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

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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 (PubMed), Cochrane library, CINAHL, PsycINFO, and EMBASE for quantitative studies on 6 classes of factors (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. 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 LTx. 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 modifiable factors related to post-LTx body weight parameters is still scarce, as definition variability limits data extraction and pooling for 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.

Keywords: obesity, weight gain, immunosuppressive medication, framework

Abbreviations

BMI, body mass index

CI, confidence interval

IQR, interquartile range

LTx, liver transplantation

OR, odds ratio

Mo, months

NA, not available

PROSPERO, international prospective register of systematic reviews

RCT, randomized controlled trial

SD, standard deviation

SE, standard error

US, United States

WHO, World Health Organization

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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], sociodemographic (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 due to 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.

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.

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 of the studies included in the meta-analysis was performed independently by two researchers (SB, GD). In cases 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 weight categories with 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 of the meta-analyzed studies was assessed independently by two researchers (SB, GD) via a 19-item instrument (see supplemental digital content, table 1), 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].

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 Cochrane Q test (with a p value <0.1 indicating significant heterogeneity) and I^2 statistics, with values 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).

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].

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.

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; p = 0.21; I^2 = 29.75%). A subgroup analysis based on year of study publication did not show a significant result (β = 0.05; p = 0.18); nor did 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; p = 0.46; I^2 = 0.00%). As with the tacrolimus analysis, cyclosporine yielded no significant difference 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).

Quality assessment

The results of the quality assessment are shown in the supplementary material Figure 4. All studies had retrospective study designs (n = 6, 100%); four (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.

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 were 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 emphasize behavior's relationships with other factors (e.g., psychological [i.e., fear, anxiety], biomedical [i.e., pain], and sociodemographic [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 number 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, the literature search retrieved 8 studies which examined tacrolimus or cyclosporine with weight gain after LTx, however, none of those 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, although we applied no time limit for the search, data extraction from studies performed more than 10 years ago was sometimes limited due to information missing from reports or articles, as authors did not typically archive their data or respond to requests for additional information. 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, due to a lack of reported data, we were not able to include information 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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References

[1] World Health Organization, 2012. Obesity, Situation and trends, GHO (GHO), Editor.

[2] Kim WR, Stock PG, Smith JM, Heimbach JK, Skeans MA, Edwards EB et al., OPTN/SRTR 2011 Annual Data Report: liver. Am. J. Transplant. 2013. 13 Suppl 1: p. 73-102.

[3] Everhart JE, Lombardero M, Lake JR, Wiesner RH, Zetterman RK, and Hoofnagle JH, Weight change and obesity after liver transplantation: incidence and risk factors. Liver Transpl. Surg. 1998. 4(4): p. 285-96.

[4] Richards J, Gunson B, Johnson J, and Neuberger J, Weight gain and obesity after liver transplantation. Transpl. Int. 2005. 18(4): p. 461-6.

[5] Wawrzynowicz-Syczewska M, Karpinska E, Jurczyk K, Laurans L, and Boron-Kaczmarska A, Risk factors and dynamics of weight gain in patients after liver transplantation. Ann. Transplant. 2009. 14(3): p. 45-50.

[6] Beckmann S, Nikolic N, Denhaerynck K, Binet I, Koller M, Boely E et al., Evolution of body weight parameters up to 3 years after solid organ transplantation: The prospective Swiss Transplant Cohort Study. Clin. Transplant. 2017. 31(3).

[7] Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D et al., European Guidelines for Obesity Management in Adults. Obes Facts 2015. 8(6): p. 402-24.

[8] Huscher D, Thiele K, Gromnica-Ihle E, Hein G, Demary W, Dreher R et al., Dose-related patterns of glucocorticoid-induced side effects. Ann. Rheum. Dis. 2009. 68(7): p. 1119-24.

[9] Watt KD, Metabolic syndrome: is immunosuppression to blame? Liver Transpl. 2011. 17 Suppl 3: p. S38-42.

[10] Aberg F, Jula A, Hockerstedt K, and Isoniemi H, Cardiovascular risk profile of patients with acute liver failure after liver transplantation when compared with the general population. Transplantation 2010. 89(1): p. 61-8.

