <10% (Tables 1 and 2). The prevalence of overweight and obese was lower at baseline and higher at one year after Tx for ≥10% when compared to <10% weight gain. The Tx organ differed between ≥10% and <10% for both A and B samples. The kidney was the most prevalent Tx organ in both groups. The second most prevalent Tx organ in the ≥10% weight gain

group was the lung while the heart and the liver were the third most frequently Tx organs. In the <10% weight gain group, the liver and the lung were among the second and the third most frequently Tx organs. Additionally, in sample A donors were younger and individuals had higher cholesterol levels at 12 months in the ≥10% weight gain group (median: 50 years and 5.0 cholesterol mmol/L, p = 0.04 and p = 0.01, respectively). In sample B, significant differences were found in the prescribed immunosuppressive treatments; CSA was highly prescribed in the ≥10% weight gain when compared to the <10% weight gain group (73.8% versus 52.7%, respectively; p = 0.02).

Genetic Risk Score analysis

Weighted genetic risk score with GWAS polymorphisms.

In samples A and B, w-GRS ranged from 16 to 40 (SNP group #1) and from 63 to 107 (SNP group #2), respectively. The association between w-GRS and BMI over time for sample A is shown in Table 3. w-GRS built from the SNP group #1 was significantly associated with BMI, showing a 0.16 BMI units increase per additional risk allele and an explained variability of 1.46%. When stratified by the median of age (w-GRS*age p = 0.001 and p = 0.02 for SNP group #1 and #2, respectively) individuals older than 54 years old had 0.23 BMI unit increase per additional risk allele and an explained BMI variability of 2.74% whereas those at 54 years or younger showed a trend of 0.10 units increase and 0.56% of explained BMI variability after multiple test correction (p = 0.08). For SNP group #2, the effect was slightly lower (0.11 units of BMI per risk allele increase, explained variability of 2.08%). These results could be partially replicated in sample B (Table 4) for SNP group #1 with an effect of 0.20 BMI units per risk allele increase and explained variability of 2.40%. Analysis stratified by sex (w-GRS*sex, p = 0.03 for SNP group #1) showed no significant associations after multiple test correction (Table 4). Additionally, a significant interaction between w-GRS and organ (i.e. kidney/non-kidney) was found for sample B and SNP group #1 (n = 83, p = 0.04) showing a slightly higher effect (0.30 units of BMI per risk allele increase) in kidney Tx individuals when compared to the overall 0.20 units. When combining samples A and B, BMI increased by 0.14 [0.09–0.19] and 0.11 [0.07–0.15] units per additional risk allele in SNP group #1 and #2, respectively, p-values < 0.001).

	n	Effect on BMI per additional risk allele [CI 95%]	p-value*	Explained Variability (%)
SNP group #1				
All population	881	0.16 [0.11 - 0.23]	**p<0.008**	1.46
Age 18 – 54 years	444	0.10 [0.01 - 0.17]	*0.08*	0.56
Age > 54 years	437	0.23 [0.14 - 0.32]	**p<0.008**	2.74
SNP group #2				
All population	854	0.11 [0.07 - 0.15]	**p<0.008**	2.08
Age 18 – 54 years	452	0.08 [0.03 - 0.13]	**p<0.008**	1.10
Age > 54 years	426	0.13 [0.07 - 0.19]	**p<0.008**	2.90

BMI, body mass index; SNP, single nucleotide polymorphisms; CI, confidence interval
* p-value corrected by multiple test

Table 3. Weighted Genetic Risk Scores from GWAS SNPs and their associations with BMI in Sample A.
Source: Own Illustration

	n	Effect on BMI per additional risk allele [CI 95%]	p-value*	Explained Variability (%)
SNP group #1				
All population	124	0.20 [0.07 - 0.35]	**0.02**	2.40
Men	82	0.14 [-0.01 - 0.31]	0.05*	°
Women	61	0.28 [-0.05 - 0.63]	0.05	°
SNP group #2				
All population	117	0.02 [-0.08 - 0.11]	0.28	°
Men	69	-0.03 [-0.18 - 0.07]	0.33	°
Women	53	0.04 [-0.16 - 0.25]	0.34	°

BMI, body mass index; SNP, single nucleotide polymorphisms; CI, confidence interval
° not calculated because of non-significant association and/or low sample size
* p-value corrected by multiple test

Table 4. Weighted Genetic Risk Scores from GWAS SNPs and their associations with BMI in Sample B.
Source: Own Illustration.

Weighted genetic risk score in Candidate Gene polymorphisms (SNP group#3).

No association of w-GRS from SNP group#3 and BMI was found in sample A whereas an increase of 0.05 units of BMI per additional risk allele was found in sample B (p = 0.048) with an explained BMI variability of 1.72%. In addition, in sample B, when SNPs group#3 and #1 were combined (49 SNPs excluding repeated SNPs) a significant association with BMI was found with an increase of 0.16 BMI units per additional risk allele and an explained BMI variability of 4.1% (p = 0.001). The w-GRS from group SNP#3 in the combined A and B sample showed an effect of 0.01 kg/m^2 per additional risk allele (p = 0.04).

Prediction of 10% weight gain one year after Tx.

For the models in which the w-GRS was significantly associated with BMI, we evaluated the ability of the model to discriminate between gainers of ≥10% of weight and those who gained <10% the first year after Tx. In sample A, a model adjusted by clinical covariates (i.e., age, sex, immunosuppressant treatment (TAC and/or CSA), baseline BMI and Tx organ) as well as genetic factors (i.e., SNP group #1) performed better than a model adjusted only by clinical covariates (Likelihood Ratio Test p = 0.0004). The predictive value for gaining 10% or more weight when including SNP group #1 in the model resulted in an AUROC of 0.74, a specificity of 0.61, a sensitivity of 0.77 and an accuracy of 0.65, whereas the model without genetic components had 0.66, 0.59, 0.66 and 0.61 of AUROC, specificity, sensitivity and accuracy, respectively (Table 5).

Similarly, the genetic model including SNP group #2, performed better (Likelihood Ratio Test p = 0.008) and had higher AUROC (0.80) than the non-genetic model (AUROC non-genetic: 0.66). Similarly, for sample B, the genetic model including clinical covariates and SNP group #1 was significantly different from the clinical model, (Likelihood Ratio Test p = 0.04) had an AUROC of 0.89 and a specificity, sensitivity and accuracy of 0.78, 0.88 and 0.81, respectively (Table 5). The prediction performance of the genetic model compared to the non-genetic one was significantly improved as shown by the Integrated Discrimination Improvement score. A statistically significant Integrated Discrimination Improvement ($p < 0.01$, sample A, SNP group #2, Table 5) means a significant improvement of the genetic model prediction, by increasing the average of sensitivity and one minus specificity of the model. The lowest Number Needed to Genotype in order to detect one misclassified case of ≥10% weight increase one year after Tx (Table 5) was 6 (obtained for sample B, SNP group #1). In sample A, the Number Needed to Genotype was 13 for SNP group #2 and 24 for SNP group #1.

		AUROC [95% CI]	Specificity	Sensitivity	Accuracy	Likelihood Ratio tests-p	Integrated Dis-crimination Im-provement [95% CI]*	Number Needed to Genotype
Sample A	**SNP group #1**							
	Non-genetic model	0.66 [0.58 - 0.72]	0.59	0.66	0.61	0.0004	0.08 [0.06 - 0.10]	24
	Genetic model	0.74 [0.70 - 0.83]	0.61	0.77	0.65			
	SNP group #2							
	Non-genetic model	0.66 [0.54 - 0.69]	0.65	0.62	0.64	0.008	0.17 [0.14 - 0.20]	13
	Genetic model	0.80 [0.71 - 0.84]	0.70	0.77	0.72			
Sample B	**SNP group #1**							
	Non-genetic model	0.67 [0.61 - 0.88]	0.55	0.76	0.63	0.04	0.36 [0.28 - 0.45]	6
	Genetic model	0.89 [0.79 - 0.97]	0.78	0.88	0.81			

SNP, single nucleotide polymorphisms; CI, confidence interval; AUROC, area under the receiver operating characteristic curve

Table 5. Comparison of genetic versus non-genetic model for 10% weight gain prediction at one year after Tx. *p < 0.01
Source: Own Illustration.

5.5 Discussion

To our knowledge, this is the first study examining the association of clinical and genetic risk scores with weight gain in Tx patients. Our results showed that, in Tx populations, previously GWAS-BMI related SNPs in general populations, were associated with BMI when combined in w-GRS. These results could be partly replicated in a second sample (i.e., sample B).

The influence of weighted score including SNP group #1 on BMI has been extensively replicated in several general populations from different ethnicities.[29-32] This is the first study evaluating the effect of these polymorphisms on BMI in Tx recipients (kidney, liver, lung, heart, or multi-organ) and weight gain, with positive results being found in both samples. SNPs group#2 was recently published[27] and contained a higher number of SNPs (including those from SNP group# 1 except of 2 SNPs). However, significant results were found only in sample A. The non-replication using SNPs group#2 in sample B could be attributed either to no effect at all or to the low number of patients in the latter sample and the large number of polymorphisms in group#2, each

one of small effect size, thus necessitating large sample sizes in order to observe an effect.[48]

In addition, an exploratory analysis of 19 polymorphisms combined in a w-GRS (SNP group#3) showed an association with BMI in sample B. These variants were selected from a microarray study examining subcutaneous gene expression which was correlated with weight change in kidney Tx recipients.[25] These findings should be considered as preliminary as they were not further replicated nor corrected for multiple test. In sample B individuals were younger, had lower percentage of living donors and gained more weight after the first year of Tx compared to sample A. Young age, low BMI at baseline and deceased donors increase the risk of gaining weight, as previously described in the literature.[15,49] Adding SNP group#3 to SNP group #1 resulted in an increased explained BMI variability of 4.1%. However, when all SNPs were combined (i.e., SNP group #2 and SNP group#3), no significant results were found, probably due to the low effect and sample size.

In a second step, we showed that a combination of extensive genetic factors and clinical data predicts better a 10% weight gain after the first year of treatment than considering the model with clinical data alone, increasing AUROC and accuracy. When examining genetic factors in sample A, several polymorphisms were significantly associated with 10% weight gain one year post-Tx. Interestingly, when looking at SNPs individually, only *MC4R (rs571312*, *rs6567160)* and *SEC16B (rs543874)* remained significant in both SNP group #1 and #2 analyses. *MC4R* is one of the most common genetic causes of obesity and this gene participates in appetite regulation and energy balance.[50] *SEC16B* has been associated with obesity-related phenotypes but the mechanism behind remains unknown. In sample B, 4 SNPs in or near *MTIF3*, *ETV5*, *GNPDA2* and *FAIM2* gene regions *(rs1006353*, *rs7647305*, *rs10938397* and *rs7138803)* were associated with 10% weight gain one year post-Tx (data not shown). Most of these gene functions are not clear yet. *ETV5* modulates circulating glucocorticoids levels[51] and *GNPDA2* regulates metabolic pathways leading to insulin resistance.[52] Interestingly, the best group of polymorphisms predicting 10% weight gain at 12 months post-Tx was SNP group #2 (n = 97 SNPs) for sample A and SNP group #1 (n = 32 SNPs) for sample B. This could be tentatively explained by the fact that a higher sample size (i.e., sample A) is necessary to demonstrate the association with larger set of SNPs (i.e., SNP group #2). Finally, only the SNP group #1 was associated with BMI change over time in both samples A and B.

In samples A and B, the mean of weight gain after one year post-Tx is 3.5% and 6.3%, respectively, i.e. much lower than the 10% mean value described in the litera-

ture.[15] It should be noted that a solid consensus does not exist yet regarding weight gain after the first year post-Tx; a mean of 10% has been described but a range from 3.5 kg to 10 kg as well. A weight gain of 10 kg over the first year following kidney[12,13,53] liver[14] and cardiac[10] Tx as described in some studies would correspond to an increase of 14% of weight in our samples (considering a mean baseline weight in sample A and B of 71 kg and 69.5 kg, respectively) which would be much higher than the weight gain mean in our samples.

Some limitations of the present study should be acknowledged. These results can only be extrapolated to Caucasians. We could not obtain all genotypes, in particular those from the SNP group#3 and possible co-medications influencing weight in addition to the immunosuppressant treatment were not reported and/or considered. Finally, sample B size was small and other replication in larger cohorts should be tested. However, both samples were obtained from naturalistic setting studies, which should represent the real cases in clinical practice. Further studies should analyze whether graft rejection in less than one year would influence weight gain (out of the scope of the present study). Also, further analysis stratified by type of Tx organ should be conducted, as weight gain may differ depending on this factor as recently described.[54]

5.6 Conclusion

To conclude, this is the first study evaluating extensively the association of w-GRS with BMI and the influence of clinical and genetic components on ≥10% weight gain over the first year post-Tx. The results obtained in the present study, showed the importance of integrating genetic factors in the final model, since they contain predictive information on ≥10% weight gain. Genetics of obesity among Tx recipients remains an important issue and will definitely contribute towards treatment personalizing and prediction improvement of weight gain in these populations by identifying at risk-individuals.

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Chapter 6. New-Onset Obesity after Liver Transplantation - Outcomes and Risk Factors. The Swiss Transplant Cohort Study

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6.1 Abstract

Weight gain after liver transplantation (LTx) facilitates development of new-onset obesity; however, the risk factors and outcomes of post-LTx new-onset obesity are poorly understood. This study aimed to identify the impact of new-onset obesity on cardiovascular events (CVEs) and patient survival, and to identify its risk factors. Using the prospective Swiss Transplant Cohort Study's sociodemographic, behavioral, biomedical, psychological and genetic data we tested possible risk factors for post-LTx new-onset obesity. Using multiple Cox regression models, we examined risk factors for CVEs, patient survival and new-onset obesity in 253 adults (mean age 52.2 ± 11.6 years, male gender 63.6%, mean follow up 5.7 ± 2.1years). During follow-up, cumulative incidence of CVE was 28.1%; that of new-onset obesity was 21.3%. In multivariable analysis, regardless of CVE status at LTx, risk factors identified for post-LTx CVEs were new-onset obesity (Hazard Ratio (HR) 2.95; 95% confidence interval (CI), 1.47-5.95; p = 0.002) and higher age at LTx (HR, 1.05; 95% CI, 1.02-1.08; p < 0.001). In patients with no pre-transplantation CVEs (n = 214), risk factors for post-LTx CVEs included new-onset obesity (HR, 2.59; 95% CI, 1.21-5.53; p = 0.014) and higher age (HR, 1.04; 95% CI, 1.02-1.07; p = 0.001). Survival was not associated with new-onset obesity (HR, 0.84; 95% CI, 0.34-2.04; p = 0.696). Independent predictors of new-onset obesity were male gender (HR, 0.39; 95% CI, 0.16-0.93; p=0.034) and alcoholic liver disease (HR, 3.37; 95% CI, 1.17-9.71; p = 0.025). In a subsample of patients with available genetic data, (n = 114), male gender (HR, 0.26; 95% CI, 0.076-0.889; p = 0.032) and genetic risk score (HR, 21.83; 95% CI, 1.50-317.64; p = 0.024) predicted new-onset obesity. In conclusion, as post-LTx new-onset obesity predicted CVEs, early introduction of post-LTx weight management programs may suggest a potential pathway to reduce CVE risk.

6.2 Background

Following liver transplantation (LTx), weight gain is common. Studies from diverse geographical regions describe mean weight gain of 2–9 kg within the first year after transplantation.[1-4] After one year post-LTx, weight gain slows, but typically continues, leading to a new-onset obesity incidence of 22% at 2 years[1,2] and up to 38% at 3 years post-LTx.[3,4]

Long-term post-LTx survival is affected by the development of metabolic and cardiovascular comorbidities,[5-7] as they increase the risk of death due to cardiovascular events (CVEs).[8,9] However, evidence regarding the impact of post-LTx obesity on CVE is scarce.[10] Albeldawi et al. found patients with obesity at 1 year post-LTx more likely to experience CVEs compared to their non-obese counterparts (49% versus 35%, p = 0.06).[11] However, as the authors did not differentiate between patients who were consistently obese over the course of LTx and those who became obese only after LTx, the impact of new-onset obesity on CVE remains unclear. Additionally, their cross-sectional study design precluded causal inferences. As CVEs also develop over the long-term post-LTx trajectory,[9,10,12,13] post-LTx body weight parameters should be considered as influencing factors.

The complex mechanisms leading to weight gain and subsequent obesity are driven by an interplay of genetic, physiological, behavioral, and environmental factors.[14,15] Still, despite frequent reports of weight gain and development of new-onset obesity after LTx, few studies have examined risk factors in this specific population. Multivariate analysis of independent factors shows that several, i.e., higher recipient and donor BMI at LTx, being married, and absence of post-LTx rejection, predicted new-onset obesity at 2 years post-LTx. Univariate analysis showed that factors associated with new-onset obesity were older age, former smoking, family history of overweight, pre-LTx diabetes, dialysis in the week before LTx, and higher Model for End-Stage Liver Disease (MELD) scores at LTx.[1,2,16] Another study, not differentiating between new-onset and continuing obesity, found that age, pre-LTx BMI, and post-LTx diabetes predicted obesity at 1 year post-LTx.[12] Understanding factors contributing to new-onset obesity in LTx, building on current evidence and including new types of potentially modifiable but unstudied factors would provide a much-needed evidence base to identify intervention leverage points.

The open, nationwide Swiss Transplant Cohort Study (STCS) provides a research framework to assess new-onset obesity, its consequences, and risk factors. Its prospective pre- and post-transplant data collection allows the capture and examination of time-dependent events such as CVE. It also includes a set of sociodemograph-

ic, behavioral, biomedical, psychological, and genetic variables, allowing assessment of the broadest range of potential risk factors for new-onset obesity assessed to date. The aims of the current study were therefore to examine the impact of new-onset obesity on CVE (primary outcome) and patient survival (secondary outcome) as well as to determine risk factors for the development of new-onset obesity after LTx.