[11] Rezende Anastacio L, Garcia Ferreira L, Costa Liboredo J, de Sena Ribeiro H, Soares Lima A, Garcia Vilela E et al., Overweight, obesity and weight gain up to three years after liver transplantation. Nutr. Hosp. 2012. 27(4): p. 1351-6.

[12] Anastacio LR, Ferreira LG, de Sena Ribeiro H, Lima AS, Vilela EG, and Toulson Davisson Correia MI, Body composition and overweight of liver transplant recipients. Transplantation 2011. 92(8): p. 947-51.

[13] Fussner LA, Heimbach JK, Fan C, Dierkhising R, Coss E, Leise MD et al., Cardiovascular disease after liver transplantation: When, What, and Who Is at Risk. Liver Transpl. 2015. 21(7): p. 889-96.

[14] Laish I, Braun M, Mor E, Sulkes J, Harif Y, and Ben Ari Z, Metabolic syndrome in liver transplant recipients: prevalence, risk factors, and association with cardiovascular events. Liver Transpl. 2011. 17(1): p. 15-22.

[15] Madhwal S, Atreja A, Albeldawi M, Lopez R, Post A, and Costa MA, Is liver transplantation a risk factor for cardiovascular disease? A meta-analysis of observational studies. Liver Transpl. 2012. 18(10): p. 1140-6.

[16] Anastacio LR, Ferreira LG, Ribeiro Hde S, Liboredo JC, Lima AS, and Correia MI, Metabolic syndrome after liver transplantation: prevalence and predictive factors. Nutrition 2011. 27(9): p. 931-7.

[17] Lucey MR, Terrault N, Ojo L, Hay JE, Neuberger J, Blumberg E et al., Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver Transpl. 2013. 19(1): p. 3-26.

[18] Watt KD, Pedersen RA, Kremers WK, Heimbach JK, and Charlton MR, Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. Am. J. Transplant. 2010. 10(6): p. 1420-7.

[19] Daniel KE, Eickhoff J, and Lucey MR, Why do patients die after a liver transplantation? Clin. Transplant. 2017. 31(3).

[20] Heimbach J, Surgical advances in obese candidates and recipients. Liver Transpl. 2016. 22(S1): p. 62-67.
[21] Charlton MR, Roadmap for improving patient and graft survival in the next 10 years. Liver Transpl. 2016. 22(S1): p. 71-78.
[22] Higgins JPT and Green S, Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. 2011, The Cochrane Collaboration. Available from http://www.cochrane-handbook.org/.
[23] Moher D, Liberati A, Tetzlaff J, Altman DG, and Group P, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009. 339: p. b2535.
[24] Beckmann S, Ivanovic N, Drent G, Ruppar T, and De Geest S, Weight gain, overweight and obesity in solid organ transplantation--a study protocol for a systematic literature review. Syst Rev 2015. 4: p. 2.
[25] World Health Organization, Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ. Tech. Rep. Ser. 2000. 894: p. i-xii, 1-253.
[26] Butland B, Jebb S, Kopelman P, McPherson K, Thomas S, Mardell J et al., Foresight. Tackling Obesities: Future Choices – Project Report, 2007. London: Government Office for Science.
[27] Downs SH and Black N, The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J. Epidemiol. Community Health 1998. 52(6): p. 377-84.
[28] Duerinckx N, Burkhalter H, Engberg SJ, Kirsch M, Klem ML, Sereika SM et al., Correlates and Outcomes of Posttransplant Smoking in Solid Organ Transplant Recipients: A Systematic Literature Review and Meta-Analysis. Transplantation 2016. 100(11): p. 2252-2263.
[29] Review Manager (RevMan) [Computer program], Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.
[30] Higgins JP, Thompson SG, Deeks JJ, and Altman DG, Measuring inconsistency in meta-analyses. BMJ 2003. 327(7414): p. 557-60.
[31] Akarsu M, Bakir Y, Karademir S, Unek T, Bacakoglu A, and Astarcioglu I, Prevalence and risk factors for obesity after liver transplantation: a single-center experience. Hepat. Mon. 2013. 13(8): p. e7569.
[32] Bianchi G, Marchesini G, Marzocchi R, Pinna AD, and Zoli M, Metabolic syndrome in liver transplantation: relation to etiology and immunosuppression. Liver Transpl. 2008. 14(11): p. 1648-54.
[33] Canzanello VJ, Schwartz L, Taler SJ, Textor SC, Wiesner RH, Porayko MK et al., Evolution of cardiovascular risk after liver transplantation: a comparison of cyclosporine A and tacrolimus (FK506). Liver Transpl. Surg. 1997. 3(1): p. 1-9.
[34] Fernandez-Miranda C, Sanz M, dela Calle A, Loinaz C, Gomez R, Jimenez C et al., Cardiovascular risk factors in 116 patients 5 years or more after liver transplantation. Transpl. Int. 2002. 15(11): p. 556-62.
[35] Rabkin JM, Corless CL, Rosen HR, and Olyaei AJ, Immunosuppression impact on long-term cardiovascular complications after liver transplantation. Am. J. Surg. 2002. 183(5): p. 595-9.
[36] Li DW, Lu TF, Hua XW, Dai HJ, Cui XL, Zhang JJ et al., Risk factors for new onset diabetes mellitus after liver transplantation: A meta-analysis. World J. Gastroenterol. 2015. 21(20): p. 6329-40.
[37] Devaux M and Sassi F, Social inequalities in obesity and overweight in 11 OECD countries. Eur. J. Public Health 2013. 23(3): p. 464-9.
[38] Herzog B, Lacruz ME, Haerting J, Hartwig S, Tiller D, Medenwald D et al., Socioeconomic status and anthropometric changes-A meta-analytic approach from seven German cohorts. Obesity (Silver Spring) 2016. 24(3): p. 710-8.

[39] Preiss K, Brennan L, and Clarke D, A systematic review of variables associated with the relationship between obesity and depression. Obes. Rev. 2013. 14(11): p. 906-18.
[40] Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR et al., Genetic studies of body mass index yield new insights for obesity biology. Nature 2015. 518(7538): p. 197-206.
[41] Greenway FL, Physiological adaptations to weight loss and factors favouring weight regain. Int. J. Obes. (Lond.) 2015. 39(8): p. 1188-96.
[42] Bray GA, Fruhbeck G, Ryan DH, and Wilding JP, Management of obesity. Lancet 2016. 387(10031): p. 1947-56.
[43] Palmer M, Schaffner F, and Thung SN, Excessive weight gain after liver transplantation. Transplantation 1991. 51(4): p. 797-800.
[44] Stanfill A, Bloodworth R, and Cashion A, Lessons learned: experiences of gaining weight by kidney transplant recipients. Prog. Transplant. 2012. 22(1): p. 71-8.
[45] LaMattina JC, Foley DP, Fernandez LA, Pirsch JD, Musat AI, D'Alessandro AM et al., Complications associated with liver transplantation in the obese recipient. Clin. Transplant. 2012. 26(6): p. 910-8.
[46] Singhal A, Wilson GC, Wima K, Quillin RC, Cuffy M, Anwar N et al., Impact of recipient morbid obesity on outcomes after liver transplantation. Transpl. Int. 2015. 28(2): p. 148-55.
[47] Hakeem AR, Cockbain AJ, Raza SS, Pollard SG, Toogood GJ, Attia MA et al., Increased morbidity in overweight and obese liver transplant recipients: a single-center experience of 1325 patients from the United Kingdom. Liver Transpl. 2013. 19(5): p. 551-62.
[48] IOM (Institute of Medicine), 2012. Accelerating Progress in Obesity Prevention: Solving the Weight of the Nation. The National Academies Press.: Washington, DC.
[49] National Institute for Health and Clinical Excellence (2014), Managing overweight and obesity in adults – lifestyle weight management services. NICE public health guidance 53, in *NICE public health guidance 53*.
[50] Organisation for Economic Co-operation and Development (OECD), Obesity Update 2017. http://www.oecd.org/health/obesity-update.htm.
[51] Hill JO, Understanding and addressing the epidemic of obesity: an energy balance perspective. Endocr. Rev. 2006. 27(7): p. 750-61.
[52] Hill JO, Thompson H, and Wyatt H, Weight maintenance: what's missing? J. Am. Diet. Assoc. 2005. 105(5 Suppl 1): p. S63-6.
[53] McAlister VC, Haddad E, Renouf E, Malthaner RA, Kjaer MS, and Gluud LL, Cyclosporin versus tacrolimus as primary immunosuppressant after liver transplantation: a meta-analysis. Am. J. Transplant. 2006. 6(7): p. 1578-85.
[54] Desai S, Hong JC, and Saab S, Cardiovascular risk factors following orthotopic liver transplantation: predisposing factors, incidence and management. Liver international : official journal of the International Association for the Study of the Liver 2010. 30(7): p. 948-57.
[55] European Association for the Study of the Liver. Electronic address eee, EASL Clinical Practice Guidelines: Liver transplantation. J. Hepatol. 2016. 64(2): p. 433-485.