Materials and Methods

Design, sample and setting

Since May 2008, the STCS has enrolled LTx patients from 3 Swiss transplant centers. Data are collected at LTx, 6- and 12-months post-LTx, then yearly thereafter. Inclusion criteria for this analysis were: receiving a first and solitary LTx between May 5, 2008 and May 31, 2012, age ≥18 years, and available data about weight and height at time of LTx. Patients who were obese at LTx but lost weight after LTx and were therefore categorized as non-obese in at least the first post-LTx measurement (at 6 months) were included. This procedure was chosen because weight at LTx could not be corrected for possible fluid overload, e.g., ascites, which might have led to a false high assessment of obesity at LTx. Patients with obesity at LTx who remained continuously obese after LTx were excluded. Patients who did not have at least 1 post-LTx measurement at 6 months because of death or re-transplantation were also excluded.

Variables and Measurement

The STCS dataset includes clinical and genetic data as well as sociodemographic, psychosocial, behavioral and quality of life variables. The latter factors are assessed via the STCS Psychosocial Questionnaire (PSQ). More information about the STCS methodology is provided elsewhere.[17,18] The STCS was approved by all relevant Swiss cantonal ethics committees.

Body weight parameters

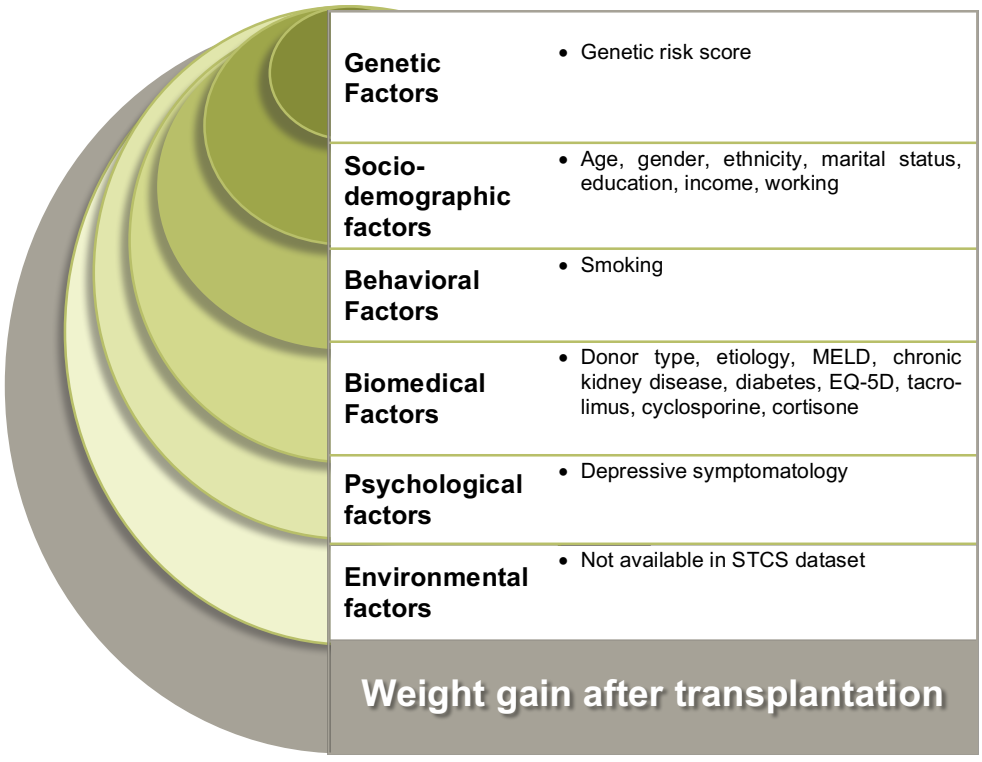
BMI was calculated as weight in kg divided by the square of height in meters and categorized as follows: underweight <18.5 kg/m^2, normal weight 18.5-24.9 kg/m^2, overweight 25-29.9 kg/m^2, obesity ≥30 kg/m^2, obesity class I 30-34.9 kg/m^2, obesity class II 34.9-40 kg/m^2, and obesity class III ≥40 kg/m^2.[19] *Weight changes* over time were examined in relation to the measurement at LTx. *New-onset obesity* was defined at the first assessment of BMI ≥30 kg/m^2 in the post-LTx follow up. Once categorized as new-onset obese, patients remained in this group for further analysis.

Clinical outcomes

The primary clinical outcome was any CVE during post-LTx follow-up. Consistent with the World Health Organization,[20] the STCS defined CVE as including coronary heart disease, coronary heart disease event, cerebral vascular disease event, peripheral vascular disease, peripheral vascular disease event, left ventricular dysfunction, pulmonary embolism or venous thrombosis, and others (e.g., myocardial infarction, circulatory failure). The first occurrence of post-LTx CVE was considered for analysis. The secondary outcome *was patient survival*. Patients without death were censored to the last known assessment date or the date of data extraction from the database (January 17, 2017).

Risk factors for new-onset obesity

We assessed sociodemographic, behavioral biomedical, psychological, and genetic variables as potential risk factors for new-onset obesity. Variables were assigned to the categories of our theoretical framework (Figure 1), which was developed based on previous evidence.[14,15]



LTx: liver transplantation, MELD: Model for End-Stage Liver Disease, STCS: Swiss Transplant Cohort Study

Figure 1. Framework of factors influencing post-LTx weight gain included in this study. Source: Own Illustration.

The baseline STCS PSQ is usually distributed at time of LTx listing. Given that the median waiting list time in Switzerland ranged from 204 to 319 days across the previous 5 years,[21] selected PSQ variables at 6 months post-LTx were considered more appropriate for examination in relation to post-LTx body weight parameters.

Sociodemographic factors were: age (years), gender (male/female), ethnicity (Caucasian/African/Asian/other), marital status (living alone/partnership), level of education (<9 years, 10 – 13 years, >14 years), and monthly income in Swiss Francs at LTx (<4500, 4501 – 6000, >6001). Working capacity was assessed at 6 months post-LTx (0%, 1 – 50%, >51%).

The *behavioral factor* was smoking, evaluated at LTx with the question "Do you smoke?" with the answer options yes/no.[22]

Biomedical factors were: type of organ donor (deceased/living), etiology of liver disease (viral hepatitis/alcoholic liver disease/hepatocellular carcinoma/nonalcoholic steatohepatitis/other), MELD score (calculated at LTx as raw laboratory MELD without exception points), presence of comorbidities (chronic kidney disease/diabetes mellitus) at LTx, and type of immunosuppressive medication at 6 months post-LTx (most commonly used drugs and combined regimen). *Perceived health status* at 6 months post-LTx was assessed by the EQ-5D in view of mobility, self-care, usual activities, pain/discomfort, anxiety/depression.[23] For our analysis, we dichotomized each dimension's answer categories as: no problem/problems (i.e., some problems or extreme problems). On the EQ-visual analogue scale, patients self-rated their health between 0 (worst imaginable health state) and 100 (best imaginable health state), which was treated as continuous variable.

The *psychosocial variable* assessed was depressive symptomatology at 6 months post-LTx, measured via a 7-item subscale from the Hospital Anxiety and Depression Scale, a self-report non-diagnostic screening instrument integrated in the PSQ.[24] Each of the 7 items was answered on a 4-point Likert scale from 0 (not at all) to 3 (most of the time) and summed up (range 0 to 21). The presence of depressive symptomatology was noted if the calculated score was ≥8.[25]

Genetic factor: Genetic data were available in 1100 STCS patients with Caucasian origin. The generation of the genetic risk score was based on 97 single nucleotide polymorphisms (SNPs), associated with BMI in a recent genome-wide association study in the general population.[26] For each SNP, genotypes in our sample were coded as 0, 1 or 2, depending on the number of specific BMI risk alleles. The additive number of alleles corresponds to an unweighted genetic score. But as the effect on BMI differs

among SNPs, each SNP was weighted for its relative effect size by the β-coefficient as mentioned in the genome-wide association study.[26] The weighted genetic risk score has been used previously in an STCS sample; more detailed information on the calculation have been described elsewhere.[27-29]

Data analysis

Patient characteristics and weight changes were described using frequency and percentage, mean and standard deviation (SD) as appropriate for the data measurement level and distribution. The mean weight change over time in relation to LTx was shown graphically.

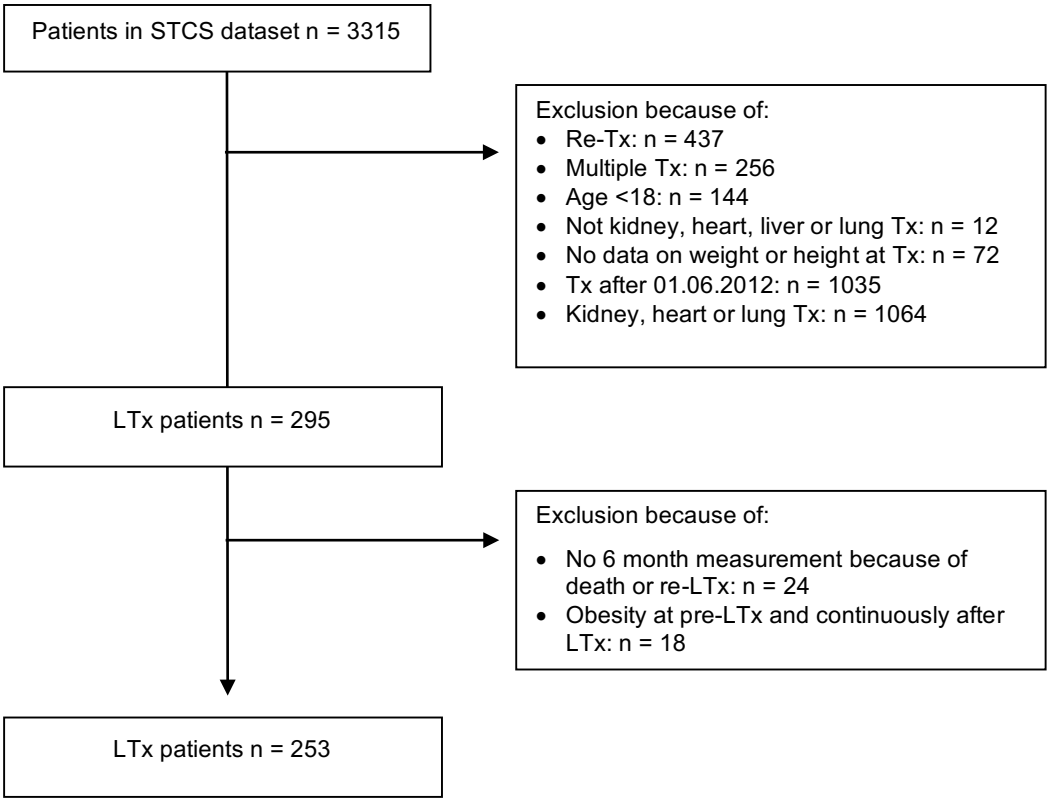
Multiple Cox regression models examined the risk factors for new-onset obesity in 2 patient groupings: those who became obese and those who did not. Manual backward elimination was used to purge the model to only its significant predictors. The same method was used to test new-onset obesity's relationships with patient survival and CVE outcomes.

In the model examining CVE, new-onset obesity was entered as a time-dependent variable. The following covariates were included: age at LTx, gender, smoking at LTx, diabetes at LTx, etiology, tacrolimus, cyclosporine and cortisone at 6 months, income and CVE at time of LTx. As cardiovascular disease is a chronic and progressive process,[30] some patients had already been assessed with CVE at LTx. We therefore performed two analyses to examine the link between new-onset obesity and CVE: First, we considered all patients irrespective of their CVE status at LTx. Second, we only considered patients without CVE at LTx. Statistical analyses were conducted using IBM SPSS Version 23 and SAS version 9.4 software. A two-tailed p-value <.05 was considered statistically significant.

5.3 Results

Patient characteristics

Of 3315 solid organ transplant recipients in the STCS dataset, 253 LTx patients met our inclusion criteria and were analyzed (Figure 2). Sample characteristics are presented in Table 1.



STCS, Swiss Transplant Cohort Study; Tx, transplantation; LTx, liver transplantation

Figure 2. Flowchart of the sample
Source: Own Illustration.

Variables	valid n	Total group	valid n	New-onset obesity	valid n	No new-onset obesity
Body weight parameters						
New-onset obesity, n (%)			54	21.3%	199	78.7%
Weight at LTx						
mean ± SD	253	75.5 ± 15	54	84.3 ± 13.4	199	70.6 ±14
Weight at 6 months						
mean ± SD	225	68 ± 12.6	49	78 ± 11.1	176	65.4 ±11.7
BMI at LTx						
mean ± SD	253	24.9 ± 3.9	54	28.1 ± 3.6	199	24 ± 3.5
BMI at 6 months						
mean ± SD	225	23.1 ± 3.2	49	26 ± 2.5	176	22.3 ± 2.9
BMI category at LTx*						
Underweight; n (%)	253	9 (3.6)	54	0 (0)	199	9 (4.5)
Normal weight; n (%)	253	137 (54.2)	54	9 (16.7)	199	128 (64.3)
Overweight; n (%)	253	77 (30.4)	54	30 (55.6)	199	47 (23.6)
Obesity; n (%)	253	30 (11.9)	54	15 (27.8)	199	15 (7.5)

BMI category at 6 months*						
Underweight; n (%)	225	18 (8.0)	49	0 (0)	176	18 (10.2)
Normal weight; n (%)	225	138 (61.3)	49	15 (30.6)	176	123 (69.9)
Overweight; n (%)	225	69 (30.7)	49	34 (69.4)	176	35 (19.9)
Clinical outcomes						
CVE at LTx; n (%)	253	39 (15.4)	54	8 (14.8)	199	31 (15.6)
CVE after LTx; n (%)	253	71 (28.1)	54	25 (46.3)	199	46 (23.1)
Death until end of follow up; n (%)	253	52 (20.6)	54	6 (11.1)	199	46 (23.1)
Re-LTx later than 6 months; n (%)	253	9 (3.6)	54	0 (0)	199	9 (4.5)
Rejection episode after LTx; n (%)	253	125 (49.4)	54	18 (33.3)	199	107 (53.8)
Follow up, mean ± SD	253	5.7 ± 2.1	54	6.4 ± 1.5	199	5.5 ± 2.2
Sociodemographic risk factors						
Age in years at Tx						
mean ± SD	253	52.2 ± 11.6	54	54.9 ± 9	199	51.5 ± 12.1
Sex						
Male; n (%)	253	161 (63.6)	54	44 (81.5)	199	117 (58.8)
Ethnicity						
Caucasian; n (%)	253	240 (94.9)	54	52 (96.3)	199	188 (94.5)
African; n (%)	253	7 (2.8)	54	1 (1.9)	199	6 (3)
Asian; n (%)	253	6 (2.4)	54	1 (1.9)	199	5 (2.5)
Marital status at LTx						
Living alone; n (%)	218	68 (31.2)	48	15 (31.3)	170	53 (31.2)
Living in a partnership; n (%)	218	150 (68.8)	48	33 (68.8)	170	117 (68.8)
Level of education at LTx						
≤ 9 years; n (%)	243	66 (27.2)	53	15 (28.3)	190	51 (26.8)
10 to 13 years; n (%)	243	108 (44.4)	53	26 (49.1)	190	81 (43.2)
≥ 14 years; n (%)	243	69 (28.4)	53	12 (22.6)	190	57 (30)
Working capacity at 6 months						
0%; n (%)	206	135 (65.5)	44	35 (79.5)	162	100 (61.7)
1 to 50%; n (%)	206	29 (14.1)	44	4 (9.1)	162	25 (15.4)
> 50%; n (%)	206	42 (20.4)	44	5 (11.4)	162	37 (22.8)
Income at LTx						
< 4500 CHF; n (%)	184	85 (46.2)	42	21 (50)	142	64 (45.1)
4501 - 6000 CHF; n (%)	184	45 (24.5)	42	14 (33.3)	142	31 (21.8)
> 6000 CHF; n (%)	184	54 (29.3)	42	7 (16.7)	142	47 (33.1)
Behavioral risk factors						
Smoking at LTx						
Smoker; n (%)	219	61 (27.9)	48	13 (27.1)	171	48 (28.1)
Non-Smoker; n (%)	219	158 (72.1)	48	35 (72.9)	171	123 (71.9)
Biomedical risk factors						
Donor type						
Deceased donor; n (%)	253	235 (92.9)	54	53 (98.1)	199	182 (91.5)
Etiology						
Viral hepatitis; n (%)	253	89 (35.2)	54	15 (27.8)	199	74 (37.2)
Alcoholic liver disease; n (%)	253	57 (22.5)	54	20 (37)	199	37 (18.6)
Hepatocellular carcinoma; n (%)	253	22 (8.7)	54	8 (14.8)	199	14 (7)
Nonalcoholic steatohepatitis; n (%)	253	7 (2.8)	54	3 (5.6)	199	4 (2)
Other; n (%)	253	78 (30.8)	54	8 (14.8)	199	70 (35.2)

Severity of disease - MELD						
mean ± SD	253	18 ± 10.4	54	17.1 ± 8.8	199	18.4 ±10.8
Comorbidities						
Chronic Kidney Disease at LTx; n(%)	253	53 (20.9)	54	9 (16.7)	199	44 (22.1)
Diabetes Mellitus at LTx; n (%)	253	52 (20.6)	54	16 (29.6)	199	36 (18.1)
Immunosuppressive drugs at 6 months						
Cyclosporine; n (%)	253	53 (20.9)	54	14 (25.9)	199	39 (19.6)
Tacrolimus; n (%)	253	140 (55.3)	54	29 (53.7)	199	111 (55.8)
Cortisone; n (%)	253	94 (37.2)	54	14 (25.9)	199	80 (40.2)
Cortisone and Cyclosporine; n (%)	253	21 (8.3)	54	3 (5.6)	199	18 (9.0)
Cortisone and Tacrolimus; n (%)	253	60 (23.7)	54	10 (18.5)	199	50 (25.1)
Perceived Health Status at 6 months						
Mobility problems; n (%)	211	71(33.6)	48	13 (27.1)	163	58 (35.6)
Self-care problems; n (%)	212	17 (8.0)	48	5 (10.4)	164	12 (7.3)
Activity problems; n (%)	209	102 (48.8)	47	18 (38.3)	162	84 (51.9)
Pain problems; n (%)	208	130 (62.5)	47	29 (61.7)	161	101 (62.7)
Anxiety problems; n (%)	210	80 (38.1)	46	13 (28.3)	164	67 (40.9)
EQ-VAS; mean ± SD	209	69.6 ± 19.2	48	72.6 ± 18	161	68.7 ± 19.5
Psychological risk factors						
Depression at 6 months; n (%)	214	34 (15.9)	48	5 (10.4)	166	29 (17.5)
Genetic risk factor						
Genetic Risk Score, mean ± SD	114	2.15 ± 0.16	29	2.18 ± 0.14	85	2.14 ± 0.17

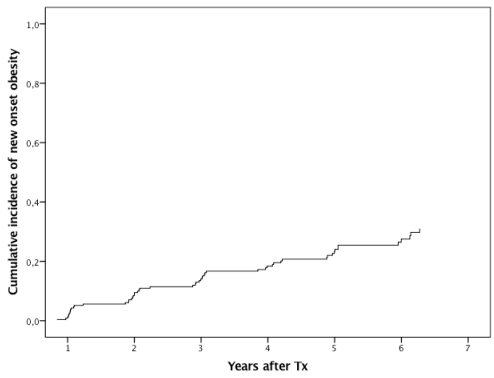
LTx, liver transplantation; BMI, body mass index; SD, standard deviation; MELD, Model for End-Stage Liver Disease; VAS, visual analogue scale

Table 1. Clinical patient characteristics and risk factor variables.
Source: Own Illustration.

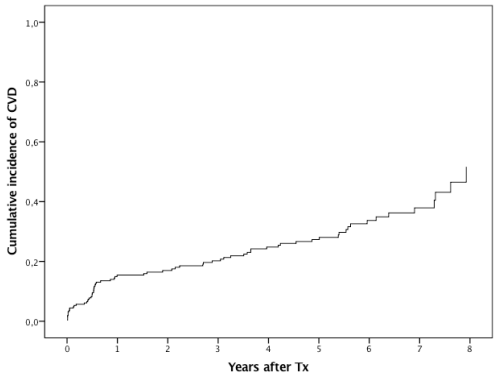
New-onset obesity after LTx

The cumulative incidence of new-onset obesity during post-LTx follow up was 21.3% (n = 54, Figure 3A). With one exception, all patients were categorized as obesity class I (BMI 30-34.9 kg/m^2). Therefore, we did not distinguish between obesity classes.

A



B

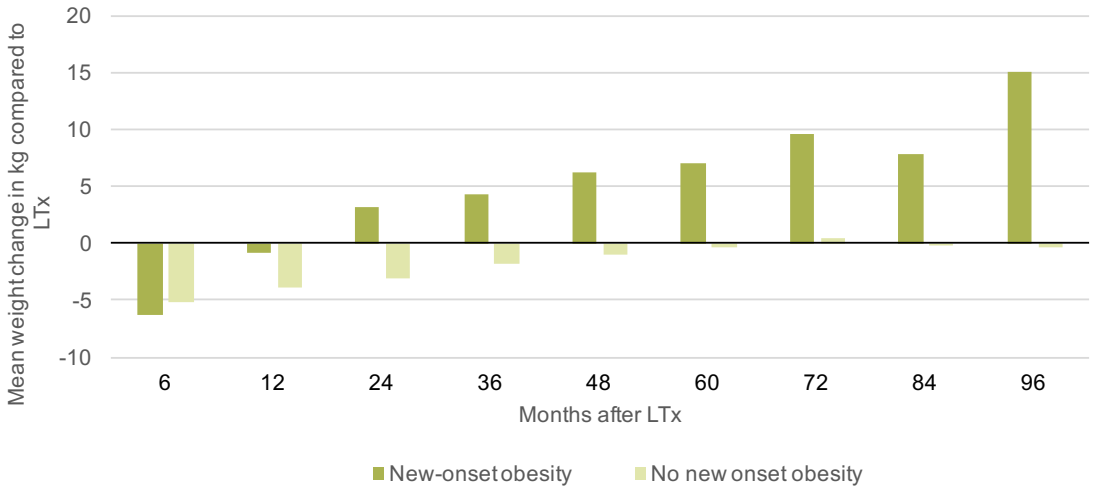


Numbers at risk	6 mo	1y	2y	3y	4y	5y	6y	7y	8y
Patients, n	225	221	193	170	178	149	102	61	24
New-onset obesity, n	0	12	25	35	42	49	54	54	54
CVE after LTx, n	23	36	39	45	53	57	64	67	71

LTx: liver transplantation; CVE: cardiovascular event, mo: months, y: year

Figure 3. Cumulative incidence of new-onset obesity and CVE in LTx patients
Source: Own Illustration.

Overall, both groups, with and without new-onset obesity, lost weight from LTx to 6 months post-LTx and gained weight afterwards (see Figure 4). Those who became obese had their highest proportional weight gain between 6 months and 2 years post-LTx.

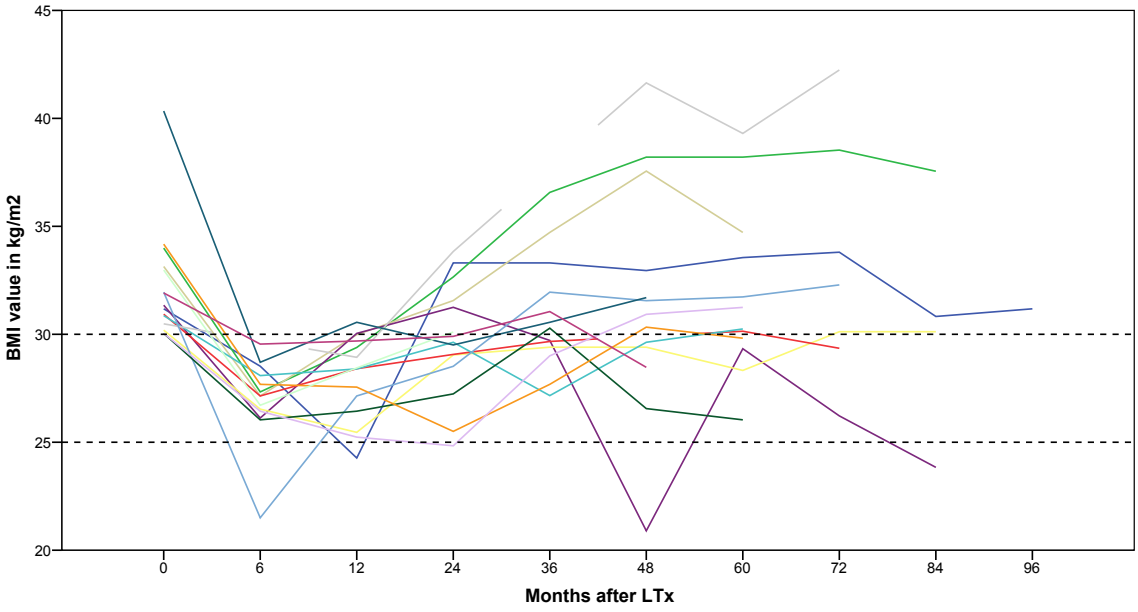


	6 mo	12 mo	24 mo	36 mo	48 mo	60 mo	72 mo	84 mo	96 mo
Total, n	225	221	193	170	178	149	102	61	24
New-onset obesity, valid n	49	51	50	43	43	39	29	16	7
weight change (kg), mean ± SD	-6.3 ± 9.8	-0.9 ± 10.7	3.2 ± 10.6	4.3 ± 13.3	6.3 ± 13.2	7.1 ± 11.0	9.6 ± 12.3	7.8 ± 15.6	15.1 ± 17.3
No new-onset obesity, valid n	176	170	143	127	135	110	73	45	17
weight change (kg), mean ± SD	-5.2 ± 7.9	-3.9 ± 8.9	-3.1 ± 9.1	-1.8 ± 9.8	-1.0 ± 9.3	-0.4 ± 9.6	0.4 ± 10.2	-0.1 ± 10.3	-0.4 ± 12.2

LTx, liver transplantation; SD, standard deviation; mo, months

Figure 4. Mean weight change compared to LTx in patients with or without new-onset obesity. Mean weight changes in kg were calculated as difference between each measurement point and the weight at LTx.
Source: Own Illustration.

Of the 54 patients who developed new-onset obesity, 15 were obese at LTx. Those patients lost weight early after LTx and had fallen below the obesity threshold, shifting to overweight (n = 13) or normal weight (n = 2). The majority (n = 8) developed new-onset obesity by 2 or 3 years post-LTx. The evolution of their BMI over time is shown in Figure 5.



LTx, liver transplantation; BMI, body mass index

Figure 5. Evolution of the BMI in 15 patients, who were obese at LTx and developed new-onset obesity after a period of being overweight or normal weight. The dashed horizontal lines represent the cutoffs for overweight (BMI ≥25kg/m2) and obesity (≥30 kg/m^2).
Source: Own Illustration.

CVE and patient survival

In the total cohort, 71 patients (28.1%) had a CVE during follow-up, mostly within the first year post-LTx (Figure 3B). Patients with new-onset obesity had a greater incidence of CVE than those without (46.3% versus 23.1%). Between 6 months and end of follow up, 52 patients (20.6%) died. The group of patients who did not become obese had a higher mortality compared to those who developed new-onset obesity (23.1% vs.11.1%).

Impact of new-onset obesity on patient outcomes

The multivariable analysis identified the following independent risk factors for CVE: new-onset obesity (Hazard Ratio (HR) 2.95; 95% Confidence Interval (CI) 1.47-5.95; p = 0.002) and higher age (HR 1.05; 95% CI 1.02-1.08; p < 0.001). In the sensitivity

analysis, using a sample of 214 patients without CVE at LTx, new-onset obesity (HR, 2.59; 95% CI, 1.21-5.53; p = 0.014) and higher age (HR, 1.04; 95% CI, 1.02-1.07; p = 0.001) remained predictors for CVE after LTx. However, new-onset obesity was not associated with increased mortality (HR, 0.84; 95% CI, 0.34-2.04; p = 0.696).

Risk factors for new-onset obesity after LTx

Given the complex mechanisms of weight gain and subsequent new-onset obesity, we intended to include risk factors from each of the framework's categories in our analysis. As the low number of new-onset obesity events (n = 54) required a reduction of factors, the final selection of variables was based on evidence from the literature and availability of relevant data in the STCS dataset: genetic risk score, age at LTx, gender, smoking at LTx, etiology, use of tacrolimus, cyclosporine and cortisone at 6 months, and income at LTx. Independent risk factors for new onset obesity were male gender (HR, 0.26; 95% CI, 0.076-0.889; p = 0.032) and genetic risk score (HR, 21.83; 95% CI, 1.50-317.64; p = 0.024). Given the limited sample of 114 patients for whom the genetic risk score was available and the broad confidence intervals observed, we performed another analysis excluding the genetic risk score. In this model, male gender (HR, 0.39; 95% CI, 0.162-0.930; p = 0.034) and alcoholic liver disease were independent predictors for new-onset obesity (HR, 3.37; 95% CI, 1.17-9.71; p = 0.025).

6.4 Discussion

Weight gain and obesity are well-known health issues in LTx recipients.[31] This analysis of a nationwide prospective transplant cohort study contributes to our understanding of both, the impact of new-onset obesity on clinical outcomes and of new-onset obesity's risk factors. After nearly 6 years of follow-up, the cumulative incidence of new-onset obesity was 21.3%, which is comparable to studies with shorter follow-up from the United States (21.6% at 2 years),[2] Brazil (23.7% at 3 years),[1] and the United Kingdom (26.3% at 3 years).[3] Male gender, etiology of alcoholic liver disease and genetic risk score were independent predictors for new-onset obesity. From transplantation until end of follow up, CVE occurred in nearly one-third of recipients. Independent of the presence of CVE at LTx, patients with new-onset obesity had a nearly 3-fold higher risk for CVE. New-onset obesity was not associated with increased mortality.

Impact of new-onset obesity on outcomes

Our analyses revealed mixed results regarding the impact of new-onset obesity on the two examined patient outcomes. Our sample's CVE incidence was within the range of

CVE later than 6 months after liver Tx reported by a systematic review (mean 11.8%; range 0% to 31.4%).[10] To the best of our knowledge, this study was the first to show that new-onset obesity predicts CVE after LTx. Fussner et al.[12] also studied post-LTx body weight parameters in a single center cohort of 455 LTx patients. In that study, nearly 30% of recipients experienced a CVE after 8–12 years of follow-up. Post-LTx BMI change, defined as a change of at least 1 BMI point in relation to the BMI at 4 months post-LTx, was not associated with CVE. A recent systematic literature review aimed to identify risk factors for CVE after LTx (e.g., individual cardiac events or combined outcomes, e.g., coronary artery disease, myocardial ischemia, heart failure, arrhythmias).[10] Of the 29 studies retrieved, only 3 examined post-LTx body weight parameters. Via multivariate analyses, none found any association between BMI at 1 year post-LTx and CVE.

To date, very few studies have examined post-LTx body weight parameters (i.e., post-LTx BMI or BMI change) in relation to CVE after LTx. This is rather surprising as CVE is a common post-LTx complication, increasing the mortality risk.[8,9] In light of the existing literature, which has showed no relationship between post-LTx body weight parameters and CVE, our finding in a prospective cohort is novel. We excluded patients who were continuously obese from pre- to post-LTx, meaning at least between LTx and the first measurement at 6 months post-LTx, all patients were under-, normal-, or overweight. The operationalization of new-onset obesity and the results of our analyses emphasize the need of weight gain prevention to avoid new-onset obesity. If the prevention of new-onset obesity might also have the potential to lower the risk of CVE will require further investigation.

In multivariable analysis, new-onset obesity did not predict mortality. Moreover, the descriptive results actually showed lower mortality in those who became obese compared to those who did not (11% versus 23%). Data published in 2016 show that weight gain and obesity may actually convey a survival benefit. Using data from 2968 patients with initial BMI values between 16 and 25 kg/m^2, Martinez-Camacho et al. examined weight gain at 2 years post-LTx.[16] Recipients who had gained weight (increase of >1 BMI point) showed significantly increased 5-year patient and graft survival compared to those whose weight decreased (decline of >1 BMI point) or remained stable. Additionally, patients who became obese by 2 years post-LTx (4.7%) had significantly longer patient and graft survival compared to those whose BMIs remained stable. Although the findings of this study support our observation, the methodology differed between the two studies. First, in that study, new-onset obesity was examined at 1 year post-LTx, while we analyzed it as a time-dependent event; second, the sample was

limited to patients with BMIs between 16 and 25 kg/m^2. This was probably why that study showed a lower incidence of new-onset obesity compared to our result (4.7% versus 21.3%). However, this issue requires further examination, especially as the results in LTx contradict studies in the kidney transplant population, where weight gain and obesity at 1 year after transplant are associated with increased risks of cardiovascular and all-cause mortality[32-34] as well as graft failure.[32-35]

Risk factors for new-onset obesity

It is well established that genes contribute to obesity in the general population;[26] and in the present study, the genetic risk score predicted new-onset obesity. Unfortunately, as the genetic risk score was only available in a subsample of the patients, the power of our analysis was limited. However, another STCS study examined two samples of kidney, liver, heart, lung and multi-organ transplant patients (total n = 1151), showing that the genetic risk score predicted 10% of weight gain in the first year after transplant.[29] The authors also found that the multivariable models with genetic variables better predicted weight gain compared to those with none.

To date, evidence on the impact of genes on body weight parameters in the transplant population is scarce. Of the few studies to examine candidate genes or SNPs, though, all found significant associations between the genetic variables and increased risk for weight gain and obesity after liver[36,37] and kidney transplant.[38]

While the results from candidate gene studies can be used to identify patients at risk of weight gain after transplantation, the clinical interpretation of a genetic risk score is limited, as it is calculated as the mean of BMI risk alleles. However, given that weight gain is driven by a complex interplay of factors, these results highlight the importance of incorporating genes in studies examining weight gain and obesity.

Another predictor for new-onset obesity indicated in our sample but not in previous research was male gender. Interestingly, in the general population, the global prevalence of obesity is higher in women than in men.[39] Despite the multitude of factors contributing to weight gain, gender specific risk factors such as hormones, menopause, and pregnancy place women at higher risk of developing obesity.[40] The reason why males were more likely than women to become obese following LTx remains unclear. However, the likelihood for males to gain rather than lose weight has also been shown in a large database study comparing male and female recipients with BMI changes after LTx.[16] In that study, 65% of patients who gained weight, and 56% of those who lost weight by 2 years post-LTx were male.

Our indication that alcoholic liver disease is a risk factor for new-onset obesity is also novel. Previous research showed a nearly 4-fold higher risk for post-LTx metabolic syndrome in patients with pre-Tx alcohol disorder;[41] however the mechanism driving this remains unclear. Brunault et al. hypothesized that LTx patients with previous alcohol use disorder switch from alcohol addiction to food addiction, leading to their higher post-Tx prevalence of obesity and metabolic syndrome.[42] This issue however, warrants further investigation.