Legend of Tables and Figures

Supplementary material

Table 1. Detailed PubMed search string

(("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 2. Characteristics of studies included in meta-analysis

Study Year	Country	Design Setting	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 (37.1) Obese: 33 (14.6)
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

Figure 1. Flowchart according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement

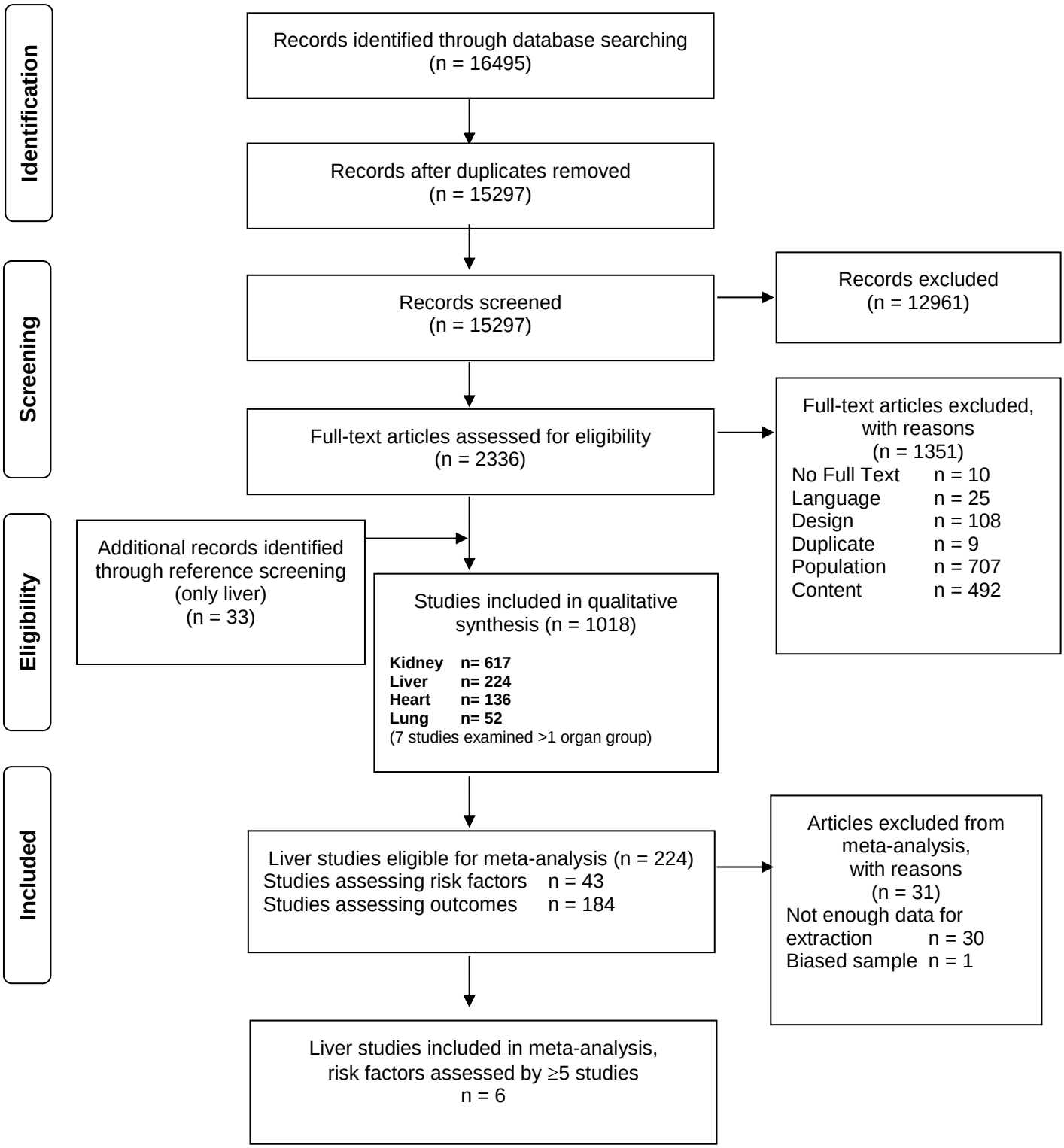
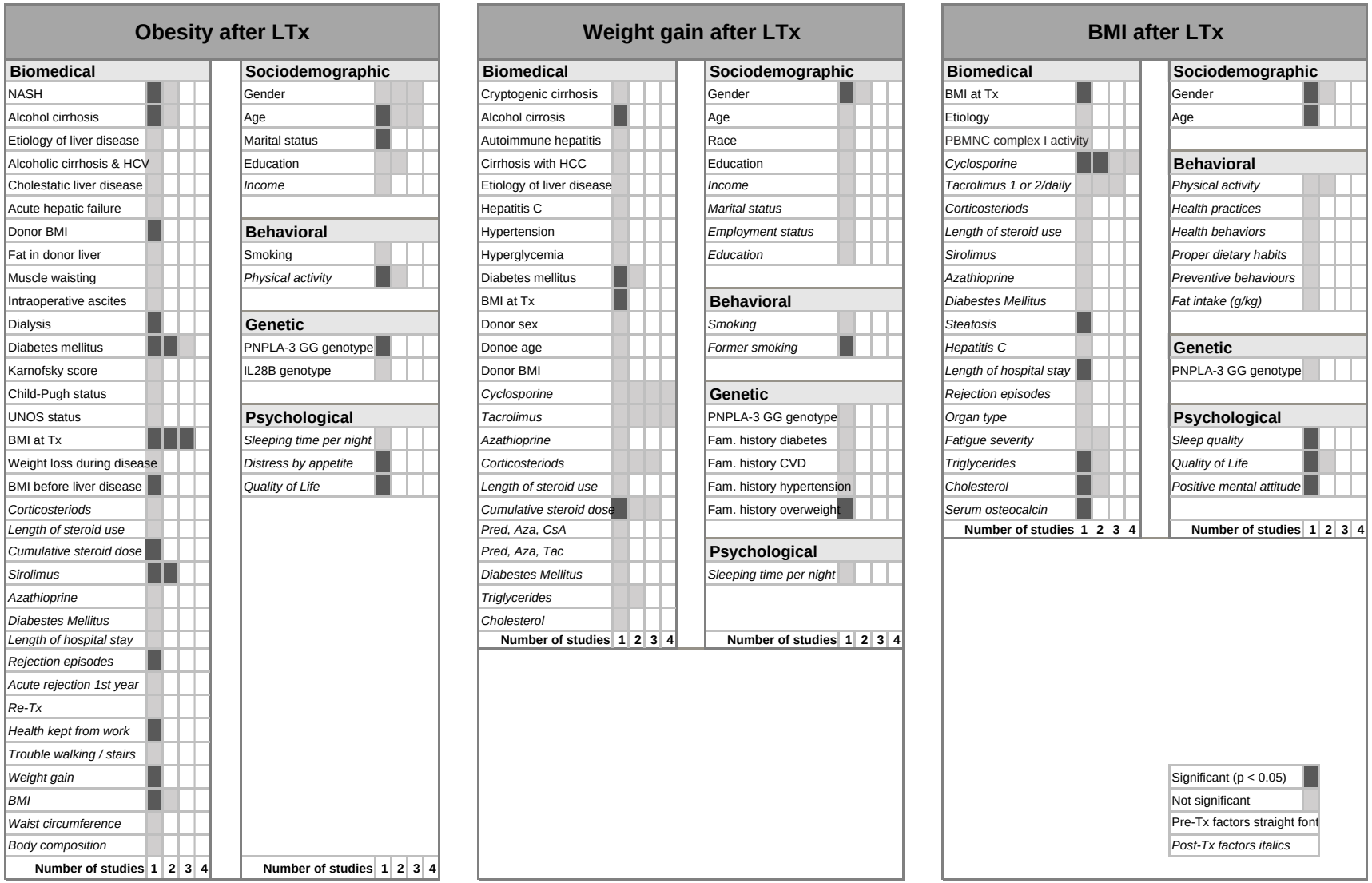