While the present study showed meaningful and partly novel results, some limitations should be mentioned. First, physical activity is an important variable regarding weight gain and obesity. However, as it has only been measured in the STCS since 2012, too many data were missing to include it. Therefore, two EQ-5D dimensions–mobility and usual activity–were considered as proxies for activity level at 6 months post-LTx, although these dimensions might not effectively reflect the behavior performed. Second, we could not correct the weight and BMI at time of LTx for possible fluid overload (e.g., ascites). Therefore, we included patients with obesity at LTx only if they lost enough weight afterwards to shift them into a lower BMI category for at least the first measurement at 6 months post-LTx. It is likely that some of those patients did not have fluid overload at LTx but were obese because of increased fat mass. Third, we had no data on body weight parameters before liver disease was diagnosed. Therefore, while an elevated BMI before liver disease has been shown to predict post-LTx weight gain,[1] it could not be included as a covariate in our multivariate model. Finally, the risk factors included were measured at specific time points. As some risk factors (e.g., income, perceived health status) might be subject to change over the post-LTx course, future studies might consider them time-dependent variables.

Future research is needed not only to better understand individual risk factors for weight gain and subsequent obesity, e.g., genetic factors, gender and alcoholic liver disease, but also to identify interrelationships and combined effects based on the interplay of those risk factors. Healthcare professionals in follow-up care should consider that new-onset obesity gradually increases over time. Therefore, to prevent the development of new-onset obesity, patients who are normal weight or overweight after LTx, males and those transplanted because of alcoholic liver disease should be subject to long-term weight gain monitoring after LTx. Although older patients and those who became obese were at higher risk for CVE, prevention of CVE should be considered in all LTx recipients as adherence to a healthy lifestyle (diet, physical activity and non-smoking) has the potential to prevent 80% of CVE.[30]

Conclusion

In conclusion, post-LTx new-onset obesity had an incidence of 21.3% in our sample, and was predicted by the genetic risk score, male gender and alcoholic liver disease. However, it was not associated with patient survival. Independent of a history of pre-LTx CVE, both new-onset obesity and older age predicted CVE after LTx. Therefore, prevention of weight gain and new-onset obesity via a weight management program early after LTx might reduce the risk for CVE.

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Chapter 7. Development of the BALANCE Intervention with the COM-B Model and the Behavior Change Wheel

Weight gain is in itself a hugely complex issue that demands an appropriately creative solution.[1] When it leads to obesity, the problem becomes what Finegood et al. labeled "wicked": it is easily perceived as policy resistant and has no clearly described single true solution.[1] While numerous approaches exist to tackle obesity, evidence suggests that interventions are most effective if they follow three basic guidelines: (a) target the individual instead of a larger population, because policy changes do not sufficiently support behavior change;[2,3] (b) focus on the prevention of weight gain instead of weight loss, because weight loss maintenance is far more challenging;[4-7] and (c) integrate multiple components, including physical activity, advice for healthy eating and promotion of behavior change.[8-10] Therefore, regarding intervention development, no one-size-fits-all solution exists.[4,5] A tailored approach, considering personal, behavioral and contextual factors, is recommended.[8-10]

The results of the studies conducted under the BALANCE project increased our understanding of the target population and to some extent of energy balance-related behaviors. This is the crucial first step of behavioral intervention development following the COM-B model and the behavior change wheel. The following section provides a theoretical introduction about the COM-B model and the behavior change wheel, then follows the three stages of the behavior change wheel, leading finally to the suggestion of the BALANCE intervention in the liver Tx population.

7.1 The COM-B model and the behavior change wheel

Harmful behaviors such as unhealthy eating and physical inactivity are major drivers of weight gain and the development of obesity. However, behavior change is challenging and requires careful consideration not only of the individual but of the social, economic and political context in which the behavior occurs.[11] Also, before behavior change can be tackled via interventions, a profound knowledge of the target behavior is crucial.[11,12] Therefore, the application of theoretical models is a key factor in the development of weight-reduction interventions.

A variety of frameworks can be used to explain behavior and view it in the context of variables such as beliefs, norms, attitudes, skills, preferences, experiences or barriers.[13] One particularly useful framework is the COM-B model (Figure 1).[14] "COM-B" stands for **C**apability, **O**pportunity, **M**otivation, and **B**ehavior. Each of these components can be divided into two types: *capability* can be physical (strength/skills) or psychological (knowledge/skills), *motivation* can be reflective (conscious planning) or automatic (desire/impulse), and *opportunity* can be physical (environmental re-

sources/facilitators) or social (cues/norms). In Figure 1, which depicts the theoretical model, the double-ended arrows indicate interactions among the determinants and the behavior.

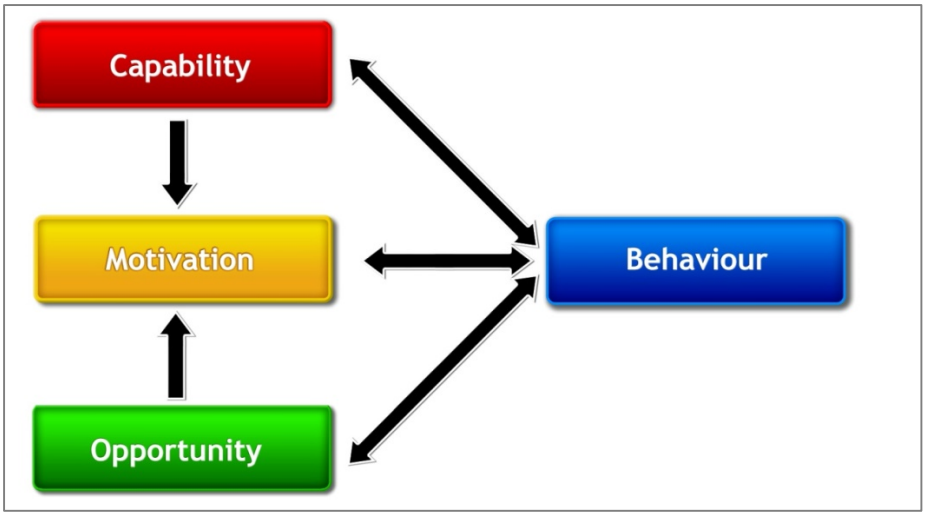

Figure 1. The COM-B model.
Source: Illustration from: Michie S, Artkins L, West R. *The behaviour change wheel. A guide to designing interventions.* Great Britain: Silverback Publishing; 2014.

The COM-B model is the core of the behavior change wheel, an intervention design tool derived from 19 behavior change frameworks identified in a systematic literature review (Figure 2).[14] While the COM-B serves as an explanatory model by characterizing the sources of behavior, the behavior change wheel guides the systematic development and evaluation of a behavioral intervention. It can be applied at any level from the individual to groups or populations; and, acknowledging the complexity of real world problems, its systematic step-by-step approach forces the intervention developer to think on multiple levels, e.g., from individual-, social- and system-level perspectives.

In the behavior change wheel, the COM-B model is surrounded by 2 outer layers: intervention functions and policy categories.[12,14] As behavior change tools, the 9 intervention functions can be combined as appropriate, i.e., an intervention may include multiple functions. The 7 policy categories support the delivery of the chosen intervention functions. All three layers of the wheel are closely interlinked via empirical evidence from the literature.[12,14]

Suggested by Michie et al., behavior change techniques are important additions to the behavior change wheel.[15] Though not depicted in Figure 2, these are integral to the intervention functions.[12] As the smallest active intervention components, behavior change techniques are by definition observable, replicable and irreducible, and are usable alone or in combination. The behavior change technique taxonomy currently

provides 93 distinct techniques, grouped into 16 clusters (e.g., goals and planning, feedback and monitoring, social support).

Some techniques have been more effective compared to others in supporting behavior change. They are summarized in separate taxonomies for specific behaviors, e.g., physical activity and healthy eating,[16,17] smoking cessation,[18,19] reduction of excessive alcohol consumption,[20] or medication adherence.[21,22]

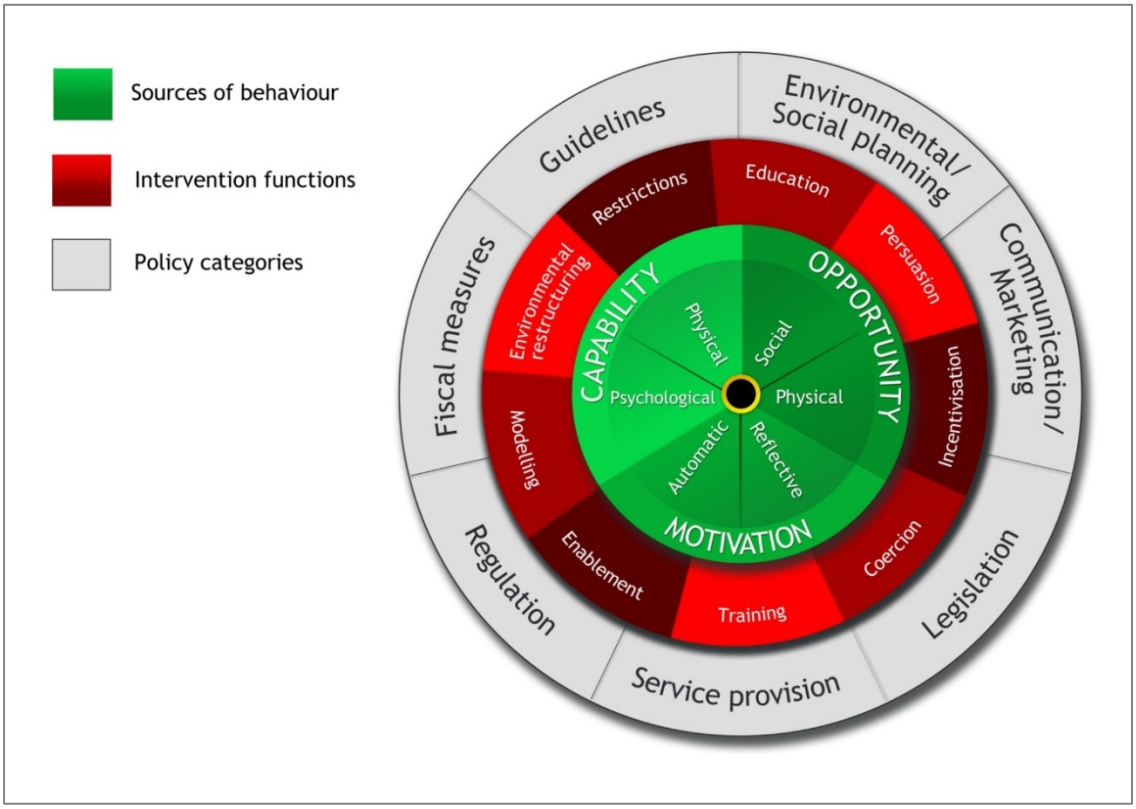

Figure 2. The behavior change wheel.
Source: Illustration from: Michie S, Artkins L, West R. *The behaviour change wheel. A guide to designing interventions.* Great Britain: Silverback Publishing; 2014.

7.2 The three stages of intervention development

Michie et al. suggested a 3-stage process of behavioral intervention design[12,14] (Figure 3). The first stage involves understanding the behavior itself and the target population via a behavioral diagnosis. The second requires identification of intervention functions and policy categories that will be effective in relation to the target behavior(s). For the third level, the intervention developers select optimal content (behavior change techniques) and decide on the delivery mode that best facilitates implementation.

For all 3 stages, evidence from diverse sources and multiple perspectives, using a variety of methods, is needed to inform decisions. And for each, patients' preferences and needs are at the center of the decision-making process. As related studies in the

liver Tx population can be scarce, evidence from other Tx groups may also be considered.

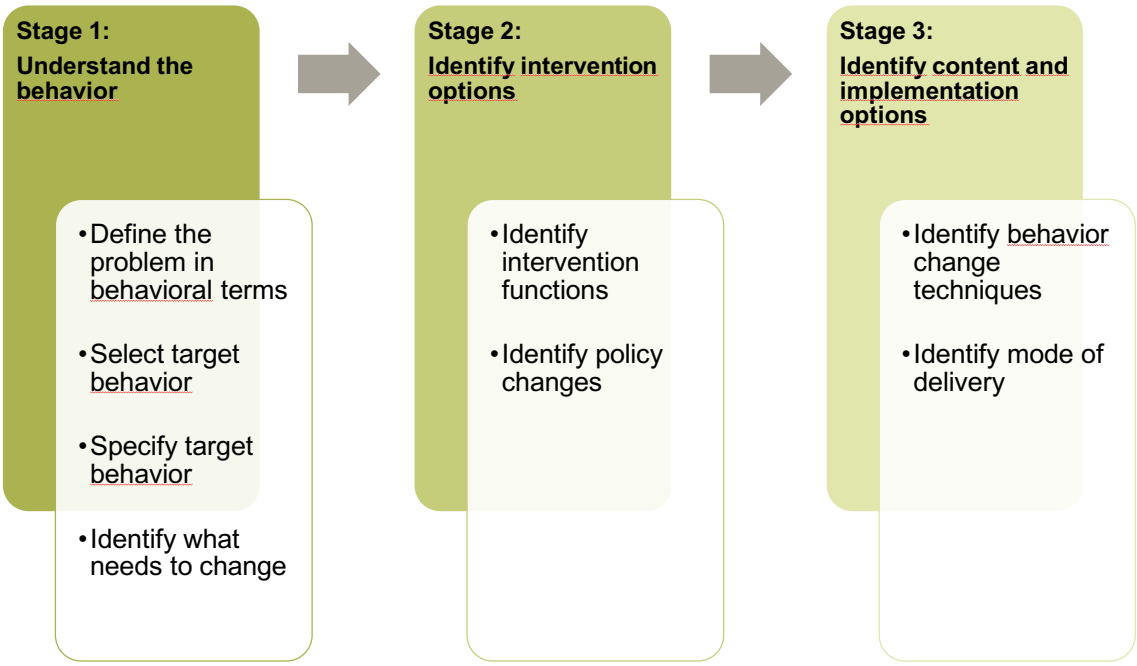

Figure 3. Designing an intervention by applying the behavior change wheel. Source: Illustration adapted from: Michie S, Artkins L, West R. *The behaviour change wheel. A guide to designing interventions.* Great Britain: Silverback Publishing; 2014.

Understand the behavior

a) Define the problem in behavioral terms

The first step towards understanding the target problem is to examine and define its characteristics in behavioral terms within the target population. The evidence base for this step of intervention development has already been introduced and discussed in the previous sections of this dissertation. The following passage is an example of a problem statement:

> ***In conclusion, the definition of the problem in behavioral terms is as follows:*** Weight management behavior in liver Tx recipients who are normal weight or overweight at 6 months after liver Tx.

b) Select the target behavior

Target behaviors should be selected within the specific context in which they occur. Behaviors do not occur in isolation but they are part of interlinked systems. Depending on the importance of a target behavior, it might impact related behaviors via the so-

called spillover effect (e.g., targeting healthy eating impacts shopping for fruits and vegetables, preparation of healthy food at home, and food choices in the workplace canteen).

In the ongoing discussion of the obesity epidemic, reduced to its simplest possible form, the fundamental mechanism of weight change is an imbalance between calories consumed and calories expended.[23] While it is important to acknowledge that increased intake of energy-dense foods and decreased physical activity are closely related to an obesogenic environment (e.g., easy access to high-fat, low-fiber foods, urban planning that discourages walking or cycling, workplace changes that minimize physical movement…),[24] an understanding of relevant and modifiable behavioral factors is crucial to body weight management. This statement is supported by two studies in which liver Tx patients were asked about the reasons for their weight gain.[25,26] Among the most common causes mentioned were reduced physical activity (24% and 36%), and increased food intake (48%). Energy balance related behaviors such as healthy eating and physical activity should therefore be considered core behaviors to prevent weight gain.

Naturally, a healthy diet is recommended after liver Tx; however, for many graft recipients, current evidence suggests that adherence to dietary guidelines is a serious challenge. One longitudinal study found that the total energy intake (carbohydrates, fat and protein) at 3-, 6-, and 9 months after Tx was greater than pre-Tx.[27] As an unfavorable development, the proportion of dietary fat increased from 35% to 40% after liver Tx–far more than the maximum of 10% recommended.[28] However, at 9 months post-Tx, fat intake was not associated with BMI.[27] Unfortunately, the current European clinical guidelines in liver Tx mention only dietary counseling to prevent weight gain and obesity, but recommend no specific content or other details.[29]

Increased physical activity has been identified as an essential component of comprehensive lifestyle interventions to manage weight in the general population.[3] Physical activity can be differentiated according to the subject's activity level and intention to perform the behavior. The American College of Sports provides the following definitions: "*Physical activity* refers to any bodily movement produced by skeletal muscles that results in energy expenditure above resting levels. Physical activity broadly encompasses exercise, sports, and physical activities done as part of daily living, occupation, leisure, and active transportation. *Exercise* refers to physical activity that is planned, structured, and repetitive with the final or intermediate objective to improve or maintain physical fitness. *Sedentary behavior* is activity that involves little or no movement or physical activity."[30]

For healthy adults, national and international health organizations recommend performance of at least 30 minutes of moderate-intensity physical activity (working hard enough to break a sweat, but still able to carry on a conversation) five days per week, or 20 minutes of more vigorous activity three days per week.[7,30,31] A combination of moderate- and vigorous- intensity activity is also possible. The same amount and intensity of physical activity is recommended for older adults or people with chronic conditions. However, the American College of Sports Medicine guidelines emphasize that if people "cannot perform 150 minutes of moderate-intensity aerobic activity per week because of chronic conditions, they should be as physically active as their abilities and conditions allow".[32]

In the liver Tx population, physical activity is linked to more health benefits than only weight gain prevention. For example, smaller studies have also found associations with increased muscle mass,[33] increased functional capacity,[34] decreased fat mass and blood lipids,[33] fewer comorbidities and a higher quality of life.[35] Moreover, lower exercise intensity has been associated with the development of metabolic syndrome.[36] A systematic review examined health outcomes of supervised exercise training programs reported in 15 randomized controlled trials in solid organ Tx recipients.[37] In heart Tx patients, regular exercise improved exercise capacity compared to standard care. The authors were unable to examine long-term patient outcomes such as cardiovascular risk factors and survival because no included studies were adequately powered.