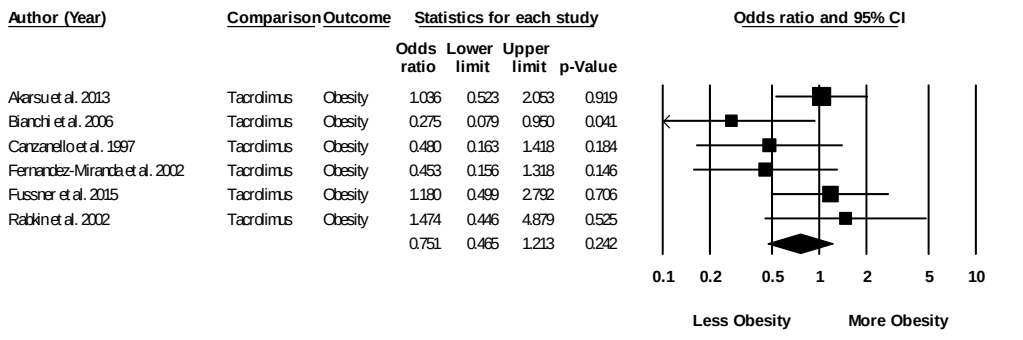
Figure 2. Pre- and post-LTx risk factors of post-LTx obesity, weight gain and BMI assessed by 1 to 4 studies



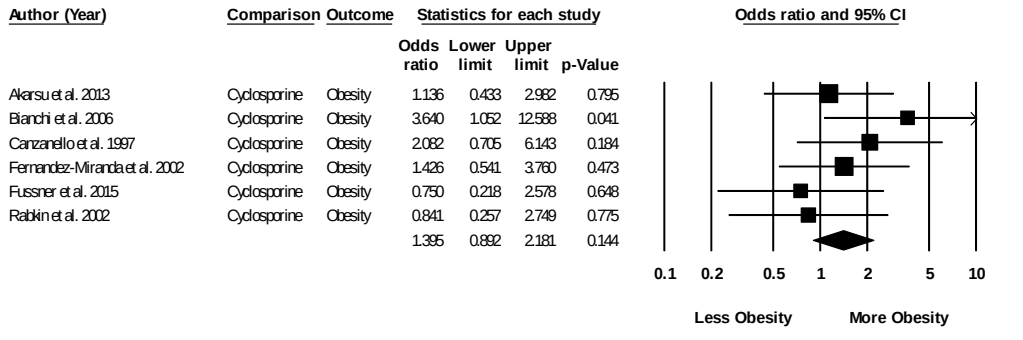
NASH, nonalcoholic steatohepatitis; HCV, hepatitis C Virus; BMI, body mass index; UNOS, United Network for Organ Sharing; Tx, transplantation; HCC, hepatocellular carcinoma; Pred, prednisone; Aaz, Azathioprine, CsA, cyclosporine; Tac, Tacrolimus; CVD, cardiovascular disease