Despite the beneficial effects of being active, physical inactivity is a serious issue in the liver Tx population. Immediately following Tx, this might be related to the severity of disease, ongoing fatigue, and decreased functional capacity after hospital and intensive care stay.[38-40] However, even in the long term, only 24% to 50% of liver Tx recipients engage in regular physical activity,[41,42] with performance below recommended levels.[43,44] One study that measured activity levels among patients from different BMI categories found that, compared to normal-weight patients, those who were overweight or obese were significantly less active.[45] Within the BMI groups, most notable difference was found in vigorous activity, with the highest levels reported in normal weight and lowest levels in obese patients.[45] Interestingly, though, total physical activity was associated with neither post-Tx obesity[46] nor BMI.[47]

Overall, research on physical activity and exercise in the Tx population lacks high quality studies.[38] Although the European liver Tx guidelines recommend integrating physical activity into the therapeutic regimen, they provide no further specifications regarding activity levels or amounts of activity.[29] This lack of specific recommendations

hinders evidence based decision-making in view of timing, frequency, duration and intensity of physical activity after Tx.

In considering intervention development, selection of the target behavior is guided by the following questions: What is the expected impact of the behavior change? What is the likelihood of changing this behavior? Is a spillover effect expected? Can the behavior be measured? Given the importance of physical activity regarding weight regulation,[48] its association with health benefits in the general[30,32] and Tx populations,[38] and the possibility to objectively measure physical activity, it might be the preferred target behavior over healthy eating. In addition, changes in physical activity might also provoke a spillover effect by leading to healthy eating. The following is an example of a clear statement regarding the selection of a specific target behavior.

In conclusion, the suggested target behavior is: physical activity (150 min/week with moderate-intensity OR 60 min/week with vigorous intensity). Depending on their physical condition, patients might start with a lower amount of activity and follow a stepwise approach to increase that until the recommendations are achieved.

c) Specify the target behavior

A detailed specification of the selected target behavior includes details about who, what, when, how often, where, and with whom the behavior is to be performed. The previous behavioral analysis steps have already covered ‘who’ and ‘what’. As no detailed recommendations are available for liver Tx patients, further decisions about specified target behavior need to be based on the best available evidence relating to the general and overall Tx populations.[38]

Specification	Evidence
Who	• Patients who are normal weight or overweight at 6 months after liver Tx (Chapter 3 and 6)
What	• Being physically active for 150 min/week with moderate-intensity OR 60 min/week with vigorous intensity (stepwise increase of activity is possible to reach the goal)[7,30,31]
When	• After 6 months post-Tx the immunosuppressive regimen is usually reduced to the minimum dose and the risk for opportunistic infection is decreased. Quality of life, mental and physical functioning, and satisfaction with life increase within the first year after Tx[29] • The most effective interventions start within 1 year after Tx[37] • The highest proportional weight gain in our liver Tx patients occurred between 6 months and 1 year after Tx (Chapter 3)
How often	• Comprehensive weight loss interventions should cover at least 14 sessions over 6 months[6] Exercise training over 12 to 24 weeks increased oxygen consumption and exercise capacity in heart Tx[37] • Weight gain in our liver Tx patients leveled off after 2nd year post-Tx (Chapter 3)
Where	• Most effective interventions included supervision (not specified by whom)[37] • Kidney Tx patients' intervention needs: support for help in lifestyle changes by various healthcare providers (dieticians, nurses, physicians)[49] → Expert supervision and coordination of diverse healthcare professionals can best be provided or at least initiated in the Tx center setting
With whom	• Peer support and exercise partners are perceived as important[49]: • In Switzerland only 3 Tx centers perform liver Tx, covering a wide geographic region. For some patients, the effort and time needed to travel to the Tx center is an organizational and financial burden and should not be underestimated → Provision of a physical activity group at the Tx center and a home-based training program

In conclusion, the specified target behavior is as follows:

Who:	Liver Tx patients with normal or overweight at 6 months after Tx
What:	Being physically active for 150 min/week with moderate intensity OR 60 min/week with vigorous intensity (stepwise increase of activity is possible to reach the goal)
When:	At 6 months after Tx (if the recipient is medically stable)
How often:	12-week program with a follow up until 2 years post-Tx
Where:	Initiated in the Tx center
With whom:	Physical activity group at the Tx center and a home-based training program

d) Identify what needs to change

The fourth step is to identify the changes needed in the individual and/or the environment to accomplish behavior change. This step includes an analysis of the behavior in its context using the COM-B model. Behavior change is expected if one or more of the

3 behavior determinants change. The need for change is summarized in the following table:

COM-B	What needs to happen for the target behavior to occur?	Is there a need for change?	Evidence
Capability - Physical	• **Having the physical skills to be active for 150 min/week with moderate-intensity OR 60 min/week with vigorous intensity (stepwise increase of activity is possible to reach the goal)**	**Yes**	**Evidence from liver Tx:** • **Calcineurin inhibitors are associated with prolonged muscle regeneration[38]** • **Risk for post-Tx comorbidity: metabolic, cardiovascular, renal and bone disease malignancy[50]** • **Ongoing fatigue post-Tx decreases functional capacity[40]**
Capability - Psychological	• **Knowing activities categorized as moderate or vigorous intensity** • **Knowing the benefits of physical activity and its impact on outcomes**	**Yes**	• **Kidney Tx: 29% believed they could lose weight by exercising and changing diet[49]** • **Heart Tx: recipients with adequate health literacy had higher odds of engaging in sufficient physical activity[51]**
Opportunity - Physical	• Environment allows physical activity	No	
Opportunity - Social	• Being physically active is socially accepted, culturally integrated, and enforced on a policy level in Switzerland	No	
Motivation - Reflective	• **Belief that one's physical capabilities are sufficient to be physically active** • **Belief that being physically activity helps to prevent weight gain** • **Intention to be more physically active** • **Setting goals to achieve the aim of being physically active**	**Yes**	**Evidence from kidney Tx:** • **Belief that the ability to be physically active was important facilitator (81%)[52]** • **Lack of motivation was most frequent barrier (62%) for physical activity[52]** • **Fear of injuring the new kidney[49]** • **Fear of movement associated with lower daily physical activity[53]**
Motivation - Automative	• **Have established the routine to integrate physical activity into daily life** • **Feeling satisfied after being physically active**	**Yes**	**Evidence from liver Tx:** • **Only 24% to 50% engaged in regular physical activity post-Tx[41,42]** • **Physical activity associated with increased quality of life[35]**

In conclusion, via the COM-B, following needs to change: capability (physical and psychological), and motivation (reflective and automatic)

Identify intervention options

a) Identify intervention functions

The fifth step links the specific target behavior to one or more intervention functions likely to be effective to change behavior. Selection of the most appropriate intervention requires guidance from the existing evidence and a systematic rating against the APEASE criteria: affordability, practicability, (cost-)effectiveness, acceptability, side-effects/safety, equity. The 9 intervention functions requiring modification are defined in the following table:

Intervention function	Definition	Is there a need for change?	Evidence
Education	**Increase knowledge or understanding**	**Yes**	**Evidence from kidney Tx:** • **Patients want to receive written information on diet and physical activity[49]** • **86% want personal contact for help in lifestyle changes[49]**
Persuasion	**Using communication to induce positive or negative feelings or stimulate action**	**Yes**	**Evidence from kidney Tx:** • **Most important facilitators for physical activity: positive feelings such as feeling healthy, wanting to improve health and increase energy[52]**
Incentivisation	Creating an expectation of reward	Not feasible because of limited resources	
Coercion	Creating an expectation of punishment or cost	Not acceptable	
Training	Imparting skills	Possible, but being physically active can be covered with the 'enablement' function in this context	
Restriction	Using rules to reduce the opportunity to engage in the target behavior	Not appropriate in this context	
Environmental restructuring	**Changing the physical or social context**	**Yes**	**Evidence from kidney Tx:** • **Implementation of a collaborative interprofessional chronic care team providing consultations and self-management support improved outcomes[54]**
Modelling	**Providing an example for people to aspire to or imitate**	**Yes**	• **Kidney Tx patients perceived peer pressure as a positive motivator for change[49]**

			• **Peer support strengthened self-management tasks**[55]
Enablement	**Increasing means or reducing barriers to increase capability (beyond education and training) or opportunity (beyond environmental restructuring)**	**Yes**	**Evidence from general population:** • **Increase capability and motivation by targeting the underlying subdomains such as self-regulation, goals, beliefs and self-efficacy**[12] • **Interventions are more successful if they include behavior change components**[8-10]

Based on the evidence from the literature, Michie et al. connected each of the 9 listed intervention functions to one or more components of the COM-B model (green cells), see table below.[12] The 'x' indicates the intervention function requiring modification in relation to the previously chosen COM-B dimension (in bold).

	Intervention functions								
COM-B	**Education**	**Persuasion**	Incentivisation	Coercion	Training	Restriction	**Environmental restructuring**	**Modelling**	**Enablement**
Capability - Physical									x
Capability - Psychological	x								x
Opportunity - Physical									
Opportunity - Social									
Motivation - Reflective	x	x						x	
Motivation - Automatic		x					x	x	x

Based on the international evidence, we identified the following intervention functions as requiring change: education, persuasion, environmental restructuring, modeling, and enablement

b) Identify policy change

The sixth step is to determine which policy category would best support the delivery of the chosen intervention. The selection of the policy categories is again based on the best evidence available and evaluated against the APEASE criteria. The policy categories that require change are identified in the following table:

Policy category	Definition	Is there a need for change
Communication/ marketing	**Using print, electronic, telephonic or broadcast media**	**Yes**
Guidelines	Creating documents that recommend or mandate practice	Are already available
Fiscal policy	Using the tax system to reduce or increase the financial cost	Not practicable in this context
Regulation	Establishing rules or principles of behavior or practice	Not practicable in this context
Legislation	Making or changing laws	Not practicable in this context
Environmental/social planning	**Designing and/or controlling the physical or social environment**	**Yes**
Service provision	**Delivering a service (e.g. counseling, training, other support…)**	**Yes**

From a content and delivery perspective, the three chosen policy categories are closely interrelated and can be elegantly combined in the category of 'service provision'. Given that the intervention should be initiated in the Tx center, service provision can be realized with a care re-organization according to a chronic care model. This possibility will be elaborated in Chapter 12.4 (Implications for clinical practice). Again, each policy category is connected to one or more intervention functions (green cells), see table below.[12] The 'x' indicates the policy chosen as needing change in relation to the previously chosen intervention function (in bold).

	Policy category						
Intervention function	**Communication / marketing**	Guide-lines	Fiscal policy	Regulation	Legislation	**Environmental/ social planning**	**Service provision**
Education	x						x
Persuasion	x						x
Incentivisation							
Coercion							
Training							
Restriction							
Environmental restructuring						x	
Modelling	x						x
Enablement						x	x

Based on international evidence, we identified the following policy categories as requiring change: communication /marketing, environmental/social planning, and service provision.

Identify content and implementation options

a) Identify behavior change techniques

The seventh step is identification of the most appropriate behavior change techniques. Based on the chosen target behavior for the final intervention, the results of two meta-analyses guided the preliminary selection of techniques effective as intervention components to increase physical activity and healthy eating.[16,17] The selection of the final technique is again based on the best available evidence and evaluated against the APEASE criteria.

Intervention function	Effective behavior change techniques in meta-analyses	Techniques meeting the APEASE criteria
Education	2.2 Feedback on behavior 2.3 Self-monitoring of behavior 2.4 Feedback on outcome(s) of the behavior 5.1 Information about health consequences 7.1 Prompts/cues	2.2 Feedback on behavior 2.3 Self-monitoring of behavior 2.4 Feedback on outcome(s) of the behavior 5.1 Information about health consequences
Persuasion	2.2 Feedback on behavior 2.4 Feedback on outcome(s) of the behavior 5.1 Information about health consequences	2.2 Feedback on behavior 2.4 Feedback on outcome(s) of the behavior 5.1 Information about health consequences
Environmental restructuring	7.1 Prompts/cues 12.1 Restructuring the physical environment	7.1 Prompts/cues
Modelling	6.1 Demonstration of the behavior	6.1 Demonstration of the behavior
Enablement	1.1 Goal setting (behavior) 1.2 Problem solving 1.3 Goal setting (outcome) 1.4 Action planning 1.5 Review behavior goal(s) 1.7 Review outcome goal(s) 2.3 Self-monitoring of behavior 3.1 Social support (unspecified) 3.2 Social support (practical) 12.1 Restructuring the physical environment	1.1 Goal setting (behavior) 1.2 Problem solving 1.4 Action planning 1.5 Review behavior goal(s) 1.7 Review outcome goal(s) 2.3 Self-monitoring of behavior

Based on international evidence, we identified following behavior change techniques: goal setting (behavior), problem solving, action planning, review behavior goal(s), review outcome goal(s), feedback on behavior, self-monitoring of behavior, feedback on outcome(s) of the behavior, information about health consequences, demonstration of the behavior, prompts/cues

b) Identify mode of delivery

The eighth step is the identification of the delivery mode for the intervention (Figure 4). Based on the decisions made in the previous steps, selection of the delivery mode is again evidence based and evaluated against the APEASE criteria.

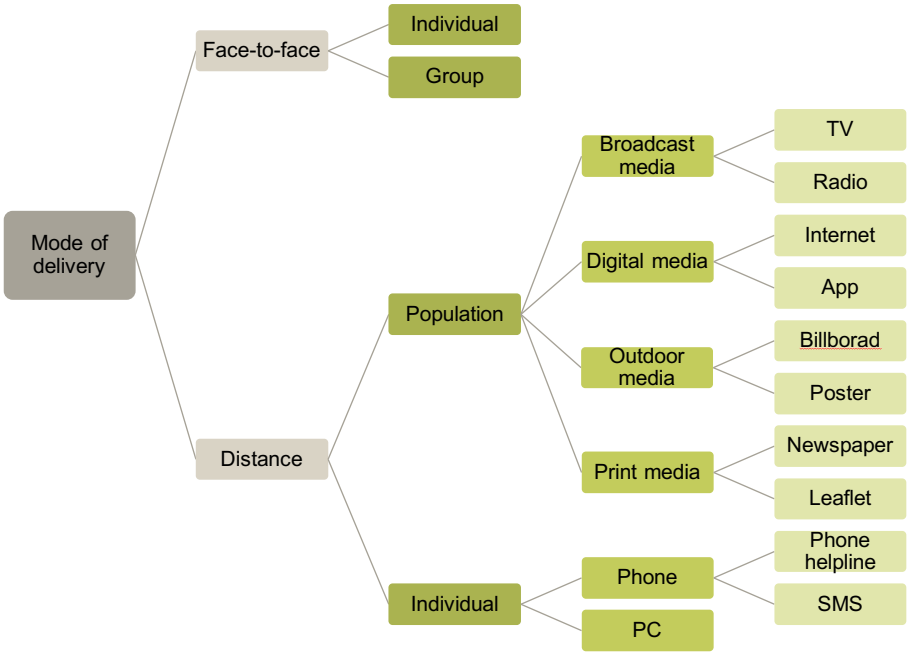

Figure 4. Delivery modes for the intervention.
Source: Illustration adapted from: Michie S, Artkins L, West R. *The behaviour change wheel. A guide to designing interventions.* Great Britain: Silverback Publishing; 2014.

Mode of delivery	Evidence
Face-to-face	Evidence from kidney Tx: • Face-to-face support was preferred to text or e-mail messages[49] Evidence from the general population: • Individual-level interventions should be favored to target obesity[2,3] • Comprehensive interventions delivered on-site lead to more weight loss compared to those via internet or e-mail[6] • Groups who received personal contact in weight loss maintenance trials had less weight re-gain compared to the self-directed control group members during the study period[56-58]
Distance	• Some patients have to travel long distances to Tx center, which can be a financial burden or resource-intense • It is possible to connect via telephone or digital media to support a home-based training program

Based on international evidence, we identified following delivery mode: individual level interventions, using a face-to-face approach in a combination with eHealth technology.

7.3 Summary of the intervention's components

Aim	• Weight management behavior in liver Tx patients who are normal weight or overweight
Target behavior	• Being physically active for 150 min/week with moderate-intensity OR 60 min/week with vigorous intensity • Patients might start with a lower activity and follow and increase stepwise to achieve recommendations
Timeline of the intervention	• Start of the 12-week program at 6 months after liver Tx (if clinically stable) • Follow up until 2 years post-Tx
Setting	• Outpatient clinic in the Tx center • Delivery of the intervention within a healthcare system structured according to a chronic care model
Interprofessional Team	• Nurse / Advanced Practice Nurse, Hepatologist, Surgeon, Physiotherapist, Nutritionist, Psychiatrist, Social worker

Capability	Motivation		Intervention Function	Description	Example for a specific intervention	Behavior change technique
		Automatic	Education	Provide information on relevant topics to increase knowledge	Group sessions and written information material about • Comorbidity and side effects of immunosuppressive drugs • Healthy lifestyle after Tx • Impact of physical activity on health • Healthy eating Individual counseling (face to face, telephone, Skype) • Review results of self-monitoring • Provide feedback on the physical activity performed and measured weight	• Self-monitoring of behavior • Feedback on behavior • Feedback on outcome of the behavior • Information about health consequences
	Reflective	X				
X						
		Automatic	Persuasion	Talk about benefits and harm caused by physical activity or inactivity to induce emotions	• Peers share success stories • Oral and written feedback on individual's success of reaching the goal (e.g., be physically active, maintain stable weight)	• Feedback on behavior • Feedback on outcome of the behavior • Information about health consequences
	Reflective	X				
		Automatic	Environmental restructuring	Establishment of a chronic care model with an interprofessional team supporting weight management Training group for Tx patients	Scheduled counseling sessions with expert • Group • Individual Written reminders from team (telephone, text message) • Perform physical activity • Training group meetings	• Prompts/cues • Demonstration of the behavior
		X				
		Automatic	Modelling	Collaborate with other Tx recipients serving as peers and role models	• Peers talk about their physical activities in the educational group sessions • Establish a buddy system for shared training sessions	• Demonstration of the behavior
	Reflective	X				
		X				
		Automatic	Enablement	Self-management support and application of behavior change techniques	• Integration of behavior change techniques in the individual counseling sessions and in the written material • Support patients to define goals for physical activity, to plan the behavior, to perform self-monitoring to overcome barriers	• Goal setting of behavior • Problem solving • Action planning • Review behavior goal • Review outcome goal • Self-monitoring of behavior
		X				
X						

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Chapter 8. Discussion

As in the general population, the health risks of weight gain and obesity have been recognized in the Tx populations. The introduction of this dissertation outlined post-Tx weight gain and obesity's associations with morbidity and mortality, the complex system of factors influencing weight gain, the importance of energy balance-related behaviors (i.e., healthy eating and physical activity), and arguments for favoring interventions to prevent weight gain over those focused on weight loss. Given the lack of interventions targeting the liver Tx population, the aim of this thesis was to develop a behavioral intervention focusing on physical activity and diet to support effective weight management and a healthy lifestyle after liver Tx.

This final section discusses the included studies' key findings according to two clinical questions that helped conceive, drive and direct the BALANCE project's research aims; it suggests implications for future research and clinical practice; and finally, acknowledges the project's strengths and limitations.

8.1 How important is the prevention of weight gain after transplantation?

Our analysis of STCS data was the first simultaneous comparison of body weight parameters in all solid organ Tx recipients going beyond the first year after Tx. Although the evolution of obesity and weight gain varied among the organ groups, both issues are health concerns in all solid organ Tx recipients. First, the majority of patients who were obese at 6 months post-Tx remained obese at 3 years post-Tx. Second, post-Tx weight gain was common. Although our sample's mean weight gain in the first year after Tx was less excessive than described in the international Tx literature,[1-8] we showed that weight gain continues beyond the first year post-Tx, leading, in many cases, to new-onset obesity. This finding should be considered in long-term follow-up care as, compared to the early post-Tx period, clinically stable Tx recipients are usually scheduled less often for Tx center follow-up appointments. Therefore, early post-Tx education should both include information on the risk for post-Tx weight gain and support patients to monitor their weight also long-term after Tx.

The need to prevent weight gain after liver Tx was reinforced by the findings of our second STCS analysis, involving post-Tx new-onset obesity. Indeed, patients who developed new-onset obesity after liver Tx had a 3-fold higher risk for CVE. This result is novel as our study was the first to examine the impact of post-liver Tx new-onset obesity on CVE.

Following liver Tx, cardiovascular and metabolic comorbidities have been shown to increase the risk for CVEs and mortality compared to age and gender-matched general populations.[9,10] This is one reason why long-term post-liver Tx outcomes have not reflected improvements in short-term patient- and graft survival.[11] Therefore, non-obese liver Tx recipients should be supported to prevent weight gain.

However, it is important to mention that in our research, over a follow-up of nearly 6 years, new-onset obesity had no negative impact on patient survival after liver Tx. While a recent study suggested that patients with new-onset obesity actually had a survival benefit compared to those who maintained a stable weight,[12] this issue has not been examined by other studies in this population.

Overall, another systematic review by our group showed a serious shortage of studies examining post-Tx weight gain and obesity in relation to outcomes in liver Tx. While we did not include the findings of this systematic review in this thesis as some sub-analyses were still pending at the time of submission, the lack of research, especially on post-Tx body weight parameters and outcomes, was substantiated in this review by the limited available evidence that was usable for meta-analysis. More specifically, of 184 studies that met our inclusion criteria, 37 were eligible for inclusion in our meta-analysis, whereof only 6 examined one post-Tx body weight parameter (i.e., post-Tx BMI). The reason so few were usable was the huge variation in outcome and body weight parameter definitions used among the studies. To extend the value of future studies, we recommend that prospective researchers intensify exploration of the link between post-Tx weight gain parameters (including new onset obesity) and patient outcomes.

In summary, both in the short- and long-term periods following Tx, weight gain prevention is important to avoid the development of new-onset obesity. Intuitively, this is hardly surprising; however, our research showed that in liver Tx recipients, preventing weight gain leading to new-onset obesity is particularly important, as it might improve cardiovascular outcomes.

8.2 Which factors are related to weight gain and obesity after transplantation?

Modifiable risk factors can make excellent targets for intervention development aiming to prevent weight gain and obesity. However, the current shortage of research guided by theoretical frameworks precludes a deeper understanding of factors influencing weight gain after liver Tx.

Through the use of our theoretical framework as a working model to guide the design of two BALANCE project studies, we were able to systematically map and better understand a number of variables related to body weight parameters. We were the first to summarize the literature and examine pre- and post-Tx factors from multiple categories associated with body weight parameters after liver Tx. The framework was then adapted according to the evidence generated in this dissertation, Figure 1. Overall, our findings highlight that, as in the general population,[13] weight gain in the Tx population is driven by a complex interplay of multiple factors.

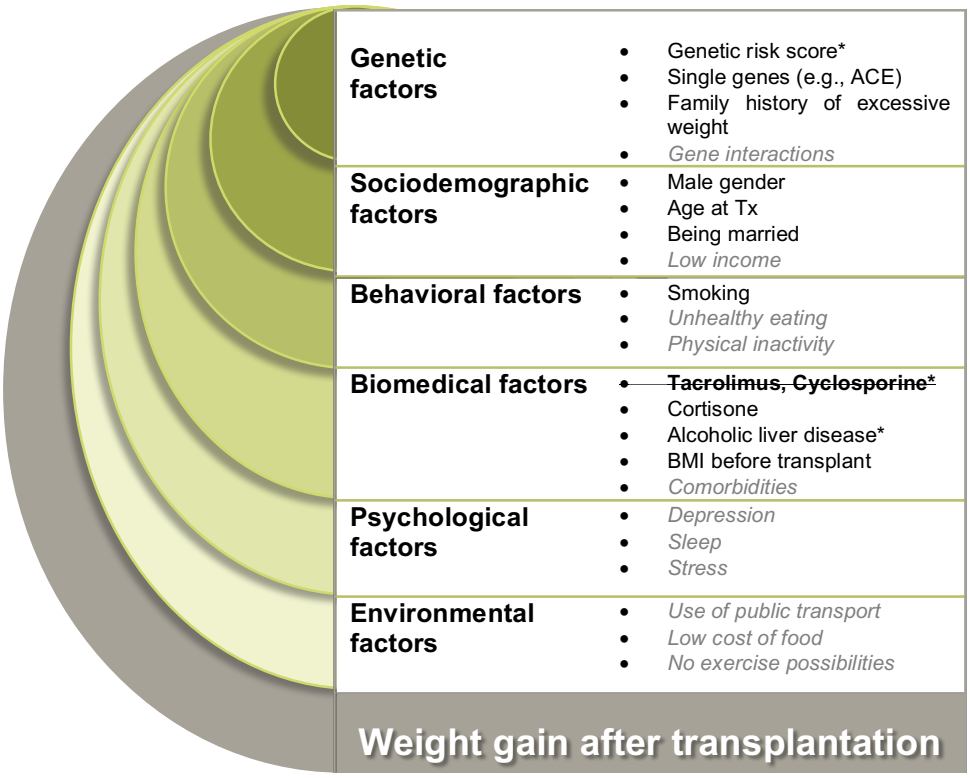

Figure 1. Theoretical framework of factors influencing weight gain in the BALANCE project. The variables assigned to the categories are: evidence from meta-analysis (bold, crossed factors were non-significant), evidence from single studies in liver Tx (* from the BALANCE project), and selected variables in the general population (in grey color and italics)
Source: Own Illustration.

Regarding suspected biomedical factors, our meta-analysis revealed that neither tacrolimus nor cyclosporine was associated with obesity after liver Tx. This is an important finding, as the results from single studies remain conflictive regarding the impact of immunosuppressive drugs on post-Tx weight gain and obesity.[14] Our synthesis of 6 studies provides higher-level evidence that might also guide clinicians' decision-making, as most liver Tx recipients receive either cyclosporine or tacrolimus.[15] It is no-

table that, although neither tacrolimus nor cyclosporine were associated with obesity, the systematic review and meta-analysis provided no evidence regarding either their impact on weight gain per se or their potential interplay with factors with known relationships to weight gain and obesity. Therefore, independent of the immunosuppressive drug used, prevention of weight gain should be included in routine follow-up care after liver Tx.

Our analysis regarding new-onset obesity identified two distinct risk factors. Both male recipients and those who received liver Tx for alcoholic liver disease had a significantly higher risk of developing new-onset obesity. To our knowledge, no other study has specifically examined gender and the impact of etiology on weight gain and obesity after liver Tx. Therefore, both these factors and the specific underlying pathways leading to new-onset obesity warrant further investigation. However, our results support the theoretical assumption that factors from various categories drive post-liver Tx weight gain.

Additionally, we examined genetic factors in combination with sociodemographic, behavioral, and biomedical factors derived with the guidance of our theoretical framework. In both of our relevant studies examining genetic risk scores, these scores were significantly associated with post-Tx body weight parameters. More specifically, over a mean follow-up period of nearly 6 years after liver Tx, the genetic risk score predicted new-onset obesity; and it predicted ≥10% weight gain at 1 year after Tx in a mixed sample of kidney, liver, heart, lung and multi-organ Tx recipients. Importantly, in the study sample of all four solid organ Tx groups, the models including genetic risk scores better predicted weight gain than models not including them.

The clinical interpretation of this finding, as well as the identification of patients at risk for weight gain and obesity based on a genetic risk score are limited, as the genetic risk score is based on the mean of BMI risk allele values. This means a genetic risk score does not facilitate the tailoring of interventions to specific genotypes. However, our results regarding the genetic risk score's predictive value emphasize the importance of including this and similar information in studies examining weight gain and obesity in Tx.

To the best of our knowledge, no other studies to date have examined the impact of genetic risk scores on body weight parameters in the Tx population, although they have been studied more frequently in the general population. Interestingly, in the general population, genetic risk scores were associated not only with BMI[16] and weight gain,[17] but also with gene-environment interactions such as socio-economic situation

(with larger BMI increases in people in the most deprived situations compared to their more affluent counterparts), self-reported physical activity (with larger BMI increases in physically inactive than active people),[18] and dietary fat and energy intake.[19]

Although we have examined the genetic risk score in combination with other factors from our theoretical framework, we were unable to study gene-environment interactions: to allow meaningful effects, a study design with such a focus would require much larger sample sizes, along with precise definitions of environmental contexts,[16] neither of which was available in the STCS database. Therefore, interactions between genetic risk scores and the environment remain a topic for future research.

Although we identified specific factors and categories impacting post-Tx weight gain, our systematic literature review also detected several areas that remain poorly understood. Despite retrieving 43 articles studying a total of 82 distinct factors related to post-liver Tx body weight parameters, we were unable to perform meta-analyses regarding gender, age or cortisone use, which are all common sociodemographic and biomedical factors and are often included in data collection as sample characteristics. The reason we could not use them was the variety of definitions and operationalization of variables among the studies (e.g., steroid use was defined as use of cortisone (yes/no), cumulative steroid dose, length of steroid use, or use of steroids combined with other immunosuppressive drugs).

Furthermore, behavioral variables such as energy balance-related behaviors (i.e., eating and physical activity) are key factors in relation to weight gain and subsequent obesity.[20,21] However, our literature search identified no studies examining either eating or physical activity in relation to post-Tx weight gain and obesity. This could be because of the methods applied, as our research questions were not specifically formulated to examine this relationship. Still, even our broad search strategy returned no results regarding energy balance-related behaviors in relation to body weight parameters after liver Tx. Finally, very few articles retrieved covered psychological or environmental factors, leading to the conclusion that these factors are generally understudied.

8.3 Implications for future research

While the findings of the studies included in this dissertation contributed to the evidence base on evolution of body weight parameters in Tx, as well as weight gain and new-onset obesity after liver Tx, they also identified the following implications for future research: First, risk factors and outcomes related to post-Tx weight gain and obesity should be determined via theoretical frameworks and defined outcome measures using

standardized operational definitions; second, patients' perspectives should be explored concerning weight management and weight gain; and third, weight management interventions should be developed, implemented, and evaluated in the Tx populations.

Given that post-Tx weight gain and obesity have been issues for more than 2 decades in the liver Tx population, the shortage of studies examining risk factors for weight gain and obesity or their impacts on morbidity and mortality calls for immediate action. From a methodological perspective, longitudinal data collection, including repeated measurements over the full course of Tx, as well as the assessment of diverse risk factor and patient outcome categories would provide an optimal basis for further research. Yet, while we strongly suggest conducting more studies, the value of such studies will be greatly enhanced via the application of the quality criteria suggested in the following paragraphs.

In view of studies examining risk factors for weight gain and obesity, any future research should use a theoretical framework to guide study design. Theoretical guidance has been proved beneficial in other research contexts examining multifaceted issues. For example, a theoretical model can be a basis for the development of evidence-based behavioral interventions;[22] a comprehensive framework can be used to guide the evaluation of interventions in implementation science;[23] and the effectiveness of a dietary or physical activity intervention can be assessed based on a theoretical model.[24]

A theory driven approach would not only facilitate a systematic research procedure, but would allow researchers to name and highlight research gaps regarding weight gain risk factors. The BALANCE project, for example, identified the need for more research in view of energy balance-related behaviors, as well as psychological, environmental and even genetic factors. Although we examined the genetic risk score in relation to weight gain and obesity, evidence on the impact of candidates' genes is still scarce. The few studies examining genetic impact found significant associations between 4 genes (CPE, LEP, NPY1R, and NPY5R) and weight gain at 6 months post-kidney Tx,[25] an ACE polymorphism and weight gain at 1 year post-liver Tx,[25,26] and between the PNPLA-3 genotype and obesity at 1 and 3 years post-liver Tx.[27] These results suggest that body weight parameters are impacted not only by genetic risk scores, but by specific genes or their polymorphisms. Expanding research in this area might provide information as to whether genes important for obesity in the general population, e.g., FTO and MC4R,[28] influence weight gain and obesity after Tx.

Finally, as with the genetic risk score, single genes should be examined in gene-environment and gene-behavior interactions, as they play a significant role in the etiology of obesity.[29-31] For example, strong evidence supports a gene-behavior interaction between the FTO gene (an important obesity-linked gene) and physical activity.[32,33] Meaning, the association of the FTO risk allele with weight gain and obesity is attenuated by approximately 30% in individuals who are physically active compared to those who are inactive. Gene-interactions may also account for why some people tend to gain weight faster and sooner than others in times of ongoing high energy intake. Likewise, they might account for outcome variability in randomized controlled trials using standardized dietary and physical activity interventions.[34] Research on gene-interactions related to weight gain and obesity in the general population has grown rapidly[35] and should also be pursued in Tx patients.

The research infrastructure in single center studies and registries might not always support the collection of measures beyond baseline clinical and sociodemographic data. However, in the era of big data, the opportunities to merge clinical and scientific databases and collaborate with other research groups might allow the inclusion of genetic, behavioral, psychological, and environmental data to study body weight parameters in the Tx population. In combination with a more systematic and theory driven approach, this is expected to enhance our understanding of post-Tx weight gain and obesity.

In view of relevant patient outcome measures, clear identification and standardized definition of terms is crucial. In our ongoing systematic review, the variety in outcomes measured was a major limitation, hindering both the comparison of studies and the performance of meta-analyses. Konerman et al. faced a similar challenge in their systematic review on risk factors for CVE after liver Tx.[36] The authors reported substantial heterogeneity among their final selection of 29 studies (i.e., definition of outcomes, inclusion and exclusion criteria), which hampered their meta-analysis.

While we acknowledge that measures need to be operationalized to serve the aims and methods of the study employing them, the Tx research community would benefit from a consensus to harmonize outcome research in relation to body weight parameters. Two recent applications of this principle have been reported in nephrology, concerning the development of standardized core outcomes to be considered in trials in hemodialysis [37] and in kidney Tx.[38] The standardization of outcomes (i.e., classification of outcomes relevant to researchers, clinicians and patients; identification of specific assessment instruments; definition of thresholds) is expected to improve both the quality of reporting and the relevance of trials in nephrology patients.

While recommendations for core outcomes in relation to body weight parameters are missing in the Tx population, one initiative guiding the movement in this direction could be the 2017 consensus statement about the management of modifiable risk factors in kidney and liver Tx.[39] An international interprofessional expert panel developed specific practical recommendations to manage risk factors for decreased graft and patient survival beyond the first year post-Tx. After summarizing causes for graft loss, their statement provided information on cardiovascular and metabolic comorbidities, which would also be relevant for examination in relation to body weight parameters. Reaching consensus in view of outcome measures is expected to improve research quality across all Tx populations. The resulting improvement of evidence quality would facilitate the performance of systematic reviews and meta-analyses.