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

Tacrolimus



Cyclosporine



CI, confidence interval

Supplementary material Table 1: Quality assessment instrument

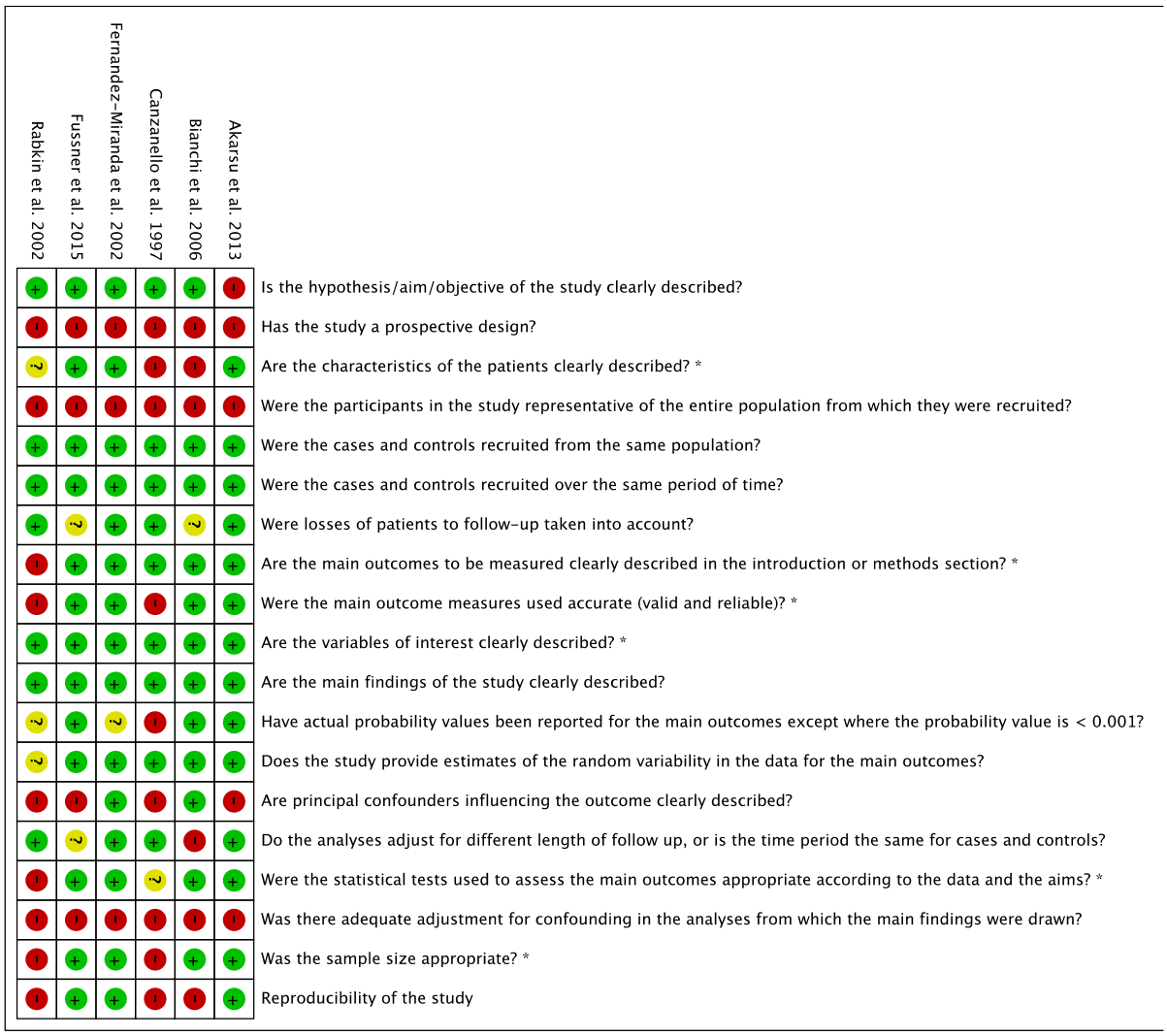
No	Question	Definition	Rating
Aim			
1	Is the hypothesis / aim / objective of the study clearly described?		• Yes • No • Unable to determine
2	Does the study have a prospective design?	Yes: • Prospective data collection	• Yes • No • Unable to determine
Participants			
3	Are the characteristics of the 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 were the cases and controls (case-control studies) recruited from the same population?	Yes: • Patients for all comparison groups were selected from the same hospital / population / cohort Unable to determine: • In cohort and case-control studies: no information concerning the source of patients included	• Yes • No • Unable to determine
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	• Yes • No • Partially

		• Consequences / outcomes	
Results			
11	Are the main findings of the study clearly described?	Yes: • Simple outcome data reported for all major findings This question does not cover statistical tests.	• Yes • No • Partially
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 to distribution of data, results include: o Non-normal: IQR o 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 drawn?	Randomized studies: No: • Main conclusions of the study were based on analyses of treatment rather than intention 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	• Yes • No • Unable to determine
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; RCT, randomized controlled trial; 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.

Supplementary material Figure 4. Quality assessment of the 6 studies included in the meta-analysis



Reproducibility of a study was rated with ‘yes’ when all items with an asterisk* were rated ‘yes’ in this study.