The second implication for future research is related to the patients' perspective, i.e., how liver recipients perceive their post-Tx weight gain and its potential causes, as such reports inform intervention development. When two quantitative studies asked recipients about the causes of their post-liver Tx weight gain, their most commonly reported answers included constant hunger–leading to increased food intake–and reduced daily physical activity.[40,41] However, further in-depth insights into these patients' perceptions with weight gain need to be explored through qualitative methodology.

The BALANCE project has already picked up this issue and is currently conducting a qualitative study to explore patients' perceptions regarding weight gain after liver Tx. Unfortunately, we were not able to finalize the qualitative study and include the results in this dissertation; however, the data will be available in the coming months. This study of patients' perceptions is expected to improve our understanding of how liver recipients perceive post-Tx weight management and weight gain.

A deeper understanding of patients' engagement in physical activity and healthy eating also has the potential to lower barriers and enhance facilitators of energy balance-related behaviors. As the COM-B model was used to guide our research (i.e., development of the interview questions, analysis guidelines), the results are expected to contribute significantly to the suggested BALANCE intervention. Integrating participants' preferences should enhance their adherence to and acceptance of a weight management program, which is essential for success.[42]

Finally, more research is needed to implement and evaluate behavioral weight management interventions. These will include both preventive interventions, which should be favored because of the physiological mechanisms of weight re-gain, and weight loss interventions in obese recipients, which might require a longer follow-up to

support participants to maintain weight loss.[43-45] In our analysis of the Swiss cohort, two patient groups qualified for behavioral weight management interventions.

Kidney Tx patients had continuously high prevalence rates of obesity over the course of Tx (19% to 22%). Given that 81.4% of these patients remained obese after Tx, this group might benefit from a weight loss intervention. Before kidney Tx, intentional weight loss in patients with chronic kidney disease is debated as a survival benefit in high-BMI patients requiring hemodialysis has been reported.[46,47] However, regarding a nonrandomized 12-month weight loss program in 169 obese patients with chronic kidney disease,[48] MacLaughlin et al. reported that after 1 year, their intervention group lost significantly more weight than their control group (-4.3 ± 5.5 kg versus -1.9 ± 6.6 kg, p = 0.001). During the median follow-up of 32 months, although weight loss had no impact on the likelihood of being waitlisted for kidney Tx, the intervention group had fewer combined events (i.e., death, myocardial infarction, stroke, hospitalization for congestive heart failure) compared to the control group (12% versus 20%, p = 0.055). The authors concluded that participation in this weight loss program might be beneficial for patients with chronic kidney disease, independent of kidney function or need for hemodialysis. In the post-Tx course, however, there have been no studies published on weight loss interventions after kidney Tx.[49,50] This lack of evidence is rather surprising, as both weight gain and obesity are known to increase the risk for graft loss and mortality.[4,8,51]

The second group from the Swiss STCS cohort to qualify for a weight loss intervention consisted of liver Tx recipients. By 3 years post-Tx, this group had the greatest weight gain of any organ group (mean 4.8 kg), the highest incidence of obesity (38.1%), and normal- or overweight patients who gained weight and became obese had increased CVE risk. These patients would benefit from an intervention to prevent weight gain after liver Tx. However, to the best of our knowledge, no post-liver Tx weight management intervention study–either to prevent weight gain or to promote weight loss–has been published to date.

In summary, although increasing rates of post-Tx weight gain and obesity have long been reported in both kidney and liver Tx patients, published studies on post-Tx weight management interventions targeting either remain scarce. The development of programs to support weight management and a healthy lifestyle in both populations is urgently needed, as would likely improve long-term morbidity and mortality.

For the implementation and evaluation of a behavioral intervention, the study design should take into account several methodological aspects: to use a conceptual

framework guiding implementation in clinical practice (e.g., Consolidated Framework for Advancing Implementation Research),[52] to assess additional measures of body weight parameters (e.g., body composition), to measure low levels of physical activity (e.g., sedentary behavior), to combine various research methods (e.g., mixed method design to examine clinical outcomes and acceptance of the behavioral intervention), to consider study designs other than randomized controlled trials (e.g., realist randomized controlled trials, which acknowledge the dynamic structures, mechanisms and contexts influencing the research setting),[53] and to integrate e-Health technology that facilitates data collection (e.g., smart phones, step trackers).

8.4 Implications for the clinical practice

Although evidence on the impact of post-Tx body weight parameters on patient outcomes remains scarce, interventions to prevent post-Tx weight gain and obesity should be considered based on the best available information. Prevention of excessive weight gain has also been suggested by clinical guidelines in the liver, kidney and heart Tx populations; however, these guidelines made no recommendations specifying intervention content.[54-56]

The BALANCE project's findings support the organization of post-Tx follow-up care based on a chronic disease model supported by eHealth technology.[57] Structuring the healthcare system according to a chronic disease model shifts the focus from traditional symptom-driven management of acute conditions to an approach that addresses the needs of chronically ill people and empowers patients to take an active part in the management of their illness.[58] A proactive, evidence-based, patient-centered approach is a key component to increasing the quality of care and improving outcomes.[59-61]

Wagner et al.'s Chronic Care Model (CCM)[58,62] is one of the most studied chronic disease models.[63] It will be used to describe and elaborate on 6 components, all of which the healthcare system needs to address to support effective weight management after Tx: self-management support, delivery system design, decision support, clinical information systems, organization of health care, and community.

1. Self-management support: This element highlights the patients' roles in managing their own health issues. To be optimally prepared to manage daily life with a chronic condition, patients need information on their conditions, assistance in skill building, and support from their social and professional surroundings.

Regarding weight management, a behavioral intervention would mainly target this CCM element. As outlined in Chapter 7, service provision (i.e., delivering special-

ized services or offering specific consultations) is the policy category best suited to the delivery of intervention functions (i.e., the component expected to support behavior change, e.g., education, persuasion, environmental restructuring, modeling, or enablement). In a weight management program, self-management support may cover a broad range of aspects; however, the amount of support, i.e., the intervention dosage, should follow a step-wise approach tailored to the Tx patients' specific needs.

As indicated above, all Tx recipients should receive information regarding the potential impacts of weight gain and obesity on their health and the value of post-Tx energy balance-related behaviors. This information should be supplemented by weight measurement and review during each Tx center follow-up consultation. Moreover, over the long-term post-Tx period, all solid organ Tx recipients are encouraged to regularly monitor and log their weight at home.

Patients with increasing weight and especially those at risk of becoming obese need additional self-management support. This should cover building skills to self-monitor their physical activity, setting goals to increase activity levels, solving problems to reduce barriers for activity, and obtaining support both from the interprofessional healthcare team and from their peers.

Supporting patients in self-monitoring is particularly important. Self-monitoring includes, for example, recording body weight, dietary intake and physical activity. This increases individuals' awareness of their current behaviors.[64] Conclusive evidence has showed that self-monitoring is crucial to successful weight management and maintenance of a healthy lifestyle.[65]

2. Delivery system design: This component covers the structures necessary within the organization to deliver all necessary care. It includes the definition of roles within the organization, clarity regarding the amount and intensity of care appropriate for specific patients, and the implementation of healthcare innovations.

Regarding weight management, the importance of a multidisciplinary healthcare team has already been outlined.[39,54] On a regular basis, this team evaluates whether an intervention needs to be adapted, e.g., if a patient is unable to increase physical activity.

Another important component in this element is the use of new technologies such as eHealth to facilitate intervention delivery. eHealth has been defined as "the use of information and communication technologies for health".[66] Due to rapid recent technical developments, eHealth has become an effective, accessible and common delivery mode for behavioral interventions focusing on weight management.[67,68] Additional-

ly, eHealth tools can be used to enhance self-management in people living with chronic conditions.[57]

The application of eHealth technology is also increasing in the Tx population, and has recently been reviewed by Fleming et al.[69] The authors found potential benefits of eHealth applications both pre- and post-Tx. The greatest success was noted in multicomponent interventions (i.e., use of electronic devices with multiple applications, reminders and alert functions), which were effective in view of increased self-monitoring, increased adherence to medication taking and blood monitoring, as well as decreased blood pressure levels. However, no study has yet found a beneficial effect regarding graft outcomes, few have aimed to control post-Tx chronic conditions such as hypertension or diabetes and none have focused on weight management or post-Tx energy balance-related behaviors.[69]

Although patients' overall acceptance and willingness to use eHealth devices after Tx appears high,[69] the sustained use of eHealth technology remains challenging. It could be argued that eHealth applications embedded in a chronic care model and supported by a healthcare team might improve eHealth tools' sustainability.

In this regard, a recent randomized controlled trial in 46 kidney Tx recipients reported interesting results. Schmidt et al. combined telemedical technology (i.e., remote telemonitoring, real-time video consultations) with a case management approach in the first year of post-Tx follow up care.[70] Compared to the usual care group, the intervention group had higher adherence rates with immunosuppressive medication, fewer unplanned hospital admissions, better disease-specific quality of life, and higher post-Tx employment rates. Additionally, the authors reported high patient engagement with the telemedical intervention.

3. Decision support: Treatment decisions should be rooted in evidence-based guidelines. *Regarding weight management*, specific treatment guidelines in the Tx population (e.g., diet and physical activity, management of cardiovascular risk factors) have yet to be developed. Until they become available, healthcare professionals are advised to follow guidelines for the general population.[39]

4. Clinical information systems: Electronic information systems facilitate rapid information exchange both between healthcare professionals and between the care team and the patient. *Regarding weight management*, the inclusion of eHealth technology would provide a stable platform for information access and data sharing (e.g., electronic patient records, use of a website with secured log in, data transfer via smartphone applications).

5. Organization of health care: Teamwork and leadership within the organization both drive and guide the implementation of the CCM.

Regarding weight management, the interprofessional healthcare team could be led by an advanced practice nurse, which has been successfully tested in kidney Tx.[71] Advanced practice nurses have at least a master degree in nursing science and are prepared to care for complex patient populations. The integration of specialized nurses into Tx teams is highly recommended. They provide expert care and guidance in pre- and post-Tx settings, especially in supporting patient self-management.[72,73]

6. Community: Community-based resources and programs can expand the services offered by clinics. *Regarding weight management*, a broad variety of external programs are available, many of which support healthy post-Tx lifestyle choices. This can include offers from sport clubs, cooking classes, peer groups, or weight loss programs. Given that some patients have to travel longer distances to their Tx centers, attending programs in their areas or neighborhoods might be more feasible for them.

The rationale for suggesting the CCM to support effective weight management in Tx recipients is 2-fold. First, as a chronically ill population, Tx patients need complex medical and therapeutic regimens to manage the risk of Tx-related, metabolic or cardiovascular comorbidities.[54-56] This involves lifelong self-management in view of following a healthy lifestyle (e.g., weight management, physical activity, healthy eating), adherence to medication taking, and symptom management.[73] Implementation of chronic illness management (in place of the current acute care model) is expected to improve long-term outcomes and has been postulated by Tx experts.[74] The benefits of restructuring the healthcare system according to a chronic disease model go well beyond facilitating follow-up care and improving clinical patient outcomes,[60,61,71] it is also an optimal structure to provide behavioral interventions to prevent weight gain and obesity.

Second, obesity belongs to the chronic diseases. The World Obesity Federation labeled obesity as a chronic, relapsing, progressive disease process, and emphasized the need to prevent and control the global epidemic.[75] And as with other chronic diseases, acute-care treatments do nothing to change its driving mechanisms. Therefore, targeting weight gain and subsequent obesity requires a shift from the existing acute-care paradigm to a comprehensive patient-centered approach based on the target population's long-term needs and incorporating coordinated care from multidisciplinary teams.[76,77] The implementation of a chronic disease model was also recommended by the *2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults*.[78]

Assessing the effectiveness of chronic disease models, two recent literature reviews[63,79] found promising results in view of improved clinical outcomes (e.g., measurements of blood pressure, lipid or blood sugar, adherence to treatment) and process outcomes (e.g., adherence to guidelines for the performance of routine tests) in various patient groups with chronic conditions (e.g., diabetes, cardiovascular disease or chronic obstructive pulmonary disease). The most commonly studied and applied chronic disease model elements were self-management support and delivery system design. Those two elements have been suggested as the effective key components of chronic disease models.[59] However, in the literature review the variability of studies examining such models (e.g., study design, implementation of specific elements) limited direct comparison of the components. Davy et al. therefore concluded that it remains unclear which element of the chronic disease model most effectively improves outcomes.[60,61,79]

In kidney Tx, Bissonnette et al.'s 2013 study elegantly described the successful application of a chronic disease model.[71] The authors re-organized their follow-up care and tested the effectiveness of a nurse-led interprofessional collaborative chronic care clinic. The team intervention was designed to support disease self-management, shared decision making and adherence-enhancing behavior.

Over the 3.5-year period, intervention patients had significantly fewer emergency room visits and hospital admissions compared to the control group. Clinical outcome parameters including systolic and diastolic blood pressure, carbon dioxide, hemoglobin, or phosphate parameters did not differ between the groups. Although this intervention did not focus on post-Tx body weight parameters, the implementation of a chronic disease model is also expected to improve post-Tx weight management outcomes.

The organization of the healthcare system according to the CCM is expected to support patients not only to effectively self-manage the Tx-related recommendations, but to augment that care with post-Tx weight management. However, experts have argued that comprehensive programs supporting lifestyle changes might be beyond the resources of some Tx centers.[80] If the implementation of a CCM is not feasible, or if it takes some time to realize, the interprofessional healthcare team should at least address the following issues in regular follow-up appointments:

– Measurement of body weight parameters: weight, BMI, and body composition (if available)
– Review and feedback on the evolution of the patient's body weight parameters
– Normal weight, overweight and obese patients should be advised not to gain weight

– Normal weight and overweight liver Tx patients (especially males and those with alcoholic liver disease) should be informed about the relationship between new-onset obesity and CVE
– Physical activity: note the amount, intensity and duration of daily physical activity, advise on beneficial effect of physical activity and national recommendations (150 min/week with moderate-intensity OR 60 min/week with vigorous intensity). In cases where the patient does not meet the recommendations, encourage goal-setting to increase daily physical activity, refer to local training groups
– Diet: advise on healthy eating, encourage recipients to favor healthy food

8.4 Strengths and Limitations of the BALANCE project

One strength of this dissertation was the inclusion of various methods and study designs to comprehensively examine body weight parameters in the Tx populations. Not only did the meta-analyses provide important evidence by summarizing the current literature, the accompanying systematic literature review allowed a mapping of the remaining gaps, which imply recommendations for future research.

Additionally, three studies used data from the prospective nationwide STCS, including genetic, sociodemographic, behavioral, biomedical, and psychological variables. This comprehensive dataset allowed us to take into consideration the complexity of weight gain and obesity. Additionally, we used a theoretical framework to examine many individual factors and their interrelationships. This was novel, as previous studies lacked theoretical guidance, hampering their research quality. Our framework guided the design and realization of 2 studies. Regarding our findings on obesity, which is characterized by complex mechanisms, the results of our theory-driven approach not only add to the body of evidence, but potentially will advance the field of obesity research.

Besides its strengths, this thesis has also several methodological limitations. Several variables important to the examination of body weight were not available for analysis in the BALANCE project. For example, we were unable to integrate data on energy balance-related behaviors including physical activity and eating–which Tx recipients themselves consider key factors of weight gain and obesity.[40,41] While the measure of eating behavior was not included in the STCS dataset, a measure of activity was added to the regular STCS data collection in 2012. However, a preliminary data analysis in an early phase of the dissertation revealed questionable results in view of that item's validity in relation to the concept of physical activity. It was therefore not possible

to include this variable in our analyses. Instead, the item was revised for the benefit of future STCS data studies examining body weight parameters.

Another component which could not be captured was body composition, as it also was not included in STCS data collection. This variable would have been useful to verify and differentiate post-Tx weight gain in view of possible miscalculation of BMI due to unusual levels of fluids, muscle or fat mass. Finally, we were unable to include information about body weight parameters previous to end-stage organ disease. Given the action of physiological mechanisms that compensate for energy shortages–i.e., that drive weight re-gain after weight loss–[43-45] it is possible that some of those physiological mechanisms contributed to post-Tx weight gain. However, we could not distinguish this aspect in our analysis.

Another limitation is the short follow-up period in our studies using data from the STCS database. The STCS was established in 2008 as an open cohort, i.e., a cohort which not only follows participants included since the beginning, but also adds every Swiss Tx patient willing to sign an informed consent form. In practical terms, this meant that while some of our participants had a follow-up period of 8 years, many had been followed up over much shorter periods. A longer follow-up time would have provided an opportunity to examine whether weight gain eventually levels off. Additionally, a longer follow-up would also have been favorable to better examine outcomes such as CVE and survival.

Although we performed a systematic literature search in all 4 solid organ groups, we only had the time and resources for data extraction in the liver Tx population. Since the BALANCE project commenced, five systematic reviews examining the impact of pre-Tx body weight parameters on patient survival have been published (kidney n = 3,[81-83] liver n = 1,[84] and lung n = 1[85]). This emphasizes first how timely the topic itself is, second, that our ongoing review will be the first to also look explicitly at post-Tx body weight parameters, and third, that a systematic review is still missing in heart Tx.

8.5 Conclusion

In conclusion, the BALANCE project contributed to the evidence base regarding the evolution of body weight parameters in kidney, liver, heart and lung Tx, as data on these groups were compared concurrently for the first time, thereby highlighting how their trajectories differ up to 3 years post-Tx. Additionally, the thesis increased the limited evidence on the impact of new-onset obesity on morbidity and mortality following liver Tx. Finally, its findings provided new insights regarding the broad examination of ge-

netic, biomedical, behavioral, sociodemographic, and psychological risk factors related to post-Tx weight gain, obesity and new onset obesity.

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Institute of Nursing Science, University of Basel, Switzerland

1999 – 2001 **Diploma in Intensive and Anesthesiology Care**
Kliniken Ludwigsburg Bietigheim gGmbH, Germany

1994 – 1997 **Diploma Registered Nurse in General Nursing**
Kliniken Ludwigsburg Bietigheim gGmbH, Germany

1985 – 1994 **Abitur (General qualification for university entrance)**
Friedrich-Abel-Gymnasium Vaihingen / Enz, Germany

APPOINTMENTS AND PROFESSIONAL EXPERIENCE

Academic

2018 – present **Clinical Nurse Scientist**
Center for Clinical Nursing Science
University Hospital of Zurich, Switzerland

2018 – present **Scientific Collaborator**
Institute of Nursing Science, University of Basel, Switzerland

2018 – present **Student Advisor**
Institute of Nursing Science, University of Basel, Switzerland

2012 – 2017 **Research Assistant**
Institute of Nursing Science, University of Basel, Switzerland

Clinical and non-academic

2012 – present	Administrative Coordinator Psychosocial Interest Group of the Swiss Transplant Cohort Study, Switzerland, Swiss National Science Foundation Grant numbers 134267 and 148512, status employee
2011 – 2017	Advanced Practice Nurse Liver Transplantation - Department for abdomen and Metabolism University Hospital of Zurich, Switzerland
2008 – 2011	Staff Nurse Intensive Care Unit for Visceral and transplant Surgery University Hospital of Zurich, Switzerland
2004 – 2008	Staff Nurse and Assistant Head Nurse Surgical and Medical Intensive Care Unit St. Franziskus Hospital Münster Münster, Germany
2001 – 2003	Staff Nurse Intensive Care Unit for Trauma Surgery Städtisches Klinikum Braunschweig gGmbH, Germany
1997 – 2001	Staff Nurse Interdisciplinary Intensive Care Unit Kliniken Ludwigsburg Bietigheim gGmbH, Germany

ADDITIONAL PROFESSIONAL AND ACADEMIC TRAINING

2016	Behavior Change - Principles and Practice Summer School, Center for Behavioral Change, UC London
2016	Genomics and Science of Symptom Management Summer School, SPINE, University of Basel
2015	Introduction to Human Behavioral Genetics, Coursera - University Of Minnesota's Online Course
2015	Hochschuldidaktik, Modul 2 University of Basel
2015	Better data for better patient safety! Summer School, SPINE, University of Lausanne
2014	Developing Behavioral Interventions for Older Adults Summer School, Institute of Nursing Science, University of Basel
2013 - 2015	European Academy of Nursing Science (EANS) Summer School for Doctoral Studies, 3-year program

MEMBERSHIPS AND SCIENTIFIC SOCIETIES

Since 2011	International Transplant Nursing Society – ITNS
Since 2011	Swiss Network of Transplant Nurses (ANTS)
Since 2011	Leuven Basel Adherence Research Group (LBARG)
Since 2012	Psychosocial Interest Group, Swiss Transplant Cohort Study

Since 2013	Schweizer Berufsverband der Pflegefachfrauen und Pflegefachmänner
Since 2013	European Academy of Nursing Science (EANS)
Since 2014	The Transplantation Society (TTS)
Since 2014	European Society for Organ Transplantation (ESOT)

OTHER ACTIVITIES

2015 Member of the Scientific committee of the 1st Annual SPINE Doctoral Student Research Day, November 19th, 2015

FUNDED RESEARCH

Beckmann S, Ivanović N, Denhaerynck K, Binet I, Koller MT, Boely Janke E, De Geest S, for the STCS Psychosocial Interest Group and the Swiss Transplant Cohort Study. Weight gain, overweight and obesity in solid organ transplantation – evolution from pre- to post transplant, risk factors and clinical outcomes, Role: principal investigator, Time Period: 2014-2015, Swiss National Science Foundation STCS Grant (number 134267), **Direct costs: 20'000 CHF**

Beckmann S, Drent G, Ivanović N, De Geest S. Systematic Literature Review on Weight Gain, Overweight, and Obesity in Solid Organ Transplantation, Role: principal investigator, Time Period: 2014-2015, International Transplant Nurses Society Research grant award, **Direct costs: 2'500 US Dollar**

Beckmann, S. Top-up stipend for PhD studies in Nursing Science, Time Period: 2015-2016, PhD Educational Platform for Health Sciences (PPHS) University of Basel: **5'500 CHF**

AWARDS

2016 Best Oral Presentation Award for the presentation entitled *Postoperative delirium after liver transplantation is associated with increased length of stay and lower survival in a prospective cohort.* Nursing Science Congress Groningen, The Netherlands

PUBLICATIONS

Peer reviewed publications

Valenta S, De Geest S, Fierz K, **Beckmann S**, Halter J, Schanz U, Nair G, Kirsch M. *Perception of late effects among long-term survivors after haematopoietic stem cell transplantation: Descriptive analysis and validation of the Brief Illness Perception Questionnaire. A substudy of the PROVIVO study*. European Journal of Oncology Nursing 27 (2017) 17e27.

Beckmann S, Nikolic N, Denhaerynck K, Binet I, Koller M, Boely Janke E, De Geest S. for the Psychosocial Interest Group, Swiss Transplant Cohort Study. *Evolution of body weight parameters up to 3 years after solid organ transplantation: the prospective Swiss Transplant Cohort Study.* Clinical transplantation 2016;00:e12896. doi:10.1111/ctr.12896.

Vogel B, De Geest S, Fierz K, **Beckmann S**, & Zúñiga F. *Dementia care worker stress associations with unit type, resident, and work environment characteristics: a cross-sectional secondary data analysis of the Swiss Nursing Homes Human Resources Project (SHURP).* International Psychogeriatrics, online first. 2016 DOI: 10.1017/S1041610216002027

Beckmann S, Schubert M, Burkhalter H, Dutkowski P, De Geest S. *Postoperative delirium after liver transplantation is associated with increased length of stay and lower survival in a prospective cohort.* Progress in Transplantation 2017, 27(1): 23-30. DOI: 10.1177/1526924816679838

Saigi-Morgui N, Quteineh L, Bochud PY, Crettol S, Kutalik Z, Wojtowicz A, Bibert S, **Beckmann S,** Mueller NJ, Binet I, van Delden C, Steiger J, Mohacsi P, Stirnimann G, Soccal P, Pascual M, Eap CB and the Swiss Transplant Cohort Study. *Weighted genetic risk scores and prediction of weight gain in Solid Organ Transplant populations.* PLoS ONE 11(10): e0164443. doi:10.1371/journal. pone.0164443

Beckmann S, Künzler-Heule P, Biotti B, Spirig R, *Mastering Together the Highs and Lows: Patients' and Caregivers' Perceptions of Self-Management in the Course of Liver Transplantation*. Progress in Transplantation 2016, 26(3):215-23. DOI: 10.1177/1526924816654769

Künzler-Heule P, **Beckmann S,** Mahrer-Imhof R, Semela D, Händler-Schuster D, *Being an informal caregiver for a relative with liver cirrhosis and overt hepatic encephalopathy: a phenomenological study.* Journal of Clinical Nursing, DOI: 10.1111/jocn.13298

Beckmann S, Ivanović N, Drent G, Ruppar T, De Geest S, *Weight gain, overweight and obesity in solid organ transplantation—a study protocol for a systematic literature review*. Systematic Reviews 2015, 4:2. DOI: 10.1186/2046-4053-4-2

Non peer reviewed publications

Beckmann S, Künzler-Heule P, Odermatt R, Biotti B und Staudacher D. *Ich lebe von Tag zu Tag*. Clinical Update, SBK, Krankenpflege, 2017, 5: 32-33

Beckmann S und De Geest S. *Adipositas und Gewichtszunahme bei Organtransplantation*. Clinical Update, SBK, Krankenpflege, 2015, 7: 34-35

Group authored papers

Danuser B, Simcox A, Studer R, Koller M, Wild P for the Psychosocial Interest Group, Swiss Transplant Cohort Study. *Employment 12 months after kidney transplantation: An in-depth bio-psycho-social analysis of the Swiss Transplant Cohort*. PLoS ONE 12(4): e0175161.

Mauthner O, Claes V, Walston J, Engberg S, Binet I, Dickenmann M, Golshayan D, Hadaya K, Huynh-Do U, Calciolari S, De Geest S. For the GERAS study consortium, For the Psychosocial Interest Group, Swiss Transplant Cohort Study (STCS). *Exploring frailty and mild cognitive impairment in kidney transplantation to predict biomedical, psychosocial, and health cost outcomes (GERAS): Protocol of a nationwide prospective cohort study.* Journal of advanced nursing. 2016 Oct 12. doi: 10.1111/jan.13179.

De Geest S, Burkhalter H, Bogert L, Berben L, Glass TR, Denhaerynck K for the Psychosocial Interest Group, Swiss Transplant Cohort Study. *Describing the evolution of medication non-adherence from pre-transplant until 3 years post-transplant and determining pre-transplant medication non-adherence as risk factor for post-transplant non-adherence to immunosuppressives: The Swiss Transplant Cohort Study*. Transplant International 2014 Jul;27(7):657-66. doi: 10.1111/tri.12312. Epub 2014 Apr 29

De Geest S, Burkhalter H, Berben L, Bogert LJ, Denhaerynck K, Glass TR, Goetzmann L, Kirsch M, Kiss A, Koller MT, Piot-Ziegler C & Schmidt-Trucksäss A, For The Psychosocial Interest Group Swiss Transplant Cohort Study (2013). *The Swiss Transplant Cohort Study's framework for assessing lifelong psychosocial factors in solid-organ transplants*. Progress in Transplantation, 23(3), 235-246. doi: 10.7182/pit2013250

Bonzanigo, A, Burkhalter, H, De Geest, S for the Psycho-Social Interest Group, Swiss Transplant Cohort Study. *Subjektive Patientenergebnisse vor und nach der Transplantation: Daten der Swiss Transplant Cohort Study*. News. Schweizerischer Transplantierten Verein 2013; 42: 13-16

SUPERVISED MASTER THESIS

Ivanović N, Beckmann S, Denhaerynck K, Binet I, Koller M, Boely Janke E, De Geest S for the Psychosocial Interest Group, Swiss Transplant Cohort Study. *Overweight, obesity and weight gain from pre- to post-transplant following solid organ transplantation: A prospective swiss cohort study.* 2014, unpublished thesis

Kabut K, Beckmann S, Mauthner O. *Erfahrungen von Patientinnen und Patienten mit einer Gewichtszunahme nach Lebertransplantation – eine qualitative Studie*, ongoing

ORAL PRESENTATION

Beckmann S, Künzler-Heule P, Biotti B, Spirig R. *Mastering Together the Highs and Lows: Patients' and Caregivers' Perceptions of Self-Management in the Course of Liver Transplantation.* Oral presentation at the 25th Annual ITNS Symposium (2016, October 16), Pittsburgh, United States of America

Beckmann S, Drent G, Nikolic P, Ruppar T, De Geest S. *A systematic literature review on weight gain and obesity in solid organ transplantation.* Oral presentation at the 25th Annual ITNS Symposium (2016, October 16), Pittsburgh, United States of America

Beckmann S, Schubert M, Burkhalter H, Dutkowski P, De Geest S. *Postoperative delirium after liver transplantation is associated with increased length of stay and lower survival in a prospective cohort.* Oral presentation at the 25th Annual ITNS Symposium (2016, October 15), Pittsburgh, United States of America

Beckmann S, Schubert M, Burkhalter H, Dutkowski P, De Geest S. *Postoperative delirium after liver transplantation is associated with increased length of stay and lower survival in a prospective cohort.* Oral presentation at the Nursing Science Congress Groningen (2016, May 30 & June 1), The Netherlands

Beckmann S, Künzler-Heule P, Biotti B, Spirig R. *Mastering Together the Highs and Lows: Patients' and Caregivers' Perceptions of Self-Management in the Course of Liver Transplantation.* Oral presentation at the Nursing Science Congress Groningen (2016, May 30 & June 1), The Netherlands

Valenta S, **Beckmann S**, Fierz K, De Geest S, & Kirsch M. (2016). *Validation of the German Brief Illness Perception Questionnaire among Long-Term Survivors after Hematopoietic Stem Cell Transplantation - A Sub-Study of the PROVIVO Study*. Bone Marrow Transplantation, 51(S1), 42nd Annual Meeting of the European Society for Blood and Marrow Transplantation, p. 515-516. doi:10.1038/bmt.2016.50.

Gerwig N, Kirsch M, Fierz K, **Beckmann S**, De Geest S. (2016). *Low Well-Being and Higher Supportive Care Needs are Related to Increased Levels of Depressive, Anxiety and Physical Symptoms among Long-Term Survivors after Hematopoietic Stem Cell Transplantation. A Mixed Methods Analysis of the PROVIVO study.* Bone Marrow Transplantation 2016; 51(S1): 544. doi:10.1038/bmt.2016.50.

Beckmann S. *Übergewicht und Adipositas nach Organtransplantation – Grund zur Sorge? Erkenntnisse aus der Schweizerischen Kohortenstudie.* Oral presentation at the 11. Symposium für Transplantierte (2015, November 21), Inselspital Bern, Switzerland

Beckmann S, Nikolic N, Denhaerynck K, Binet I, Koller M, Boely Janke E, De Geest S. for the STCS Psychosocial Interest Group and the Swiss Transplant Cohort Study. *Pretransplant risk factors for obesity at 1 year after organ transplantation. A secondary data analysis of the Swiss Transplant Cohort Study.* Oral presentation at the 1st SPINE Doctoral Student Research Day (2015, November 19), Basel, Switzerland.

Beckmann S, Künzler-Heule, P. *Kontinuität in der Patientenversorgung vor und nach Lebertransplantation - spitalübergreifende Zusammenarbeit von APNs*. Oral presentation at the Wissenschaftskonferenz-Gesundheitsberufe (2015, September 23), Inselspital Bern, Switzerland

Künzler-Heule P, **Beckmann S**, Mahrer Imhof R, Semela D, Händler-Schuster D. *"As if the brain had been turned off" - Caregiver's Experiences of Overt Hepatic Encephalopathy.* Presentation at the Congrès Annuel Interlaken Kongress (2014, September 11-12), Kongresszentrum Interlaken: SGG - SGVC - SASL.

Beckmann S, Künzler-Heule P. *Kontinuität in der Patientenversorgung vor und nach Lebertransplantation- spitalübergreifende Zusammenarbeit von APNs.* Oral presentation at the 3rd International APN ANP Congress "Sein oder nicht Sein" (2015, September 4-5), Munich, Germany.

Beckmann S, Künzler-Heule P. *Bridging the gap between institutions: Continuous nursing care and self-management support throughout the liver transplant process*. Oral presentation at the 6th Symposium of the Swiss Clinical Trial Organisation (2015, June 17), St.Gallen, Switzerland

Beckmann S. *Weight gain, overweight and obesity in solid organ transplantation: Need for action?* Oral presentation at the 50th International Liver Congress, Organised by EASL, The European Association for the Study of the Liver (2015, April 22-26), Vienna, Austria.

Beckmann S. *Keep the BALANCE - eating and physical activity as key behaviors for a healthy lifestyle after transplantation.* Oral presentation at the 1st ETAHP Meeting - European Transplant Allied Healthcare Professionals Meeting (2014, October 3-4), Budapest, Hungary.

Beckmann S, Kirsch M, Mauthner O. *Selbstmanagement & Transplantation Neues aus Forschung & Praxis, Pflegesprechstunde Lebertransplantation am UniversitätsSpital Zürich.* Oral presentation at the SBK-Kongress (2014, June 4 – 6), Basel, Switzerland

Beckmann S, Schubert M, Burkhalter H, Dutkowski P, De Geest S. *Postoperative delirium in liver transplant recipients: Incidence, impact on clinical patient outcomes and risk factors. A preliminary data analysis*. Oral presentation at the Joint Congress of the International Transplant Nurses Society (ITNS) and the Italian Society for Safety and Quality in Transplantation (SISQT) (2013, April 8-12), Florence, Italy.

Beckmann S, Duerinckx N, Ivanovic N, De Geest S. *Weight gain and obesity in solid organ transplantation - results from a structured literature review.* Oral presentation at the Joint Congress of the International Transplant Nurses Society (ITNS) and the Italian Society for Safety and Quality in Transplantation (SISQT) (2013, April 8-12), Florence, Italy.

POSTER PRESENTATION

Beckmann S, Dutkowski P, Nikolic N, Denhaerynck K, Binet I, Koller M, Boely E, De Geest S for the Psychosocial Interest Group, Swiss Transplant Cohort Study. *Evolution of body weight parameters up to 3 years after liver transplantation: the prospective Swiss Transplant Cohort Study.* Poster presentation at the International Liver Congress (2017, April 19-23), Amsterdam, The Netherlands.

Künzler-Heule P, Semela D, Müllhaupt B, **Beckmann S**. *Nurse-led self-management support across two hospitals in liver transplantation: a win-win situation for patients and health care professionals.* Poster presentation at the International Liver Congress (2017, April 19-23), Amsterdam, The Netherlands.

Beckmann S, Ivanović I, Denhaerynck K, Binet I, Koller M, Boely Janke E, De Geest S, for the STCS Psychosocial Interest Group and the Swiss Transplant Cohort Study. *Pre-transplant risk factors for obesity at 1 year after solid organ transplantation: a secondary data analysis of the prospective, nationwide Swiss Transplant Cohort Study.* 17th Congress of the European Society for Organ Transplantation (2015, September 13-16), Brussels, Belgium.

Beckmann S, Schubert M, Burkhalter H, Dutkowski P, De Geest S. *Postoperative Delirium after Liver Transplantation is Associated with Higher Health Care Utilization and Lower Survival.* Poster presentation at the World Transplant Congress (2014, July 26-31), San Francisco (US). Abstract Supplement jointly published by the American Journal of Transplantation 14 (S3): 745, DOI: 10.1111/ajt.12892.